

Clinical Trial Protocol

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EudraCT No.:	2015-002634-41	
BI Trial No.:	1297.3	
BI Investigational Product:	BI 695501	
Title:	Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis (RA): an open-label extension trial for patients who have completed trial 1297.2 and are eligible for long-term treatment with adalimumab	
Brief Title:	Open-label, long-term extension trial of BI 695501 in patients with rheumatoid arthritis	
Clinical Phase:	IIIb	
Trial Clinical Monitor:	<p>Phone: _____</p> <p>Fax: _____</p>	
Coordinating Investigator:	<p>Tel.: _____</p> <p>Fax: _____</p>	
Status:	Final Protocol (revised protocol based on global amendment 01)	
Version and Date:	Version:	Date:
	2.0	19 FEB 2016
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 19 Feb 2016	Trial number: 1297.3		Revision date: NA
Title of trial:	Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis (RA): an open-label extension trial for patients who have completed trial 1297.2 and are eligible for long-term treatment with adalimumab		
Coordinating Investigator:			
Trial site(s):	Multinational, multicenter trial in approximately 80 clinical sites across approximately 15 countries. Since this is an extension to Trial 1297.2, the actual number of sites and countries will be determined by the sites participating in Trial 1297.2 that have patients eligible for Trial 1297.3.		
Clinical phase:	IIIb		
Objective(s):	The objective of this trial is to provide long-term safety, efficacy, pharmacokinetics (PK), and immunogenicity data on BI 695501 administered via prefilled syringe in patients with RA who have completed Trial 1297.2.		
Methodology:	<p>BI 695501 is a proposed biosimilar to adalimumab (Humira®). Humira has received regulatory approval for RA in the United States (US), the European Union (EU) and many other countries.</p> <p>This is an open-label trial of BI 695501 with a 48-week treatment period in patients with RA continuing to receive methotrexate (MTX) within the dose range of the 1297.2 trial for at least 12 weeks. After Week 12, the MTX dose will be at the Investigator's discretion.</p> <p>Each patient who meets all the inclusion criteria and none of the exclusion criteria will self-administer 40 mg of BI 695501 every 2 weeks.</p> <p>The trial is designed to generate data on long-term safety, efficacy, PK, and immunogenicity with BI 695501 in patients who have completed Trial 1297.2. This will include:</p> <ul style="list-style-type: none">• patients who were previously treated with BI 695501 in Trial 1297.2 for 48 weeks,• patients who were previously treated with US-licensed Humira® for 24 weeks followed by BI 695501 for 24 weeks in Trial 1297.2,• patients who were previously treated with US-licensed Humira® in Trial 1297.2 for 48 weeks		
No. of patients:			
total entered:	It is anticipated that approximately 300 to 400 patients will be eligible and willing		

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Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 19 Feb 2016	Trial number: 1297.3		Revision date: NA
	to participate in this extension trial.		
each treatment:	All patients will receive BI 695501.		
Diagnosis :	Moderately to severely active RA.		
Main criteria for inclusion:	<p>Adult patients with moderately to severely active RA who completed Trial 1297.2, wish to participate in this extension trial and in the Investigator's assessment can benefit from receiving BI 695501. Patients must not have experienced Investigator-reported drug-related serious adverse events (SAEs) during the 1297.2 trial.</p> <p>Patients willing and able to self-administer BI 695501 using a pre-filled syringe.</p>		
Test product:	BI 695501, solution for injection		
dose:	40 mg/0.8 mL every 2 weeks via single pre-filled glass syringe		
mode of administration:	Subcutaneous (SC) injection		
Comparator product:	Not applicable		
Duration of treatment:	<p>Each patient will be treated with BI 695501 every 2 weeks.</p> <p>The trial will consist of a 48-week treatment period.</p> <p>Every effort should be made for all patients who complete the 48-week treatment period or who discontinue the trial early (and do not withdraw their consent), to return for a safety follow-up visit 10 weeks after the last administration of trial medication.</p>		
Safety endpoints:	The primary endpoint of this trial is defined as the number (proportion) of patients with drug-related adverse events (AEs) during the treatment phase.		

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Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 19 Feb 2016	Trial number: 1297.3		Revision date: NA
Criteria for efficacy, immunogenicity and pharmacokinetics:	<p>There is no primary efficacy endpoint in this trial.</p> <p>Unless otherwise specified, all endpoints will be assessed using the 1297.2 baseline values.</p> <p><u>Secondary efficacy endpoints</u></p> <ul style="list-style-type: none">• The change from Baseline in Disease Activity Score in 28 joints (DAS28) (erythrocyte sedimentation rate [ESR]) at Week 48• The proportion of patients meeting American College of Rheumatology 20% (ACR20) response criteria at Week 48• The proportion of patients who meet the ACR/European League Against Rheumatism (EULAR) definition of remission at Week 48• The proportion of patients with EULAR response (good response, moderate response or no response) at Week 48		

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Criteria for efficacy, immunogenicity and pharmacokinetics, continued:	<p><u>Other endpoints</u></p> <ul style="list-style-type: none">• The proportion of patients with antidrug antibodies (ADAs) at Week 12, Week 24, and Week 48• The proportion of patients with neutralizing antidrug antibodies (nADAs) at Week 12, Week 24, and Week 48• The proportion of patients who discontinue due to lack of efficacy• The proportion of patients who discontinue due to a drug-related AE <p><u>PK Analysis</u></p> <p>A population PK analysis with sparse blood sampling throughout the treatment period and at follow-up will be carried out to assess the PK of BI 695501. The PK analysis might involve combining data with data from other BI 695501 studies. If relevant, a relationship will be investigated between selected safety and efficacy parameters including the development of ADA/nADA.</p>		
Statistical methods:	Descriptive statistics for safety, efficacy, and other endpoints will be provided. Analyses will be based on data obtained in the current 1297.3 trial, and comparisons will be made depending on the treatment assignment in Trial 1297.2. The results will also be analyzed overall, according to the single open-label treatment in 1297.3.		

FLOW CHART

Visit	1	2	3	4	5	6	7	8	9	10
Week	Screening ¹	Baseline	6 ²	12	18 ²	24	32 ²	40 ²	48 EoT ³	58 SFU
Day	-14	1	43	85	127	169	225	281	337	407
Permitted visit window (days)	±3	±1	-	±2	-	±2	-	-	±2	±2
Informed consent	X									
Assessment of eligibility	X									
Self-administration evaluation ⁴	X									
Demographics	X									
LABS/SAFETY ASSESSMENTS										
Infection screen: Hepatitis B (HbsAg); HCV and optional HIV test	X									
RF and anti-CCP antibodies		X							X	
TB test ⁵	X								X	
ESR (local)	X	X		X		X			X	X
CRP	X	X		X		X			X	X
Pregnancy test ⁶	X	X		X		X			X	X
Physical examination	X	X		X		X			X	X
Vital signs ⁷	X	X		X		X			X	X
Laboratory tests (serum chemistry, hematology, urinalysis) ⁸	X	X		X		X			X	X
12-lead ECG ⁹	X	X								X
Previous and concomitant therapy	X	X		X		X			X	X
Adverse events ¹⁰	X	X		X		X			X	X

FLOW CHART (CONT'D)

Visit	1	2	3	4	5	6	7	8	9	10
Week	Screening ¹	Baseline	6 ²	12	18 ²	24	32 ²	40 ²	48 EoT ³	58 SFU
Day	-14	1	43	85	127	169	225	281	337	407
Permitted visit window (days)	(±3)	±1	-	±2	-	±2	-	-	±2	±2
EFFICACY ASSESSMENTS										
Swollen and tender joint counts	X	X		X		X			X	
Patient's global assessment VAS ¹¹	X	X		X		X			X	
Physician's global assessment VAS	X	X		X		X			X	
HAQ-DI ¹¹	X	X		X		X			X	
SF-36 v2 ¹¹	X	X		X		X			X	
OTHER ASSESSMENTS										
Pharmacokinetics ¹²		X		X		X			X	X
Antidrug antibody sampling ¹²		X		X		X			X	X
Neutralizing antidrug antibody sampling ¹²		X		X		X			X	X
TRIAL MEDICATION										
Contact IRT	X	X	X	X	X	X	X	X	X	
Review patient diary			X	X	X	X	X	X	X	X
Administration of trial medication	(X) ¹³	X ¹⁴	X ¹⁵ -----X							
Dispense trial medication ¹⁶		X	X	X	X	X	X	X		
Termination of trial medication									X	
End of participation										X

anti-CCP: anti-cyclic citrullinated peptide; CRP: C-reactive protein; EoT: End of Treatment; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; HAQ-DI: Health Assessment Questionnaire – Disability Index; HbsAg: Hepatitis B surface antigen; HCV: hepatitis C; HIV: human immunodeficiency virus; IRT: Interactive Response Technology; RF: rheumatoid factor; SF-36 v2: 36-item Short Form Health Survey version 2; SFU: Safety Follow-up; TB: tuberculosis; VAS: visual analogue scale.

- The Screening visit will be the Week 48 visit in Trial 1297.2 and the same visit window applies (±3 days). Informed consent for this extension trial must be obtained prior to conducting the Week 48 assessments in Trial 1297.2, in order for those assessments to serve as the screening assessments in this extension trial. VAS assessments and completion of the HAQ-DI and SF-36 v2 questionnaires must be done prior to any visit procedures at this day. Patient questionnaires completed for the 1297.2 trial will be used as baseline questionnaires for the 1297.3 trial. Trial medication should be administered after completion of all assessments at the Screening visit; this will be the last administration of trial medication in Trial 1297.2.

2. The Week 6, Week 18, Week 32, and Week 40 visits will be trial medication administration only visits, however the patient may choose to administer the trial medication at home and collect dispensed medication at a later date. At each visit, the Investigator/designee will dispense sufficient trial medication so that patients can continue to self-administer trial medication at home until the next site visit.
3. Patients who discontinue the trial early will, at discontinuation, have an End of Treatment (EoT) Visit equivalent to the Week 48 assessments; patients who discontinue early will also return for a safety follow-up visit 10 weeks after the last dose of BI 695501. Every effort should be made for all patients who complete the total 48-week treatment period to return for a safety follow-up visit at Week 58.
4. Patients will be assessed at screening if they are willing and able, per investigator judgment, to self-administer the trial medication.
5. Patients must have a negative tuberculosis (TB) test, including a QuantiFERON TB Gold test. A TB test can be performed at any time during the trial if the Investigator considers it clinically necessary.
6. Females only; a urine pregnancy test will be performed at Screening, on Day 1 (Baseline), and all subsequent visits (does not include trial medication only visits).
7. Includes measurement of blood pressure, respiratory rate and pulse rate (all sitting after 5 minutes rest). The patient's body temperature will also be recorded.
8. Findings of alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal or hemoglobin <8.0 g/dL at baseline are criteria for exclusion.
9. Two consecutive recordings need to be taken.
10. Adverse events will be collected from the time of informed consent. Adverse events continuing at the EoT Visit must be followed to resolution or follow up as agreed by the Investigator and medical monitor. For patients who complete the trial or who discontinue the trial early, AEs will be captured for 10 weeks after the EoT visit.
11. Questionnaires will be completed at the site by the patient before any investigations or discussions about their disease with the clinic staff.
12. Pharmacokinetic (PK) and anti-drug antibody (ADA) samples (including neutralizing ADA samples) should be taken at each visit designated with an "X", and can be taken at any time during the visit (PK and ADA/neutralizing ADA samples will be taken at the same time point). For all PK samples, the day and time of sampling must be accurately recorded. All dosing dates and times must be accurately entered in the patient diary. See also [Table 5.4: 1](#) for PK sampling time points.
13. At the Screening visit, the administration of BI 695501 will be performed by a suitably qualified, designated trial personnel at the site and patients will be trained on self-administration. This will be the last administration of trial medication in Trial 1297.2.
14. The first dose of trial medication in the extension trial will be administered at the Baseline visit, which is approximately 2 weeks after the Screening visit (the Week 48 visit of Trial 1297.2). The patients will self-inject BI 695501 with the support of the suitably qualified, designated trial personnel.
15. For all subsequent injections. Patients will self-inject the trial medication every 2 weeks until trial completion or early withdrawal.
16. 1 to 5 syringes will be dispensed to the patient at each visit.

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ABBREVIATIONS

ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response criteria
ACR50	American College of Rheumatology 50% response criteria
ACR70	American College of Rheumatology 70% response criteria
ADA(s)	Antidrug antibody(ies)
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
Anti-CCP	Anti-cyclic citrullinated peptide
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
CRP	C-reactive protein
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DAS	Disease Activity Score
DAS28	Disease Activity Score in 28 joints
DILI	Drug-induced liver injury
DMARD	Disease-modifying antirheumatic drug
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EoT	End of Treatment
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GH	General Health
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
LOCF	Last observation carried forward

MedDRA	Medical Dictionary for Regulatory Activities
MMP	Matrix metalloproteinase
MTX	Methotrexate
nADA	Neutralizing ADAs
NSAIDs	Nonsteroidal anti-inflammatory drugs
PK	Pharmacokinetics
PPK	Population pharmacokinetic
RA	Rheumatoid arthritis
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SC	Subcutaneous
SF-36 v2	36-item Short Form Health Survey version 2
SFU	Safety Follow-up
SJC	Swollen joint count
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TJC	Tender joint count
TNF	Tumor necrosis factor
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
US	United States of America
VAS	Visual analogue scale
VCA	Virus capsid antigen

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder characterized by synovial inflammation in the joints and consequently, progressive joint destruction. Depending on the severity of the disease, systemic manifestations may occur including lung, cardiovascular, hematologic and ocular effects. If left untreated, RA may lead to severe functional disabilities, and therefore a considerable reduction in quality of life for the patient ([R11-4384](#), [R11-4383](#)). The prevalence of RA varies with factors such as gender, race and smoking status and is approximately 0.5% to 1% ([R07-0637](#)).

The cytokine tumor necrosis factor (TNF)-alpha is involved in inflammatory and immune responses. Elevated levels of TNF-alpha are found in the synovial fluid of RA patients, including juvenile idiopathic arthritis and psoriatic arthritis patients and it has been demonstrated that TNF-alpha (hereafter also referred to as TNF) plays a crucial role in both the pathologic inflammation and the joint destruction characteristic of these diseases. Thus, TNF targeted therapy plays an important role in RA through a reduction in the TNF-mediated downstream effects on other cell types involved in the inflammatory response.

There are five anti-TNF drugs that have been approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to treat moderate to severe RA that has not responded to one or more of the traditional disease-modifying antirheumatic drugs (DMARDs). These currently approved therapies include: adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab. Efficacy has been demonstrated in all five therapies, in combination with methotrexate (MTX), by greater American College of Rheumatology 20%/50%/70% (ACR20/50/70) responses, an improvement in Disease Activity Score in 28 joints (DAS28), less radiographic progression, and an improvement in quality of life (Health Assessment Questionnaire – Disability Index [HAQ-DI], 36-item Short Form Health Survey version 2 [SF-36 v2]) ([R12-2515](#)).

1.2 DRUG PROFILE

BI 695501 is a monoclonal antibody being developed as a proposed biosimilar to the TNF-alpha blocker, adalimumab (US-licensed Humira[®] and EU-approved Humira[®]). Adalimumab is a recombinant human monoclonal immunoglobulin (Ig) G1 antibody specific to human TNF-alpha. It has human-derived heavy and light chain variable regions and human IgG1:k constant regions and is produced in a mammalian expression system ([R15-0739](#) and [R15-3225](#)).

Humira[®] binds specifically to TNF-alpha (and not TNF-beta) and blocks its interaction with the p55 and p75 cell surface TNF receptors. Humira[®] has also been shown to lyse cells expressing surface TNF in vitro in the presence of complement and modulate biological responses that are induced or regulated by TNF, including changes in adhesion molecules responsible for leukocyte migration (endothelial leukocyte adhesion molecule-1, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1) ([R15-0739](#)).

After subcutaneous (SC) administration of a single 40 mg dose in healthy adult subjects, peak serum concentrations of Humira® are reached approximately 5 days after administration. The average absolute bioavailability of Humira® estimated from three studies following a single 40 mg SC dose was 64%. Following SC administration of 40 mg of Humira® every second week in adult RA patients, the mean steady-state trough concentrations were approximately 5 µg/mL (without concomitant MTX) and 8 to 9 µg/mL (with concomitant MTX), respectively. The serum Humira® trough levels at steady-state increased roughly proportionally with dose following 20, 40 and 80 mg SC dosing every other week and every week ([R15-0739](#) and [R15-3225](#)).

Population pharmacokinetic (PPK) analyses showed a trend toward higher apparent clearance of Humira® with increasing body weight. After adjustment for weight differences, gender and age appeared to have a minimal effect on Humira® clearance ([R15-0739](#) and [R15-3225](#)).

Humira® was evaluated in over 3000 patients in all RA trials that were performed prior to approval, with some patients treated for up to 60 months duration. In the EMA label, five randomized, double-blind and well-controlled studies were reported for Humira®, which assessed the efficacy and safety of Humira® for the treatment of RA ([R15-3225](#)).

In two of the five studies, long-term administration of Humira® was evaluated; patients received Humira® for ≥52 weeks.

In one study, 114 patients were enrolled to the open-label study and continued to receive Humira® 40 mg every other week for 60 months. Of these patients 86, 72 and 41 patients had ACR20, ACR50 and ACR70 responses, respectively, at Month 60 ([R15-3225](#)).

In a trial of 799 MTX-naïve, adult patients with moderate to severe active early RA, 42.9% of patients who received Humira®/MTX combination therapy achieved clinical remission (DAS28 <2.6) at Week 52 compared to 20.6% and 23.4% of patients receiving MTX monotherapy and Humira® monotherapy, respectively. Humira®/MTX combination therapy was clinically and statistically superior to MTX ($p < 0.001$) and Humira® monotherapy ($p < 0.001$) in achieving a low disease state ([R15-0739](#) and [R15-3225](#)).

In addition, it has been shown that individual components of the American College of Rheumatology (ACR) response criteria (number of tender and swollen joints, physician and patient assessment of disease activity and pain, and disability index scores) improved at 24 or 26 weeks compared to placebo ([R15-0739](#) and [R15-3225](#)).

Humira® treatment in RA patients has been associated with a decrease in levels of acute phase reactants of inflammation, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and serum cytokines (interleukin-6), compared to Baseline. Serum levels of the matrix metalloproteinases (MMP)-1 and MMP-3 that induce the tissue remodelling responsible for cartilage destruction were also decreased and patients experienced improvement in hematological signs of chronic inflammation after Humira® administration ([R15-3225](#)).

In addition to the analytical and pharmacological assays, the similarity between BI 695501 and US-licensed Humira[®] was assessed in a single-dose pharmacokinetic (PK) study in the cynomolgus monkey and a local tolerance study in rabbits. Additionally, the three-way PK similarity between BI 695501, US-licensed Humira[®] and EU-approved Humira[®] was demonstrated in a Phase I clinical study in healthy volunteers. The results of these studies are provided in the Investigator's Brochure (IB).

For a more detailed description of the drug profile, refer to the current IB which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Adalimumab (Humira®) has received regulatory approval for treatment of patients with RA in the US, the EU, and many other countries ([R15-0739](#) and [R15-3225](#)). BI 695501 is being developed as a proposed biosimilar to US-licensed Humira® and EU-approved Humira®.

This trial will be conducted in compliance with the Clinical Trial Protocol (CTP), the International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP) and with all applicable and current regulatory requirements.

The rationale for conducting this trial is to generate long-term safety, efficacy, and immunogenicity data for the administration of the proposed biosimilar BI 695501 in patients with RA. This is a 1-year extension trial to Trial 1297.2, in which patient will have received 48 weeks of treatment with US-licensed Humira® or BI 695501, or with US-licensed Humira® for 24 weeks then BI 695501 for 24 weeks.

2.2 TRIAL OBJECTIVES

The objective of this trial is to provide long-term safety, efficacy, PK, and immunogenicity data on BI 695501 administered via prefilled syringe in patients with RA who have completed Trial 1297.2.

2.3 BENEFIT - RISK ASSESSMENT

Patient risk will be minimized in this trial by implementing conservative eligibility criteria. Due consideration has been given to previous experience with US-licensed Humira® and EU-approved Humira® in RA patients and side effect management advice (e.g., for hypersensitivity reactions) is provided for in this CTP. All trial personnel are directed to the BI 695501 IB for a description of the non-clinical and clinical experience with BI 695501. To date, a total of 175 healthy male volunteers (includes data from Trial 1297.8 and Trial 1297.1) have received BI 695501. As of 01 July 2015, 465 patients were included in Trial 1297.2.

Representatives from Boehringer Ingelheim (BI) and Safety, Clinical and Quality functions will review accumulating safety data at the monthly Medical and Quality Review Meeting.

Given the progressive nature of the disease, each patient will receive active RA treatment throughout the trial.

Patients will be carefully monitored during ambulatory (outpatient) visits for any safety signs and symptoms that may occur or arise following trial treatment. Adverse events (AEs), body temperature, vital signs, electrocardiograms (ECGs) and safety laboratory assessments as

well as immunogenicity data will be collected throughout the trial; therefore monitoring patients for safety outcomes over a prolonged period of time will be possible.

A potential for drug-induced liver injury (DILI, a rare event) is under constant surveillance by sponsors and regulators. Therefore, timely detection, evaluation, and follow-up of alterations of selected liver laboratory parameters to ensure patients' safety will be performed in this trial (see [Section 5.3.6](#)).

In addition, hypersensitivity reactions, anaphylaxis, and serious infections are considered adverse events of special interest (AESI), see Section 5.3.6.

In patients treated with Humira[®], common adverse reactions reported in greater than 10% of patients include infections (e.g., upper respiratory tract infections, sinus infections), injection site reactions, headache and rash. Allergic reactions (e.g., allergic rash, anaphylactic reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients ([R15-0739](#) and [R15-3225](#)).

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. Carriers of HBV and patients with a history of HBV infection will be excluded from the trial.

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. Patients will be evaluated for TB risk factors and tested for latent infection prior to and during the trial due to the increased risk of opportunistic infections with Humira[®].

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, the possible risk for the development of malignancies cannot be excluded.

Further information regarding relevant contraindications, special precautions, adverse reactions and other recommendations for the use of US-licensed Humira[®] and EU-approved Humira[®] in RA patients are described in the prescribing information ([R15-0739](#) and [R15-3225](#)).

BI 695501, as a proposed biosimilar product, is expected to provide comparable efficacy, safety, tolerability and immunogenicity in patients with RA and therefore is expected to provide a similar benefit-risk profile as US-licensed Humira[®] and EU-approved Humira[®].

An Independent Data Monitoring Committee (IDMC) is monitoring the 1297.2 trial and an IDMC safety review will be completed prior to the first patient's enrolment in the extension trial.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is an open-label trial of BI 695501 with a 48-week treatment period in patients with RA continuing to receive MTX within the dose range of the 1297.2 trial for at least 12 weeks. After Week 12, the MTX dose will be at the Investigator's discretion.

The trial will consist of a Screening visit 14 days prior to Day 1, a 48-week treatment period and a 10-week safety follow-up visit. The Screening visit will be the Week 48 visit in Trial 1297.2. Informed consent for this extension trial must be obtained prior to conducting the Week 48 assessments in Trial 1297.2, in order for those assessments to serve as the screening assessments in this extension trial. Trial medication should be administered after completion of all assessments at the Screening visit; this will be the last administration of trial medication in Trial 1297.2.

Patients who discontinue the trial medication early (and do not withdraw consent) should return to the site for an End of Treatment (EoT) visit equivalent to the Week 48 assessments as soon as possible after last trial medication administration. For patients who discontinue treatment early, a safety follow-up visit should be performed 10 weeks after the last administration of BI 695501. All patients who complete the trial should return for a safety follow-up visit at Week 58.

It is anticipated that approximately 300 to 400 patients with moderately to severely active RA who have completed Trial 1297.2 will be eligible and willing to participate in this extension trial. Each patient who provides informed consent and meets all the inclusion criteria and none of the exclusion criteria will self-administer 40 mg of BI 695501 every 2 weeks by SC injection.

Patients will undergo up to 10 visits over the duration of the trial (58 weeks). The trial procedures to be undertaken at each visit are shown in the [Flow Chart](#).

The primary endpoint of this trial is defined as the number (proportion) of patients with drug-related AEs during the treatment phase. Efficacy and other safety parameters will be assessed as secondary and other endpoints. For more details, see [Section 5.1](#).

Up to Week 12, patients will continue to take their regular MTX therapy and the associated stable weekly dose of adequate folic acid (at least 5 mg per week or as per local practice) or folinic acid (at least 1 mg per week or as per local practice) from their usual source. After Week 12, MTX therapy may be adjusted based on Investigator assessment. Patients may also continue to receive treatment with oral corticosteroids at a dose of ≤ 10 mg/day prednisolone or equivalent.

Patients may return for unscheduled visits should their medical condition warrant urgent attention at the discretion of the Investigator.

The trial is designed to generate data on long-term safety, efficacy, PK, and immunogenicity with BI 695501 in patients who have completed Trial 1297.2. This will include:

- patients who were previously treated with BI 695501 in Trial 1297.2 for 48 weeks,
- patients who were previously treated with US-licensed Humira[®] for 24 weeks followed by BI 695501 for 24 weeks in Trial 1297.2, and
- patients who were previously treated with US-licensed Humira[®] in Trial 1297.2 for 48 weeks.

3.1.1 Administrative structure of the trial

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

A Coordinating Investigator will be nominated and 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.

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

This is a long-term, open-label extension trial to assess the safety, efficacy, PK, and immunogenicity of BI 695501 in patients with RA who have completed Trial 1297.2 and are eligible for long-term treatment with adalimumab. The trial has a 48-week treatment period in patients with RA continuing to receive MTX within the dose range of the 1297.2 trial for at least 12 weeks. After Week 12, the MTX dose will be at the Investigator's discretion. All patients will be treated with BI 695501. No comparator was chosen as the purpose of the trial is to collect data on the long-term safety (and efficacy) and to better characterize PK and immunogenicity of BI 695501.

Each patient who meets all the inclusion criteria and none of the exclusion criteria will self-administer 40 mg of BI 695501 every 2 weeks. This is the same dosing regimen the patients received in Trial 1297.2.

3.3 SELECTION OF TRIAL POPULATION

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

The main requirements for trial entry include patients who completed Trial 1297.2, wish to participate in this extension trial, and in the Investigator's assessment can benefit from receiving BI 695501.

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

3.3.2 Inclusion criteria

1. All patients must sign and date an Informed Consent Form consistent with ICH GCP guidelines and local legislation prior to participation in the trial (i.e., prior to any trial procedures, which include medication washout and restrictions) and be willing to follow the protocol.
2. Adult patients with moderately to severely active RA who have completed Trial 1297.2, and who wish to participate in this extension trial and in the Investigator's assessment can benefit from receiving BI 695501.
3. Patients willing and able to self-administer BI 695501 pre-filled syringe.
4. For participants of reproductive potential (males and females), a reliable means of contraception has to be used throughout trial participation. Acceptable methods of birth control include, for example, birth control pills, intrauterine devices, surgical sterilization, vasectomized partner and double barrier method (for example male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream/suppository). All patients (males and females of child-bearing potential*) must also agree to use an acceptable method of contraception for 6 months following completion or discontinuation from the trial medication.

*Women of childbearing potential are defined as:

- Any female who has experienced menarche and does not meet the criteria for "women not of childbearing potential" as described below

Women not of childbearing potential are defined as:

- Women who are postmenopausal (12 months with no menses without an alternative medical cause) or who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy)

3.3.3 Exclusion criteria

1. Patients who experienced Investigator-reported drug-related serious adverse events (SAEs) in Trial 1297.2.
2. ACR functional Class IV (see [Appendix 10.1](#)) or wheelchair/bed bound.
3. Primary or secondary immunodeficiency (history of, or currently active).
4. Positive QuantiFERON test.

5. Known clinically significant coronary artery disease or significant cardiac arrhythmias or severe congestive heart failure (New York Heart Association Classes III or IV), or interstitial lung disease observed on chest X-ray.
6. Anaphylactic reaction or hypersensitivity to adalimumab received in Trial 1297.2.
7. History or recent evidence of cancer including solid tumors, hematologic malignancies, and carcinoma in situ (except participants with previous resected and cured basal or squamous cell carcinoma, treated cervical dysplasia, or treated in situ Grade I cervical cancer within 5 years prior to the Screening Visit).
8. Positive serology for HBV or hepatitis C virus (HCV).
9. Patients who are expecting to receive any live virus or bacterial vaccinations during the trial, or up to 3 months after the last dose of trial drug.
10. Any treatment (including biologic therapies) that, in the opinion of the Investigator, may place the patient at unacceptable risk during the trial.
11. Patients with a significant disease other than RA and/or a significant uncontrolled disease (such as, but not limited to, nervous system, renal, hepatic, endocrine, 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.
12. Premenopausal (last menstruation 1 year prior to screening), sexually active women who are pregnant or nursing, or are of child-bearing potential and not practicing an acceptable method of birth control, or do not plan to continue practicing an acceptable method of birth control throughout the trial (acceptable methods of birth control are intrauterine devices, surgical sterilization, double barrier, or vasectomized partner).
13. Current inflammatory joint disease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease) or other systemic autoimmune disorder (e.g., systemic lupus erythematosus, inflammatory bowel disease, pulmonary fibrosis, or Felty's syndrome, scleroderma, inflammatory myopathy, mixed connective tissue disease, or any overlap syndrome). Secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA is permitted.
14. Any planned surgical procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) for the duration of the trial.
15. Known active infection of any kind (excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with intravenous (i.v.) anti-infectives within 4 weeks of the Screening Visit or completion of oral anti-infectives within 2 weeks of the Screening Visit.
16. Serious infection or opportunistic infection during the 1297.2 trial.
17. Any acquired neurological, vascular, systemic or demyelinating disorder that might affect any of the efficacy assessments, in particular, joint pain and swelling (e.g., Parkinson's disease, cerebral palsy, diabetic neuropathy) that occurred during the 1297.2 trial.
18. Currently active alcohol or drug abuse.

19. Treatment with i.v. Gamma Globulin or the Prosorba® Column during the 1297.2 trial.
20. Planned treatment with i.v. intramuscular, intra-articular and parenteral corticosteroids.
21. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >1.5 times upper limit of normal (ULN).
22. Hemoglobin <8.0 g/dL.
23. Platelets <100,000/μL.
24. Leukocyte count <4000/μL.
25. Creatinine clearance <60 mL/min.
26. Patients who are currently participating in another clinical trial other than Trial 1297.2.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

Patients who do not meet all of the inclusion criteria or who meet one or more of the exclusion criteria will not be enrolled in this extension trial. The primary reason for the screen failure will be recorded on the electronic Case Report Form (eCRF).

Patients have the right to withdraw from this trial at any time for any reason.

Two situations can occur in this trial and need to be documented accordingly, as follows:

1. An individual patient is to be withdrawn from the trial if:
 - The patient decides to discontinue participation in the trial by withdrawal of consent. In this case, no more investigations will be performed. The patient does not have to justify the decision.
2. Based on assessment by the Investigator, and after consultation with the trial medical advisor, an individual patient may be discontinued from treatment with the investigational compound if:
 - The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication
 - The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse or drug-related events, other diseases, or pregnancy)
 - Repeated protocol violation after documented discussion with the medical monitor
 - Lack of efficacy
 - The patient has an AE that is categorized as a serious infection. A serious infection is defined as infections requiring i.v. antibiotics or those that meet the regulatory definition of a SAE (including, but not limited to, systemic fungal infections, human immunodeficiency virus [HIV], HBV, HCV, infected joint prosthesis)
 - Patient lost to follow-up despite reasonable efforts to make contact with the patient

If a patient permanently discontinues trial medication for any reason, every effort should be made for the patient to attend the EoT Visit as soon after trial treatment discontinuation as possible. Every effort should be made for all patients who discontinue the trial treatment early, to return for a safety follow-up visit 10 weeks after the last dose of trial medication. For details of assessments to be performed at the Week 48 visit and the Week 58 visit, see [Sections 6.2.2](#) and [6.2.3](#), respectively.

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

3.3.4.2 Discontinuation of the trial by the sponsor

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 CTP, or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product(s) and comparator product(s)

Details of the trial medication are provided in [Table 4.1.1: 1](#).

Table 4.1.1: 1 Trial medication

Trial Medication	Dosage form (concentration)	Manufacturer
BI 695501, sterile solution consisting of: sodium acetate, acetic acid, trehalose, polysorbate 80 and water for injection.	Solution for SC injection (40 mg/0.8 mL)	Boehringer Ingelheim Pharma GmbH & Co KG, Germany

SC: subcutaneous.

BI 695501 will be provided in 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.

Any unused product or waste material will be disposed of in accordance with local requirements.

4.1.2 Method of assigning patients to treatment groups

This is an open-label, single-arm trial. Once patients have completed screening, have met all the inclusion criteria and none of the exclusion criteria, they will all be treated with BI 695501.

4.1.3 Selection of doses in the trial

The dose of BI 695501 for the treatment of RA in this trial is the same dose used in Trial 1297.2, and is based on the clinically effective dose of currently available forms of US-licensed Humira® and EU-approved Humira®. The recommended dose for use in patients with RA is 40 mg by SC injection every 2 weeks and therefore BI 695501 will be administered at 40 mg by SC injection every 2 weeks.

4.1.4 Drug assignment and administration of doses for each patient

Each patient will receive up to 25 SC drug injections (40 mg/0.8 mL) of BI 695501 during the treatment period.

Prefilled syringes will be used for the injections (see [Section 4.1.1](#)). Injections will be administered subcutaneously.

At the Screening visit (Week 48 visit of Trial 1297.2), trial medication will be administered by a suitably qualified, designated trial personnel. This will be the last administration of trial

medication in Trial 1297.2. Detailed training and instruction on self-administration will be provided to the patient at this visit and a self-administration guide will be provided to the patient. Patients will be instructed to accurately record the dates and times of BI 695501 dosing, and the occurrence of any AEs and use of concomitant medications, on the provided diary cards between the ambulatory visits.

The first administration of trial medication in this extension trial will be at the Baseline visit (Day 1). After the first injection (Baseline, Day 1), the patient will remain at the clinical site for at least 1 hour for observation of any AEs.

All subsequent injections of BI 695501 will be administered by the patients themselves, these injections may be performed at the site or at the patients home, as specified in the [Flow Chart](#).

At each visit, 1 to 5 syringes will be dispensed to the patient so that patients can continue to self-administer trial medication at home until the next site visit.

Handling and administration of trial medication will be described in detail in the handling instructions, which will be provided in the ISF.

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. In the event of an anaphylactic or other serious allergic reaction, the administration of trial medication will be discontinued immediately, and appropriate therapy instituted.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open-label, single-arm trial. No blinding of BI 695501 will be performed. The patients, Investigators, and site staff will know that the patients are receiving treatment with BI 695501.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

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 Good Manufacturing Practice and GCP. The medication must be stored in a refrigerator at a controlled temperature (2 to 8°C [36 to 46°F]) and must not be frozen. A

temperature log will be kept at the trial site, and will be completed (with a minimum and maximum reading) on each business date. Syringes will be kept in the outer carton in order to protect from light. Detailed storage conditions will be described on the trial medication labels.

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

4.1.8 Drug accountability

Drug supplies will be provided by the Sponsor.

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

- Approval of the CTP 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
- Availability of the curriculum vitae of the principal Investigator
- Availability of a signed and dated CTP or immediately imminent signing of the CTP
- Availability of the proof of a medical license for the principal Investigator
- Availability of Form 1572 for sites in the US

The designated person must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the preparation of the trial medication. Unused trial medication will be destroyed as per local standard operating procedures.

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 return to the Sponsor and/or the Clinical Research Organization, the designated 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.

Patients will be instructed to return all unused drug supplies to the site.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

Patients will continue to take their usual prescribed concomitant medications as allowed by the CTP, including MTX (within the dose range of the 1297.2 trial, up to Week 12) from their usual source. After Week 12, the dosing regimen for MTX and associated folic acid or folinic acid intake may be adjusted at the Investigator's discretion. In this case, MTX treatment can be combined with or replaced by other non-biologic DMARDs (as described in [Table 4.2.2.1: 1](#)). Non-biologic DMARD therapy may be modified during the trial, per Investigator assessment. Certain side effects are commonly associated with MTX treatment and therefore patients are required to take folic acid (a stable dose of at least 5 mg/week or as per local practice) or folinic acid (at least 1 mg/week or as per local practice), from their usual source, to minimize MTX-related toxicity.

All patients should also continue to receive any oral nonsteroidal anti-inflammatory drugs (NSAIDs) at a stable dose or background oral corticosteroids as required throughout the trial. There are no special emergency procedures to be followed.

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](#).

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 Sponsor's physician representative.

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
DMARD therapy	Patients may continue receiving or have previously received conventional DMARD therapy, for the treatment of RA. Non-biologic DMARD therapy may be modified during the trial, per Investigator assessment
MTX	Patients must continue to receive and tolerate oral or parenteral MTX within the dose range of the 1297.2 trial up to Week 12. After Week 12, MTX therapy may be adjusted based on Investigator assessment.
Folic acid/folinic acid	Patients must be taking oral folic acid (at least 5 mg/week or as per local practice) or folinic acid (at least 1 mg/week or as per local practice) during treatment with MTX. The dosing regimen is at the Investigator's discretion.
Intravenous, intramuscular, intra-articular or parenteral corticosteroids	Parenteral administration of corticosteroids should be avoided to the extent possible.
Oral corticosteroids	If receiving current treatment with oral corticosteroids (other than intra-articular or parenteral corticosteroids), the dose should not exceed 10 mg/day prednisolone or equivalent.
NSAIDs	At the discretion of the Investigator.
Leflunomide	Not permitted.
Hydroxychloroquine/chloroquine	Patients may take oral hydroxychloroquine provided that the dose is not >400 mg/day or chloroquine provided that the dose is not >250 mg/day. Dose and route of administration must remain throughout the entire trial period where possible.
Analgesics (other than NSAIDs)	Analgesics up to the maximum recommended doses may be used for pain as required. However, patients must not take analgesics within 24 hours prior to a visit where clinical efficacy assessments are performed and recorded.
Prosorba® Column	Not permitted.
IV Gamma Globulin	Not permitted.
Live/attenuated vaccine	Not permitted for the duration of the trial, and up to 3 months after the last dose of trial drug
Anti-infective agents	At the discretion of the Investigator.
Any drug/therapy that has not received regulatory approval for any indication	Not permitted.
Non-pharmacological treatments (e.g., physical therapy)	Permitted freely.

It is recommended that, in case of an unplanned surgical procedure, including bone/joint surgery/synovectomy (including joint replacement or fusion), the Investigator should consult with the trial medical advisor to discuss issues surrounding cessation of trial medication administration.

4.2.2.2 Restrictions on diet and life style

Not applicable.

4.3 TREATMENT COMPLIANCE

Compliance will be assessed by a count of syringe boxes and/or labels by a Clinical Research Associate.

The prescribed dosage, timing, and mode of administration of trial medication may not be changed. Any deviation from the intended regimen must be recorded in the eCRF.

For all injections patients will be asked to complete a patient diary documenting the date and time of the injections. All used and unused syringes must be returned to the site at each visit.

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

5. VARIABLES AND THEIR ASSESSMENT

Please refer to the [Flow Chart](#) for the schedule of assessments for the trial.

The primary endpoint is described in [Section 5.1.1](#) below. Secondary endpoints are described in [Section 5.1.2](#), and other endpoints are described in [Section 5.1.3](#).

Unless otherwise specified, all endpoints will be assessed using the 1297.2 baseline values.

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the number (proportion) of patients with drug-related AEs during the treatment phase (refer to [Section 7.3.1](#) for the definition of treatment phase).

5.1.2 Secondary Endpoints

Long-term efficacy will be assessed as a secondary objective in this trial.

- The change from Baseline in DAS28 (ESR) at Week 48
- The proportion of patients meeting ACR20 response criteria at Week 48
- The proportion of patients who meet the ACR/European League Against Rheumatism (EULAR) definition of remission at Week 48
- The proportion of patients with EULAR response (good response, moderate response, or no response) at Week 48.

5.2 ASSESSMENT OF EFFICACY

The following assessments will be made at the time points indicated in the [Flow Chart](#) for the purposes of calculating the DAS28 (ESR and CRP) and ACR response scores.

5.2.1 Joint assessments

Wherever possible, the same person will perform the joint assessment throughout the trial (i.e., for all patients at each trial site). Standardized training will be provided to the independent joint assessor via the training modules provided in the specific study portal. This training will be documented and filed in the ISF.

Each of the 66/68 joints will be evaluated for tenderness and swelling, respectively (prior to taking any required analgesic that day if possible). The 66/68 joint count includes the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of the hands, the metatarsal phalangeal and distal interphalangeal joints of the feet, and the shoulder, elbow, wrist, hip, knee, ankle, tarsus, and temporomandibular, sternoclavicular, and acromio-clavicular joints. Artificial, missing, and ankylosed joints, and data from joints following intra-articular injections are excluded from both tenderness and swelling assessments ([R11-4385](#)).

5.2.2 Patient's global assessment of disease activity VAS

Patients will mark on a visual analogue scale (VAS) their overall assessment of how their RA affects them, rating how they are managing from 0 (very well) to 100 (very poor). This is equivalent to the General Health component of the Disease Activity Score (DAS) (see [Appendix 10.2](#)).

5.2.3 Patient's assessment of pain

Patient's assessment of pain will be assessed using the VAS provided in the HAQ-DI questionnaire (see [Appendix 10.3](#)).

5.2.4 Physician's global assessment of disease activity VAS

The physician's global disease assessment will be documented on a VAS, ranging from no arthritis activity (0) to extremely active arthritis (100) (see [Appendix 10.2](#)).

5.2.5 Patient's assessment of disability

The physical functioning of the patient will be assessed using the HAQ-DI questionnaire. This is a widely used patient self-report tool which assesses the degree of difficulty a person has had in accomplishing tasks in eight functional areas, over the previous week, taking into account any aids or help required. It consists of eight component sets: (1) dressing and grooming, (2) rising, (3) eating, (4) walking, (5) hygiene, (6) reach, (7) grip and (8) common daily activities. In addition, patients will mark on a VAS the severity of pain that they have had because of their RA in the past week, ranging from 0 (no pain) to 100 (severe pain) (see [Appendix 10.3](#)).

5.2.6 SF-36 v2

Patients will complete the SF-36 v2, a generic health survey consisting of 36 questions, yielding eight health-related quality of life domains (physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health) as well as a psychometrically-based physical component score and mental component score (see [Appendix 10.4](#)).

5.2.7 Systemic inflammation: CRP level and ESR

A blood sample for CRP and ESR assessments will be taken at the visits indicated in the [Flow Chart](#).

Analysis of CRP will be conducted by a suitably qualified laboratory using validated methods.

A whole blood sample (2 mL) will be collected for the ESR values to be measured locally.

5.2.8 Calculation of DAS28 and ACR scores

The DAS28 score will be derived using the following formulas:

$$\text{DAS28 (ESR)} = 0.56 \cdot \sqrt{(\text{TJC28})} + 0.28 \cdot \sqrt{(\text{SJC28})} + 0.014 \cdot (\text{GH}) + 0.7 \cdot \ln(\text{ESR})$$

$$\text{DAS28 (CRP)} = 0.56 \cdot \sqrt{(\text{TJC28})} + 0.28 \cdot \sqrt{(\text{SJC28})} + 0.014 \cdot (\text{GH}) + 0.36 \cdot \ln(\text{CRP}+1) + 0.96$$

Where:

- TJC28 = 28 joint count for tenderness
- SJC28 = 28 joint count for swelling
- Ln(ESR) = natural logarithm of ESR
- Ln(CRP) = natural logarithm of CRP
- GH = the General Health component of the DAS (see [Section 5.2.2](#))

Improvement in DAS28 will also be categorized using the EULAR response criteria (see [Table 5.1.2.8: 1](#)).

Table 5.1.2.8: 1 DAS28 EULAR response

DAS28 at Endpoint	DAS28 Improvement		
	≥1.2	>0.6 and <1.2	≤0.6
≤3.2	Good Response	Moderate response	No Response
>3.2 and ≤5.1	Moderate response	Moderate response	No Response
>5.1	Moderate response	No Response	No Response

Low disease activity is defined as a DAS28 score of ≤ 3.2 and DAS28 remission is defined as a DAS28 score of < 2.6 . A clinically relevant change in DAS28 score is defined as an improvement in DAS28 score of at least 1.2.

A patient has an ACR20 response if all of the following occur:

- A $\geq 20\%$ improvement in the SJC (66 joints)
- A $\geq 20\%$ improvement in the TJC (68 joints)
- A $\geq 20\%$ improvement in at least three of the following assessments:
 - Patient's assessment of pain
 - Patient's global assessment of disease activity
 - Physician's global assessment of disease activity
 - Patient's assessment of physical function, as measured by the HAQ-DI
 - Acute phase reactant (CRP)

Patients will be considered to have had an ACR50 or ACR70 response if a 50% or 70% improvement from Baseline of Trial 1297.2, respectively, was observed in the criteria specified above for ACR20.

5.2.9 Definition of ACR/EULAR remission

Boolean-based definition:

At any time point, the patient must satisfy all of the following:

- $TJC \leq 1^a$
- $SJC \leq 1^a$
- $CRP \leq 1$ mg/dL
- Patient global assessment of disease activity ≤ 10 (on a 0 to 100 scale) (see [Appendix 10.2](#))

^a For TJC and SJC, use of a 28-joint count may miss actively involved joints, especially in the feet and ankles, and it is preferable to include feet and ankles also when evaluating remission.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at the visits indicated in the [Flow Chart](#).

Whenever possible, the same person should perform the physical examination throughout the trial (i.e., for all patients at each trial site). The physical examination will include assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular, neurological, thyroid, musculoskeletal/extremities, respiratory and abdomen. Body weight will also be measured. Height will be measured at Screening only.

5.3.2 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 Investigator must assess all vital signs findings at each visit. If the Investigator finds any clinically relevant abnormalities, these must be reported as AEs/SAEs as appropriate (see [Section 5.3.6](#)).

5.3.3 Safety laboratory parameters

Blood and urine samples for determination of serum chemistry, hematology and urinalysis will be taken at the times indicated in the [Flow Chart](#).

The following laboratory parameters will be measured:

- Serum chemistry: creatinine, alkaline phosphatase, AST, ALT, gamma glutamyl transpeptidase, bilirubin (total and direct), glucose, total cholesterol, total protein, albumin, sodium, potassium, chloride, calcium

- Hematology: hemoglobin, hematocrit, platelets, white blood cells, lymphocytes, neutrophils
- Urinalysis: protein, glucose, blood

In addition, the following parameters will be analyzed at the visits indicated in the [Flow Chart](#):

- Infection screen: patients must have a negative serological test for hepatitis B surface antigen (HBsAg), for hepatitis C serology
- HIV screen (at the discretion of the Investigator where clinically indicated, and per local regulations)
- TB test (QuantiFERON[®] Gold assay)
- ESR and CRP
- Pregnancy testing for females of child-bearing potential only (serum human chorionic gonadotropin or urine)
- ADAs and nADAs

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies will be analyzed at Baseline (Day 1) and Week 48.

The Investigator must assess all laboratory results. The Investigator will evaluate any change in laboratory values and all clinical laboratory tests will be reviewed for potential clinical significance at all time points throughout the trial. The Investigator should endeavor to provide a reason for all results deemed not clinically significant. If the Investigator determines a laboratory abnormality to be clinically significant, it will be considered an AE/SAE (see [Section 5.3.6](#)); however, if the laboratory value abnormality is consistent with a current diagnosis, it will be documented accordingly.

Blood samples will be analyzed by a central laboratory (except ESR). The central laboratory provider will also provide the materials for blood sampling. Instructions for the labelling, storage and shipment of the samples can be found in the Laboratory Manual. 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 or local laboratory using urine at all applicable visits thereafter.

Estimated blood volumes are shown in [Section 6.1](#).

5.3.4 Electrocardiogram

A resting 12-lead ECG will be performed at the visits indicated in the [Flow Chart](#).

Patients should rest for at least 5 minutes in a supine position before ECG evaluations. Two consecutive recordings will be made.

The original ECG traces and variables must be stored in the patients' medical record as source data. The Investigator or designee will evaluate the ECG from a clinical perspective

and the result (whether the ECG result is normal or abnormal) will be recorded on the appropriate section of the eCRF.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the Investigator. Any ECG abnormalities, judged as clinically relevant, will be monitored carefully and, if necessary, the patient will be discontinued from the trial medication and will receive the appropriate medical treatment.

5.3.5 Other safety parameters

Tuberculosis Assessment

A QuantiFERON[®]-TB Gold test will be used to assess TB status at Screening and at Week 48.

5.3.6 Assessment of adverse events

Adverse event

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

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

Serious adverse event

A SAE is defined as any AE which:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect
- or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered “Always Serious”

In accordance with the EMA initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as given above.

A copy of the latest list of “Always Serious AEs” can be found in the ISF. These events should always be reported as SAEs as described in [Section 5.3.7](#).

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/Sponsor’s designee Pharmacovigilance Department within the same timeframe that applies to SAEs, see [Section 5.3.7](#).

The following are considered as AESIs:

- Hepatic injury

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

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

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory 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 laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

- Anaphylactic reactions
- Serious infection (defined as infections requiring i.v. antibiotics or meeting the regulatory definition of a SAE)
- Hypersensitivity reactions.

Protocol-specified AESIs can be classified as serious or nonserious, but all AESIs must be reported in an expedited manner similar to SAEs on an SAE form (i.e., nonserious AESIs must be reported on the SAE form and follow SAE reporting timelines).

Intensity of AEs

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

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

Causal relationship of AEs

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

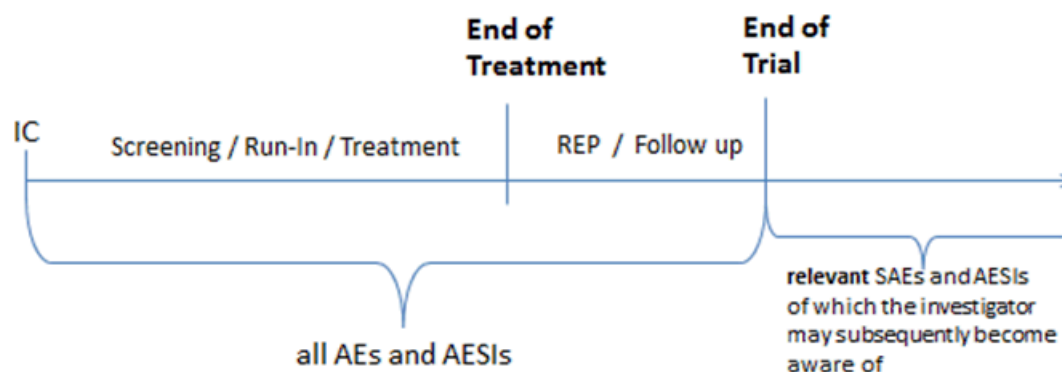
- Yes: There is a reasonable causal relationship between the investigational product administered and the AE
No: There is no reasonable causal relationship between the investigational product administered and the AE

The causal relationship must be provided by the Investigator for the trial drug (BI 695501). The reason for the decision on causal relationship needs to be provided in the eCRF and on the SAE form (if applicable).

5.3.7 Adverse event collection and reporting**AE Collection**

The following must be collected and documented on the appropriate eCRF by the Investigator:

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



The REP for BI 695501 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 that occur after the REP will be considered as post-treatment events.

AE reporting to sponsor and timelines

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

Information required

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

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator. If such abnormalities already pre-exist prior to trial inclusion, they will be considered as baseline conditions

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

Pregnancy

In rare cases, pregnancy might occur in a trial. Once a patient has been enrolled into the clinical trial after having taken trial medication the Investigator must report any drug exposure during pregnancy which occurred in a female patient or in a partner to a male patient to the Sponsor/Sponsor's designee 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).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be

completed. If there is an SAE associated with the pregnancy, then the SAE has to be reported on the SAE form in addition.

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Blood samples for the determination of concentrations of BI 695501 will be obtained from each patient at the visits specified in the [Flow Chart](#) and [Table 5.4: 1](#).

Table 5.4: 1 Pharmacokinetic estimated sample time points

Visit	Week	Day	PK Sample ^a	ADA/nADA sample ^b
2	Baseline	1	X (predose)	X (predose)
			X (between 1 and 6 hours after dosing)	
4	12	85	X	X
6	24	169	X	X
9	48/EoT	337	X	X
10	58/SFU	407	X	X

ADA = antidrug antibody; EoT = End of Treatment; nADA = neutralizing antidrug antibody; PK = pharmacokinetics; SFU = Safety Follow-up.

- a. PK samples collected from Visit 4 onwards can be taken at any time during each designated visit.
b. ADA and nADA samples will be collected at the same time as PK samples.

5.4.1 Assessment of Pharmacokinetics

The PK analysis will be based on a population-based approach. Therefore, although samples may be taken at any time during each designated visit starting at Visit 4, it will be essential for the Investigator or designated staff to document the exact time each sample is taken. The exception is at Visit 2. At that visit, one sample must be taken from each patient before dosing begins. A second sample should be taken between 1 and 6 hours after dosing. If the sample on the visit day is taken after the dose on that visit day, the dosing time will be collected in the eCRF as well as in the diary.

5.4.2 Methods of sample collection

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

Plasma sampling for pharmacokinetic analysis

Samples of whole blood (2.7 to 3 mL) will be taken (in tubes containing K₂EDTA anticoagulant) at the time points shown in [Table 5.4: 1](#) for the determination of the concentration of BI 695501.

Immediately after blood sampling, the drawing tubes will be transferred into ice water or on ice until centrifugation.

After completion of the trial, selected PK samples may be retained and used for further methodological investigations, e.g., stability testing. The PK samples will be discarded after the completion of the additional investigations upon the Sponsor's written approval. The PK samples may be destroyed 5 years after the final Clinical Trial Report (CTR) has been signed, and in accordance with local regulation.

Wherever possible, PK blood samples will be taken at the same time as blood is drawn for other analyses to limit repeated venipuncture.

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](#).

5.4.3 Analytical determinations

Analyte concentrations in plasma samples for all patients that receive active drug will be determined by a fully validated enzyme-linked immunosorbant assay. Detailed descriptions of the assay methods will be available prior to the start of sample analysis.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKER(S)

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Immunogenicity – Antidrug antibodies

Blood samples (2.7 to 3 mL) will be taken at the visits shown in the [Flow Chart](#) and [Table 5.4: 1](#) to determine the number (proportion) of patients with ADAs.

Plasma sampling for ADA characterization

For characterization of human anti-BI 695501 antibodies (ADAs), 2.7 to 3 mL of blood will be collected from a forearm vein in a dipotassium ethylenediaminetetraacetic acid (K₂EDTA) anticoagulant blood drawing tube at time points indicated in the [Flow Chart](#). Immediately after blood sampling, the drawing tubes should be placed in ice water or on ice until centrifugation.

Antidrug antibody will be detected in human plasma samples by a validated method. A screen positive response in a patient will be confirmed in a drug-competition assay. Confirmed positive samples will be further characterized in a titer assay and in a neutralizing antibody assay.

After completion of the trial, selected PK and immunogenicity 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. The ADA samples will be discarded after the completion of the additional investigations upon the Sponsor's written approval. The ADA samples may be destroyed 5 years after the final CTR has been signed, and in accordance with local regulation.

Plasma sampling for Neutralizing Antibody characterization

For characterization of human neutralizing anti-BI 695501 antibodies (nADA), 6 mL of blood will be collected from a forearm vein in a K₂EDTA-anticoagulant blood drawing tube at the same time points as ADA samples are collected. Immediately after blood sampling, the drawing tubes will be placed in ice water or on ice until centrifugation.

Neutralizing antibodies will be detected in human plasma samples by a validated method. Full instructions for collection, labeling, analysis, storage and shipment of samples are provided in the Laboratory Manual.

5.6.2 Lack of efficacy

Discontinuation due to lack of efficacy, as judged by the Investigator, will be captured in the eCRF.

5.6.3 Adverse Event leading to discontinuation

Discontinuation due to a drug-related AE will be captured in the eCRF.

5.7 APPROPRIATENESS OF MEASUREMENTS

The efficacy endpoints (ACR20) are standard outcome criteria that are widely accepted for regulatory purposes to demonstrate efficacy on signs and symptoms of RA.

These endpoints were chosen to comply with the recommendations of both the EU and US regulatory authorities for studies in RA ([R11-4337](#), [R03-1444](#)).

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 pre-planned schedule:

- The first dose is to be administered approximately 2 weeks after the Screening visit (Week 48 of Trial 1297.2). A visit window of ± 1 day is permitted for Visit 2; trial medication will be administered on the day of the Baseline visit
- A visit window of ± 2 days is permitted for Visits 4, 6, 9 and 10
- Trial medication should be administered every 2 weeks (± 2 days after the Baseline visit)
- No visit window will apply to Visits 3, 5, 7, and 8

On ambulatory visit (outpatient) days, all assessments should be performed prior to trial medication 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, CRP)	3	6	18
Hematology	2	6	12
ADAs	3	5	15
nADAs	6	5	30
ESR (local)	2	6	12
Pharmacokinetics	3	6	18
RF, anti-CCP	1	2	2
Infection screen	4	1	4
TB test	3	2	6
Approximate total			117

ADAs: antidrug antibodies; anti-CCP: anti-cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; nADAs: neutralizing ADAs; RF: rheumatoid factor; 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 period

Screening Period (Day -14)

Once the patient has provided informed consent (before any 1297.2 or 1297.3 trial-specific procedures or assessments are performed) and meets all inclusion criteria and none of the exclusion criteria (see [Section 3.3](#)), the trial site will enter the screened patient into the system using the Interactive Response Technology (IRT).

The following will also be performed/collected:

- Demographic information (including gender, date of birth, ethnicity and race), and medical and surgical history (including RA history and history of opportunistic infection)
- Evaluation of patient's willingness and ability to self-administer trial medication
- Physical examination, including height (cm) and weight (kg) (see [Section 5.3.1](#))
- Infection screen (HBsAg, HCV and HIV test, per the Investigator's discretion)
- Urine pregnancy test for women of child-bearing potential
- Patient questionnaires: global VAS, HAQ-DI and SF-36 v2 (see [Section 5.2](#))
- Joint assessment (see Section 5.2)
- TB test (QuantiFERON[®]-TB Gold test)
- ESR and CRP
- Physician questionnaire: global VAS (see Section 5.2)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see [Section 5.3.2](#))
- Laboratory testing (serum chemistry, hematology and urinalysis; see [Section 5.3.3](#))
- 12-lead ECG (see [Section 5.3.4](#))
- Previous and concomitant therapy (see [Section 4.2](#))
- Assessment of AEs (see [Section 5.3.6](#))

Once patients have signed the ICF, completed screening, and eligibility is confirmed, the Investigator will contact IRT and patients will be assigned to treatment with BI 695501. As part of the Trial 1297.2 Week 48 assessments, trial medication is administered. This is the last trial medication administration of the 1297.2 trial. During this visit, the Investigator/designee will train the patient on how to self-administer the trial medication. See [Section 4.1.4](#) for details.

6.2.2 Treatment period(s)

For the duration of the trial, BI 695501 will be administered by the patients themselves. Trial medication will be administered every 2 weeks (± 2 days).

Baseline, Visit 2 (Day 1)

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

The following will also be performed/collected:

- Physical examination, including weight (kg) (see [Section 5.3.1](#))
- RF and anti-CCP antibodies
- Patient questionnaires: global VAS, HAQ-DI and SF-36 v2 (see [Section 5.2](#))
- Joint assessment (see Section 5.2)
- ESR and CRP
- Physician questionnaire: global VAS (see Section 5.2)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see [Section 5.3.2](#))
- Urine pregnancy test for women of child-bearing potential
- Laboratory testing (serum chemistry, hematology and urinalysis; see [Section 5.3.3](#))
- 12-lead ECG (see [Section 5.3.4](#))
- Previous and concomitant therapy (see [Section 4.2](#))
- Assessment of AEs (see [Section 5.3.6](#))
- Blood PPK samples (see [Section 5.4](#))
- Blood samples for the level of ADAs and nADAs (see [Section 5.6.1](#))
- Contact IRT and administration of trial medication
- Dispense trial medication

Patients will be instructed to accurately record the dates and times of BI 695501 dosing, and the occurrence of any AEs and use of concomitant medications, on the provided diary cards between the ambulatory visits.

The Investigator should plan with the patient when Visit 3 (Week 6) will occur and 3 syringes will be dispensed to the patient.

Visits 3, 5, 7, and 8 (Days 43, 127, 225 and 281, respectively)

The patient may choose to attend the site to self-inject the trial medication with the support of the suitably qualified, designated trial personnel or may self-inject the trial medication at home.

At all visits, the Investigator/designee will contact IRT and will dispense trial medication to the patient (see [Section 4.1.4](#) for details). The Investigator should plan with the patient when administration only visits will occur and 1 to 5 syringes will be dispensed to the patient at each visit. Patients may choose to administer the trial medication at home for these visits and collect dispensed medication at a later date. The Investigator/designee will review the patient diary card entries.

Visits 4 and 6 (Days 85 and 169, respectively)

The following will be performed/collected:

- Physical examination, including weight (kg) (see [Section 5.3.1](#))
- Patient questionnaires: global VAS, HAQ-DI and SF-36 v2 (see [Section 5.2](#))
- Joint assessment (see Section 5.2)
- ESR and CRP
- Physician questionnaire: global VAS (see Section 5.2)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see [Section 5.3.2](#))
- Urine pregnancy test for women of child-bearing potential
- Laboratory testing (serum chemistry, hematology and urinalysis; see [Section 5.3.3](#))
- Previous and concomitant therapy (see [Section 4.2](#))
- Assessment of AEs (see [Section 5.3.6](#))
- Review of patient diary card entries
- Blood PPK samples (see [Section 5.4](#))
- Blood samples for the level of ADAs and nADAs (see [Section 5.6.1](#))
- Contact IRT and administration of trial medication
- Dispense trial medication

Visit 9 (Day 337): End of Treatment Visit

The following will be performed/collected:

- Physical examination, including weight (kg) (see Section 5.3.1)
- RF and anti-CCP antibodies
- Patient questionnaires: global VAS, HAQ-DI and SF-36 v2 (see Section 5.2)
- Joint assessment (see Section 5.2)
- TB test (QuantiFERON[®]-TB Gold test)
- ESR and CRP
- Physician questionnaire: global VAS (see Section 5.2)
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see Section 5.3.2)
- Urine pregnancy test for women of child-bearing potential
- Laboratory testing (serum chemistry, hematology and urinalysis; see Section 5.3.3)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Review of patient diary card entries
- Blood PPK sample (see Section 5.4)
- Blood samples for the level of ADAs and nADAs (see Section 5.6.1)
- Administration of trial medication

Visit 10 (Day 407): Safety follow-up Visit

The following will be performed/collected:

- Physical examination, including weight (kg) (see [Section 5.3.1](#))
- ESR and CRP
- Vital signs (blood pressure, pulse rate, respiratory rate, and body temperature; see [Section 5.3.2](#))
- Urine pregnancy test for women of child-bearing potential
- Laboratory testing (serum chemistry, hematology and urinalysis; see [Section 5.3.3](#))
- 12-lead ECG (see [Section 5.3.4](#))
- Previous and concomitant therapy (see [Section 4.2](#))
- Assessment of AEs (see [Section 5.3.6](#))
- Review of patient diary card entries
- Blood PPK sample (see [Section 5.4](#))
- Blood samples for the level of ADAs and nADAs (see [Section 5.6.1](#))
- End of participation

6.2.3 Follow-Up Period and Trial Completion

End of Treatment Visit

Patients who 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 48 Visit as soon after trial discontinuation as possible.

Every effort should be made for all patients who complete the total 48-week treatment period or who discontinue the trial early, to return for a safety follow-up visit 10 weeks after the last dose of trial medication.

End of trial definition

The trial will be considered to be complete once the last patient in the trial meets one of the following:

- Completes the last trial visit (Week 58 or safety follow-up visit 10 weeks after the last trial medication administration); or
- Dies; or
- Is lost to follow-up

The Sponsor may also elect to discontinue clinical investigations under this trial for any reason at any time.

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 Phase IIIb, open-label, single arm extension of Trial 1297.2.

The objective of this trial is to provide long-term efficacy, safety, PK and immunogenicity data on BI 695501 administered via prefilled syringe in patients with RA who have completed the trial 1297.2.

No formal hypothesis testing will be performed. The analysis of the data will be performed descriptively.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No formal hypothesis testing will be performed. If confidence intervals or p-values are presented, they will be interpreted in an exploratory fashion only.

7.3 PLANNED ANALYSES

All patients treated with at least one dose of trial medication during the 1297.3 trial (Safety Analysis Set) will be included in the safety evaluations.

The Full Analysis Set (FAS) will be the basis for efficacy analyses. The FAS consists of all patients who received at least one dose of trial medication in Trial 1297.3 and had at least one DAS28 (ESR or CRP) or ACR20 measured during the 1297.3 trial.

The “All Enrolled Patients” analysis set will include all patients who provide informed consent for this trial.

For presentation of results in the report, three groups of patients will be created depending on treatments assigned in Trial 1297.2. The first group will consist of patients who were randomized to BI 695501 in Trial 1297.2 and will continue to receive BI 695501 in Trial 1297.3 but via self-administration. The second group will consist of patients who were initially randomized to receive US-licensed Humira® in Trial 1297.2, continue to receive US-licensed Humira® after Week 24 re-randomization in Trial 1297.2 and will transition to BI 695501 via self-administration in the Trial 1297.3. The third group will consist of patients who were initially randomized to receive US-licensed Humira® in Trial 1297.2, transitioned to BI 695501 following the re-randomization at Week 24 in the Trial 1297.2 and continue to receive BI 695501 in Trial 1297.3 but via self-administration. [Table 7.3: 1](#) gives an overview of the above-defined patient groups.

Table 7.3: 1 Patient groups for presentation of analysis results

Patient group	1	2	3
Randomized treatment in Trial 1297.2	BI 695501	US-licensed Humira®	US-licensed Humira®
Re-randomized treatment in Trial 1297.2 (Week 24)	BI 695501	US-licensed Humira®	BI 695501

The descriptive statistics for safety, efficacy and other endpoint will be presented for these three groups and overall for all patients combined.

Unless otherwise specified, baseline for this trial (1297.3) is defined as the baseline of Trial 1297.2 and all endpoints are those assessed in Trial 1297.3.

7.3.1 Primary endpoint analyses

The primary endpoint is defined as the number (proportion) of patients with drug-related AEs during the treatment phase.

The primary safety analysis will be performed using the Safety Analysis Set.

All AEs with an onset date between start of treatment and end of the REP, a period of 10 weeks after the last dose of trial medication, will be assigned to the treatment phase for evaluation. Adverse events will be classified by system organ class and term using the Medical Dictionary of Regulatory Activities (MedDRA) coding dictionary.

The proportion of patients with drug-related AEs during the treatment phase will be analyzed descriptively by MedDRA system organ class and preferred term. In addition, patient incidence and/or event incidence per 1000 patient-years exposure will be provided. No formal inferential analyses are planned.

7.3.2 Secondary endpoint analyses

The secondary efficacy endpoints (see [Section 5.1.2](#)) will be summarized descriptively for the FAS.

7.3.4 Safety analyses

Adverse events will be coded using the MedDRA coding dictionary. Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the residual effect period (REP), a period of 10 weeks after the last dose of trial medication, will be assigned to the treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be presented by MedDRA system organ class and preferred term. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA.

In addition, for infections/serious infections, hypersensitivity reactions, drug-induced liver injury (DILI) and injection-site reactions, patient incidence and/or event incidence per 1000 patient-years exposure will be displayed.

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

Vital signs (blood pressure, pulse rate, respiratory rate and body temperature), physical examinations, 12-lead ECGs, 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 analyses

A PPK analysis with sparse blood sampling throughout the treatment period and at follow-up will be carried out to assess the PK of BI 695501. The PK analysis might involve combining data with data from other BI 695501 studies. If relevant, a relationship will be investigated between selected safety and efficacy parameters including the development of ADA/nADA. The population PK will be described in a separate analysis plan and will be reported separately to the CTR. Raw concentration data will be reported in the CTR. Reporting of the raw concentration data will be described in the trial statistical analysis plan (TSAP).

7.3.6 Immunogenicity analyses

If data allow, the antibody response, antibody titer and neutralizing antibody response will be summarized as appropriate (frequency/proportions for ADA positive samples, descriptive statistics for titer and frequency/proportions of characterization of the neutralizing potential of the ADA for ADA positive samples assayed) by scheduled assessments (Week 12, Week 24 and Week 48) and overall (for ADA positive patients only). Further, the potential relationship between safety and antibody response will be explored if appropriate. Details of the analyses will be described in the TSAP.

7.4 INTERIM ANALYSES

No formal interim analysis will be performed for this trial. However, based on regulatory requirements safety snapshots may be provided.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety and other endpoints

For the aim of primary and secondary analyses, in case of missing AE relationship status, the AE will be considered as related.

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

7.5.2 Efficacy endpoints

Missing ACR20 data will be imputed using the last observation carried forward (LOCF) 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 endpoint assessment will be considered as a non-responder. This is referred to as 'NRI' (missing data imputation of primary analysis in 1297.2).

. For missing data, LOCF will be applied on the component variables prior to the DAS28(ESR) score.

Other missing efficacy data will not be imputed.

Further details will be given in the TSAP.

7.6 RANDOMISATION

This is an open-label, single-arm trial. No randomization will be performed.

7.7 DETERMINATION OF SAMPLE SIZE

All patients from the initial randomized controlled Trial 1297.2 willing and able to self-administer BI 695501 pre-filled syringe, and who are eligible for further treatment courses will be offered an additional treatment course with BI 695501. Patients are deemed eligible for further treatment courses if they have not experienced Investigator-reported drug-related SAEs during the 1297.2 trial, and in the Investigator's assessment can benefit from receiving BI 695501. It is anticipated that approximately 300 to 400 patients will be eligible to participate in this roll-over extension trial.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

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

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

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, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Electronic CRFs for individual patients will be provided by the Sponsor. For drug accountability, refer to [Section 4.1.8](#).

8.3.1 Source documents

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

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

For eCRFs, all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfill the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular AE is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For BI 695501, this is the current version of the IB.

For non-investigational medicinal products, for both MTX and folic acid, the reference document is the Summary of Product Characteristics.

The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC/IRB

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 END OF TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

- R11-4384 Ku IA, Imboden JB, Hsue PY, Ganz P. Rheumatoid arthritis: model of systemic inflammation driving atherosclerosis. *Circ J* 2009. 73(6): 977-85.
- R11-4383 Scott DL. Early rheumatoid arthritis. *Br Med Bull* 2007. 81-82: 97-114.
- R07-0637 Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. *Arthritis Res* 2002. 4: 265-72.
- R15-0739 Humira® (adalimumab) injection, for subcutaneous use (AbbVie) (U.S. prescribing information, revised: 12/2014 website rxabbvie.com/pdf/humira.pdf
- R15-3225 Humira® 40 mg/0.8 mL solution for injection for paediatric use, 40 mg solution for injection in pre-filled syringe, 40 mg solution for injection in pre-filled syringe with needleguard, 40 mg solution for injection in pre-filled pen (AbbVie) (summary of product characteristics, manufacturer(s) of the biological active substance and manufacturer(s) responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet, last updated: 12/05/2015). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (access date: 26 June 2015) (2015)
- R11-4385 Sokka T and Pincus T. Quantitative joint assessment in rheumatoid arthritis. *Clin Exp Rheumatol* 2005. 23(Suppl. 39): S58-62.
- R11-4337 Points to consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. CPMP/EWP/556/95 rev 1/Final. 17 December 2003. [ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003439.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003439.pdf).
- R03-1444 Food and Drug Administration. Guidance for Industry: Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). February 1999.
- R12-2515 Kukar M, Petryna O, Efthimiou P. Biological targets in the treatment of rheumatoid arthritis: a comprehensive review of current and in-development biological disease modifying anti-rheumatic drugs. *Biologics* 2009. 3:443-57.

9.2 UNPUBLISHED REFERENCES

Not applicable.

10. APPENDICES

10.1 FUNCTIONAL CLASS

American College of Rheumatology Revised Criteria for Classification of Functional Status in Rheumatoid Arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
Class II	Able to perform self-care and vocational activities, but limited in avocational activities
Class III	Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV	Limited in ability to perform usual self-care, vocational, and avocational activities

* Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age-and-sex specific.

10.2 PATIENT AND PHYSICIAN GLOBAL ASSESSMENT VAS

Patient's Global Assessment VAS

Considering all the ways that your arthritis affects you, rate how you are doing on the following scale by placing a single vertical mark (|) on the line.

VERY WELL

O

VERY POOR

100

Physician's Global Assessment VAS

Global assessment of rheumatoid arthritis activity today.

NO
RHEUMATOID
ARTHRITIS
ACTIVITY

_____0_____

EXTREMELY
ACTIVE
RHEUMATOID
ARTHRITIS

100

10.3 HAQ DISABILITY INDEX

HEALTH ASSESSMENT QUESTIONNAIRE

Name _____ Date _____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

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

	Without ANY <u>Difficulty</u>	With SOME <u>Difficulty</u>	With MUCH <u>Difficulty</u>	UNABLE To Do	
DRESSING & GROOMING					PATKEY# QUESTDAT
Are you able to:					HAQADMIN
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____	QUESTYPE
- Shampoo your hair?	_____	_____	_____	_____	PMSVIS
ARISING					RASTUDY
Are you able to:					QUESTNUM
- Stand up from a straight chair?	_____	_____	_____	_____	
- Get in and out of bed?	_____	_____	_____	_____	DRESSNEW
EATING					
Are you able to:					
- Cut your meat?	_____	_____	_____	_____	
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____	
- Open a new milk carton?	_____	_____	_____	_____	EATNEW
WALKING					
Are you able to:					
- Walk outdoors on flat ground?	_____	_____	_____	_____	
- Climb up five steps?	_____	_____	_____	_____	WALKNEW
Please check any AIDS OR DEVICES that you usually use for any of these activities:					
_____ Cane		_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)			
_____ Walker		_____ Built up or special utensils			
_____ Crutches		_____ Special or built up chair			
_____ Wheelchair		_____ Other (Specify: _____)			DRSGASST
Please check any categories for which you usually need HELP FROM ANOTHER PERSON:					
_____ Dressing and Grooming		_____ Eating			EATASST
_____ Arising		_____ Walking			WALKASST

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	HYGNNEW
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	REACHNEW
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	GRIPNEW
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	ACTIVNEW
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	
Please check any AIDS OR DEVICES that you usually use for any of these activities:					
_____ Raised toilet seat	_____ Bathtub bar				
_____ Bathtub seat	_____ Long-handled appliances for reach				
_____ Jar opener (for jars previously opened)	_____ Long-handled appliances in bathroom				
	_____ Other (Specify: _____)				
Please check any categories for which you usually need HELP FROM ANOTHER PERSON:					
_____ Hygiene	_____ Gripping and opening things				
_____ Reach	_____ Errands and chores				
We are also interested in learning whether or not you are affected by pain because of your illness.					
How much pain have you had because of your illness IN THE PAST WEEK:					
PLACE A <u>VERTICAL</u> (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.					
NO PAIN 0	_____			SEVERE PAIN 100	PAINSCAL

10.4 SF-36 V2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day. **Does your health now limit you in these activities? If so, how much?**

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c. Lifting or carrying groceries	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d. Climbing <u>several</u> flights of stairs.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e. Climbing <u>one</u> flight of stairs.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f. Bending, kneeling, or stooping.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g. Walking <u>more than a mile</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h. Walking <u>several hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i. Walking <u>one hundred yards</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j. Bathing or dressing yourself.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

4. During the **past 4 weeks**, how much of the time have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. <u>Accomplished less</u> than you would like.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. Were limited in the <u>kind of</u> work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort).....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent on work or other activities	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. <u>Accomplished less</u> than you would like	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. Did work or other activities <u>less carefully than usual</u>	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5






6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5






7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
				
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
					
a Did you feel full of life?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b Have you been very nervous?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Have you felt calm and peaceful?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e Did you have a lot of energy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f Have you felt downhearted and low?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g Did you feel worn out?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h Have you been happy?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i Did you feel tired?	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	▼	▼	▼	▼	▼
a. I seem to get ill more easily than other people.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b. I am as healthy as anybody I know.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c. I expect my health to get worse	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d. My health is excellent	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

Thank you for completing these questions!

10.5 CLINICAL EVALUATION OF LIVER INJURY

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

Repeat the following laboratory tests: ALT, AST and bilirubin (total and direct) within 48 to 72 hours and provide the additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters.

Only in cases whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient's repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST and bilirubin (total and direct) will be evaluated by a local laboratory and the results made available to the Investigator and to Boehringer Ingelheim as soon as possible. If in such a case it is confirmed that ALT and/or AST are ≥ 3 times ULN combined with an elevation of total bilirubin ≥ 2 times ULN, results of the laboratory parameters described below must be made available to the Investigator and to Boehringer Ingelheim 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 eCRF.

The Investigator is to follow the laboratory testing and assessments as noted in the DILI checklist in the ISF. These assessments include but are not limited to:

Clinical chemistry

- Alkaline phosphatase, albumin, prothrombin time or International Normalized Ratio, creatine kinase, creatine kinase muscle-brain, coaguloplasmin, α -1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides, cholinesterase

Serology

- Hepatitis A (Anti-IgM, total Ig), hepatitis B (hepatitis B surface antigen, antiHBs, DNA), hepatitis C (antiHCV, RNA if antiHCV positive), hepatitis D (anti-IgM, total Ig), hepatitis E (antihepatitis E virus [HEV], antiHEV IgM, RNA if antiHEV IgM positive), antiSmooth Muscle antibody (titer), antinuclear antibody (titer), antiliver-kidney microsomes antibody, antimitochondrial antibody, Epstein Barr Virus (virus capsid antigen [VCA] IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

Hormones, tumor marker

- Thyroid stimulating hormone

Hematology

- Complete blood count (including differential counts)

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

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

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		01
Date of CTP revision		19. February 2016
EudraCT number		2015-002634-41
BI Trial number		1297.3
BI Investigational Product(s)		BI695501
Title of protocol		Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis (RA): an open-label extension trial for patients who have completed trial 1297.2 and are eligible for long-term treatment with adalimumab
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input checked="" type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input type="checkbox"/>
Section to be changed		Clinical Trial Protocol Synopsis - Trial Clinical Monitor
Description of change		Change of the name and contact details (phone and fax number) regarding the Trial Clinical Monitor from _____ to _____.
Rationale for change		The responsibility as Trial Clinical Monitor for this trial has been transferred.
Section to be changed		Clinical Trial Protocol Synopsis - Flow Chart
Description of change		The following three changes are made to the flow

		<p>chart:</p> <ol style="list-style-type: none"> 1. Change of the permitted visit window for the Screening Visit from ± 1 day to ± 3 days. 2. Inclusion of the following sentence in the footnotes: <u>‘VAS assessments and completion of the HAQ-DI and SF-36 v2 questionnaires must be done prior to any visit procedures at this day. Patient questionnaires completed for the 1297.2 trial will be used as baseline questionnaires for the 1297.3 trial.’</u> 3. Inclusion of the following footnote regarding ECG: <u>‘Two consecutive recordings need to be taken.’</u>
Rationale for change		<p>Ad 1) The visit window for the screening visit for study 1297.3 is changed to ± 3 days to be in line with the permitted visit window for the End of Treatment Visit (Week 48) of the parent trial 1297.2, as these two visits coincide.</p> <p>Ad 2) Emphasis of the order of the assessments to be performed at the visits to avoid that the patients are biased before doing the questionnaires.</p> <p>Ad 3) Emphasis that in study 1297.3 two ECGs are to be taken (as in the parent study 1297.2).</p>
Section to be changed		3.3.3: Exclusion Criteria
Description of change		<p>Deletion of exclusion criteria #2</p> <p>Original text:</p> <p>Patients with major protocol deviations in Trial 1297.2</p>
Rationale for change		<p>The term “major protocol deviations” was not further defined in the clinical study protocol (CTP). The vast majority of currently known major protocol deviations is of administrative nature and not relevant for safety of the patients. As judged by BI, these administrative deviations do not justify exclusion of patients who would be otherwise eligible for participation in 1297.3 based on the clinical and safety assessments performed at the screening/baseline visit and are expected to have a continued benefit from further treatment in the 1297.3 study.</p>

		Patients having any major protocol violations in study 1297.2 related to safety will be excluded from the study 1297.3 based on the other specific exclusion criteria listed in the CTP.
Section to be changed		5.2.1 Joint assessments
Description of change		<p>Correction of the text regarding training of independent joint assessor</p> <p>Original text:</p> <p>Wherever possible, the same person will perform the joint assessment throughout the trial (i.e., for all patients at each trial site). <u>Standardized training will be provided to the independent joint assessor during the Investigator Meeting via the training portal.</u> This training will be documented and filed in the ISF.</p> <p>Amended text:</p> <p>Wherever possible, the same person will perform the joint assessment throughout the trial (i.e., for all patients at each trial site). <u>Standardized training will be provided to the independent joint assessor via the training modules provided in the specific study portal.</u> This training will be documented and filed in the ISF.</p>
Rationale for change		The original CTP states that standardized training will be provided to the independent joint assessor (IJA) during the Investigator Meeting via the training portal. Based on the fact that no investigator meeting will take place for this extension study, training of the IJAs will be conducted via the respective training modules posted in the study portal.
Section to be changed		5.4.2 Methods of sample collection
Description of change		<p>Revision of wording regarding storage of PK samples</p> <p>Original text:</p> <p>After completion of the trial, selected PK samples may be retained and used for further methodological investigations, e.g., stability testing. The PK samples will be discarded after the completion of the additional investigations <u>and after the Sponsor has approved this in writing, but not earlier than 5 years after the final Clinical Trial</u></p>

		<p>Report (CTR) has been signed.</p> <p>Amended text:</p> <p>After completion of the trial, selected PK samples may be retained and used for further methodological investigations, e.g., stability testing. The PK samples will be discarded after the completion of the additional investigations <u>upon the Sponsor's written approval. The PK samples may be destroyed 5 years after the final Clinical Trial Report (CTR) has been signed, and in accordance with local regulation.</u></p>
Rationale for change		<p>Reworded for clarity and because the storage of samples for PK analyses at the central laboratory should be limited to 5 years, where possible. The storage time needs to be in line with the local regulations.</p>
Section to be changed		5.6.1 Immunogenicity – Antidrug antibodies
Description of change		<p>Amendment of wording regarding storage of ADA samples</p> <p>Original text:</p> <p>The ADA samples will be discarded after the completion of the additional investigations <u>and the Sponsor has approved this in writing, but not earlier than</u> 5 years after the final CTR has been signed.</p> <p>Amended text:</p> <p>The ADA samples will be discarded after the completion of the additional investigations <u>upon the Sponsor's written approval. The ADA samples may be destroyed 5 years after the final CTR has been signed, and in accordance with local regulation.</u></p>
Rationale for change		<p>Reworded for clarity and because the storage of samples for biological analyses at the central laboratory should be limited to 5 years, where possible. The storage time needs to be in line with the local regulations.</p>
Section to be changed		<p>7.3.1 Primary endpoint analysis</p> <p>7.3.4 Safety Analysis</p>
Description of change		<p>Correction of patient incidence</p>

		<p>Original text (section 7.3.1):</p> <p>In addition, patient incidence and/or event incidence per <u>100</u> patient-years exposure will be provided. No formal inferential analyses are planned.</p> <p>Corrected text:</p> <p>In addition, patient incidence and/or event incidence per <u>1000</u> patient-years exposure will be provided. No formal inferential analyses are planned.</p> <p>Corrected text (section 7.3.4):</p> <p>In addition, for infections/serious infections, hypersensitivity reactions, drug-induced liver injury (DILI) and injection-site reactions, patient incidence and/or event incidence per <u>1000</u> patient-years exposure will be displayed.</p>
Rationale for change		Correction of an error in the original protocol to be in line with the protocol for the 1297.2 study.
Section to be changed		7.5.2 Efficacy endpoints
Description of change		<p>Revision of</p> <p>Original text:</p> <p><u>For DAS28 secondary endpoint, off-treatment assessments will not be taken into account.</u> For missing data, LOCF will be applied on the component variables prior to the DAS28(ESR) score.</p> <p>Other missing efficacy data will not be imputed. Further details will be given in the TSAP, <u>including an additional analysis strategy using patients' off-treatment results.</u></p> <p>Corrected text:</p> <p>For missing data, LOCF will be applied on the component variables prior to the DAS28(ESR) score.</p> <p>Other missing efficacy data will not be imputed. Further details will be given in the TSAP.</p>
Rationale for change		Correction of an error in the original protocol. No off-treatment efficacy data will be collected and no analysis regarding off-treatment efficacy will be

		done for study 1297.3.
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APPROVAL / SIGNATURE PAGE**Document Number:** c03635799**Technical Version Number:**2.0**Document Name:** clinical-trial-protocol-revision-01

Title: Long-term assessment of safety, efficacy, pharmacokinetics and immunogenicity of BI 695501 in patients with rheumatoid arthritis (RA): an open-label extension trial for patients who have completed trial 1297.2 and are eligible for long-term treatment with adalimumab

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		19 Feb 2016 15:28 CET
Author-Clinical Monitor		19 Feb 2016 15:35 CET
Approval-Therapeutic Area		19 Feb 2016 15:40 CET
Approval-Clinical Pharmacokinetics		19 Feb 2016 17:44 CET
Approval-Biostatistics		22 Feb 2016 08:32 CET
Verification-Paper Signature Completion		24 Feb 2016 09:31 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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