16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

Version 1.0, 23 August 2016

Clinical Trial Protocol

	Document Number:	**c11534380-01**
EudraCT No.: **EU Trial No:**	2016-003158-34	
BI Trial No.:	1297.13	
BI Investigational Product(s):	BI 695501	
Title:	Randomized, single-dose, parallel-arm, open-label Phase I trial to compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously via prefilled syringe or autoinjector	
Clinical Phase:	I	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol	
Version and Date:	**Version:1.0**	**Date:23 August 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: 23 Aug 2016	**Trial number:** 1297.13		**Revision date:**

Title of trial:	Randomized, single-dose, parallel-arm, open-label Phase I trial to compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously via prefilled syringe or autoinjector
Coordinating Investigator:	[redacted]
Trial sites:	Multicenter trial to be conducted in three two countries: SGS Life Science Services – Clinical Research Clinical Pharmacology Unit Antwerpen Lange Beeldekenstraat 267 B-2060 Antwerpen, Belgium PRA HealthSciences Van Swietenlaan 6, 9728 NZ Groningen. PO Box 8144, 9702 KC Groningen
Clinical phase:	I
Objective(s):	The primary objective of this trial is to characterize and compare the pharmacokinetics of BI 695501 after subcutaneous injection using either a prefilled syringe or an autoinjector. Additionally, safety, tolerability and immunogenicity will be assessed.
Methodology:	This is a randomized, single-dose, open-label trial in healthy volunteers in two sites. This trial will consist of two parallel arms receiving BI 695501 by either a prefilled syringe or an autoinjector.
No. of patients:	160 healthy male and female subjects with evaluable PK data for primary analysis. At least 30% of each gender will be included in the study.
total entered:	Consisting of: • subjects with a baseline body weight ≤ 60.0 kg, • subjects with a body weight >60.0 - <90.0 kg, • subjects with a body weight ≥90.0 kg
each treatment:	BI 695501/ prefilled syringe – up to 80 subjects BI 695501/ autoinjector – up to 80 subjects
Diagnosis :	Not applicable

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 23 Aug 2016	**Trial number:** 1297.13		**Revision date:**

Main criteria for inclusion:	Healthy male and female subjects aged ≥18 to ≤65 years and body mass index range: >17.5 to < 35.0
Test product(s): **dose:** **mode of administration:**	BI 695501 solution for injection/autoinjector 40 mg (0.8 mL) Subcutaneous injection via autoinjector
Comparator products: **dose:** **mode of administration:**	BI 695501 solution for injection/pre-filled syringe 40 mg (0.8 mL) Subcutaneous injection via prefilled syringe
Duration of treatment:	Single dose administration trial followed by a 57-day observation period and up to 70 days safety follow up period
Endpoints	**Criteria for pharmacokinetics:** Primary endpoints: The following primary endpoints will be determined for BI 695501 administered via prefilled syringe and autoinjector: • AUC_{0-1368} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1368 hours after dose) • C_{max} (maximum measured concentration of the analyte in plasma) • $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity) [redacted]

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 23 Aug 2016	**Trial number:** 1297.13		**Revision date:**
	[redacted]		
Safety criteria:	**Criteria for safety:** Secondary endpoints: The number (proportion) of subjects with drug-related treatment emergent adverse events (TEAEs) occurring from Day 1 through Day 70. [redacted]		
Statistical methods:	Primarily, all PK endpoints will be presented descriptively. $C_{max,}$ $AUC_{0-\infty}$ and AUC_{0-1368} will be evaluated descriptively using scatterplots and boxplots for prefilled syringe versus autoinjector administration of BI 695501, by baseline body weight, and overall. Additionally, and in an exploratory manner, the relative bioavailability of BI 695501 using autoinjector compared to BI 695501 using prefilled syringe will be estimated using an analysis of variance (ANOVA) model on the logarithmic transformed primary PK parameters (C_{max}, $AUC_{0-\infty}$ and AUC_{0-1368}), adjusting for baseline body weight (continuous). In addition to the ratio of the geometric means, the 90% confidence intervals will also be presented. [redacted]		

FLOW CHART

Treatment period	Visit	Day	Planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	Laboratory/ Urinalysis[4]	Injection Site Reaction Assessment	PK_{blood}	Anti-drug antibodies	Neutralizing antibodies	Physical Exam[3]	12-lead ECG	Vital signs (BP, PR and Temperature[3])	AE/Concomitant Mediation
	1	-28 to -2			Screening	X					X	X	X	▲ | ▼
1	[1,2]	-1			Admission to trial center	X					X	X	X	X
		1	-1:00	7:00	Predose		X	X	X	X				X
			0:00	8:00	Drug administration									|
			0:30	8:30			X							X
			1:00	9:00				X						X
			4:00	12:00			X	X					X	X
			8:00	16:00				X						
			12:00	20:00				X						X
		2	24:00	8:00			X	X						X
		3	48:00	8:00				X						X
			60:00	20:00				X						▲
		4	72:00	8:00				X						|
			84:00	20:00				X						|
		5	96:00	8:00				X						|
			108:00	20:00				X						|
		6	120:00	8:00				X						|
			132:00	20:00				X						|
		7	144:00	8:00				X						|
		8	168:00	8:00	Discharge from trial site	X		X			X	X	X	|
	[1,2]	10	216:00	8:00	Ambulatory visit			X						|
	[1,2]	15	336:00	8:00	Ambulatory visit			X						|
	[1,2]	22	504:00	8:00	Ambulatory visit	X		X	X	X	X	X	X	|
	[1,2]	29	672:00	8:00	Ambulatory visit			X						|
	[1,2]	36	840:00	8:00	Ambulatory visit			X						|
	[1,2]	43	1032	8:00	Ambulatory visit			X						|
	9	57	1368	8:00	Ambulatory e.o.t. End of Treatment	X		X	X	X	X	X	X	|

Treatment period	Visit	Day	Planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	Laboratory/ Urinalysis[4]	Injection Site Reaction Assessment	PK_{blood}	Anti-drug antibodies	Neutralizing antibodies	Physical Exam[3]	12-lead ECG	Vital signs (BP, PR and Temperature[3])	AE/Concomitant Medication
	10	70			Safety Follow-up[5] End of Trial									X

Note: Please refer to table 1 for specific planned time points.

1. Days -1 to 8 will be inpatient visits. Days 10 to 57 (e.o.t.) will be outpatient/ambulatory visits.
2. Subjects who discontinue the trial early will have all assessments completed as identified for the e.o.t visit.
3. Temperature may be measured orally or aurally; however, should be consistent for all assessments at a given trial site.
4. Full laboratory testing as outlined in Table 5.3.3:1 inclusive IGRA-T will be performed at screening and e.o.t.; Abbreviated laboratory testing as outlined in section 5.3.3 will be performed on Day -1, 8, 22 and at the investigator's discretion.
5. Day 70: subjects will be contacted to collect safety data.
6. Flowchart represents an example based on a drug administration time of 8:00 in the morning. If the drug administration time is shifted, all other measurements specified in the flowchart have to be shifted accordingly.

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ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug antibody
AE	Adverse event
AI	Autoinjector
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP/ALP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-1368}	Area under the concentration curve of the analyte in plasma from time zero to 1368 hours
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from zero to infinity
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma following extravascular administration
CK	Creatine kinase
C_{max}	Maximum measured concentration of the analyte in plasma
CPM	Clinical Project Manager
CRA	Clinical Research Associate
CRP	C-reactive protein
eCRF	Electronic Case Report Form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CTSU	Clinical Trial Supplies Unit
DILI	Drug-induced liver injury
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
e.o.t.	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GGT	Gamma glutamyl transferase
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IGRA	Interferon-gamma release assay
IGRA-T	Interferon-gamma release assay testing
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regualtory Activities
nAb	Neutralizing antibody
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic analysis set
PFS	Prefilled syringe
PR	Pulse rate
RA	Rheumatoid arthritis
RBC	Red Blood Cell(s)
RDC	Remote data capture
REP	Residual effects period
SAE	Serious adverse event
s.c.	Subcutaneous
SOP	Standard operating procedure
SPC	Summary of Protocol Characteristics
SUSAR	Serious unexpected suspected adverse reactions
TB	Tuberculosis
t_{max}	Time to reach maximum concentration
TSAP	Trial Statistical Analysis Plan
TNF	Tumor necrosis factor
$t_{1/2}$	Terminal half-life of the analyte in plasma
ULN	Upper limit of normal
US	United States
V_z/F	Apparent volume of distribution during the terminal phase λz following an extravascular dose
WBC	White Blood Cell(s)
λ_z	Terminal rate constant in plasma
V_z/F	Apparent volume of distribution during the terminal phase λz following an extravascular dose

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by synovial inflammation in the joints and consequently, progressive joint destruction. The prevalence of RA varies with factors such as gender, race, and smoking status, and ranges from 0.5% to 1% (R07-0637).

The biologic tumor necrosis factor (TNF) antagonists, including the human monoclonal antibody (mAb) adalimumab (Humira®, Abbott), are generally preferred as first-line biologic therapy. Tumor necrosis factor is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of patients with inflammatory joint disease (e.g., RA and psoriatic arthritis).

The use of adalimumab (Humira®) and other TNF antagonists in RA therapy are endorsed in the current RA treatment recommendations of the American College of Rheumatology (ACR) (R13-3614) and the European League Against Rheumatism (R14-3385). Humira has also gained approval for the treatment of polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and moderate to severe chronic plaque psoriasis.

1.2 DRUG PROFILE

BI 695501 is a monoclonal antibody being developed as a proposed biosimilar to the TNF-alpha blocker US-licensed and EU-approved Humira (adalimumab). Adalimumab is a recombinant human monoclonal immunoglobulin (Ig) GI antibody specific to human TNF-alpha. Humira binds specifically to TNF-alpha (and not TNF-beta) and blocks its interaction with the TNF receptors, TNFR1 and TNFR2. 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).

The preclinical studies that support the clinical program included:

- A comparative 5-week toxicology trial with an 8-week recovery in cynomolgus monkeys comparing BI 695501 and EU-approved Humira. There was no difference in systemic exposure between BI 695501 and EU-approved Humira with repeated dosing. This trial demonstrated the similarity of the toxicology profile for BI 695501 and EU-approved Humira.
- A single dose pharmacokinetic (PK), subcutaneous (s.c.) trial in cynomolgus monkeys comparing BI 695501 to EU-approved Humira. There were no differences in the exposure or antidrug antibody (ADA) response in cynomolgus monkeys to BI 695501 and EU-approved Humira.
- A comparative human tissue cross-reactivity trial of BI 695501, US-licensed and EU-approved Humira. This trial showed that the patterns of staining of BI 695501, US-licensed and EU-approved Humira were similar with minor differences

attributable to section to section variation, rather than any true staining differences. All of the tissue cross-reactivity staining was consistent with reported sites of TNF expression and/or previously reported sites of reference product cross-reactivity.

- A determination of the potential other cytokines to bind to BI 695501 or inhibit binding of BI 695501 to TNF compared to US-licensed and EU-approved Humira. None of the three antibodies bound to any of the 8 other cytokines that were tested. Additionally, there was no difference in the effect of these cytokines on the binding of TNF between BI 695501, US-licensed and EU-approved Humira.
- The potential for BI 695501 to induce *in vitro* cytokine release or directly activate complement compared to EU-approved Humira. The results from this trial demonstrated that BI 695501 and EU-approved Humira are not anticipated to induce cytokine release in humans and do not directly activate complement.
- An irritation potential trial in rabbits with BI 695501 demonstrated that BI 695501 did not cause irritation.

To date, a total of 175 male healthy subjects were treated with 40 mg s.c. of BI 695501 administered via prefilled glass syringe in two healthy subject trials 1297.1 and 1297.8 (U13-1096-01 and c03070713). The PK similarity of BI 695501 to US-licensed Humira and EU-approved Humira was demonstrated in a healthy volunteers study using the final commercial formulation (c03070713) in study 1297.8. Single s.c. doses of 40 mg BI 695501, US-licensed Humira and EU-approved Humira were generally well tolerated by healthy male subjects. There were no notable differences between the 3 treatment arms with respect to safety, tolerability and immunogenicity.
Additionally, 71 healthy volunteers were treated in a Phase I trial (1297.6, c02715841), comparing the PK of BI 695501 administrated using an autoinjector or a prefilled syringe following s.c. injection in the abdominal area. Preliminary results of 66 completed subjects showed no clinically relevant differences in PK, safety and immunogenicity.Overall, the adverse events (AEs) seen in three healthy subject trials for BI 695501 and both EU-approved Humira and US-licensed Humira were in line with the known safety profile presented in the US prescribing information for US-licensed Humira (R16-2901) and in the summary of product characteristics (SPC) for EU-approved Humira (R16-2926).

A phase III trial (1297.2) in patients with moderate to severe RA is ongoing and recruitment has been completed; 645 patients with moderate to severe RA were included and randomized to treatment with BI 695501 or US-licensed Humira in a blinded manner. The observed blinded AE profile revealed no unexpected safety findings and showed no clinically relevant safety concerns. The extension trial to the RA trial (1297.3) is ongoing where patients with benefit on the pivotal trial are treated with Bi 695501 in an open label fashion.
In addition, 77 patients with RA were enrolled in an open label real life handling study (1297.11) and received 4 doses of BI 695501 by AI. Patients completing the AI part of the study are being continued in an extension phase and will self-inject BI 695501 via PFS for additional 42 weeks. No unexpected safety concerns have been observed in this study till date.

For further details see ‘Investigator’s Brochure’ (c01843589).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 695501 is being developed in two different presentations – prefilled syringe and autoinjector, both containing the same drug product of 40 mg BI 695501 per 0.8 mL solution. Pursuant to the draft guidance published by the FDA (R13-5230), additional considerations for drug products developed as a drug-device combination for the treatment of RA should be addressed throughout the entire development program. Changes in the device components may affect the drug product delivery characteristics and clinical performance of the drug-device combination product.

This PK bridging trial aims to demonstrate similar delivery of the drug product to the same biospace across a range of body weights for the two delivery devices for BI 695501 in development (a prefilled syringe and an autoinjector); additionally, clinical data to support the safety, including immunogenicity and local tolerability will be evaluated. Humira is approved for administration in abdomen and thigh as injection sites. In contrast to 1297.6 study which evaluated abdomen as an injection site, this study is designed to compare the PK between BI 695501 PFS vs AI, when administered in the thigh.

[redacted]

The primary objective of this trial is to compare the PK of 40 mg of BI 695501 administered using an autoinjector and 40 mg of BI 695501 administered using a prefilled syringe following a single s.c. injection in the thigh. In particular: $C_{max,}$ AUC_{0-1368} and $AUC_{0-\infty}$.

The assessment of safety (proportion of subjects with drug-related TEAEs) will be the secondary objective of this trial.

[redacted]

2.3 BENEFIT - RISK ASSESSMENT

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance to the development of the BI 695501 autoinjector. The subjects are exposed to the risks of the trial procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venepuncture for blood sampling.

The total volume of blood withdrawn during the entire trial per subject will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

The needle cap on the prefilled syringe contains dry natural rubber. In rare cases this may cause severe allergic reactions. However, since the injection will be performed by the experienced medical personnel, the risks will be minimized. Subjects with a known history of allergic reactions will not be included into the trial.

Drug-related risks and safety measures

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

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

Tuberculosis (TB) reactivation or new TB infections have been observed in patients receiving Humira and other TNF-inhibitors, including patients who had previously received treatment for latent or active TB.
To avoid a risk of reactivating TB and other infections, TB tests (interferon-gamma release assay [IGRA]), Hepatitis B Surface Antigen (qualitative), Hepatitis B Antibody (qualitative), Hepatitis C Antibodies (qualitative), human immunodeficiency virus (HIV)-1 and HIV-2 Antibody (qualitative) will be performed prior to dosing to exclude subjects tested positive. Risk to subjects will also be minimized in this trial by implementing conservative eligibility criteria.

In the controlled portions of clinical trials of some TNF-inhibitors, including Humira, more cases of malignancies have been observed among TNF-inhibitor-treated adult patients compared to control-treated adult patients when treated with multiple doses. However, 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 are described in the prescribing information (R16-2901 and R16-2926).

The PK similarity of BI 695501 to US-licensed and EU-approved Humira was established in the phase I trial 1297.8 (c03070713). Additionally, there were no notable differences with respect to safety, tolerability and immunogenicity between the three groups in this phase I trial and the dose of 40 mg BI 695501 was safe and well tolerated in young healthy volunteers. The AE with the highest incidence in the 108 subjects who received BI 695501 in trial 1297.8 was headache (25 subjects, 23.1%), followed by upper respiratory tract infections (19 subjects, 17.6%). However, there was no difference in the AE profile between BI 695501 to US-licensed and EU-approved Humira®. There were no clinically relevant findings with respect to clinical laboratory evaluation, vital signs, electrocardiograms (ECGs), or injection site reactions.

The subjects will be kept in a Phase I unit for 8 days after trial medication administrationfor safety evaluations and blood samples draws. A careful clinical examination will be performed before the subjects are discharged from the clinic, during the trial and at the end of trial visit.

Subjects will be followed up during outpatient ambulatory visits. The ambulatory visits will occur on Days 10, 15, 22, 29, 36, 43 and 57 (End-of-Treatment [e.o.t.]) and will allow for collection of safety signs and symptoms that may occur or arise following trial treatment. Adverse events, body temperature, vital signs, ECGs and safety laboratories as well as immunogenicity will be monitored at different time points during the trial. During the long term safety follow-up period all AEs, regardless of relatedness, will be collected until 10 weeks after the administration of trial medication.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also section 5.3.7.1.
In addition, hypersensitivity reactions, anaphylaxis, and serious infections are considered as adverse events of special interest (AESI), see Section 5.3.7.1.

Based upon preclinical and clinical information available to date, healthy subjects in this trial will not be exposed to undue safety risks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be performed as a randomized, single-dose, open-label, parallel arm trial in healthy male and female subjects aged ≥18 to ≤65 years, in order to evaluate and to compare the PK and safety of the test treatment (A/BI 695501 in autoinjector) to the reference treatment (B/ BI 695501in prefilled syringe) in a broad weight range . The subjects will be allocated to 3 weight groups: ≤ 60.0 kg, >60.0 - <90.0 kg, ≥90.0 kg. The subjects will be randomly allocated to one of the two treatments (A or B). The treatments will be one 40 mg BI 695501/ autoinjector (A) or one 40 mg BI 695501 / prefilled syringe (B) followed by approximately 57 days of observation period.

It is planned to include 160 healthy male and female subjects (at least 30% of each gender will be included in the study) with a broad range of weight for the primary analysis report describing the PK profiles of BI 695501 given in a prefilled syringe and an autoinjector as well as the assessments of safety and immunogenicity. All efforts will be made to enroll subjects in all subgroups, in order to ensure a wide distribution of weight in the study.

This trial will have a screening period of up to 28 days. The subject will check-in to the trial center on Day -1, will be dosed on Day 1 and be resident until the Day 8 discharge procedures are complete. All subjects will remain in the clinic until day 8 after dosing. The subject will then return to the clinic for 7 ambulatory visits on Days 10, 15, 22, 29, 36, 43 and 57 (e.o.t.).
Additionally, all AEs, regardless of relatedness, will be collected until 10 weeks after the administration of trial medication. Adverse events not fully resolved at the Safety Follow-up visit will be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.

For details for treatments to be administered refer to Section 4.1.

An overview of all relevant trial activities is provided in Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Section 6.1 and Section 6.2, respectively.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) International GmbH.
A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial.
Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating the activities required to manage the trial in accordance with applicable regulations and Standard Operating Procedures (SOPs).

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

The trial will be conducted at two clinical sites in two countries:
- Clinical Pharmacology Unit Antwerpen of SGS Life Science Services – Clinical Research, Antwerpen, Belgium under the supervision of the principal investigator.
- PRA Health Sciences, Van Swietenlaan 6, 9728 NZ Groningen. PO Box 8144, 9702 KC Groningen

Details of the investigators and other personnel whose participation may materially affected the conduct of the trial, including their curricula vitae are provided in Clinical Trial Master File.

Safety laboratory tests will be performed by the local laboratory of the trial sites. ZNA Klinisch Laboratorium, Lange Beeldekensstraat 267, 2060 Antwerpen, Belgium and PRA HS Clinical Chemistry Lab, Van Swietenlaan, 6 9728 NZ Groningen.
The analyses of BI 695501 PK, ADA and neutralizing antidrug antibody (nAb) samples will be performed by [redacted].

The organisation of the trial (including but not limited by Project Management, Clinical Field Monitoring, Medical Monitoring, On-site monitoring, Data Management) in the participating countries will be performed by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.
Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

This is a 14-week, open-label, randomized, single dose, parallel arm trial to investigate and compare the PK, safety, tolerability and immunogenicity of BI 695501 administered subcutaneously in the thigh via prefilled syringe or autoinjector.

Due to the long half-life of BI 695501, a parallel group design was selected, with administration of BI 695501 as a single dose only. Additionally, randomization minimizes selection bias between the treatment groups.

Blinding is not possible because the BI 695501 presentations are visually distinguishable. The open-label treatment is not expected to bias the PK results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte provided by a bioanalytical laboratory which is blinded to treatment allocation.

It is not expected that the device itself, being a prefilled syringe or an autoinjector, has an influence on the bioavailability in terms of rate and extent of absorption especially considering the long half-life of the compound. The most likely important variable is the reliability of the injection with regards the depth of the injection and thus the tissue reached as well as the amount of drug being injected by the device. The injection characteristics are

more likely influenced by the amount of s.c. fat tissue. Body mass index and weight have a good correlation with s.c. fat tissue thus the inclusion of healthy subjects having a broad range of weight would give a better estimation of the reliability and performance of the devices.

The group size of up to 80 subjects per treatment group is considered adequate for an evaluation of the PK, safety, tolerability, and immunogenicity for the primary analysis report to support the primary objective of the study.

3.3 SELECTION OF TRIAL POPULATION

It is planned that in total up to 160 healthy male and female subjects will enter the trial. All efforts will be made to enroll in all 3 weight categories, in order to ensure a wide distribution of weight in the study.
Subjects, who prematurely discontinue the trial due to any reason, may be replaced to ensure sufficient numbers complete the trial. Thus the planned number of subjects entered may exceed a total of 160. They will be recruited from the volunteers' pool of the trial sites.

Male and female healthy subjects with a weight in the indicated weight groups will be included into the trial. This will ensure that performance of the devices is tested in a wide range of weight ranges and is representative of wider patient population.
A log of all subjects 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 trial will be performed in healthy male and female subjects.

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

3.3.2 Inclusion criteria

1. Age between 18 and 65 years (inclusive)
2. BMI of >17.5 to <35.0 kg/m^2
3. Healthy male or female subjects, according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (blood pressure [BP], pulse rate [PR]), 12-lead ECG, and clinical laboratory tests.
4. Subjects who meet any of the following criteria:

- Surgically sterilized (confirmed 6 month prior to enrollment)
- Have surgically sterilized sexual partner (confirmed 6 month prior to enrollment)

- Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

5. Subjects agree to use an adequate contraception, starting from the begin of the trial and until 6 months after the dose of the trial drug: e.g. any of the following methods plus condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
6. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. Previous exposure to adalimumab or proposed adalimumab biosimilar drugs.
2. Any finding in the medical examination (including BP, PR or ECG) that deviates from normal and judged as clinically relevant by the investigator.
3. Any evidence of a concomitant disease judged as clinically relevant by the investigator including gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal disorders or diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders.
4. History of relevant orthostatic hypotension, fainting spells, or blackouts.
5. Chronic or relevant acute infections.
6. Positive result for HIV, HBV, and hepatitis C (Hep C) at screening.
7. History of relevant allergy or hypersensitivity including allergy to the trial medication, its excipients or device materials (e.g. natural rubber or latex).
8. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial.
9. Intake of an investigational drug in another trial within 2 months or 5 half-lives (whichever longer) prior to planned administration of the trial medication in this trial or intake of an investigational drug during the course of this trial.
10. Alcohol abuse (consumption of more than 28 units/week).
11. Unwillingness/inability to refrain from intake of alcoholic beverages from 48 hours prior to the trial medication administration and until Day 14 post trial medication administration; and/or to limit alcohol intake to a maximum of 3 units per day until e.o.t.
12. Drug abuse or positive drug screening.
13. Blood donation of more than 500 mL within 30 days prior to administration of trial medication or intended donation during the trial.
14. Intention to perform excessive physical activities within 4days prior to administration of trial medication or contact sport during the entire trial and unwilling to avoid vigorous exercise for 14 days post dosing.
15. Inability to comply with dietary regimen of trial site.
16. Any out-of-range laboratory values considered clinically significant by the investigator; (subjects with creatine kinase (CK) values 2 times the upper limit of normal (ULN) at Day -1 are to be) excluded from participation).

17. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because he is considered not able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial.
18. Subjects with any immunological disorders or auto-immune disorders, (e.g., RA, lupus erythematosus, scleroderma, etc.).
19. Subject has received a live vaccine within 12 weeks prior to enrolling in the trial.
20. History of TB or positive finding in IGRA.
21. Evidence of skin irritation or infection at the planned injection place.
22. Currently enrolled in another investigational device or drug study
23. Any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial
24. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep subjects in the trial as scheduled. This includes careful subject selection and appropriate explanation of the trial requirements and procedures prior to enrolment.

An individual subject is to be withdrawn from trial if:

- The subject withdraws consent for trial participation, without the need to justify the decision. In this case, no more assessments/investigations will be performed.
- The subject needs to take concomitant drugs that interfere with the investigational product
- The subject can no longer participate for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the subject's agreement, the subject will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and section 6.2.3.
For all subjects, the reason for withdrawal (e.g. adverse events) must be recorded in the CRF. 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 reasons including but not restricted to:

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

In case the planned number of subjects cannot be randomized, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if the available sample size is sufficient to complete the trial.
The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products have been manufactured and will be provided by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in autoinjector
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	40 mg / 0.8 mL
Posology:	1-0-0*
Route of administration:	s.c.
Duration of use:	single dose

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	40 mg / 0.8 mL
Posology:	1-0-0*
Route of administration:	s.c.
Duration of use:	single dose

*administered in the morning

BI 695501 autoinjector will be provided as sterile, preservative-free, non-pyrogenic, single-use prefilled syringes in autoinjectors containing 40 mg of BI 695501 per 0.8 mL. One autoinjector will be used per injection. The needle cap of the autoinjector syringe contains dry, natural rubber. BI is the final manufacturer of the BI 695501 autoinjector.

BI 695501 prefilled syringe will be provided as sterile, preservative-free, non-pyrogenic, single-use prefilled glass syringes containing 40 mg of BI 695501 per 0.8 mL. One syringe will be used per injection. The needle cap of the syringe contains dry, natural rubber.

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

4.1.2 Selection of doses in the trial

The dose selected for this trial reflects the standard clinical dose, and established similarity to the originator compound (see Section 1.2). The design and handling of the BI 695501 prefilled syringe and autoinjector do not significantly differ from the originator products as well and both presentations are intended to be marketed.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted and informed about the planned visit dates.

Once subjects have completed screening, have met all the inclusion criteria and none of the exclusion criteria, randomization can occur prior to the planned dosing on Day 1. Subjects will be stratified by weight and site, and randomized sequentially.

Each prefilled syringe and autoinjector of the trial medication will be labeled with the trial code and a unique medication identification number.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This is a single dose trial. All subjects will receive one of two possible treatments in a randomized order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
A	BI 695501	Solution for injection in autoinjector	40 mg	0.8 mL	40 mg
B	BI 695501	Solution for injection in prefilled syringe	40 mg	0.8 mL	40 mg

The autoinjector and prefilled syringe should be removed from refrigeration approximately 30 minutes before administration, to permit the medication to warm. Injecting cold medication can cause discomfort.

Trial medication will be administered as a single, s.c. injection while the subject is in a supine position by the trained investigator or designee. The time, injection location, and any difficulties with injection of the trial medication administration will be recorded in the eCRF. The location for the injection is the front of the thigh. Detailed "Instructions for use" for autoinjector and prefilled syringe will be provided in the ISF. Subjects will be kept under close medical surveillance until 24 hours following trial medication administration.

Standardized meals will be served during the residential period.

For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

No blinding will be performed because the treatments are distinguishable from each other. This Phase I trial will be handled in an open-label fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias is low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since all subjects will receive the same dose of the same drug via different presentations in an open-label design.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site and the bioanalyst will remain blinded.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).
For details of packaging, retention sampling, and description of the labels refer to the ISF.
Re-supply of the trial medication may occur on an as-needed basis during the trial.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the labelled storage conditions. 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 must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA) (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB / ethics committee 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 clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator
- Availability of Form 1572, if applicable

Only authorized personnel as documented in the form 'Trial Staff List' (site delegation log) may dispense medication to trial subjects. The identification of drug kits for retention sampling must be completed by the designated site personnel.

The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorization by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is expected in this healthy volunteers trail. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the eCRF. Hormonal contraceptives are allowed for women of child-bearing potential; limited amounts of paracetamol (or ibuprofen) are allowed to treat aches and pains.

Supplements and herbal preparations are discouraged from use during the course of the trial. Vitamins may be used during the trial based on the discretion of the investigator.

Any live or attenuated vaccines are strictly prohibited during the course of the trial.
Use of any prescribed or over-the counter drugs should be reported and discussed with the investigator.

> The subjects are instructed not to undergo any medical treatment or any surgical procedure 14 days prior to, during and until the end of the trial without having informed the investigator or his deputy unless necessary to treat medical emergencies.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from smoking, consuming any food or drink other than those provided by the site staff.

On all days when laboratory sampling is planned, subjects must have fasted for 4 hours prior to blood samples being collected.

Excessive exercise should be avoided from 4 days prior to and up to 14 days after trial medication administration. Contact sport must be avoided for the duration of the trial.

Female subjects and Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 6 months after the dose of trial drug. Males and male partners of female subjects should use a condom.

Female subjects and female partners of male subjects must additionally use one of the following methods if they are not pregnant: implants, injectables, combined oral or vaginal contraceptives, intrauterine device.
Male subjects must also agree to not donate sperm during the trial and for a period of 6 months after the last dose of trial drug.

Subjects should abstain from alcoholic beverages for 24 hours prior to each trial visit. Alcoholic beverages are not permitted from 48 hours prior to the first trial medication administration on Day 1 and until Day 14 and then no more than three units of alcohol per day are allowed until e.o.t.

One unit of alcohol is 10 mL (1 cL) by volume, or 8 g by weight, of pure alcohol. For example:
One unit of alcohol is about equal to:

- Half a pint (290 mL) of ordinary strength beer, lager, or cider (3% to 4% alcohol by volume); or
- A small pub measure (25 mL) of spirits (40% alcohol by volume): or
- A standard pub measure (50 mL) of fortified wine such as sherry or port (20% alcohol by volume).

There are one and a half units of alcohol in:

- A small glass (125 mL) of ordinary strength wine (12% alcohol by volume); or
- A standard pub measure (35 mL) of spirits (40% alcohol by volume).

4.2.2.3 Restrictions regarding women of childbearing potential

A serum beta-human Chorionic Gonadotropin (β-hCG) test will be performed at Screening in women of childbearing potential. A local urine pregnancy test will be then performed as indicated in the Flow Chart. Any woman with a confirmed positive pregnancy test during screening is not eligible for the trial. A positive urine pregnancy test during the study duration should be reported and followed up. Female subjects of childbearing potential must use the contraception methods described in Section 4.2.2.2 and the subject information.
Acceptable methods of birth control include, for example, birth control pills, intrauterine devices (IUDs), surgical sterilization, vasectomized partner and for example male condom in combination with female implants, injectables, combined oral or vaginal contraceptives, intrauterine device).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication at the trial center by the investigator or an authorised designee. The measured plasma concentrations will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the eCRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

The following primary endpoints for PK will be determined for BI 695501 administered via PFS and AI:

- $AUC_{0\text{-}1368}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 1368 hours after dose)
- C_{max} (maximum measured concentration of the analyte in plasma)
- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

5.1.2 Secondary Endpoints

For safety:
Number (proportion) of subjects with drug-related TEAEs occurring from Day 1 through Day 70.

For PK/immunogenicity:

No secondary endpoints for PK and immunogenicity are defined.

[redacted]

5.2 ASSESSMENT OF EFFICACY

No efficacy will be evaluated.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A physical examination will be performed at the visits indicated in the Flow Chart.
At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, temperature), 12-lead ECG, laboratory tests (including drug and virus screening, IGRA-T), and a physical examination. At the e.o.t. examination, the medical examination will include review of vital signs, 12-lead ECG, laboratory tests (including IGRA-T), and a physical examination with determination of weight. Adverse events and concomitant therapies will be assessed throughout the trial.
The physical examination will include assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen.

5.3.2 Vital Signs

Systolic and diastolic BP as well as PR or heart rate (heart rate is considered to be equal to PR) will be measured by means of a validated BP device at the times indicated in the

Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of BP recording instrument on the same arm if possible.

The method of measuring body temperature (oral/aural) should be consistent at a specific trial site.

5.3.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 hours (or 4 hours before admission on Day -1). Overnight fasting is not required at the discretion of the investigator or designate for retests.

Required sample volumes for safety/serology laboratory assessments may vary between local laboratories. Sample amount may be exceeded if unscheduled (additional) monitoring of laboratory results is warranted.

The parameters that will be determined are listed in Table 5.3.3: 1 and Table 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is a relevant abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.3.3: 1 Routine laboratory tests

Functional lab group	Test name
Hematology	Hematocrit Hemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count
Automatic WBC differential (relative)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (at the investigator's discretion)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Coagulation[1]	Activated partial thromboplastin time (Aptt) Prothrombin time (Quick's test and international normalized ratio [INR]) Fibrinogen
Enzymes	Aspartate aminotransferase (AST/GOT) Alanine aminotransferase (ALT/GPT) Gamma glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated
Substrates	Plasma glucose Creatinine Total bilirubin Direct bilirubin Bilirubin indirect Total protein Albumin C-Reactive Protein (CRP) Total cholesterol
Electrolytes	Sodium Potassium Calcium
Serum Pregnancy test (only for female subjects of childbearing potential) at screening and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine erythrocytes
Urine Pregnancy test (only for female subjects of childbearing potential) at randomization and continued as indicated in the Flow Chart (including EoT	Human Chorionic Gonadotropin in the urine

[1] at screening only

The tests listed in Table 5.3.3: 1 will be performed at screening, and as part of the end of trial examination.

The tests listed in Table 5.3.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the eCRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to treatment period on Day -1.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine Barbiturates Benzodiazepine THC Cocaine Methadone Methamphetamines Opiates PCP Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Tuberculosis	IGRA-T (e.g. QuantiFERON®-TB Gold IT Test)

The following laboratory parameters will be analyzed at all other visits indicated in Flow Chart:

- Serum chemistry: creatinine, alkaline phosphatase, AST, ALT, GGT, CK, bilirubin (total and direct), glucose, total cholesterol, total protein, albumin, sodium, potassium, calcium
- Hematology: hemoglobin, hematocrit, platelets, red blood cells, white blood cells, lymphocytes, neutrophils
- Urinalysis: protein, glucose, erythrocytes

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to the treatment period, and may be repeated at any time during the trial at the discretion of the investigator or designee. Alternately, alcohol screening may be done as part of urine drug screening. The results will not be included in the CTR.

The laboratory tests listed in Table 5.3.3: 1 and Table 5.3.3: 2 will be performed at the local site laboratory with the exception of the drug screening tests. These tests will be performed at the trial sites.

Laboratory data will be transmitted electronically from the laboratory to the trial site.

5.3.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, Avr, Avl, Avf, V1 – V6) will be recorded using a computerized electrocardiograph as scheduled in the Flow Chart.

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

All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the only valid ECG will be used for analysis and reported in CRF. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

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 subject will be removed from the trial and will receive the appropriate medical treatment. A physician familiar with interpretation of ECG will evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal, abnormal not clinically relevant or abnormal clinically relevant) will be recorded in the appropriate section of the eCRF. The digitally recorded ECGs will be electronically stored.

5.3.5 Other safety parameters

Local tolerability
Injection site reaction assessment will be performed by investigator or site staff according to “swelling”, “induration”, “heat”, “redness”, “pain”, or “other findings”. Tolerability will be assessed at Day 1 from the time of the injection until Day 2. If any injection site reactions are observed, these findings should also be reported on the AE eCRF page.

5.3.6 Immunogenicity evaluation

The following further parameters of interest will be evaluated:

- The proportion of subjects with antidrug antibodies (ADAs) at baseline (pre-dose), Day 22, and Day 57.
- ADA titers of ADA positive subjects at baseline (pre-dose), Day 22, and Day 57
- The proportion of subjects with neutralizing antidrug antibodies (nAbs) at baseline (pre-dose), Day 22, and Day 57

5.3.7 Assessment of adverse events

5.3.7.1 Definitions of AEs

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

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

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- 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 jeopardise the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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

AEs considered "Always Serious"
Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as given above.

The latest list of "Always Serious AEs" can be found in the ISF. A copy of the latest list of "Always Serious AEs" will be provided to you upon request.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs:

1. Hepatic injury

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

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

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

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

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

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

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

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

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

- The event is consistent with the known pharmacology of the drug

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

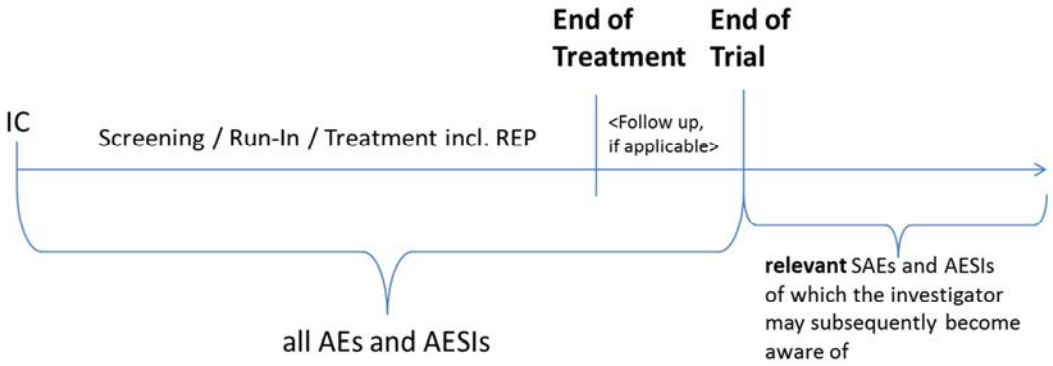
Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

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

5.3.7.2 Adverse event collection and reporting

AE <u>Collection</u>
The Investigator shall maintain and keep detailed records of all AEs in their subject files. The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until individual subject's end of trial:
  -all AEs (serious and non-serious) and all AESIs.
  However, if an individual subject discontinues trial assessments but stays in the trial (i.e. if further visits incl. telephone visits, or vital status assessments are planned) from then on and until the individual subject's end of the trial the Investigator must report related SAEs and related AESIs.
- After the individual subject's end of trial:
  the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.



- The REP is defined as 10 weeks after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

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

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship of AE to the trial medication.
The following should also be recorded as an (S)AE in the CRF and SAE form (if applicable):

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

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

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

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a subject has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately

(within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's/sponsor designee'sunique entry point (contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Date and clock time of drug administration and PK sampling will be recorded in the eCRFs.

The actual sampling times will be used for determination of PK parameters.

The PK endpoints to be evaluated are outlined in Section 5.1.

5.4.2 Methods of sample collection

Plasma sampling for pharmacokinetic analysis
Samples of whole blood (approximately 3 mL) will be taken (in tubes containing dipotassium ethylenediaminetetraacetic acid [K_2EDTA] anticoagulant) at the time points shown in the Flow chart for the determination of concentrations of BI 695501.
Method to process the sample after collection will be described in the laboratory manual.
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 completion of the additional investigations, but not later than 5 years after the final Clinical Trial Report (CTR) has been signed.

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

5.4.3 Analytical determinations

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

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

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

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Not applicable.

5.5 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Assessment of immunogenicity

5.6.1.1 Plasma sampling for Anti-Drug-antibodies characterization

For characterization of human anti-BI 695501 antibodies (ADA), approximately 3 mL of blood will be collected from a forearm vein in a K_2EDTA anticoagulant blood drawing tube at time points indicated in Flow Chart.

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

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

5.6.1.2 Plasma sampling for neutralizing antibody characterization

For characterization of human neutralizing anti-BI 695501 antibodies (nAb), approximately 6 mL of blood will be collected from a forearm vein in a K_2EDTA anticoagulant blood drawing tube at the same time points as ADA samples are collected. Method to process the sample after collection will be described in the laboratory manual.

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

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine PK parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of a subcutaneously administered drug, and are widely used in clinical trials. The PK parameters and measurements outlined in Section 5.1 are generally used assessments of drug exposure. Therefore, the appropriateness of all measurements applied in this trial is confirmed.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for all visits are given in Flow Chart.

- General medical examination: at screening (2 to 28 days prior to the first trial day);
- Trial measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 hour period prior to the trial drug administration.
- The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests PK, ADA, nAb sampling) will be:
  - ±15 minutes for Day 1
  - ±2 hours from Day 2 to Day 10;
  - ±1 day from Day 15 to Day 57
  - The e.o.t. IGRA may be performed up to 72 hours prior to the other e.o.t. assessments.

If scheduled in the Flow Chart at the same time as a meal, vital signs, 12-lead ECG recordings and blood sampling have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times refer to Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of PK parameters.

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening Period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.
For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.3.1 to 5.3.5.
If possible, spare subjects will be provided for each group to guarantee the start of a complete group. The spare subjects will participate in all trial activities up to Day 1, i.e. on Day -1 they will be admitted to the clinic and all examinations, which have been scheduled up to drug administration on Day 1 will be performed. The spare subjects from one group will be given the option to participate in the next planned group.

6.2.2 Treatment period(s)

Subjects will be randomly allocated to the treatment (autoinjector or prefilled syringe).

On Day -1 trial participants will be admitted to the trial site and kept for 8 days following drug administration. The subjects will be allowed to leave the trial site from Day 8 after formal assessment and confirmation of their fitness. On all other trial days, the trial assessments will be performed in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK, ADA and nAb analysis, refer to Flow Chart and Section 5.5.

The safety measurements performed during the treatment period are specified in Section 5.3. of this CTP and in Flow Chart. For details on time points for all other trial procedures, refer to Flow Chart. Adverse events and concomitant therapy will be assessed continuously from screening until the end of trial.

6.2.3 Follow Up Period and Trial Completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of treatment (e.o.t.) visit (day 57), see Sections 5.3.1 to 5.3.5.

Subjects who discontinue trial participation before the end of the planned observational period but not withdraw consent - should undergo the e.o.t. visit and Safety Follow-up (end of trial) visit 10 weeks after administration of the trial medication.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalized or have been sufficiently characterized.

The end of the trial as a whole is defined by the ‘last regular visit completed by last subject’ or ‘end date of the last open AE’ or ‘date of the last follow-up test’ or ‘date of an AE has been decided as sufficiently followed-up’, whichever is latest.

Long-term safety follow-up observational period will continue for 10 weeks after BI 695501 administration to collect AEs (SAEs).

The subjects are to be instructed to contact the investigator or his/her designee in case of occurrence of any AEs, any additional concomitant drug or if they undergo any medical treatment or any surgical procedure during the observational period until the safety follow-up visit call. Subjects will be contacted by the investigator or designee 10 weeks after administration of the trial medication to collect the information on subject’s wellbeing and document all AEs (SAEs) and concomitant medication.

All AEs, serious and non-serious, will be followed up until they have normalized or been sufficiently characterized and documented in the safety database.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is a randomized, open-label, parallel-group, single-dose, Phase I trial.

7.1 STATISTICAL DESIGN - MODEL

For the purposes of the exploratory analysis, the primary PK endpoints for BI 695501 will be estimated using an analysis of variance (ANOVA) model on the logarithmic scale with fixed effects for treatment, and baseline body weight (continuous).

The ANOVA model is described by the following equation:

$$y_{ij} = \mu + \tau_i + \beta * weight_{ij} + e_{ij}, \text{ where}$$

y_{ij} = logarithm of PK parameter measured on subject j receiving treatment i,

μ = the overall mean,

τ_i = the i-th treatment effect, i = 1, 2 (1=Test, 2=Reference),

β = the slope parameter for the baseline body weight covariate,

$weight_{ij}$ = baseline body weight of subject j receiving treatment i,

e_{ij} = the random error associated with the j-th subject, receiving treatment i,

where $e_{ij} \sim N(0, \sigma_i^2)$ are independent random variables.

The randomisation will be stratified by site, but this is considered to be a logistical stratification and will therefore be not included in the primary model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 695501 using autoinjector (A) compared to BI 695501 using prefilled syringe (B) will be estimated, in an exploratory manner, by the ratios of the geometric means (A/B) for the primary endpoints using the ANOVA described in Section 7.1. All PK further parameters of interest will be analysed descriptively.

7.3 PLANNED ANALYSES

Primarily, all endpoints will be presented descriptively. The PK parameters (see Section 5.1.1) will be calculated according to the BI SOP ‘Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics’ (001-MCS-36-472).

The logarithmic transformed primary PK endpoints will be evaluated using scatterplots and boxplots for prefilled syringe versus autoinjector administration of BI 695501, by baseline body weight and overall.

7.3.1 Primary endpoint analyses

In an exploratory manner, the relative bioavailability of BI 695501 using autoinjector (A) compared to BI 695501 using prefilled syringe (B) will be estimated by the ratios of the geometric means (A/B) for the primary PK endpoints. Point estimates of relative bioavailability, the ratios (A/B) of the geometric means for the primary PK endpoints (see Section 5.1.1), and their two-sided 90% CIs will be provided for the overall comparison A versus B.

The PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model (see Section 7.1). For each PK endpoint, the difference between the means for log(A)-log(B) will be estimated by the difference in the corresponding adjusted means (least-squares means), and a two-sided 90% CI based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for the corresponding ratio of geometric means (A/B) for each PK endpoint.

The ANOVA will be conducted on the PK Analysis Set (PKS). The PKS will consist of all randomized subjects who receive the single dose of trial medication (BI 695501 using autoinjector or BI 695501 using prefilled syringe), and have at least one evaluable primary PK parameter, and are without important protocol deviations or violations thought to significantly affect the PK of BI 695501.

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters can for example be:

- Time deviations
- Use of restricted medications
- Dosing errors

It will also be decided in the Report Planning Meeting which subjects are to be included in the PKS.

Details of the presentation and analysis of PK data will be provided in the Trial Statistical Analysis Plan (TSAP).

[redacted]

[redacted]

7.3.4 Analysis of Safety endpoints

Safety will be assessed for the secondary and further endpoints listed in Section 5.1.2 and Section 5.1.3 using the Safety Analysis Set. All treated subjects (that is, all subjects who received one dose of trial drug), will be included in the Safety Analysis Set. Safety analyses will be descriptive in nature.

The safety summaries will be presented by treatment according to treatment received.

Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All events with an onset after the first dose of trial medication up to a period of 10 weeks after the last dose of the trial medication (i.e., end of the REP) will be assigned to the treatment phase for evaluation, and will be referred to as treatment emergent adverse events (TEAEs). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs and other significant AEs (according to ICH E3), and protocol-specified AESIs will be listed separately (see Section 5.3.7.1).

The number and percentage of subjects with injection site reactions (assessed at Day 1 from the time of the injection until Day 2, prior to discharge from the trial site) will be summarized by treatment for each injection site reaction.

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. Descriptive statistics of laboratory values over time and for the change from baseline will be provided for each treatment group. Laboratory parameters will be compared to their reference ranges and frequency tables will be provided for the number of subjects within and outside the reference range.

Observed values and changes from baseline in BP (systolic and diastolic), PR, and body temperature will be summarized by treatment group.

Details of the presentation and analysis of safety data will be provided in the TSAP.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The PK parameters listed in Section 5.1.1 and Section 5.1.3 for drug BI 695501 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.1) will be reported with their individual plasma concentrations and individual PK parameters; however, they will not be included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessment.

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

If a pre-dose concentration value is greater than 5% of Cmax, the subject's PK data will not be included in any statistical evaluations, in accordance with international guidance. The individual PK parameters of such a subject will be calculated and listed separately. If a pre-dose concentration is above below the limit of quantification (BLQ), but less than or equal to 5% of the subject's Cmax value, the subject's data without any adjustments will be included in all PK measurements and calculations.

7.4 INTERIM ANALYSES

No interim analysis is planned in this study.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

With respect to AE analysis, missing relationship will be imputed to "yes". For other safety evaluation, no imputation of missing data is planned.

7.5.2 Plasma drug concentration - time profiles

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

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ, or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point except the lag phase.

7.5.3 Pharmacokinetic parameters

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

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

Descriptive statistics of parameters are calculated only when a parameter value is available for certain for at least 2/3 of the treated individuals. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. PK parameters that cannot be determined will be identified as "not calculated".

7.6 RANDOMISATION

Subjects will be randomized to one of the two treatments in a 1:1 ratio. The block size will be documented in the CTR.

The sponsor will arrange for the randomization as well as packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable. Randomization will be stratified by:

- site (2 levels and for logistical reasons only)
- baseline body weight category with ranges:
    - low: ≤ 60.0 kg
    - medium: > 60.0 to ≤ 90.0 kg
    - high: ≥ 90.0 kg

and will be randomized sequentially (the lowest sequentially available randomization number).

The randomization list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 160 subjects for the primary analysis of this trial, because this sample size is considered sufficient to assess the primary objective of this exploratory trial. With this sample size, the precisions of the ratio of the geometric means (test/reference) to be expected with 95% probability, are presented in Table 7.7: 1. That is to say, we expect with 95% probability, that the precision is no greater than the value specified, where precision is defined as the ratio of upper CI limit to the point estimate of the geometric mean ratio.

The observed ratio of the geometric means (and geometric coefficient of variation (gCV)) in previous trials (1297.8, c03070713; 1297.6, CTR in reporting stage) were:

- 108% (45%) for $AUC_{(0-\infty)}$ in 1297.8
- 104% (54%) for $AUC_{(0-\infty)}$ in 1297.6
- 112% (32%) for Cmax in 1297.6

The values from 1297.6 are estimated from the models adjusted for BMI (continuous). Although the main analysis for this study will be adjusted for baseline body weight (continuous), these model estimates serve as a good approximation, given the high correlation expected between BMI and body weight. The values coming from 1297.8 are unadjusted.

Table 7.7: 1 Precision and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a parallel trial (N=160).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
32	1.09	112	102.44	122.45
45	1.13	108	95.53	122.09
54	1.16	104	90.01	120.17

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

The calculation was performed as described by Julious (R12-0972) using R Version 3.2.2.

Regarding the assessment of the primary PK parameters, albeit in an exploratory manner, the following table (Table 7.7: 2) provides an overview of the probability of success (power) given some assumed effect sizes and assumptions on the gCV, as described above. The calculations are based upon the overall treatment effect, adjusting for BMI continuous (as a good substitute for body weight), where data is available.

Table 7.7: 2 Power (%) for concluding bioequivalence (acceptance range 80-125%) based on a geometric coefficient of variation around 50% and for different expected ratios of geometric means (test/reference) in a parallel trial (N=160).

	Ratio [%]*			
gCV [%]	**100**	**104**	**108**	**112**
32	>99%	98%	90%	**71%**
45	89%	83%	**68%**	55%
50	81%	75%	61%	-
54	74%	**68%**	55%	-

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

The calculations were performed using nQuery Version 2.0.1.0.

Therefore, with the expectation that there is less variability in this planned trial, there should be more than 70% power to have the resulting 90% confidence interval of the ratio of the gMeans lying within the range of 80-125%. The reason for less expected variability is that the the drug is now to be administered in the thigh, and there is also expected to be slightly less variability when adjusting for baseline body weight.

Thus a total sample size of up to 160 subjects is planned for this trial and with no planned adjustment for drop-outs.

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract. The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF (Investigator Site File).

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to subject participation in the trial, written informed consent must be obtained from each subject 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 subject -information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.
The Investigator must give a full explanation to trial subjects based on the subjects information form. A language understandable to the subjects should be chosen, technical terms and expressions avoided, if possible. The subjects must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms (CRF) for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

For the CRF, all data must be derived from source documents.

The LabPas and Oracle Clinical (TD Synergy) systems is an electronic data capturing and information management system that will also serve as an e-source system for this trial. The system combines all aspects of source data capturing with process control and clinical trial management. Clinical and laboratory data, except those which are paper based, will be collected in there.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which

must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject privacy will be ensured by using subject identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.
Treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking

facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.

- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment pf the first subject in the whole trial.
The end of the trial is defined as the date of the last visit of the last subject in the whole trial ("Last Patient Out"). **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

9. REFERENCES

9.1 PUBLISHED REFERENCES

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(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).webpage.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000481/WC500050870.pdf (access date: 26 June 2015) (2015)

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10. APPENDICES

Not available

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

"This is the original protocol."

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c11534380 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: Randomized, single-dose, parallel-arm, open-label Phase I trial to compare the pharmacokinetics, safety and tolerability of BI 695501 administered subcutaneously via prefilled syringe or autoinjector

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor	[redacted]	23 Aug 2016 16:21 CEST
Approval-Clinical Pharmacokinetics	[redacted]	23 Aug 2016 16:24 CEST
Approval-Team Member Medicine	[redacted]	23 Aug 2016 16:38 CEST
Approval-Therapeutic Area Head	[redacted]	23 Aug 2016 16:56 CEST
Approval-Project Statistician	[redacted]	24 Aug 2016 15:30 CEST
Verification-Paper Signature Completion	[redacted]	24 Aug 2016 15:32 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**