Clinical Trial Protocol

	Document Number:	**c16011431-03**
EudraCT No.: **EU Trial No:**	2016-002254-20	
BI Trial No.:	1297.9	
BI Investigational Product(s):	BI 695501	
Title:	VOLTAIRE-X: Pharmacokinetics, safety, immunogenicity and efficacy 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:	The VOLTAIRE-X trial looks at the effect of switching between Humira® and BI 695501 in patients with plaque psoriasis.	
Clinical Phase:	Phase III	
Trial Clinical Monitor:	Tel.:	
Coordinating Investigator:	Tel.:	
Status:	Final Protocol (Revised Protocol [based on Global Amendment 2])	
Version and Date:	**Version: 3.0**	**Date: 25 Jul 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	NA
Active ingredient name:	BI 695501
Protocol date	Revision date 25 Jul 2019
Trial number	1297.9
Title of trial:	Pharmacokinetics, safety, immunogenicity and efficacy 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. The VOLTAIRE-X Trial.
Coordinating Investigator:	
Trial site(s):	Multi-national, multi-center trial in approximately 80 clinical sites across approximately 12 countries
Clinical phase:	Phase III
Objective(s):	The primary objective of the trial is to assess the pharmacokinetic (PK) similarity between patients receiving United States (US)-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®, in patients with moderate to severe chronic plaque psoriasis. The secondary objectives of this trial are to descriptively compare the safety, immunogenicity and efficacy profiles between patients receiving US-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®.
Methodology:	This is a 58-week, multiple-dose, active comparator trial with a single-arm run-in period of 14 weeks duration for all entered patients, followed by a randomized, double-blind, two-arm period of 34 weeks. The total treatment period will be 48 weeks followed by 10 weeks of safety follow-up. All entered patients will have a planned run-in period of 14 weeks during which they will be treated with US-licensed Humira® (last dose at Week 12/Visit 8). Each patient will receive 80 mg of US-licensed Humira® at the start of the run-in period (Day 1, Week 1) followed by 40 mg of Humira® 1 week later, and then 40 mg of Humira® every other week. At the beginning of Week 14 (Visit 9), patients achieving at least a 50% reduction in Psoriasis Area and Severity Index (PASI50) response will be randomized in a 1:1 ratio to either continue receiving US-licensed Humira® (continuous US-licensed Humira® arm) until Week 48 or receive BI 695501/US-licensed Humira®/BI 695501 alternately for three periods (switching arm) in a blinded fashion (BI 695501 at Week 14/Visit 9 and Week 16/Visit 10, US-licensed Humira® at Week 18/Visit 11 and Week 20/Visit 12, and BI 695501 every other week from Week 22/Visit 13 to Week 48/Visit 26). At Week 14, the randomization will be stratified by the level of their Week 14 PASI response (≥ PASI50 to < PASI75 and ≥ PASI75). In the switching arm, the first two treatment periods will be of 4 weeks (2 injections) duration, and the third treatment period will be of 10 weeks (5 injections) duration, with an extension period of 16 weeks beyond the primary endpoint assessed at Week 32. Those patients not achieving at least PASI50 at Week 14 will be discontinued from any further treatment in the trial, and will only be followed up for safety.

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	Starting at Week 14, the treatment regimen of the two arms will be: • Continuous Humira® arm: US-licensed Humira® (34 weeks) • Switching arm: BI 695501 (4 weeks, 2 injections)/US-licensed Humira® (4 weeks, 2 injections)/BI 695501 (10 weeks, 5 injections for primary endpoint + 16 weeks, 9 injections extension period; 26 weeks total) Patients will undergo intensive PK sampling between Weeks 12-14 (Visit 8, Visits 8a-d, and Visit 9) and 30-32 (Visit 17, Visits 17a-d, and Visit 18) to assess PK similarity between the two arms. After approximately 86 patients have had their Week 32 endpoint assessments and are PK evaluable, a blinded interim analysis with sample size re-assessment will be performed. Recruitment (for stage 2) will however not be stopped. The interim analysis will be performed in a blinded manner.
Number of patients entered:	Initial enrollment into the run-in US-licensed Humira® arm: Approximately 240 patients will be entered.
Number of patients on each treatment:	Patients will be randomized 1:1 into continuous US-licensed Humira® and switching arms at Week 14, leading to approximately 96 patients per arm, considering approximately 80% achieve PASI50 and a PK non-evaluable drop-out rate of approximately 10%-15%, to obtain approximately 86 PK evaluable patients per arm for the primary endpoint analysis.
Diagnosis :	Moderate to severe chronic plaque psoriasis.
Main in- and exclusion criteria	This trial will include male and 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 prior to randomization, and which has been stable for the last 2 months with no changes in morphology or significant flares. Patients must be suitable for systemic treatment or phototherapy. Patients must have a PASI score ≥ 12, Static Physician's Global Assessment of psoriasis (sPGA) ≥ 3 at screening and at baseline, and a body surface area (BSA) involvement ≥ 10%. Patients with prior exposure to any biologic therapy will be excluded from this trial.
Test product(s):	BI 695501 solution in a pre-filled syringe
dose:	40 mg every other week, starting at Week 14
mode of administration:	Subcutaneous (s.c.) injection
Comparator products:	US-licensed Humira® solution in a pre-filled syringe
dose:	80 mg initial dose, followed by 40 mg every other week starting 1 week after initial dose
mode of administration:	s.c. injection
Duration of treatment:	Patients will be treated with trial medication for 48 weeks.

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Active ingredient name:	BI 695501
Protocol date	Revision date 25 Jul 2019
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Endpoints	The following will be the endpoints of the trial: Primary endpoints: Pharmacokinetics • $AUC_{\tau, 30-32}$ (Area under the adalimumab plasma concentration-time curve [AUC] over the dosing interval of Week 30-32) • $C_{max, 30-32}$ (Maximum observed adalimumab plasma concentration during the dosing interval Week 30-32) Secondary endpoints: Pharmacokinetics • $C_{min, 30-32}$ (Minimum observed adalimumab plasma concentration during the dosing interval Week 30-32) • $t_{max, 30-32}$ (Time to maximum observed adalimumab plasma concentration during the dosing interval Week 30-32) Efficacy • Proportion of patients with a 75% reduction in PASI (PASI75) response at Week 32 • Proportion of patients with an sPGA ≤ 1 (clear or almost clear) at Week 32 Safety • Proportion of patients with drug-related adverse events (AEs) during the treatment phase and the safety follow-up period Immunogenicity • Proportion of patients with anti-drug antibodies (ADAs) and ADA titer at Week 32, • Proportion of patients with neutralizing ADAs (nAbs) frequency and titer at Week 32
Safety criteria:	Physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead electrocardiogram (ECG), laboratory tests, continuous AE monitoring and local tolerability.
Statistical methods:	The assessment of PK similarity will be based upon two-sided 90.2% confidence intervals (CIs) for the ratios of the means (test/reference, where the test treatment corresponds to the switching arm and the reference to the Humira®-only arm) for the primary endpoints using an acceptance range of 80.00% to 125.00%. This method is equivalent to the two one-sided t-tests procedure, each at the 4.9 % significance level The statistical model will be an analysis of covariance (ANCOVA) on the original scale including effects for “treatment”, “log(rPASI)”, “weight”, and “$AUC_{\tau, 12-14}$” or “$C_{max, 12-14}$”, where rPASI=ratio of PASI at Week 14 and PASI at Week 1. The randomization will be stratified by the level of their Week 14 response (≥ PASI50 to < PASI75 and ≥ PASI75)

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	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Trial Periods	Screening	Run-in Period							Double-blind Period					
Visit[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**[2]	**10**	**11**	**12**	**13**	**14**
Week	Screening -5 to -2	**Baseline 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Days	-38 to -15	**1**	**8**	**22**	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**
Permitted visit window (days)	-	0	± 2	± 2	± 2	± 2	± 2	± 2	0[2]	± 3	± 3	± 3	± 3	± 3
Informed consent	X													
Assessment of eligibility	X	X												
Run-in Phase/Randomization[3]		X							X					
Demographics	X													
Medical and surgical history, incl. history of opportunistic inf.	X													
LABS/SAFETY ASSESSMENTS[4]														
Infection screen: Hepatitis B (HBsAg, anti-HBc), hepatitis C (anti-HCV), HIV	X													
Chest X-ray	X[5]													
TB testing (IGRA or PPD testing)[6]	X								X					
Pregnancy test for women of childbearing potential	X	X				X			X				X	
Physical examination[7]	X	X				X			X				X	
Vital signs[7]	X	X				X			X				X	
Laboratory tests (serum chemistry, hematology, urinalysis)	X	X				X			X				X	
12-lead electrocardiogram[8]	X								X				X	
Previous and concomitant therapy	◄----------X----------►													
Adverse events[9]	◄----------X----------►													

FLOW CHART – SCREENING TO WEEK 24 (CONT'D)

Trial Periods	Screening	Run-in Period							Double-blind Period					
Visit[1]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**[2]	**10**	**11**	**12**	**13**	**14**
Week	Screening -5 to -2	**Baseline 1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
Days	-38 to -15	**1**	**8**	**22**	**36**	**50**	**64**	**78**	**92**	**106**	**120**	**134**	**148**	**162**
Permitted visit window (days)	-	0	± 2	± 2	± 2	± 2	± 2	± 2	0[2]	± 3	± 3	± 3	± 3	± 3
EFFICACY ASSESSMENTS[4]														
PASI	X	X		X		X			X		X		X	
sPGA	X	X		X		X			X		X		X	
OTHER ASSESSMENTS														
Pharmacokinetics[10]		X	X			X		X	X		X		X	
Anti-drug antibodies[11]		X	X			X		X	X		X		X	
Neutralizing anti-drug antibodies[11]		X	X			X		X	X		X		X	
TRIAL MEDICATION														
Pre-treatment call	X													
Contact IRT[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Medication[2]		X	X	X	X	X	X	X	X	X	X	X	X	X

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

FLOW CHART – WEEK 26 TO END OF TRIAL

	Double-blind Period			Extension Period									Follow-up		
Visit[1]	**15**	**16**	**17**	**18**[2]	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	
Week	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**[13]	**50**[13] **EoT**	**58** **SFU**[13]	
Days	**176**	**190**	**204**	**218**	**232**	**246**	**260**	**274**	**288**	**302**	**316**	**330**	**344**	**400**	
Permitted visit window (days)	± 3	± 3	± 3	0[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
TB testing (IGRA or PPD testing)[6]													X		
Pregnancy test for women of childbearing potential				X				X					X		
Physical examination[7]				X				X					X		
Vital signs[7]				X				X					X		
Laboratory tests (serum chemistry, hematology, urinalysis)				X				X					X		
12-lead electrocardiogram[8]				X									X		
Previous and concomitant therapy	◄----------X----------►														
Adverse events[9]	◄----------X----------►														
EFFICACY ASSESSMENTS[4]															
PASI		X		X				X					X		
sPGA		X		X				X					X		
OTHER ASSESSMENTS															
Pharmacokinetics[10]			X	X				X					X	X	
Anti-drug antibodies[11]			X	X				X					X	X	
Neutralizing anti-drug antibodies[11]			X	X				X					X	X	
TRIAL MEDICATION															
Contact IRT[12]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Trial Medication[2]	X	X	X	X	X	X	X	X	X	X	X	X			

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

1. Patients will have to visit the site for the visits where safety samples and efficacy assessments need to be conducted. Medication will be administered at the site by a qualified site staff member.
2. 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 14 onward). All assessments and procedures should be performed prior to trial medication administration.
   Note: The below trial medication administration time points will need to be strictly followed as shown.
   Trial medication at Week 14 (Visit 9) should be administered **exactly 14 days after the Week 12 Visit** (Visit 8).
   Trial medication at Week 32 (Visit 18) should be administered **exactly 14 days after the Week 30 Visit** (Visit 17).
3. Entry into the run-in phase can occur through a pre-treatment call. The pre-treatment call will be done by the site 15 days prior to Day 1, and will depend on the trial site procedure. Patients will be randomized to each treatment in a 1:1 ratio (US-licensed Humira®:Switching Arm) at Week 14.
4. All efficacy (e.g., Psoriasis Area and Severity Index [PASI] and Static Physician's Global Assessment of psoriasis [sPGA]) and safety assessments will be performed by blinded personnel.
5. 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.
6. Patients must have a negative tuberculosis (TB) assessment at screening, including a purified protein derivative (PPD) skin test or an interferon gamma-release 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. If the result is positive, patients may participate in the trial if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If latent TB is confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines.[1] Post-screening, if the patient is positive for TB tests, additional work up would be needed to conclude either latent or active TB and appropriate measures need to be taken as per the local country guidelines.
7. The physical examination will include assessment of general appearance, body weight, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen. Clinically relevant abnormal findings will be reported as baseline conditions or AEs. Vital signs include measurement of body temperature, blood pressure, and pulse rate (all in the sitting position after a 5-minute rest).
8. Patients should rest for at least 5 minutes in a supine position before electrocardiogram (ECG) evaluations.
9. Adverse events (AEs) will be collected from the time of informed consent. Adverse events continuing at the End-of-Treatment (EoT) 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 the EoT Visit.
10. Pharmacokinetics (PK) samples will be taken pre-dose at baseline visit, Week 2, Week 8, Week 12; and additionally at 72 h, 120 h, 168 h, and 240 h at sub-visits 8a, 8b, 8c, and 8d for PK sampling after the Week 12 dosing; pre-dose Week 14, Week 18, Week 22, Week 30 and 72 h, 120 h, 168 h, and 240 h at sub-visits 17a, 17b, 17c, and 17d for PK sampling after the Week 30 dosing; pre-dose Week 32 and Week 40, during follow-up at Week 50 and Week 58 (see Table 5.3.1: 1). The PK samples at sub-

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

visits 8a, 8b, 8c, 8d, 17a, 17b, 17c, and 17d may be drawn by a qualified home healthcare professional (nurse) at the patient's home or at an alternative location specified by the patient and agreed by the study team (see Section 5.3.1).

11. Anti-drug antibody (ADA) samples (including neutralizing ADA samples [nAbs]) should be taken at each visit designated with an "X" prior to dosing of trial medication.
12. Interactive Response Technology (IRT) will be contacted prior to every trial medication administration visit.
13. Patients who pre-maturely discontinue the trial at any time after Day 1 (but do not withdraw their consent) will be required to have all of the evaluations for the EoT Visit (equivalent to the Week 50 assessments) as soon after trial discontinuation as possible. Patients will then be followed for efficacy assessments until Week 50, wherever possible. Every effort should be made for all patients who complete the total 50-week treatment period, or who discontinue the trial early, to return for an SFU Visit at Week 58 or 10 weeks after the last treatment administration.

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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
anti-HCV	hepatitis C antibodies
AST	aspartate aminotransferase
AUC	area under the curve
β-hCG	beta-human chorionic gonadotropin
BI	Boehringer Ingelheim
BLQ	below the limit of quantitation
BSA	body surface area
CA	competent authority
CI	confidence interval
C_{max}	maximum concentration of the analyte in plasma
C_{min}	minimum concentration of the analyte in plasma
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	coefficient of variation
DILI	drug-induced liver injury
DRM	Data Review Meeting
ECG	electrocardiogram
eCRF	electronic Case Report Form
EoT	End-of-Treatment
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
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_2EDTA	dipotassium ethylenediaminetetraacetic acid
LPDD	Last Patient Drug Discontinuation
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTX	methotrexate
nAb	neutralizing antibody
NOA	not analysed
NOR	no valide result
NOS	no sample
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
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPD	purified protein derivative
PPS	Per-Protocol Set
PUVA	psoralen with ultraviolet light
RA	rheumatoid arthritis
REP	residual effect period
RTS	Run-in Treated Set
SAE	serious adverse event
s.c.	subcutaneous
SFU	Safety Follow-up
SOP	standard operating procedure
SPC	summary of product characteristics
sPGA	Static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
t_{max}	time to reach maximum concentration
t_{min}	time to reach minimum concentration
TNF	Tumor necrosis factor
TNFR1	tumor necrosis factor 1
TNFR2	tumor necrosis factor 2
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal
US	United States
US-PI	United States Prescribing Information
WHO	World Health Organisation

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 characterised 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 (TNF) agents, 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

Humira® (adalimumab) is a recombinant humanized monoclonal immunoglobulin (Ig)G1 antibody specific to TNF alpha and has received regulatory approval for psoriasis in the United States (US), the European Union (EU), and many other countries (R16-5078 and R16-0358). Humira® binds specifically to TNF-alpha (not to TNF-beta) and blocks its interaction with the TNF receptors 1 (TNFR1) and 2 (TNFR2). It has human-derived heavy and light chain variable regions and human IgG1:k (kappa) constant regions and is produced in a mammalian cell expression system (R16-5078 and R16-0358). Humira® is administered as a monotherapy.

Humira® has a generally favourable clinical safety profile, and is not associated with adverse events (AEs) that would suggest a high risk to patients participating in this trial. In patients treated with Humira®, the most commonly reported adverse reactions are infections (such as upper respiratory tract infection and sinusitis), nausea, headache, rash, accidental injuries and injection site reactions (erythema, itching, haemorrhage, pain or swelling).

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.

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.

The drug being studied in this trial, BI 695501, is a monoclonal antibody being developed as a proposed biosimilar to US-licensed and EU-approved Humira® (adalimumab).

The preclinical studies that support the clinical program of BI 695501 include:

- A comparative 5-week toxicology trial with an 8-week recovery in cynomolgus monkeys comparing BI 695501 and EU-approved Humira®. There was no difference in systemic exposure between BI 695501 and EU-approved Humira® with repeated dosing. This trial demonstrated the similarity of the toxicology profile for BI 695501 and EU-approved Humira®.
- A single-dose pharmacokinetic (PK), subcutaneous (s.c.) trial in cynomolgus monkeys comparing BI 695501 to EU-approved Humira®. There were no

differences in the exposure or anti-drug antibody (ADA) response in cynomolgus monkeys to BI 695501 and EU approved Humira®.

- A comparative human tissue cross-reactivity trial of BI 695501, US-licensed, and EU-approved Humira®. This trial showed that the patterns of staining of BI 695501, US-licensed, and EU-approved Humira® were similar, with minor differences attributable to section-to-section variation, rather than any true staining differences. All of the tissue cross-reactivity staining was consistent with reported sites of TNF expression and/or previously reported sites of reference product cross-reactivity.
- A determination of other potential cytokines that may bind to BI 695501 or inhibit binding of BI 695501 to TNF compared to US-licensed and EU-approved Humira®. None of the 3 antibodies bound to any of the 8 other cytokines that were tested. Additionally, there was no difference in the effect of these cytokines on the binding of TNF between BI 695501, US-licensed, and EU-approved Humira®.
- The potential for BI 695501 to induce in vitro cytokine release or directly activate complement compared to EU-approved Humira®. The results from this trial demonstrated that BI 695501 and EU-approved Humira® are not anticipated to induce cytokine release in humans and do not directly activate complement.
- A tissue irritation potential trial in rabbits with BI 695501 demonstrated that BI 695501 did not cause irritation.

To date, a total of 241 male healthy subjects were treated with 40 mg s.c. of BI 695501 in 3 phase I trials with healthy subjects: 1297.1 (U13-1096-01), 1297.6 (c09477818-01) and 1297.8 (c03070713). The PK similarity of BI 695501 to US-licensed Humira® and EU-approved Humira® was demonstrated in the healthy volunteer trial 1297.8 (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.

A phase III trial (1297.2) in patients with moderate to severe rheumatoid arthritis (RA) has recently completed. A total of 645 patients with moderate to severe RA were included in the trial and treated with either BI 695501 or US-licensed Humira®. The observed AE profile revealed no unexpected safety findings and showed no clinically relevant safety or immunogenicity differences between BI 695501 and US-licensed Humira®.

For a more detailed description of the BI 695501 profile please refer to the current Investigator's Brochure (IB) (c01843589) and for US-licensed Humira® to the United States Prescribing Information (US-PI) (R16-5078).

1.3 RATIONALE FOR PERFORMING THE TRIAL

The current trial is being performed to assess whether multiple switches between Humira® and BI 695501 lead to the same PK, safety and immunogenicity profile compared to continuous Humira® treatment, as this may happen in clinical practice.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this trial may help to improve access to and availability of the respective drug treatment for other patients in the future.

Patient risk will be minimized in this trial by implementing conservative eligibility criteria, e.g., patients with pre-existing diseases are excluded from trial participation, although in real time clinical practice, such patients might be treated.

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 5.2.6.1.

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 core 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 patients who test positive. Investigators are also expected to carefully consider the risks and benefits of treatment with adalimumab in patients who have been exposed to TB and patients who have travelled in areas of high risk of TB or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis.

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.

Tumor necrosis factor-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.

To minimize the risks, patients with a significant disease other than psoriasis will be excluded from the trial participation.

The AEs seen in 3 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 (USPI) for Humira® (R16-5078) and in the summary of product characteristics (SPC) for EU-approved Humira® (R16-0358).

The AE profile in the phase III trial 1297.2 (c02158186) revealed no unexpected safety findings and showed no clinically relevant safety differences between US-licensed Humira® and BI 695501. The review of safety data in 1297.2 trial by the Independent Data Monitoring Committee (IDMC) also did not suggest any clinically relevant differences in safety profile between Humira® and BI 695501.

There were no clinically relevant differences with respect to clinical laboratory evaluation, vital signs, ECGs, or injection site reactions in previous studies comparing BI 695501 with either US-licensed or EU-approved Humira®. Based on extensive preclinical, analytical, functional, and toxicological testing carried out prior to initiation of this trial, and the phase I and III 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 a 50% reduction in Psoriasis Area and Severity Index (PASI50) (patients showing lack of efficacy), will be discontinued from treatment after Week 14 with the trial drug, but only followed up for safety.

There are certain risks that arise when patients switch between different products. Multiple switches could theoretically lead to higher immunogenicity in patients, resulting in a higher number of hypersensitivity reactions and lower efficacy. This risk will be mitigated by closely monitoring the patient for hypersensitivity reactions, collection and follow-up of reported AEs.

The benefit-risk profile for the patients participating in this trial remains favourable and similar to the originator product Humira®. BI 695501, as a proposed biosimilar product, is expected to provide comparable efficacy, safety, tolerability and immunogenicity in patients with moderate-to-severe chronic plaque psoriasis and therefore is expected to provide a similar benefit-risk profile as US-licensed Humira®.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of the trial is to assess the PK similarity between patients receiving US-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®, in patients with moderate-to-severe chronic plaque psoriasis.

The secondary objectives of this trial are to descriptively compare the safety, immunogenicity and efficacy profiles between patients receiving US-licensed Humira® continuously vs those who switch between BI 695501 and US-licensed Humira®.

2.1.2 Primary endpoint(s)

The primary endpoints are:

- $AUC_{\tau, 30\text{-}32}$
  (Area under the adalimumab plasma concentration-time curve [AUC] over the dosing interval of Week 30-32)
- $C_{max, 30\text{-}32}$
  (Maximum observed adalimumab plasma concentration during the dosing interval Week 30-32)

2.1.3 Secondary endpoint(s)

The secondary endpoints are:

<u>Pharmacokinetic</u>

- $C_{min, 30\text{-}32}$
  (Minimum observed adalimumab plasma concentration during the dosing interval Week 30-32)
- $t_{max, 30\text{-}32}$
  (Time to maximum observed adalimumab plasma concentration during the dosing interval Week 30-32)

<u>Efficacy</u>

- Proportion of patients with a PASI75 response at Week 32
- Proportion of patients with an Static Physician's Global Assessment (sPGA) ≤ 1 (clear or almost clear) at Week 32

<u>Immunogenicity</u>

- Proportion of patients with ADAs at Week 32
- ADA titer of patients with ADAs at Week 32
- Proportion of patients with neutralizing antibody (nAb) frequency and titer at Week 32

<u>Safety</u>

- Proportion of patients with drug-related AEs during the treatment phase and the safety follow-up period

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a 58-week, multiple-dose, active comparator trial with a single-arm run-in period of 14 weeks duration for all entered patients, followed by a randomized, double-blind, two-arm period of 34 weeks. The total treatment period will be 48 weeks followed by 10 weeks of safety follow-up.

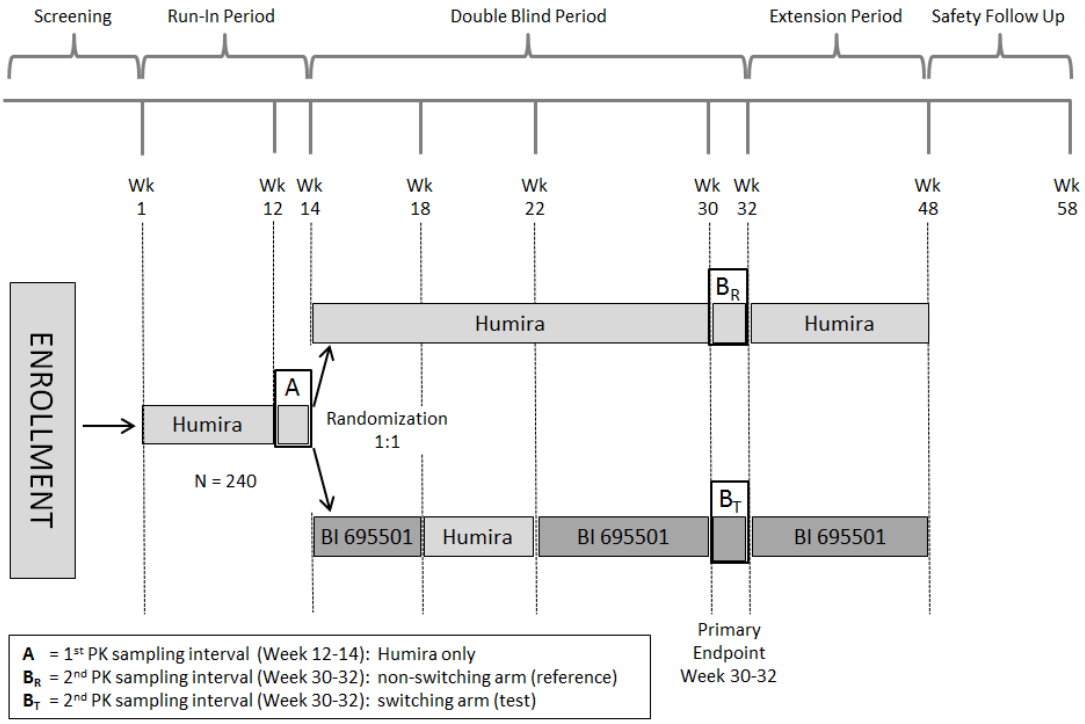
All entered patients will have a planned run-in period of 14 weeks during which they will be treated with US-licensed Humira® (last dose at Week 12/Visit 8) (see Section 4.1 for dosage). At the beginning of Week 14 (Visit 9), patients achieving at least a PASI50 response will be randomized in a 1:1 ratio to either continue receiving US-licensed Humira® (continuous US-licensed Humira® arm) until Week 48 or receive BI 695501/US-licensed Humira®/BI 695501 alternately for three periods (switching arm) in a blinded fashion (BI 695501 at Week 14/Visit 9 and Week 16/Visit 10, US-licensed Humira at Week 18/Visit 11 and Week 20/Visit 12, and BI 695501 every other week from Week 22/Visit 13 to Week 48/Visit 26). At Week 14, the randomization will be stratified by the level of their Week 14 PASI response (≥ PASI50 to < PASI75 and ≥ PASI75). All patients will continue to receive 40 mg US-licensed Humira® or BI 695501 every other week until Week 48.

Those patients not achieving at least PASI50 at Week 14 will be discontinued from any further treatment in the trial, but will undergo the End-of-Treatment (EoT) and Safety Follow-up (SFU) for safety.

Patients will undergo intensive PK sampling between Weeks 12-14 (Visit 8, Visits 8a-d, and Visit 9), and Weeks 30-32 (Visit 17, Visits 17a-d, and Visit 18) to assess PK similarity between the two arms.

The co-primary PK endpoints of the trial are $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ (see Section 2.1.2). After approximately 86 patients have had the Week 32 endpoint assessment and are PK evaluable, a statistician will perform a blinded evaluation of the variability to assess whether the initially planned sample size will be increased or not.

Figure 3.1: 1 summarizes the trial design.



Note: Trial medications are administered at the beginning of the specified week.

Figure 3.1: 1 Trial Design

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

Chronic plaque psoriasis is considered a sensitive indication to assess PK similarity in this trial as BI 695501/Humira® are administered as a monotherapy in this indication. It will be also assessed whether patients receiving Humira® and BI 695501 in an alternating fashion generate a clinically relevant different immunogenic response as compared to patients receiving Humira® continuously.

Clinical efficacy endpoints are not considered to be sufficiently sensitive to assess any impact of immunogenicity on efficacy, since patients discontinuing Humira® therapy after achieving a 75% PASI (PASI75) response may take up to 5 months to deteriorate. “Diminished efficacy”, if it occurs in the context of switching, is expected to result from the increased development of ADAs. Increased ADA formation may lead to increased drug clearance and decreased exposure which in turn would result in diminished efficacy. Therefore, the assessment of PK after switching is considered as a sensitive surrogate marker for changes in efficacy.

A total of three switches will be performed for patients randomized to the switching group. The final switching duration provides a sufficient washout period for US-licensed Humira® in switching arm to reach low plasma levels, which may potentially maximize the generation of immunogenic response. Pharmacokinetic equivalence at the end of this switching period

would suggest similar immunogenicity in switching vs non-switching arms. In the context of switching, similar PK and immunogenicity may be extrapolated to similar long-term efficacy and safety between BI 695501 and US-licensed Humira®.

3.3 SELECTION OF TRIAL POPULATION

Approximately 240 patients will be randomized in approximately 80 clinical sites across approximately 12 countries.

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

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

3.3.2 Inclusion criteria

1. Males and females aged ≥ 18 to < 80 years at screening 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 trial drug (a self-reported diagnosis confirmed by the Investigator is acceptable), and which has been stable per Investigator opinion for the last 2 months with no changes in morphology or significant flares at both screening and baseline:
    a. involved body surface area (BSA) ≥ 10% and
    b. PASI score ≥ 12 and
    c. sPGA score of ≥ 3.
2. Participants of reproductive potential (childbearing potential[2]) must be willing and able to use highly effective methods of birth control per International Council for Harmonisation (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 4.2.2.3 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 or phototherapy according to Investigator judgement.

[2] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.3 Exclusion criteria

1. Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to Investigator's judgment.
2. Prior exposure to any biologic therapies for any auto-immune diseases (eg: RA, Psoriasis, Crohns Disease, etc).
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 before enrollment 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 (in the opinion of the Investigator) 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 trial, or less than 30 days (or less than 5 half-lives, whichever is longer) since ending another investigational device or drug trial(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 trial subject or unlikely to complete the trial.
9. Women who are pregnant, nursing, or who plan to become pregnant during the course of this trial or within the period at least 6 months following completion or discontinuation from the trial medication.
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 TB; 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 trial if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If latent TB is confirmed, then treatment must have been initiated before treatment in the study and continued according to local country guidelines.[3]
13. Known clinically significant (per Investigator opinion) 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.

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

14. Patients with a history of any clinically significant adverse reaction (including serious allergic reactions, or anaphylactic reaction, or hypersensitivity) to murine or chimeric proteins, previously used biological drug or its excipients, or natural rubber and latex.
15. Positive serology for HBV or 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 hospitalisation 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. Calculated creatinine clearance < 60 mL/min at screening.

3.3.4 Withdrawal of patients from therapy or assessments

Patients who do not meet all of the inclusion criteria or who meet one or more of the exclusion criteria will not be randomized, and will be considered screen failures. Screen failure patients may be rescreened once based on Investigator judgment and prior permission from medical monitor of the trial. The primary reason for the screen failure will be recorded on the electronic Case Report Form (eCRF).

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

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the randomised patients in the trial: if possible on tretament, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

If a patient discontinues (drops out or withdraws after randomization) from this trial, the patient will not be replaced.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and eCRF.

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- Lack of efficacy defined as PASI50 not reached at Week 14.
- Development of a toxicity or AE which warrants BI 695501/ Humira® discontinuation including but not limited to 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 an 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 stick 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 (SFU Visit) and Section 6.2.3.

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

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow-up on safety cannot opccur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 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 the following reasons:

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 trial protocol, 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).

3.3.5 Replacement of subjects

In case more than 30% of the patients are not eligible for the primary endpoint analysis, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. However the total number of patients recruited will not exceed 350. A replacement patient will be assigned a unique study patient number, and will be assigned to the same treatment as the patient he or she replaces.

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 trial. 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 1

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:	40 mg at Week 14 and Week 16 (2 injections), and every other week from Week 22 to Week 48 in the switching arm (14 injections)
Route of administration:	s.c. injection
Site of administration:	Front of the thighs or abdomen/belly, at least 2 inches (about 5 centimeters) away from the navel

Table 4.1.1: 2 Reference product

Substance:	US-licensed Humira® (adalimumab)
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	.
Unit strength:	40 mg / 0.8 mL or 40 mg / 0.4 mL
Posology:	80 mg (loading dose) on Day 1, Week 1 40 mg every other week from Week 2 to Week 12 Continuous US-licensed Humira® arm: 40 mg every other week from Week 14 to Week 48 Switching arm: 40 mg at Week 18 and Week 20 (2 injections)
Route of administration:	s.c. injection
Site of administration:	Front of the thighs or abdomen/belly, at least 2 inches (about 5 centimeters) away from the navel

BI 695501 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. 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 (40 mg) will be used, except for Week 1 / 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, Humira® has received health authority approval for the treatment of RA, Crohn's disease, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, Uveitis and Hidradenitis suppurativa. The doses of BI 695501 and Humira® selected for this trial are reflective of the approved treatment regimen for plaque psoriasis of Humira® (initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose) (R16-0358).

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.

The Day 1 pre-treatment call will depend on the trial site procedure. The process for treatment assignment will 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 pre-treatment call will be made as described below and trial medication will be shipped. The pre-treatment call might be made 15 days prior to the planned first administration of trial medication.

At the beginning of Week 14, patients with at least a PASI50 response will be randomized to one of two sequences (1:1) to either switching or non-switching arm. At Week 14, the randomization will be stratified by the level of their Week 14 response (≥ PASI50 to < PASI75 or ≥ PASI75). Access to the randomization code will be controlled and documented. The block sizes of the randomization will be documented in the clinical trial report (CTR).

Randomization will be performed by the IRT. Patients will be randomized sequentially (the lowest sequentially available randomization number).

Each syringe of trial medication will be labelled 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 trial. The IRT will assign each patient a unique medication number. Details on the IRT system will be provided in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

The trial design is described in Section 3.1.

Prefilled syringes will be used for the injections (see Section 4.1.1). Injections will be administered subcutaneously to the front of the thighs or abdomen/belly, at least 2 inches (about 5 centimeters) away from the navel. Rotate injection sites and do not give injections into areas where the skin is tender, bruised, red or hard.

After the first injection (Visit 2) and at randomization (Visit 9), 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 dose is administered. As soon as possible, the dosing should return to the original schedule and refer back to baseline. A minimum interval of 1 week between 2 successive injections should be adhered to.

In the event of an anaphylactic or other serious allergic 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

The trial is carried out in a double-blind fashion. Third-party blinding will be used to administer trial medication.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct of the trial will have no access to the treatment allocation prior to final database lock (see Section 4.1.5.2).

The randomization code will be kept secret by IRT up to database lock.

It is planned to conduct the trial using pre-filled syringes of 0.8 mL Humira® (40 mg) as the reference product throughout.

However, if this 0.8 mL pre-filled Humira® syringe is not available for complete trial supply, the trial conduct may have to be continued using the 0.4 mL pre-filled Humira® syringe as the reference product. Taking into account that the 0.8 mL BI 695501 and the 0.4 mL Humira® presentations might differ, the blinding of treatments will be maintained by using a third-party blinding procedure. This means that the trial 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 trial (see Appendix 10.3 for details on third party blinding procedure). The secondary packaging (carton containing syringes) will be the same design for both BI 695501 and Humira®. The label text on secondary packaging (carton containing syringes) will be identical for both the products. However, the use-by date (expiry date) will be open.

4.1.5.2 Unblinding and breaking the code

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

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI' s Pharmacovigilance group to access the randomisation 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. Detailed storage conditions will be described on the trial medication labels.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) (as provided in the list of contacts in the ISF) 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 head of the investigational site;
- 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; and
- Availability of Form 1572 (for US).

The designated person must maintain records of the investigational 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 authorise an appropriate therapy. In those cases, patients 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 trial or must refer them for appropriate ongoing care according to local guidelines and daily practice, respectively.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Restrictions on prior and concomitant medications during the course of the trial are described in Table 4.2.2.1: 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 with 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 discuss the introduction of any of the medications listed in Table 4.2.2.1: 1 with the CRO Medical Monitor.

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

Table 4.2.2.1: 1 Prior and concomitant treatments

Treatment	Restriction
Biologic agents (e.g., TNF antagonists, anti-IL12/23 and anti-IL17)	Previous or concomitant treatment with any biologic therapy for auto-immune diseases is not permitted. Concomitant medication with either anakinra or abatacept is not recommended.
Cyclophosphamide	Cyclophosphamide will not be permitted within 6 months prior to Visit 2/Day 1 and for the duration of the trial.
Topical steroids	Topical steroid treatment applied on psoriatic lesions/scalp/nails will not be permitted within 2 weeks prior to Visit 2/Day 1 and for the duration of the trial. Occlusive topical corticosteroids in any location will not be permitted within 2 weeks prior to Visit 2/Day 1 and for the duration of the trial. Topical corticosteroids of low potency (WHO group VI/VII) are permitted during the trial except within 24 hours before trial 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 Visit 2/Day 1 and for the duration of the trial. However, use of emollients (moisturizing treatments) will be permitted during the trial duration except within the 24-hour period immediately prior to each clinic visit.
UVB or UVA or PUVA treatment	Treatment with UVB or UVA (without psoralen) will not be permitted within 2 weeks prior to Visit 2/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 Visit 2/Day 1 and for the duration of the trial.
Nutraceutical treatments	Nutraceuticals intended for the treatment of psoriasis will not be permitted within 4 weeks prior to Visit 2/Day 1 and for the duration of this trial.
Other systemic or locally acting medications	Treatment with any other systemic or locally acting medications which might counter or influence the objective of the trial (e.g., NSAID, antihistamine), or medications known to provoke/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 Visit 2/Day 1 and are planned to remain so for the duration of this trial.
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 Visit 2/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 Visit 2/Day 1 or throughout the trial.
Oral corticosteroids	Not permitted within 4 weeks prior to Visit 2/Day 1 or throughout the trial.
Prosorba® Column	Not permitted within 6 months of the Screening Visit.
Leflunomide	Not permitted. Must be withdrawn at least 8 weeks prior to Visit 2/Day 1.

Abbreviations: IL=interleukin; IV=intravenous; NSAID=nonsteroidal anti-inflammatory drugs; PUVA= psoralen with ultraviolet light; TNF=tumor necrosis factor; UVA=ultraviolet A light; UVB=ultraviolet B light; WHO=World Health Organization.

4.2.2.2 Restrictions on diet and life style

Moisturizers/emollients containing retinoids and the use of tanning beds are not allowed during the trial.

4.2.2.3 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 trial requires immediate interruption of trial 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 treatment.

Women of childbearing potential must use the contraception methods described in the patient information for 6 months after the last dose of trial drug. Acceptable methods of birth control include, for example, birth control pills, intrauterine devices (IUDs), surgical sterilization, vasectomized partner.

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).
- Women must not breast-feed for at least six months after the last adalimumab treatment.

4.2.2.4 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 described in the patient information 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, 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 patients 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 will be assured by the observation of trial medication administration (see Flow Chart) by dedicated trial personnel considered qualified to perform or observe the s.c. injections.

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.

Patients who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) will 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. ASSESSMENTS

Please refer to the Flow Chart for the schedule of assessments for the trial.

5.1 ASSESSMENT OF EFFICACY

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

5.1.1 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 (Table 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 represent 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, Table 10.2: 4)

5.1.2 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 patient's disease state at the time of the assessments, without comparison to any of the patient's previous disease states (dynamic), whether at baseline or at a previous visit (Appendix 10.2, Table 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 ASSESSMENT OF SAFETY

At the Screening Visit, the medical examination will include documentation of patient 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 other visits, it will include review of vital signs, 12-lead ECG, laboratory tests, 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).

5.2.1 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, body weight, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen. Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

5.2.2 Vital signs

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

Blood pressure, respiratory rate, 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 (see Section 5.2.6.2).

5.2.3 Safety laboratory parameters

The laboratory tests listed in Table 5.2.3: 1 will be analysed by a central laboratory. The central laboratory provider will also provide the materials for blood sampling. Instructions for the labelling, 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 5.2.6.1); however, if the laboratory value abnormality is consistent with a current diagnosis, it will be documented accordingly.

Table 5.2.3: 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) 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)	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)	Hepatitis B (HBsAg, anti-HBc) Hepatitis C (anti-HCV) HIV-1 and HIV-2 antibody (qualitative, where mandated by local authorities, at the discretion of the Investigator where clinically indicated)
Screening for infections (at screening, Visit 14, EOT, and optional retest at Unscheduled 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; GGT=gamma-glutamyl transferase; GOT=glutamic-oxaloacetic transaminase; GPT=glutamic pyruvic transaminase; Hb=hemoglobin; HBsAg= hepatitis B surface antigen; Hct=hematocrit; HIV=human immunodeficiency virus; IGRA=interferon gamma-release assay; PPD=purified protein derivative; RBC=red blood cell; 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.

5.2.4 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.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

The assessment of injection site reactions will be done by the Investigator/designee in blinded fashion 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.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

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

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

Serious adverse event
A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- 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 hospitalisation or
- requires prolongation of existing hospitalisation,
- 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 appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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 hospitalisation or development of dependency or abuse.

AEs considered “Always Serious”
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in Section 5.2.6, subsections “ AE Collection” and **AE reporting to sponsor and timelines”**

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim 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 as defined 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 (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, 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
- 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 analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

2. Anaphylactic reactions
3. Serious infection (defined as infections requiring i.v. antibiotics or meeting the regulatory definition of an SAE)
4. Hypersensitivity reactions

Intensity (severity) of AEs
The intensity (severity) 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
Medical judgement 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 trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AEs in the 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 trial drug administration), until the individual patient's end of trial:
  -all AEs (serious and non-serious) and all 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 related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g., phone call. Those AEs should however, not be reported in the CRF.

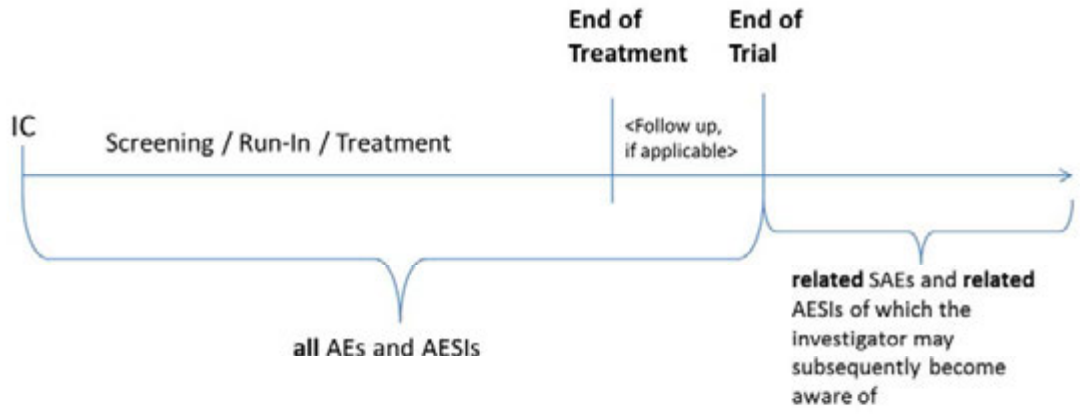


Figure 5.2.6.2: 1 Adverse event collection

The 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 unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor / 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, if applicable. 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 BI SAE form (if applicable):

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only.All (S)AEs, including those

persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Plasma samples of BI 695501 or adalimumab will be obtained from each patient at the visits specified in the Flow Chart and Table 5.3.1: 1.

Table 5.3.1: 1 Pharmacokinetic estimated sample time points

Visit	Week	Day	PTM [h]	PK Sample	ADA/nAb samples
2	Baseline	1	-1	within 3 hours before drug administration	X (predose)
3	2	8	168		X (predose)
6	8	50	1176		X (predose)
8	12	78	1848		X (predose)
8a		81	1920	72 hours ± 12 hours after the Week 12 dosing	
8b		83	1968	120 hours ± 12 hours after the Week 12 dosing	
8c		85	2016	168 hours ± 12 hours after the Week 12 dosing	
8d		88	2088	240 hours ± 12 hours after the Week 12 dosing	
9	14	92	2184	336 hours ± 3 hours after the Week 12 dosing AND within 3 hours before Week 14 dosing	X (predose)
11	18	120	2856	within 3 hours before drug administration	X (predose)
13	22	148	3528		X (predose)
17	30	204	4872		X (predose)
17a		207	4944	72 hours ± 12 hours after the Week 30 dosing	
17b		209	4992	120 hours ± 12 hours after the Week 30 dosing	
17c		211	5040	168 hours ± 12 hours after the Week 30 dosing	
17d		214	5112	240 hours ± 12 hours after the Week 30 dosing	
18	32	218	5208	336 hours ± 3 hours after the Week 30 dosing AND within 3 hours before Week 32 dosing	X (predose)
22	40	274	6552	within 3 hours before drug administration	X (predose)
27	50 / EoT	344	8232	no restrictions	X
28	58 / SFU	400	9576	no restrictions	X

Abbreviations: ADA=anti-drug antibody; EoT=End-of-Treatment; nAb=neutralizing antibody; PK=pharmacokinetic; PTM=Planned Time; SFU=Safety Follow-up.

It needs to be ensured that samples indicated to be taken before drug administration (predose) in the table above will be taken before the next injection is given. It will be essential for the

Investigator or designated staff to document the exact date and time when each sample was taken and the time of administration of the most recent dose preceding the sample in the eCRF. Pharmacokinetic parameters will be evaluated using noncompartmental analysis methods according to the derivations defined in the TSAP.

The sponsor will offer the patient a Home Health Care (HHC) service to support the patient with compliance to the multiple blood draws at specific points in time for this study. This service includes a qualified home healthcare professional (nurse) who will visit the patient outside of the clinic (at home or at an alternative location to be specified by the patient and agreed by the study team) to collect specific blood samples required after Visit 8 (Visits 8a-d) and after Visit 17 (Visits 17a-d), avoiding the requirement for the patient to come to the clinic to have these samples collected.

5.3.2 Methods of sample collection

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

In the event of early withdrawal from the trial, every effort should be made to take a PK sample as part of the early withdrawal procedures, if possible, with date and time of sample and time of dose prior to this sample recorded.

Estimated blood volumes are shown in Section 6.1.

5.3.3 Analytical determinations

Plasma concentrations of BI 695501 and adalimumab will be measured using a validated method.

After completion of the trial, selected PK samples may be retained and may be analyzed for the presence of species (e.g., soluble proteins or small molecule entities) potentially interfering with the analysis method or for generation of ADA positive control material and stability testing for use in future assays. Retained samples may also be used to further characterize the immune response (e.g., isotyping of ADA) if required and as additional assay methods are developed. The results of any additional ADA analyses of the retained samples (i.e., analyses not already specified in this protocol) will be reported separately from the CTR.

All remaining trial samples will be discarded after completion of the additional investigations upon written authorisation by the sponsor, but not later than 5 years after the final CTR has been signed.

5.3.4 Pharmacokinetic – pharmacodynamic relationship

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 OTHER ASSESSMENTS

5.5.1 Assessment of immunogenicity

5.5.1.1 Plasma sampling for anti-drug-antibodies characterisation

For characterization of human anti-BI 695501 or anti-adalimumab antibodies (ADA), approximately 3 mL of blood will be collected in a dipotassium ethylenediaminetetraacetic acid (K_2EDTA) anticoagulant blood drawing tube at time points indicated in Flow Chart and Table 5.3.1: 1.

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

After completion of the trial, selected immunogenicity (ADA and nAb) samples may be retained and may be analyzed for the presence of species (e.g., soluble proteins or small molecule entities) potentially interfering with the analysis method or for generation of ADA positive control material and stability testing for use in future assays. Retained samples may also be used to further characterize the immune response (e.g., isotyping of ADA) if required and as additional assay methods are developed. The results of any additional ADA analyses of the retained samples (i.e., analyses not already specified in this protocol) will be reported separately from the CTR.

All remaining trial samples will be discarded after completion of the additional investigations upon written authorisation by the sponsor, but not later than 5 years after the final CTR has been signed.

Estimated blood volumes are shown in Section 6.1.

5.5.1.2 Plasma sampling for neutralizing antibody characterisation

For characterization of human neutralizing anti-BI 695501 or adalimumab antibodies (nAb), approximately 6 mL of blood will be collected in a K_2EDTA anticoagulant blood drawing tube at the same time points as ADA samples are collected.

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

Neutralizing antibodies will be detected in human plasma samples using validated methods.

5.6 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.

Measurement of the drug concentrations is necessary for the determination of the PK profile. Determination of ADAs and nAbs will support the PK, efficacy and safety analysis.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

A schedule of assessments is provided in the Flow Chart.

Visits will be scheduled as close as possible to the preplanned schedule:
- No visit window is permitted for Visit 2 (Day 1).
- A visit window of ± 2 days is permitted from Visit 3 up to Visit 8
- Visit 9 has to be scheduled exactly 14 days after Visit 8
- A visit window of ± 3 days is permitted for Visit 10 to Visit 17
- Visit 18 has to be scheduled exactly 14 days after Visit 17
- A visit window of ± 3 days is permitted for Visit 19 to Visit 27
- A visit window of ± 3 days is permitted for Visit 28
- Trial medication will be administered at Day 1, with the second injection 7 days later, and subsequent injections every 2 weeks thereafter (± 2 days up to Week 12, ± 3 days from Week 14 to Week 48).

Note: The below trial medication administration time points will need to be strictly followed as shown.

Trial medication at Week 14 (Visit 9)
should be administered **exactly 14 days after Week 12 Visit** (Visit 8).

Trial medication at Week 32 (Visit 18)
should be administered **exactly 14 days after Week 30 Visit** (Visit 17).

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

Questionnaires will be completed at the site by the patient 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.

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	8	24
Hematology	3	8	24
ADAs	3	12	36
nAbs	6	12	72
Pharmacokinetics	3	20	60
Infection screen	4	1	4
TB test	3	3	9
Approximate total			229

Abbreviations: ADAs=anti-drug antibodies; nAbs=neutralizing ADAs; TB=tuberculosis.

It should also be noted that 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

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 trial site will enter the screened patient into the system using the IRT. Patients can be re-screened in case they have failed an eligibility assessment at screening that is fulfilled at a later date during the recruitment period of the trial. Screen failure patients may be rescreened once based on Investigator judgment and prior permission from medical monitor of the trial (see Section 3.3.4). All assessments have to be repeated for the rescreened patients.

The procedures and assessments performed at screening are shown in the Flow Chart.

Once patients have completed screening and have met all the inclusion criteria and none of the exclusion criteria, treatment kit assignment can occur using the IRT system.

6.2.2 Treatment period(s)

The trial medication will be administered at the site on days when trial assessments will be performed. Trial medication will be administered at Visit 2 (Day 1), at Visit 3 (± 2 days), and then every 2 weeks from Visit 4 onward.

The procedures and assessments performed at Visit 2 through Visit 8 are shown in the Flow Chart.

At Visit 9 (the beginning of Week 14), patients with at least a partial response (PASI50) at Week 14 will be randomized to one of two sequences (1:1) according to the stratification factors (see Section 4.1.3 for details).

Other procedures and assessments performed at Visit 9 through Visit 26 are shown in the Flow Chart.

End-of-Treatment procedures and assessments will be performed at Visit 27 as shown in the Flow Chart.

Safety Follow-up procedures and assessments will be performed at Visit 28 as shown in the Flow Chart.

6.2.3 Follow-up period and trial completion

End-of-Treatment Visit
Patients who prematurely discontinue the trial at any time after Day 1 (but do not withdraw their consent) will be required to have all of the evaluations for the Week 50 Visit as soon after trial discontinuation as possible.

Every effort should be made for all patients who complete the total 50-week treatment period, or who discontinue the trial early, to return for an SFU Visit at Week 58 or 10 weeks after the last treatment administration.

Unscheduled visit assessments
Patients may attend the trial site for unscheduled visits at any time for additional safety monitoring at the discretion of the Investigator.

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.

Trial objectives are as stated in Section 2.1.1.

7.2 NULL AND ALTERNATIVE HYPOTHESES

For the primary endpoint analysis the BE margins 80% – 125% on the ratio scale will be applied.

The two endpoints are considered coprimary (i.e., the trial is considered positive if the results for both endpoints are simultaneously positive), therefore no multiplicity-adjustment with respect to the alpha level will be performed.

The tests for PK similarity will be performed with respect to switching versus continuous Humira.

The hypotheses for the primary endpoint analysis can be written as follows:

H_{01}: Ratio of the means of $AUC_{\tau, 30\text{-}32}$ (switching arm versus continuous Humira® arm) is less than 80% or more than 125%

H_{11}: Ratio of the means of $AUC_{\tau, 30\text{-}32}$ (switching arm versus continuous Humira® arm) is within [80%, 125%]

and

H_{02}: Ratio of the means of $C_{max, 30\text{-}32}$ (switching arm versus continuous Humira® arm) is less than 80% or more than 125%

H_{12}: Ratio of the means of $C_{max, 30\text{-}32}$ (switching arm versus continuous Humira® arm) is within [80%, 125%]

A (one-sided) significance level 4.9% was chosen to ensure overall type I error control at 5%, in light of the adapted analysis strategy (details are described in the TSAP).

7.3 PLANNED ANALYSES

Pharmacokinetic parameters of a patient will be included in the statistical analyses of PK endpoints if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK. Whether a protocol violation is considered relevant will be decided no later than in the Data Review Meeting (DRM) prior to the data snapshot. Exclusion of a patient's data will be documented in the CTR.

Relevant protocol violations within the time period critical for primary endpoint evaluation (i.e., from Visit 2 to 18) may be:

- Incorrect trial medication taken, i.e., the patient received at least one dose of trial medication the patient was not assigned to.
- Incorrect or incomplete dose of trial medication taken.
- Missed doses of trial medication.
- Use of restricted medications with suspected impact on PK.
- Missed plasma samples during the dosing interval from Week 12 to Week 14 or from Week 30 to Week 32:
    - at two consecutive timepoints during Visits 8a-d and 17a-d
    - before dosing at Week 12, 14, 30 or 32.

Further criteria that may lead to exclusion of subjects or individual plasma concentrations from the calculation of PK parameters or exclusion of PK parameters from statistical analyses may be specified in the TSAP and in the minutes of the Data Review Meeting.

The PKS includes all patients in the Treated Set (TS, see below) who provide at least one primary PK parameter that was not excluded according to the description above.

All efficacy analyses will be based on the Per Protocol Set (PPS).

The PPS consists of all patients
- who were randomized to double-blinded treatment
- who received at least one dose of double-blinded trial medication, and
- who have all efficacy measures relevant for at least one secondary efficacy endpoint, measured prior to randomization (last non-missing value prior to randomization) and at least once post-randomization.
- who have followed the CTP in all essential criteria: 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 secondary efficacy endpoint. Important protocol violations may include: Incorrect trial medication taken, violation of treatment compliance, violation of inclusion/exclusion criteria. Protocol violations will be assessed on a case-by-case basis. Further details on the definition of the different analysis sets will be provided in the TSAP.

All patients treated with at least one dose of trial medication administered in the randomized phase will be included in the safety evaluation (TS).

All patients treated with at least one dose of Humira® during the run-in period will be included in the Run-in Treated Set (RTS).

The primary, secondary and further analysis results will be presented based on the double-blind randomization (continuous Humira® arm and switching arm).

7.3.1 Primary endpoint analyses

The analyses will be performed on the PKS and done ‘as treated’.

The PK similarity of the two treatments (switching arm versus continuous Humira® arm) will be tested for the primary parameters $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ (see Section 2.1.2 for details).

The ratios of the means including their two-sided 90.2% CIs will be calculated. The confidence interval will be calculated according to Fiellers theorem [R12-1809]. As stated in [R12-1809, chapter 10.2.1], equivalence will be concluded if Fieller's 90.2% confidence interval for the ratio of means is included in the equivalence range 80.00% – 125.00% and

$$\frac{|\bar{Y}_R|}{\hat{\sigma}\sqrt{\frac{1}{n_R}}} > t_{1-\alpha,n_T+n_R-5}$$

which is equivalent to rejecting both null hypotheses. Thereby $\bar{Y}_R$ refers to the LSMean of the reference treatment, $\hat{\sigma}$ is the residual standard deviation from the ANCOVA model (M1) below, n_T and n_R are the final sample sizes in the test and reference arm, respectively, and α = 4.9%.

The statistical model used for the analysis of $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ will be an analysis of covariance (ANCOVA) model on the original scale. This model will include effects accounting for:

- Treatment (switching arm versus continuously Humira® arm)
- Logarithm of rPASI, where rPASI is the ratio of PASI at Week 14 and PASI at Week 1 (continuous value)
- Weight at Week 14 (continuous value)
- Stage, where stage represents the two parts of the study prior to and after the blinded sample size reassessment (categorical, 1 or 2)
- $AUC_{\tau, 12\text{-}14}$ or $C_{max, 12\text{-}14}$ (continuous value)

as a source of variation. As the measurements at Week 14 will be prior to randomization and all patients will have received the same treatment with the reference treatment only, the covariates listed above are all considered adequate baseline values.

All effects will be considered as fixed. The model is described by the following equation:

(M1) response (AUC_τ or C_{max}) = overall mean + treatment effect + log(rPASI) + weight at Week 14 + stage + $AUC_{\tau, 12\text{-}14}$ or $C_{max, 12\text{-}14}$ + random error.

where the random errors are assumed to be independent and normally distributed with zero mean and variance σ_k^2 where k is either test or reference treatment.

Prior to analysis, the data will be log-transformed (see M1). In other words, the dependent variable of the primary endpoint analysis model is the primary endpoint, as stated in the M1 formula. The analysis will then be adjusted for the covariates as stated in M1. The model will be implemented with the SAS® procedure PROC MIXED in conjunction with the LSMEANS statement. The LSMEANS statement is used to estimate the treatment. LSMeans of the switching and non-switching arm which will be used to construct the point estimate for the ratio of means. The 90.2% CI will be derived based on Fieller's theorem.

All patients that finished Week 32 Visit at or before the cut-off date will be allocated to stage 1. All other patients (i.e., all patients that at cut-off date do not have a finished Week 32 Visit) will be allocated to stage 2.

7.3.2 Secondary endpoint analyses

7.3.2.1 Secondary PK endpoint analyses

The secondary PK endpoint $C_{min, 30-32}$ will be analyzed in the same way as the primary endpoints (see Section 7.3.1). However, only the mean ratio and CIs will be calculated and presented. No formal comparison to margins will be performed.

The secondary PK endpoint $t_{max, 30-32}$ will be analyzed in a descriptive manner only.

7.3.2.2 Secondary efficacy endpoint analyses

All secondary efficacy endpoint analyses will be based on the PPS and incomplete or missing data will be handled as described in Section 7.3.2.

The analysis of efficacy endpoints (see Section 2.1.3) will be based on asymptotic method.

The difference in proportions will be calculated as the difference between the observed proportions in each treatment group. Conficence intervals for the difference of proportions will be obtained using the Wald method, which is based on the asymptotically normal approximation to the distribution of the observed sample proportions.

The 90% and 95% CIs will be provided.

7.3.2.3 Secondary immunogenicity endpoint analyses

All secondary immunogenicity endpoint analyses will be based on the TS. All secondary immunogenicity endpoints will be summarized descriptively.

For analysis of the secondary endpoint dedicated to safety, see Section 7.3.4.

7.3.4 Safety analyses

The safety analyses will be descriptive in nature. The analyses will be performed based on the TS and RTS.

The proportion of patients with drug-related AEs during the treatment phase will be analyzed as a secondary safety endpoint.

For the proportion of patients with AESIs, risk ratios and 95% CIs will be provided in addition.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

Safety measurements (such as ECG, vital signs or laboratory parameters) and AEs as well as local tolerability assessments will be assigned to treatments, based on the actual treatment at the time of the measurement, or on the recorded time of AE onset (concept of treatment emergent AEs). That is, measurements and AEs recorded prior to first trial drug administration will be assigned to 'screening'; those between the first Humira® intake and up to the drug administration on Week 14 will be assigned to “run-in” period. All AEs occurring between start of treatment and end of the REP will be considered ‘treatment-emergent’ with respect to the randomized treatment arm. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’ (with respect to the randomized treatment arm).

Laboratory assessments after the first dose of trial medication up to a period of 10 weeks after the last dose of the trial medication will be assigned to the treatment phase for evaluation. Laboratory values will be compared to their reference ranges and frequency tables by visit will be provided for the number of patients within and outside the reference range.

Vital signs, physical examinations, 12-lead ECG, 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.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The PK parameters listed in Sections 2.1.2, 2.1.3, 2.1.4 for patients in the switching arm and in the US-licensed Humira®-continuous arm will be calculated using non-compartmental methods according to the relevant SOP of the sponsor and as described in the TSAP.

PKS will be used for the statistical analysis of PK parameters. Plasma concentrations will be analyzed descriptively for all patients in the run-in treated set (RTS). Moreover, PK parameters will be also descriptively analyzed for patients in the RTS.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format provided in the bioanalytical report, that is, to the same precision of decimal places or significant figures as provided in the bioanalytical report.

If a measured level for a given PK sample is BLQ then 1/2 LLOQ of the bioanalytical assay (0.0125 µg/mL) will be used for the parameter calculations. For samples taken at baseline (visit 2) BLQ values will not be replaced by 1/2 LLOQ.

If all plasma concentrations of an intensive PK interval (week 12-14 and/or week 30-32) will be replaced by ½ LLOQ, both C_{max} and C_{min} of the respective dosing interval will equal ½ LLOQ. The corresponding t_{max} and t_{min} will be the actual time of the first plasma sample in this dosing interval.

Both analyte plasma concentrations and PK parameters for the switching arm and in the US-licensed Humira®-continuous arm will be listed and presented graphically as appropriate.

At least the following descriptive statistics will be calculated for plasma concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, Q1, Q3 (Q1 and Q3 only for PK parameters), arithmetic coefficient of variation (CV), geometric mean, and geometric CV. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then, the individual PK values as well as the descriptive statistics will be reported with three significant digits in the CTR.

For the statistical analysis of the PK endpoints please refer to Section 7.3.1.

7.4 INTERIM ANALYSES

7.4.1 Blinded review of sample size

The blinded, pooled $AUC_{\tau, 30\text{-}32}$ or $C_{max, 30\text{-}32}$ will be monitored to verify the sample size assumptions.

Due to the uncertainty about the PK variability, a sample size re-assessment procedure as described in Friede and Kieser (P04-05360) and Golkowski et al (R16-4933) has been considered for this study. The initially planned total sample size is 170 PK evaluable patients (i.e., patients in the PKS and all necessary covariates are available). This is also set to be the minimum sample size for the trial.

For this study a maximum sample size to be recruited is set to 350. Taking into account the drop-out rates as described above this translates to a maximum of approximately 246 PK evaluable patients at Week 32.

After (approximately) 86 patients have had their Week 32 primary endpoints assessment and are PK evaluable the variability of $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ will be re-estimated based on the data of those 86 patients. This adequately allows the determination of the variability relevant for sample size (re-)calculation, which is in line with the primary endpoint analysis strategy. In order to mirror the primary endpoint analysis strategy the variability will be estimated after

stage 1 as the residual variance from the model as stated in Section 7.3.1 but, due to the blinded assessment, without the covariates 'Treatment' and 'Stage'.

More details will be specified in the TSAP. In addition, the TSAP will provide justification which demonstrates that the overall type I error is maintained.

No formal statistical testing for efficacy will be performed.

7.5 FINAL ANALYSIS

The final analysis as described above will take place when all data are available, clean and the database is locked.

7.6 HANDLING OF MISSING DATA

7.6.1 Pharmacokinetic data

Handling of missing PK data will be performed according to the relevant SOP of the sponsor (001-MCS-36-472).

For the non-compartmental analysis, concentration data identified with no sample (NOS), no valid result (NOR) or not analysed (NOA) will generally not be considered for the evaluations (calculations and graphical representation).

Descriptive statistics of concentrations at specific time points are calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled is based on the total number of samples that were drawn at the specific time point (i.e., below the limit of quantitation [BLQ] (only if not replaced by ½ LLOQ of the bioanalytical assay), NOR, NOA and NOS are included).

7.6.2 Efficacy data

For the analysis of secondary efficacy endpoints, missing PASI75 and sPGA data will be imputed using the multiple imputation (MI) method.

However, all patients who discontinue treatment, are lost-to-follow-up or have any severe violation related to any therapy that may significantly impact efficacy assessment (Table 4.2.2.1: 1) prior to the secondary efficacy endpoints assessment will be considered as a non-responder. This is referred to as 'NRI'.

For more details refer to the TSAP.

7.6.3 Safety data

For the aim of safety analysis, in case of missing AE relationship status, an AE will be considered as related.

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

7.7 RANDOMISATION

On Day 1, all patients meeting the eligibility criteria will be entered and receive Humira® during the run-in phase. At the beginning of Week 14, patients with at least a partial response (PASI50) will be randomized at 1:1 to either receive Humira® until Week 48 or alternatively receive BI 695501 and Humira® until Week 48. Patients not achieving at least a PASI50 response at Week 14 will be considered as non-responders and will be discontinued from the trial. At Week 14, the randomization will be stratified by the level of their Week 14 response (≥ PASI50 to < PASI75 and ≥ PASI75). 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 except for unblinded qualified staff who will prepare and administer trial medication. The block sizes of the randomization will be documented in the CTR.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

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 patients 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

eCRFs 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 patient 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 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 contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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 and regulatory reporting obligation in accordance with regulatory requirements.

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 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 Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim 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 when the first patient in the whole trial signs informed insent.

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 30 days 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 one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

Pharmacokinetic, ADA, and nAb sample analysis will be performed by

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 CLINICAL EVALUATIONS OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.6 (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, LDH, cholinesterase, haptoglobin, PT or INR, CK, CK-MB (assessed only if CK is greater than ULN at the DILI visit), coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting plasma glucose, cholesterol, triglycerides

Serology
- Hepatitis A (Anti-IgM, Total Anti-Hep A), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Total Anti-Hep D if HBsAg positive), 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, and Anti mitochondrial antibody if overall hepatitis serology is negative or non-reactive

Hormones, tumor marker
- TSH

Hematology
- CBC w/Reticulocytes (WBC, differentials, RBC, MCV, MCH, MCHC and Reticulocytes)

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

Table 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%				

Table 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.

Table 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%					

Table 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, receiving and handling the trial medication at site) will remain blinded with regard to the randomized treatment assignments until after database lock.

To prevent unblinding, a designated unblinded 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 personnel. 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 and Table 4.1.1: 2.

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
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: **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 or WebEx 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.

10.4 POTENTIAL DRUG-INDUCED LIVER INJURY (DILI) CHECKLIST

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Potential Drug-Induced Liver Injury (DILI) Checklist Page 1 of 17

(BI) Trial no: Patient no: Date:

- **The DILI Checklist provides detailed guidance for the assessment of potential drug-induced liver injury once a laboratory hepatic injury alert is received.**
- **Please follow-up the topics and questions within the specified timeframes below.**
- **Reporting procedures for new information is outlined in each section of the DILI Checklist.**
- **Keep the DILI Checklist as well as all other received information relating to the potential DILI (e.g. laboratory data, special diagnostic, expert consultations and consultant's reports) in the patient's / healthy subject's file.**
- **Data should not be unblinded for reporting purpose.**
- **Provide a copy of the DILI Checklist as well as all other received information attached to the SAE form – report according to the process outlined in the clinical trial protocol. This applies to initial information and updated information.**

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Potential Drug-Induced Liver Injury (DILI) Checklist Page 2 of 17

(BI) Trial no: Patient no: Date:

_____ _____ _____

1. Targeted questionnaire and investigator follow-up

Triggered by the laboratory hepatic injury alert / notification as defined in the CTP, the investigator initiates the collection of information as requested below in sections 1.1 to 1.5.

Investigator:
Collect the information in Section 1 within 48 hours upon laboratory hepatic injury alert/notification (or as soon as possible, in case the timelines cannot be met).

1.1 Alcohol Consumption

Reporting:

- Please add any new information on alcohol consumption to Table 1.

Table 1: Details of alcohol consumption

Number of drinks	per day / week / month*	Volume of drink and % of alcohol

* as applicable

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(BI) Trial no: Patient no: Date:

1.2 Medical history / concomitant diagnoses

Reporting:

- Please report date of diagnosis (DD), date of onset (DO), and end date (ED) of last episode in the 'Date' field in Table 2. Please specify type of date in brackets.
- Please add any medical history that is answered with 'yes' in Table 2 to the medical history/baseline condition page of the (e)CRF, if not entered there already.

Table 2: Medical history / concomitant diagnoses

Does the patient have the following conditions?				
Liver cirrhosis (of any etiology)				
cirrhosis	Yes ☐	No ☐	Not known ☐	Date _____
portal hypertension	Yes ☐	No ☐	Not known ☐	Date _____
gastrointestinal varices	Yes ☐	No ☐	Not known ☐	Date _____
Liver lesions or hepatocellular carcinoma	Yes ☐	No ☐	Not known ☐	Date _____
Portal vein thrombosis	Yes ☐	No ☐	Not known ☐	Date _____
Viral hepatitis	Yes ☐	No ☐	Not known ☐	Date _____
	specify viral hepatitis:		_____	
	serology of viral hepatitis:		_____	
Non-Alcoholic Steatohepatitis (fatty liver)	Yes ☐	No ☐	Not known ☐	Date _____
Gilbert syndrome	Yes ☐	No ☐	Not known ☐	Date _____
Signs and symptoms of encephalopathy				
mental status deterioration (e.g. confusion, disorientation)	Yes ☐	No ☐	Not known ☐	Date _____
sleepiness (somnolence)	Yes ☐	No ☐	Not known ☐	Date _____
drowsiness	Yes ☐	No ☐	Not known ☐	Date _____
flapping tremor (asterixis)	Yes ☐	No ☐	Not known ☐	Date _____

Table 2 continues on next page

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Potential Drug-Induced Liver Injury (DILI) Checklist Page 4 of 17

(BI) Trial no: _____ Patient no: _____ Date: _____

Table 2: Medical history / concomitant diagnoses (cont.)

Haematochromatosis	Yes ☐	No ☐	Not known ☐	Date _____
Biliary tract disease:				
gallstones	Yes ☐	No ☐	Not known ☐	Date _____
pancreatic disease	Yes ☐	No ☐	Not known ☐	Date _____
other				Date _____
Liver synthesis:				
factors II, VII, IX, X < ref. range	Yes ☐	No ☐	Not known ☐	Date _____
INR > ref. range	Yes ☐	No ☐	Not known ☐	Date _____
aPTT > ref. range	Yes ☐	No ☐	Not known ☐	Date _____
PT > ref. range	Yes ☐	No ☐	Not known ☐	Date _____
AT-IIIi < ref. range	Yes ☐	No ☐	Not known ☐	Date _____
serum albumin < ref. range	Yes ☐	No ☐	Not known ☐	Date _____
Thrombocytopenia	Yes ☐	No ☐	Not known ☐	Date _____
Ecchymosis	Yes ☐	No ☐	Not known ☐	Date _____
Excessive bruising on skin	Yes ☐	No ☐	Not known ☐	Date _____
Gastrointestinal bleeding				
upper GI bleeding	Yes ☐	No ☐	Not known ☐	Date _____
lower GI bleeding	Yes ☐	No ☐	Not known ☐	Date _____
obscure GI bleeding	Yes ☐	No ☐	Not known ☐	Date _____
Haemolytic disorders				
sickle cell disease	Yes ☐	No ☐	Not known ☐	Date _____
glucose-6-phosphate dehydrogenase deficiency	Yes ☐	No ☐	Not known ☐	Date _____

Table 2 continues on next page

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Potential Drug-Induced Liver Injury (DILI) Checklist Page 5 of 17

(BI) Trial no: _____ Patient no: _____ Date: _____

Table 2: Medical history / concomitant diagnoses (cont.)

Infections				
recent viral-like illness	Yes ☐	No ☐	Not known ☐	Date _____
recent travel to tropical zones	Yes ☐	No ☐	Not known ☐	Date _____
malaria	Yes ☐	No ☐	Not known ☐	Date _____
trypanosomiasis	Yes ☐	No ☐	Not known ☐	Date _____
schistosomiasis	Yes ☐	No ☐	Not known ☐	Date _____
Allergy (specify type)	Yes ☐	No ☐	Not known ☐	Date _____
Diabetes Mellitus Type 1	Yes ☐	No ☐	Not known ☐	Date _____
Diabetes Mellitus Type 2	Yes ☐	No ☐	Not known ☐	Date _____
Congestive Heart Failure	Yes ☐	No ☐	Not known ☐	Date _____
Ischemic Heart Disease	Yes ☐	No ☐	Not known ☐	Date _____
Blood Transfusion within the past 3 months	Yes ☐	No ☐	Not known ☐	Date _____
Auto-immune disorders	Yes ☐	No ☐	Not known ☐	Date _____
Recreational drug use	Yes ☐	No ☐	Not known ☐	Date _____
Special diet since 3 months	Yes ☐	No ☐	Not known ☐	Date _____
	Which diet:			
Environmental exposure to liver toxins*	Yes ☐	No ☐	Not known ☐	Date _____
collection of wild mushrooms	Yes ☐	No ☐	Not known ☐	Date _____
Other (specify)				Date _____
Current symptoms				
Fatigue	Yes ☐	No ☐	Not known ☐	Date _____
Nausea	Yes ☐	No ☐	Not known ☐	Date _____
Vomiting	Yes ☐	No ☐	Not known ☐	Date _____
Abdominal pain in right upper quadrant	Yes ☐	No ☐	Not known ☐	Date _____
Other information:				

*If yes, please see section 1.4 below

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Potential Drug-Induced Liver Injury (DILI) Checklist Page 6 of 17

(BI) Trial no: Patient no: Date:

1.3 Complete Physical Examination

Reporting:

- Please add any conditions that is answered with 'yes' in Table 3 in the Adverse Event (AE) page of the (e)CRF with the respective details, if not entered there already.

Table 3: Physical Examination

Does the patient have the following conditions?		Yes	No
Rash		☐	☐
Icterus		☐	☐
	Skin	☐	☐
	Sclerae	☐	☐
Abdominal tenderness		☐	☐
	Diffuse	☐	☐
	Right upper quadrant	☐	☐
Hepatomegaly		☐	☐
Splenomegaly		☐	☐
Blood pressure			mmHg
Body temperature			°C
Heart rate or pulse rate			/min
Dyspnea		☐	☐
Lung sounds			
	Crackle	☐	☐
	Rales	☐	☐
	Other		
Heart sounds (abnormalities?)		☐	☐
Peripheral edema		☐	☐
Jugular venous distension		☐	☐
Signs of ascites		☐	☐
recent increase in abdominal girth		☐	☐
weight gain		☐	☐
	in kg / days:		

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(BI) Trial no: Patient no: Date:

1.4 List herbal and non-herbal supplements and vitamins for past 3 months

Reporting:

- Please add herbals and non-herbal supplements and vitamins with the respective details to Table 4 and to the concomitant therapy page in the (e)CRF, if not entered there already.

Table 4: Herbal and non-herbal supplements and vitamins for past 3 months

Name	Start Date	Stop Date

1.5 List medications (prescriptions and non-prescriptions) for past 3 months

Reporting:

- Please add drugs with the respective details to Tables 5 and 6 as well as to the concomitant therapy page in the (e)CRF, if not entered there already. Add dose and concomitant alcohol intake as additional information.

Please provide information on drugs, including over the counter drugs (OTC) such as acetaminophen (= phenacetin, paracetamol). Please consider whether high doses for these drugs were taken.

Table 5: Acetaminophen use: alone or in combination with other medicines

Name	Dose	Start Date	Stop Date	In conjunction with alcohol Y/N
What was the highest dose of acetaminophen taken in a single day?				

Table 5 continues on next page

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(BI) Trial no: Patient no: Date:

Table 6: Concomitant therapies (other than acetaminophen)

Name	Dose	Start Date	Stop Date	In conjunction with alcohol Y/N

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(BI) Trial no: Patient no: Date:

2. Reflex testing from initial blood sample

Triggered by the central laboratory hepatic injury alert / notification (e.g. in Phase 1 trials) of the initial blood sample the investigator initiates the steps below.

Investigator:

Collect the information of the reflex laboratory (reflex the initial blood sample = employ available specimen) within 24 hours upon laboratory hepatic injury alert / notification.

Any elevation of ALT and/or AST and TBL qualifying as laboratory hepatic injury alert should lead to reflex testing on the initial blood sample. The reflex testing should include (if appropriate specimen is available):

- direct bilirubin
- creatine kinase
- acetaminophen level
- lactate dehydrogenase
- haptoglobin
- complete blood count and cell morphology
- reticulocyte count

The priority of the reflexing is given by the displayed order of the tests in case that the remaining specimen of the initial sample limits complete testing. If the described parameters were already part of the initial assessment, reflexing on the initial sample is not requested. Should an individual laboratory be unable to perform all specified analyses, it should perform those that are possible.

Data collection and reporting:

- Central laboratory*: reflexing is done automatically via algorithm. ALT, AST, AP, bilirubin (total and direct) will be reported automatically. Therefore, these parameters do not need to be entered into the (e)CRF.
- Local laboratory: reflexing is initiated by investigator. ALT, AST, AP, and bilirubin (total and direct) have to be reported via creation of an unplanned visit page in the (e)CRF.
- Please enter the values of the initial blood sample and the reflex testing in Table 7, irrespective of whether a central or local laboratory is applicable.

* Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient's repeat specimen would not reach the central laboratory in a reasonable timeframe), the above listed laboratory values are evaluated by a local laboratory.

The process described here for the local laboratory, might also be applicable for trials, in which a central laboratory was not set-up (e.g. in Phase 1 trials).

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(BI) Trial no: Patient no: Date:

Table 7: Reflex testing of initial blood sample

Date of reflex testing (dd-Mmm-yyyy):

Parameter	Value	Unit	Reference Range
ALT			
AST			
Direct bilirubin			
Total bilirubin			
Alkaline phosphatase			
Creatine kinase			
Acetaminophen level			
Lactate dehydrogenase			
Haptoglobin			
Complete blood count			
White blood count			
Neutrophils			
Lymphocytes			
Monocytes			
Eosinophils			
Basophils			
Red blood count			
Platelets			
MCV			
MCH			
MCHC			
Reticulocyte count			

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(BI) Trial no: Patient no: Date:

3. DILI Kit assessment and abdominal imaging

Investigator:

Follow up the potential DILI case within 48 hours of initial laboratory hepatic injury alert / notification (e.g. in Phase 1 trials), or as soon as possible if timelines cannot be met.

Investigator initiates:

- Obtain new blood sample for DILI Kit assessment within 48 hours of initial laboratory hepatic injury alert / notification
- Initiate abdominal imaging within 48 hours of initial laboratory hepatic injury alert / notification (to rule out biliary tract, pancreatic, or intrahepatic pathology, e.g. bile duct stones or neoplasm)

  Note: abdominal ultrasound is considered as minimal procedure. The most appropriate imaging should be chosen by the investigator.

Reporting:

- The investigator provides the results of the DILI Kit via the DILI Checklist in Table 8 to the TCM (via the CML of the respective country). The results are not reported via the (e)CRF.
- In case of findings: please update the AE page with the diagnosis derived from the parameters and include the result (e.g. Anti-IgM value, unit and reference range for Hepatitis A diagnosis) into the respective AE comment field.
- Any diagnosis found through abdominal imaging should be recorded on the adverse event page.

3.1 DILI Kit assessment

In case the DILI Kit was provided to a central laboratory, all parameters will be assessed automatically.

In case the DILI Kit was provided to a local laboratory, assessment of the parameters of the DILI Kit is in the responsibility of the investigator.

Should an individual laboratory be unable to perform all specified analyses, it should perform those that are possible.

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(BI) Trial no: _____ Patient no: _____ Date: _____

Table 8: DILI Kit

Date of DILI Kit (dd-Mmm-yyyy): _____

Parameter	Value	Unit	Reference Range
ALT			
AST			
Alkaline phosphatase			
Total bilirubin			
Direct bilirubin			
Lactate dehydrogenase			
Creatine kinase			
Complete blood count			
White blood count			
neutrophils			
lymphocytes			
monocytes			
eosinophils			
basophils			
Red blood count			
Platelets			
MCV			
MCH			
MCHC			
Haptoglobin			
Reticulocyte count			

Table 8 continues on next page

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(BI) Trial no: Patient no: Date:

Table 8: DILI Kit (cont.)

Parameter	Value	Unit	Reference Range
ChE (serum)			
Albumin			
PT (sec) or INR			
CK			
Coeruloplasmin			
α-1antitrypsin			
Transferrin			
Amylase			
Lipase			
Complete blood count (including differential)			
Fasting Glucose			
Cholesterol			
Triglycerides			
TSH			

Table 8 continues on next page

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(BI) Trial no: Patient no: Date:

Table 8: DILI Kit (cont.)

Immunology		Value / Unit	Reference Range		Value / Unit	Reference Range
Hepatitis A	anti–IgM			total anti HepA		
Hepatitis B	HbsAg, anti HBcIgM			DNA [1]		
Hepatitis C	anti-HCV			RNA [2]		
Hepatitis D [3]	anti–IgM			total anti HepD		
Hepatitis E	anti-HEV IgM			total anti-HEV [4]		
	RNA [5]					
ANA [6]	Positive					
	Negative					
Anti-smooth muscle cell Antibody [6]	Positive					
	Negative					
Anti-LKM antibody [6]	Positive					
	Negative					
Anti-mitochondrial antibody [6]	Positive					
	Negative					

[1] PCR

[2] if Anti-HCV positive

[3] if HbsAg positive

[4] instead of total Anti HEV, HEV IgG can be assessed (depends on assay availability)

[5] if anti-HEV IgM positive, if test is available in central laboratory provider

[6] assessed if overall hepatitis serology is negative

Either ELISA or IFA are acceptable methods. If possible provide titers.

If any of the laboratory parameters of the DILI Kit cannot be performed, e.g. due to logistics, the TMM and the RM physician (if nominated) have the decision of whether such a parameter has to be assessed.

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(BI) Trial no: Patient no: Date:

4. Long term follow-up

Investigator:

In case of persistent abnormal liver laboratory values, repeat AST, ALT, AP, bilirubin (total and direct)

- Please consider hepatology consultation and provide the consultant's report, if available.
- At least 1/week until the symptoms / laboratory abnormalities stabilize or return to normal,
- Then, according to the protocol

The investigator initiates the repeats with either central laboratory (if set up) or local laboratory.

Reporting:

- Central laboratory*: ALT, AST, AP, and bilirubin (total and direct) will be reported automatically. Therefore, these parameters are not entered into the (e)CRF.
- Local laboratory: ALT, AST, AP, and bilirubin (total and direct) have to be reported via creation of an unplanned visit page in the (e)CRF.
- Any important comment may be entered in the general comment field of the laboratory test page.

Depending on further laboratory changes, additional parameters identified e.g. by the DILI Kit may be followed up based on medical judgment.

Follow-up of findings based on the DILI Kit (e.g. Hepatitis B) are reported as AE in the (e)CRF with the corresponding laboratory values in the AE comment field.

Results of the long term follow-up are made available by the investigator to the functions on the DILI Distribution List (via the CML of the respective country).

* Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient's repeat specimen would not reach the central laboratory in a reasonable timeframe), the above listed laboratory values are evaluated by a local laboratory.

The process described here for the local laboratory, might also be applicable for trials, in which a central laboratory was not set-up (e.g. in Phase 1 trials).

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(BI) Trial no: Patient no: Date:

SIGNATURE

Signed by investigator who assessed the components of the DILI Checklist.

Signature:	**Date of signature:** / / (dd / mmm / yyyy)
Investigator (in block letters):	

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(BI) Trial no: Patient no: Date:

5. Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
AP	Alkaline Phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ChE	Cholinesterase
CK	Creatinine Kinase
CK-MB	Isoenzyme of CK
CML	Local Clinical Monitor
CRF	Case Report Form
DILI	Drug-Induced Liver Injury
(e)CRF	(Electronic) Case Report Form
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase
LKM	Liver / Kidney / Microsomal Antibody
OTC	Over the Counter
PT	Prothrombine Time
RM	Risk Managment
TBL	Total Bilirubin
TCM	Trial Clinical Monitor
TMM	Team Member Medicine
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 Nov 2017
EudraCT number		2016-002254-20
BI Trial number		1297.9
BI Investigational Product(s)		BI 695501
Title of protocol		VOLTAIRE-X: Pharmacokinetics, safety, immunogenicity and efficacy 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.
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title Page
Description of change		Lay Title revised
Rationale for change		Lay description of protocol revised for clarity.
Section to be changed		Synopsis (Trial site[s]), 3.3
Description of change		Number of clinical sites revised from 75 to 80.
Rationale for change		Number of sites updated.
Section to be changed		Synopsis (Methodology), 3.1
Description of change		Description of “Visit Days” changed to “Visit #” for Weeks 12-14 and 30-32.
Rationale for change		Changed to “visits” in case days are revised.
Section to be changed		Synopsis (Methodology), 3.1
Description of change		Drug and dosing sequence by Week/Visit # added.
Rationale for change		Text revised for clarity of dosing sequence.
Section to be changed		Flow Chart list of assessments, Flow Chart Footnote 6
Description of change		TB testing added to Week 14 and EoT visits; procedures to follow if positive TB results are obtained at screening or post-screening have been added.
Rationale for change		Additional testing added to monitor TB positivity at

		EoT.
Section to be changed		Flow Chart
Description of change		Contact IRT added to EoT visit
Rationale for change		Missed procedure for EoT added.
Section to be changed		Flow Chart (Cont'd)
Description of change		Change permitted window visit to "0" days
Rationale for change		Corrected a previous error.
Section to be changed		Flow Chart, Footnote 10, Section 5.3.1
Description of change		Added collection of PK samples that may be performed by home healthcare nurse at sub-visits.
Rationale for change		Added for clarity.
Section to be changed		Abbreviations
Description of change		List of Abbreviations updated as necessary.
Rationale for change		Consistency with revisions.
Section to be changed		2.1.4
Description of change		PK endpoints added.
Rationale for change		PK endpoints added for accuracy and completeness.
Section to be changed		3.1
Description of change		The text: "the end of the treatment period" deleted.
Rationale for change		Text revisions made for clarity.
Section to be changed		3.3.2
Description of change		"Pre-treatment call" deleted from Inclusion Criterion #1.
Rationale for change		Deleted to avoid confusion.
Section to be changed		3.3.3
Description of change		Units for calculated creatinine clearance corrected in Exclusion Criterion #23.
Rationale for change		Units corrected.
Section to be changed		Table 4.1.1: 1, Table 4.1.1: 2
Description of change		Posology revised.
Rationale for change		Posology revised for clarity.
Section to be changed		Table 4.1.1: 1, Table 4.1.1: 2, Section 4.1.4
Description of change		Site of administration added.
Rationale for change		Site of administration added for clarity and for consistency with labelling.

Section to be changed		Table 4.2.2.1: 1
Description of change		Live attenuated vaccine not permitted up to "5" months revised to "3" months.
Rationale for change		Corrected to be aligned with the label and with other studies for the same molecule.
Section to be changed		5.2
Description of change		Deleted "(including IGRA at SFU)".
Rationale for change		Change made to be consistent with Flow Chart.
Section to be changed		Table 5.2.3: 1
Description of change		Screening for hepatitis clarified; screening for infections added to Visit 14, EoT, and optional retest at Unscheduled visit.
Rationale for change		Additional TB testing added for monitoring.
Section to be changed		Table 5.3.1: 1
Description of change		Revised Visit 17 PK samples from Week "17" to Week "30" and Visit 18 PK samples from Week "18" to Week "32"; PK sampling time windows revised from "3" hours to "12" hours at Visits 8a-d and 17a-d.
Rationale for change		Revised for accuracy.
Section to be changed		Table 6.1: 1
Description of change		Number of samples and volumes revised due to TB tests added at Visits 14 and EoT.
Rationale for change		Revised for accuracy with updated testing.
Section to be changed		6.2.3
Description of change		Deleted text noting that patients will be followed for efficacy assessments until Week 50.
Rationale for change		Deleted since most patients will receive other treatments following the End-of-Treatment Visit.
Section to be changed		7.3
Description of change		Number of missed plasma samples from Week 12 to 14 or Week 30 to 32 revised to two consecutive timepoints during Visits 8a-d and 17a-d; deleted "at more than three timepoints"
Rationale for change		This scenario is redundant based on the other two defined criteria.
Section to be changed		7.3.2.1
Description of change		C_{min} revised to $C_{min, 30-32}$.
Rationale for change		Changes made for clarity and accuracy.

Section to be changed		7.4.3
Description of change		Section number revised to 7.5; description of final analyses revised.
Rationale for change		Changes made for clarity and accuracy.
Section to be changed		8.7
Description of change		Changed bioanalytical lab from to
Rationale for change		Change in laboratories.
Section to be changed		10.1.2
Description of change		Clinical chemistry, serology, and hematology assessments changed to be consistent with Section 10.4.
Rationale for change		Revisions made for internal consistency.
Section to be changed		Figure 10.2: 5
Description of change		Nail assessment deleted.
Rationale for change		Nail assessment not performed in this trial.
Section to be changed		11.1
Description of change		Description of Global Amendment 1 and summary of changes added.
Rationale for change		Description of changes and rationales added per template.

11.2 GLOBAL AMENDMENT 2

Date of amendment		25 Jul 2019
EudraCT number		2016-002254-20
BI Trial number		1297.9
BI Investigational Product(s)		BI 695501
Title of protocol		VOLTAIRE-X: Pharmacokinetics, safety, immunogenicity and efficacy 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.

To be implemented only after approval of the IRB / IEC / Competent Authorities	X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	

Section to be changed		Synopsis (Statistical methods), Sections 3.1, 4.1.5, 7.2, 7.3.1, 7.3.2.1, 7.3.5, 7.4.1, 7.8, 9.1.
Description of change		The primary statistical method and sample size calculations have been updated based on the **blinded** sample size re-assessment (BSSR) (the study is still fully blinded)
Rationale for change		The results of the BSSR revealed that the assumptions underlying the statistical analysis model in the current CTP version 2 were not valid. Therefore, the pre-specified primary statistical analysis (ANCOVA on the log scale) is considered inappropriate in this specific case. This amendment is changing the statistical analysis of the primary endpoints to adequately reflect the underlying data distribution. The primary endpoints $AUC_{\tau, 30\text{-}32}$ and $C_{max, 30\text{-}32}$ are to be evaluated on the untransformed original scale instead of on the logarithmic scale. No primary analysis with week 32 data, there will be only one final analysis with all data.
Section to be changed		Synopsis (Statistical methods)
Description of change		Confidence intervals updated to 90.2; Text revised to address the changes on pre-specified primary statistical analysis
Rationale for change		See above
Section to be changed		Sections 3.1, 7.4.2, 7.5
Description of change		The primary analysis when the last patient has completed their Week 32 assessment has been deleted.
Rationale for change		See above
Section to be changed		Section 4.1.5
Description of change		Blinding of the study staff involved in the primary analysis when the last patient has completed their Week 32 assessment has been deleted.
Rationale for change		See above
Section to be changed		Section 7.2
Description of change		1st paragraph deleted:-This is equivalent to comparing the 90% two-sided confidence intervals (CI) for the ratio of geometric means with the boundaries 80.00%

		to 125.00% used in the evaluation of PK similarity. New paragraph added: A (one-sided) significance level 4.9% was chosen to ensure overall type I error control at 5%, in light of the adapted analysis strategy (details are described in the TSAP). Means description updated (geometric deleted)
Rationale for change		See above
Section to be changed		Section 7.3
Description of change		Paragraph 1: Sentence deleted: "The Pharmacokinetic Set (PKS) is defined as follows." Paragraph 3: It was added that further criteria might be specified also "in the minutes of the Data Review Meeting."
Rationale for change		Paragraph 1: Corrected a previous error. Paragraph 3: Adapted to the actual procedure.
Section to be changed		Section 7.3.1
Description of change		Paragraph 2 added:The confidence interval will be calculated according to Fiellers theorem [R12-1809]. As stated in [R12-1809, chapter 10.2.1], equivalence will be concluded if Fieller's 90.2% confidence interval for the is included in the equivalence range 80.00% – 125.00% and $$\frac{|\bar{Y}_R|}{\hat{\sigma}\sqrt{\frac{1}{n_R}}} > t_{1-\alpha,n_T+n_R-5}$$ which is equivalkent to rejecting both null hypotheses. Thereby $\bar{Y}_R$ refers to the LSMean of the reference treatment, $\hat{\sigma}$ is the residual standard deviation from the ANCOVA model (M1) below, n_T and n_R are the final sample sizes in the test and reference arm, respectively, and $\alpha = 4.9\%$. Logarithmic scale replaced by Original. LSMEANS statement updated as follows: The LSMEANS statement is used to estimate the treatment. LSMeans of the switching and non-switching arm which will be used to construct the point estimate for the ratio of means. The 90.2% CI will be derived based on Fieller's theorem.

Rationale for change		See above
Section to be changed		Section 7.3.2.1
Description of change		gMean ratio replaced by Mean ratio
Rationale for change		See above
Section to be changed		Section 7.3.5
Description of change		Paragraph 2 was replaced by: PKS will be used for the statistical analysis of PK parameters. Plasma concentrations will be analyzed descriptively for all patients in the run-in treated set (RTS). Moreover, PK parameters will be also descriptively analyzed for patients in the RTS. Paragraph 4 was added: If a measured level for a given PK sample is BLQ then 1/2 LLOQ of the bioanalytical assay (0.0125 µg/mL) will be used for the parameter calculations. For samples taken at baseline (visit 2) BLQ values will not be replaced by 1/2 LLOQ. Paragraph 5 was added: If all plasma concentrations of an intensive PK interval (week 12-14 and/or week 30-32) will be replaced by ½ LLOQ, both C_{max} and C_{min} of the respective dosing interval will equal ½ LLOQ. The corresponding t_{max} and t_{min} will be the actual time of the first plasma sample in this dosing interval. Sentence added in paragraph 7: (Q1 and Q3 only for PK parameters)
Rationale for change		Paragraph 2: RTS will be used for the descriptive analysis of PK concentrations and PK parameters to also include patients with plasma concentrations and PK parameters determined only during the run-in period. Paragraph 4: BLQ values will be replaced by 1/2 LLOQ at visits other than baseline to acknowledge the intrinsic property of adalimumab to elicit high titer immunogenic responses with strong impact on drug exposure Paragraph 5: If all plasma conentrations during the

		intensive PK interval are replaced by ½ LLOQ the observed parameters C_{max} and C_{min} (and t_{max} and t_{min}) are identical in order to include also patients with low plasma concentrations in the analysis of these parameters. Additional sentence in paragraph 7: Section adapted according to SOP
Section to be changed		Section 7.6.1
Description of change		Sentence added: (only if not replaced by ½ LLOQ of the bioanalytical assay).
Rationale for change		Added for consistency and clarity. See also rationale for change in section 7.3.5
Section to be changed		Section 7.8
Description of change		
Rationale for change		Sample size determination is updated based on the change of the statistical analysis for primary endpoints
Section to be changed		Section 9.1
Description of change		New reference added: R12-1809, Hauschke D Steinijans V Pigeot I. Bioequivalence studies in drug development: methods and applications. Chichester: John Wiley & Sons; 2007.
Rationale for change		Added for clarity.

APPROVAL / SIGNATURE PAGE

Document Number: c16011431 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: VOLTAIRE-X: Pharmacokinetics, safety, immunogenicity and efficacy 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 Trial Leader		26 Jul 2019 12:23 CEST
Author-Trial Clinical Pharmacokineticist		26 Jul 2019 13:13 CEST
Approval-Team Member Medicine		26 Jul 2019 14:27 CEST
Approval- Medical Affairs		26 Jul 2019 18:58 CEST
Author-Trial Statistician		29 Jul 2019 07:56 CEST
Verification-Paper Signature Completion		05 Aug 2019 16:53 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed