SIGNATURE INFORMATION

Document: 1302-0001--protocol-revison-02

Document No.: U12-1288-03

Title Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study

SIGNATURES (ELECTRONICALLY OBTAINED)

Meaning of Signature:	Signed by:	Date signed: (GMT)
Author-Trial Clinical Monitor		1/11/2013 12:19:33
Author-Team Member Medicine		1/11/2013 12:23:47
Author-Trial Statistician		1/11/2013 13:04:10
Approval-Therapeutic Area		1/11/2013 14:08:30
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SIGNATURE INFORMATION (continued)

Document 1302-0001--protocol-revison-02

Document No.: U12-1288-03

Title Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study

SIGNATURES (ELECTRONICALLY OBTAINED)
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Clinical Trial Protocol

Doc. No.: U12-1288-032

BI Trial No.:	1302.1
BI Investigational Product(s):	BI 695502
Title:	Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 01 and 02)
Version and Date:	**Version: 32.0** **Date: 11 Jan 2013~~26 Nov 2012~~**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 695502			
Protocol date: 27 Mar 2012	**Trial number:** 1302.1		**Revision date:** **11 Jan 2013~~26 Nov 2012~~**
Title of trial:	Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study		
Co-ordinating Investigator			
Trial sites:	Multi-center trial in two clinical sites in one country.		
Clinical phase:	I		
Objective(s):	The primary objective of this study is to establish pairwise pharmacokinetic similarity between BI 695502, Avastin®, US origin and Avastin®, EU origin following one intravenous infusion. The secondary objective of this study is to evaluate safety of BI 695502 and bevacizumab (Avastin®) US and EU origin and other pharmacokinetic parameters.		
Methodology:	This is a randomized, single-blind, parallel-arm, single-dose, active-comparator study. The trial will consist of three parallel arms of BI 695502, bevacizumab (US-origin Avastin®), and bevacizumab (EU-origin Avastin®) with pairwise comparisons between each of the arms.		
No. of subjects:	Up to approximately 180 subjects will be enrolled (90 subjects in Stage 1; 90 subjects in Stage 2, if applicable)		
total entered:	Subjects with evaluable data		
each treatment:	• BI 695502/concentrate for solution for infusion - approximately 60 subjects (30 subjects in Stage 1 and 30 in Stage 2, if applicable) • Bevacizumab (Avastin®) / solution for intravenous infusion, US source - approximately 60 subjects (30 subjects in Stage 1 and 30 subjects in Stage 2, if applicable) • Bevacizumab (Avastin®) / concentrate for solution for infusion, EU source - approximately 60 subjects (30 subjects in Stage 1 and 30 subjects in Stage 2, if applicable) The first six subjects will be dosed over 6 days (i.e., 1 subject per day) and each subject will be required to remain in the trial center for 48 hours after dosing (overnight) for safety observations. At least one subject will receive BI 695502.		
Diagnosis :	Healthy male subjects		

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 695502			
Protocol date: 27 Mar 2012	**Trial number:** 1302.1		**Revision date:** **11 Jan 2013~~26 Nov 2012~~**

Main criteria for inclusion:	Healthy male subjects, aged 21 to 50 years, body weight 65 to 95 kg, and BMI ≤ 30 kg/m^2
Test product(s):	BI 695502/concentrate for solution for infusion
dose:	1 mg/kg
mode of admin.:	Intravenous infusion
Comparator products:	Bevacizumab (Avastin®)/solution for intravenous infusion, US source
dose:	1 mg/kg
mode of admin.:	Intravenous infusion
	Bevacizumab (Avastin®)/concentrate for solution for infusion, EU source
	1 mg/kg
	Intravenous infusion
Duration of treatment:	This study will have a screening period of up to 28 days. The subject will check-in to the study center on Day -1 and be resident until the Day 3 discharge procedures are complete. All patients will remain hospitalized for 48 hours after dosing but can be discharged after 24 hours at investigator´s discretion. The subject will then return to the clinic for 9 ambulatory visits (Days 5, 8, 15, 22, 36, 50, 64, 78, and 99 End of trial).

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 695502			
Protocol date: 27 Mar 2012	**Trial number:** 1302.1		**Revision date:** **11 Jan 2013~~26 Nov 2012~~**
Criteria for pharmacokinetics:	The primary pharmacokinetic endpoint for assessment of pharmacokinetic similarity is the following: • Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) The following secondary pharmacokinetic parameters will be evaluated: • Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable data point (AUC_{0-tz}) • Maximum measured concentration of the analyte in plasma (C_{max})		
Criteria for safety:	Physical examination, vital signs (blood pressure and pulse rate), temperature, weight, 12-lead electrocardiogram, laboratory tests, concomitant medications, and adverse events.		
Statistical methods:	The trial will be performed as a two-stage group sequential design with Pocock boundaries. At interim analysis, after approximately 50% of subjects are evaluable, an early look for similarity, will be performed. The alpha levels for the interim look and the final look are both given as 6.07% (two-sided) based on an overall (two-sided) alpha of 10%. This is equivalent to comparing the 93.93% two-sided confidence interval for the ratio of the geometric means with the boundaries of 0.80 and 1.25. The trial will be stopped at interim analysis for early similarity if the confidence intervals for $AUC_{0-\infty}$ are within these boundaries for all three comparisons (BI 695502 versus EU-sourced Avastin®, BI 695502 versus US-sourced Avastin®, and EU versus US-sourced Avastin®). Stopping after interim of a single arm is possible if both comparions for the investigated arm already show early similarity. The trial will be considered positive at final analysis if the confidence intervals for $AUC_{0-\infty}$ are within these boundaries for all three comparisons (BI 695502 versus EU-sourced Avastin®, BI 695502 versus US-sourced Avastin® and EU versus US-sourced Avastin®). Descriptive statistics for safety (e.g., vital signs, laboratory values, and adverse events) and pharmacokinetic parameters will be calculated. The statistical model for the analysis of pharmacokinetics similarity will be an analysis of variance on the logarithmic scale, including following sources of variation: 'treatment' and 'weight'. All effects will be considered as fixed. Based on the residual error from analysis of variance, two-sided confidence intervals for the inter-subject ratio will be calculated.		

FLOW CHART 1.1 SCHEDULE OF ASSESSMENTS

	Screening[1]		**Study period**											**End of study**[2]
Visit	1		2											3
Day	-28 to -2	-1	1	2	3	5	8 (±2)	15 (±2)	22 (±2)	36 (±2)	50 (±2)	64 (±2)	78 (±2)	99 (±2)
Informed consent	X													
Assessment of eligibility	X	X												
Demographics	X													
Temperature	X	X	X											
Body height(only at screening), weight, and calculation of BMI	X	X												
Medical and surgical history	X													
Drug and virus screening[8]	X	X												
Physical examination[10]	X	X	X[3]	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X[4]	X	X	X	X	X	X	X	X	X	X	X
LABS/SAFETY ASSESSMENTS														
Laboratory tests (serum chemistry, hematology, and urinalysis)	X	X		X	X		X	X	X	X	X	X	X	X
12-lead ECG	X	X	X[5]	X	X			X		X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OTHER ASSESSMENTS														
Pharmacokinetics			X[6]	X	X	X	X	X	X	X	X	X	X	X

Trial period	**Screening[1]**		**Study period 1**											**End of study[2]**
Visit	1		2											3
Day	-28 to -2	-1	1	2	3	5	8 (±2)	15 (±2)	22 (±2)	36 (±2)	50 (±2)	64 (±2)	78 (±2)	99 (±2)
TRIAL MEDICATION														
Check-in		X												
Discharge[9]					X									
Randomization (predose)			X											
Administration of trial medication[7]			X											
Ambulatory visit						X	X	X	X	X	X	X	X	X
End of participation														X

BMI: body mass index; Con med: concomitant medication; ECG: electrocardiogram.
Note: Please refer to Appendix 10.2 for specific planned time points for safety and pharmacokinetic assessments

1. Screening within 28 days before drug administration and include subject information, signed informed consent, assessment of eligibility, demographics, medical and surgical history, drug and virus screening, physical examination, ECG, vital signs, body height, weight and calculation of BMI, laboratory/urinalysis, adverse event and concomitant medication recording.
2. End-of-study examination will be Day 99 and includes physical examination, temperature, vital signs, laboratory tests, ECG, and AEs/concomitant medication recording. For subjects who discontinue from the trial early, a complete end of study visit will be performed.
3. Predose.
4. Predose and at 1, 2, 3, 4, 5, and 6 hours postdose.
5. ECG performed at end of infusion, 2, and 8 hours after start of infusion.
6. Pharmacokinetic samples to be taken predose, just before end of infusion 2, 4, and 8 hours after start of infusion.
7. Infusion for all BI 695502 and comparators will be 30 minutes.
8. Drug screening: cannabis, benzodiazepine, barbiturates, opiates, cocaine, amphetamines, and methadone. Virus screening: Hepatitis B, hepatitis C, and HIV. Virus screening only at screening.
9. All patients will remain hospitalized for 48 hours after dosing but can be discharged after 24 hours at investigator´s discretion. Patients discharged on Day 2, must return to the site on Day 3.
10. Symptom directed physical examination as clinically indicated on Day 2 to Day 78.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to time of the last quantifiable data point
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
C_{max}	Maximum measured concentration of the analyte in plasma
CRA	Clinical Research Associate
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Coefficient of variation
δ	Biosimilarity margin
DILI	Drug-induced liver injury
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDTA	Ethylendiaminetetraacetic acid
ELISA	Enzyme linked immunosorbent assay
EU	European Union
GCP	Good Clinical Practice
Hep B	Hepatitis B
Hep C	Hepatitis C
HIV	Human immunodeficiency virus
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
iv	Intravenous
mAb	Monoclonal antibody
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetic(s)
RDC	Remote Data Capture

SAE	Serious adverse event
SOP	Standard operating procedure
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Vascular endothelial growth factor (VEGF) is a key angiogenic factor mediating tumor angiogenesis. Multiple studies have described increased VEGF levels in a variety of human cancers and the VEGF expression levels have been correlated with poor survival (R10-4862, R12-0947, R12-0948).

Bevacizumab (Avastin®) is a therapeutic humanized monoclonal antibody (mAb) specific for VEGF exerting its pharmacologic antiangiogenesis effect by binding to and neutralizing VEGF, thereby blocking its signal transduction through VEGF receptors (R12-1012). This has been demonstrated in vitro through antibody inhibition of several late-phase VEGF-dependent vascular endothelial cell functions such as proliferation, migration, and survival.

Bevacizumab (Avastin®) has shown antitumor activity and clinical benefit in combination with chemotherapy in metastatic colorectal cancer, metastatic breast cancer, advanced non-small cell lung cancer, and ovarian cancer (R12-0939, R12-0971). Furthermore, clinical benefit was reported with the combination of bevacizumab and interferon in renal cell cancer (R12-0939, R12-0971) or as a single agent in glioblastoma (R12-0971).

BI 695502 is being developed as a proposed biosimilar to bevacizumab.

1.2 DRUG PROFILE

BI 695502 is a genetically engineered humanized mAb directed against human VEGF that selectively binds all isoforms of VEGF and neutralizes VEGF's biologic activity through a steric blocking of the binding of VEGF to its receptors on the surface of the endothelial cells, on tumor cells and autocrine and paracrine loops.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 695502 is being developed as a biosimilar to bevacizumab (Avastin®), which is planned to meet the need for alternatives to high-priced biologic agents in oncology treatments. The planned clinical development follows the currently understood concepts from published guidance documents and statements from regulatory authorities for biosimilar mAb development. The general approach is to demonstrate sequentially a high degree of similarity (i.e., statistical similarity) between the biosimilar and originator compound, first in PK and subsequently for efficacy. While also demonstrating a high degree of similarity (but not necessarily powered for statistical similarity) for safety and immunogenicity.

As such, trial 1302.1 is the stepping stone for successful clinical development of BI 695502 as it aims to establish PK similarity of BI 695502 to bevacizumab (Avastin®) originator compounds and will assess initial safety of BI 695502 in healthy subjects.

Since the PK of Avastin® is linear for doses ≥ 1 mg, the dose of 1 mg/kg of BI 695502 and bevacizumab (Avastin®) is the lowest dose that can allow PK extrapolation for the standard clinical dose.

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

2.2 TRIAL OBJECTIVES

2.2.1 Primary objective

The primary objective of this study is to establish pairwise PK similarity between BI 695502, Avastin®, US origin and Avastin®, EU origin following one iv infusion.

2.2.2. Secondary objectives

The secondary objective of this study is to evaluate safety of BI 695502 and bevacizumab (Avastin®) US and EU origin and other pharmacokinetic parameters.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of this new drug.

Healthy subjects who participate in study 1302.1 may be exposed to:

- The risks of the study procedures;

- The known risks related to the exposure with the study medications (tested drug and comparator drugs) ; and
- The unknown risks that might be related to the exposure with the study medication.

Procedure-related risks

The use of an indwelling cannula for the purpose of drug administration and blood sampling may be accompanied by mild bruising and in rare cases, by transient inflammation of the wall of the vein. After initial irritation, the presence of an indwelling cannula is usually painless and hardly noticeable. The same applies to vein puncturing for further blood sampling. In rare cases, a nerve might be injured while inserting the cannula. This could be followed by paresthesia, reduced sensibility, and/or pain.

Drug-related risks and safety measures

Based on safety data from over 3,500 patients with various malignancies, predominantly treated with Avastin® in combination with chemotherapy in clinical trials, the most frequently reported side effect were hypertension, proteinuria, fatigue, diarrhea, and abdominal pain. The serious adverse events (SAEs) were gastrointestinal perforation, hemorrhage, and arterial thromboembolism (R12-0939).

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin® therapy are likely to be dose-dependent.

The subject's risk will be minimized in this trial by:

- Using a low dose of Avastin® or BI 695502;
- Implementing conservative eligibility criteria; and
- Close monitoring in a Phase I study center for the first 48 hours after drug administration. Subjects will also be followed during out-patient ambulatory visits. The ambulatory visits will occur on Days 5, 8, 15, 22, 36, 50, 64, 78, and 99 and will allow for collection of safety signs and symptoms that may occur or arise following study treatment.

In addition, the first six subjects will be dosed in a sequential manner (i.e., 1 subject per day). At least one subject will receive BI 695502.

Adverse events and vital sign data will be collected throughout the trial and subjects will be monitored for safety outcomes over a prolonged period of time. Physical examinations are performed at every visit. Special attention will be given to assessment of potential drug-induced liver injury (DILI).

Although rare, a potential for DILI is under constant surveillance by sponsors and regulators. Therefore, this study will require timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure subjects´ safety.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study. Subjects will be randomly allocated to one of three treatment groups.

The treatments will be single dose of 1-mg/kg BI 695502/concentrate for solution for infusion: 1-mg/kg bevacizumab (Avastin®), US source/solution for intravenous infusion; or 1-mg/kg bevacizumab (Avastin®), EU source/concentrate for solution for intravenous infusion.

The first six subjects will be dosed over 6 days (i.e., 1 subject per day) and each subject will be required to remain in the trial center for 48 hours after dosing (overnight) for safety observations. At least one subject will receive BI 695502. This study will occur in two stages:

Stage 1 – 90 subjects (30 per treatment group)

Stage 2 – 90 subjects (30 per treatment group)

An interim analysis will be conducted and if the pre-specified criteria for early PK biosimilarity are achieved then the study may be stopped. It is also possible that a single arm is going to be stopped based on the chosen boundaries and the interim results. This is the case if both comparisons for the specific arm show an early similarity. If any comparison does not show early similarity then the trial will proceed to Stage 2.

3.1.1 Administrative structure of the trial

A data monitoring committee (DMC) will be appointed to periodically assess the trial data to ensure overall safety and integrity of the trial. Details of the DMC responsibilities will be described in the DMC charter.

Inclusion of subjects in the trial may be stopped temporarily after the assigned number of subjects for Stage 1 has been randomized. Inclusion might be restarted in case the interim analysis fails to show early PK biosimilarity.

Decisions on trial termination, amendment, or cessation of subject recruitment, based on safety or outcome findings, can be made upon agreement after recommendations from the DMC.

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

This is a randomized, single-blind, single-dose, parallel-arm, two-stage, active-comparator study to investigate the PK and safety of BI 695502, and to establish PK similarity of BI 695502 to bevacizumab (Avastin®), as US and EU source in healthy, male subjects.

Subjects will be enrolled in two sites in New Zealand. Each of the three arms (BI 695502 and bevacizumab [Avastin®], as US and EU source) will include approximately 60 subjects (totaling approximately 180 subjects), which is considered sufficient for PK testing.

Subjects will be randomized in a 1:1:1 ratio to receive BI 695502, bevacizumab (Avastin®) as US source, or bevacizumab (Avastin®) as EU source. Randomization minimizes selection bias between the treatment groups. Note that for Stage 2 it might be possible that one of the arms will be stopped for early similarity and therefore the ratio might change to 1:1 for the remaining arms. The parallel-group, active-comparator design takes into account the safety of the healthy subjects.

The trial bioanalyst as well as the trial pharmacokineticist will be blinded until final database lock to the origin of the PK samples to maintain objectivity.
The investigator and other sponsor representative will not be blinded to be able to follow the safety data of the subjects randomized into the trial.

A DMC will periodically assess the trial data as described in Section 3.1.1.

3.3 SELECTION OF TRIAL POPULATION

It is planned that up to a maximum of 180 healthy, male subjects will be randomized ~~enrolled~~ in~~to~~ th~~e~~is study (see Section 7.6).

This study will be performed in healthy subjects since this population **is most sensitive** to product differences. A healthy subject population may provide greater sensitivity to detect differences in PK profiles, as there are no underlying factors, e.g., tumor burden, which may affect the PK results.

Bevacizumab is used in the clinic mostly in combination with chemotherapy agents in treatment of solid tumors. Avastin® can be used at a low dose of 5 mg/kg every 2 weeks or 10 mg/kg every 3 weeks (dose intensity of 2.5 mg/kg/week) or at a high dose of 7.5 mg/kg every 2 weeks or 15 mg/kg every 3 weeks (dose intensity of 5 mg/kg/week). The most frequent side effects reported with bevacizumab given at this dose were hypertension, fatigue, diarrhea, and abdominal pain. Proteinuria is also a common laboratory change reported with Avastin®.

Analysis of the safety data suggests that the occurrence of hypertension and proteinuria with Avastin® therapy are likely to be dose-dependent (R12-0939).

Based on the safety profile of Avastin® (side effect dose-dependency and cumulative toxicity) it is expected that the proposed single and low dose (1 mg/kg) will be well tolerated with no or limited and mild side effects.

A log of all subjects entered into the trial (i.e., having given informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with the study medication or not.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy male subjects according to the criteria listed in Section 3.3.2 and 3.3.3.

3.3.2 Inclusion criteria

Healthy males according to the following criteria:

1. Complete medical history, including physical examination, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), and clinical laboratory tests;

2. Aged 21 to 50 years;
3. Body mass index (BMI) ≤ 30;
4. Body weight of 65 to 95 kg, inclusive;
5. Signed and dated written informed consent prior to admission to the study in accordance with GCP and the local legislation;

3.3.3 Exclusion criteria

Healthy males according to the following criteria:

1. Any finding of the medical examination (including blood pressure, pulse rate, and ECG) deviating from normal and of clinical relevance;
2. Any evidence of a clinically relevant concomitant disease, as judged by the investigator, including gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, hormonal disorders, or diseases of the central nervous system (such as epilepsy), psychiatric disorders, or neurological disorders;
3. History of relevant orthostatic hypotension, fainting spells, or blackouts;
4. Chronic or relevant acute infections. A negative result for human immunodeficiency virus (HIV), Hepatitis B (Hep B), and Hepatitis C (Hep C) testing is required for participation;
5. History of relevant allergy/hypersensitivity (including allergy to the study medications or its excipients);
6. Intake of prescribed or over-the-counter drugs within less than six half-lives of the respective drug prior to study drug administration or during the trial;
7. Participation in another trial with a study medication within two months prior to administration or during the trial (six half-lives);
8. Smoker (> 10 cigarettes or > 3 cigars or > 3 pipes/day);
9. Inability to refrain from smoking during days of confinement at the study center;
10. Current alcohol abuse as judged by the investigator;
11. Current drug abuse, as judged by the investigator;
12. Blood donation (more than 100 mL within four weeks prior to administration or during the trial);
13. Participation in collision sports (e.g. ice hockey, rugby etc.)
14. Any out-of-range laboratory values considered clinically significant by the investigator;
15. Subject considered unsuitable for inclusion by the investigator (e.g., inability to understand and/or comply with study requirements or presence of any condition which, in the opinion of the investigator, would not allow safe participation in the study);

Exclusion criteria specific for this study include:

16. Hypertension or relevant family history of hypertension, as judged by the investigator;
17. Major injuries and/or surgery or bone fracture within 4 weeks of trial inclusion, or planned surgical procedures during the trial period. Intended participation in collision sports during the study;

18. Less than 15 weeks from previous dosing of a mAb;
19. History of hemorrhagic or thromboembolic event;
20. Known inherited predisposition to bleeding or to thrombosis.
21. Pre-existing proteinuria

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

- The subject withdraws consent, without the need to justify a decision;
- The subject has to take any concomitant drugs interfering with the study medication; and
- The subject is no longer able to participate for other medical reasons (e.g., surgery, AEs, or other diseases).

A subject can be withdrawn after discussion between the sponsor and the investigator if eligibility criteria are being violated or if the subject fails to comply with the CTP (e.g., non-attendance at study assessments, incomplete, missing or wrong trial drug administration).

If a subject is withdrawn from the study prior to the randomization, the data of this subject will not be entered in the trial database and not be reported. The only exception to this rule is when the subject has a serious or significant AE. If a subject discontinues or withdraws from the study thereafter, this will be documented and the reason for withdrawal will be recorded in the electronic Case Report Forms (eCRFs), the data will be included in the trial database and will be reported. At the time of discontinuation, a complete end-of-study evaluation will be performed, if possible, and the information will be recorded in the eCRFs. Those withdrawals will be discussed in the final Clinical Trial Report (CTR).

Subjects who are enrolled in the trial and do not fulfill the inclusion / exclusion criteria or have inadequate number PK samples performed will be replaced for each stage, separately. For Stage 1, in case less than 90 subjects (30 per treatment group) complete the trial, the investigator, together with the trial pharmacokineticist and trial statistician, will decide if and how many subjects will be replaced. Similarly, subjects might be replaced for Stage 2, if applicable. Each subject will have a unique study subject number, including replacing subjects. Replacement subjects will be assigned the next available randomization number from the randomization list.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular trial site;
2. Emergence of any efficacy / safety / toxicological information that could significantly affect continuation of the trial;
3. Violation of GCP, the CTP, or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial; or

4. The recommendation of the DMC that would require discontinuation of the trial including stopping for early PK biosimilarity.

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of Boehringer Ingelheim investigational product and comparator product(s)

Details of the trial medication are provided in Table 4.1.1: 1.

Table 4.1.1: 1 Study medications

Trial medication	Dosage form (concentration)	Manufacturer
BI 695502, clear to slightly opalescent, colorless to slightly yellow, sterile, pH 6.2 concentrate for solution for infusion	Concentrate for solution for infusion (25 mg/mL)	Boehringer Ingelheim Pharma GmbH & Co KG, Germany
Bevacizumab (Avastin®), US source, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion	Solution for intravenous infusion (25 mg/mL)	Genentech, Inc.
Bevacizumab (Avastin®), EU source, clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 concentrate for solution for infusion	Concentrate for solution for infusion (25 mg/mL)	Roche Pharma AG

The pharmacist will use the appropriate aseptic technique. He/she will inspect the drug and look for particulate matter and discoloration prior to administration to the subject, if the solution and container permit such inspection. The necessary amount of study medication will be withdrawn and diluted in 0.9% of sodium chloride. Standard of concentration is 1.4 mg/ml. The volume to be administered for each subject will be calculated based on the subject's weight respecting the recommended concentration of 1.4 mg/ml. If any solution remains in the vial, the vial and solution will be discarded, as the product does not contain preservatives (R12-0939, R12-0971).

4.1.2 Method of assigning subjects to treatment groups

The allocation process of subjects to one of the three treatment groups per the randomization list (see Section 7.5 for details) is performed on Day 1 prior to administration of the study drug. The list of subject and medication numbers will be provided to the trial site in advance. Once a subject number has been assigned, it cannot be reassigned to any other subject. (The same applies for randomization numbers).

4.1.3 Selection of doses in the trial

Bevacizumab (Avastin®) is approved for the below indications (R12-0939, R12-0971):

- Metastatic colorectal cancer;
- Metastatic breast cancer (EU only);
- Metastatic or recurrent non-small cell lung cancer;
- Advanced and/or metastatic renal cell cancer;
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer (EU only); and
- Glioblastoma (US only).

Avastin® can be used at a low dose of 5 mg/kg every 2 weeks or 10 mg/kg every 3 weeks (dose intensity of 2.5 mg/kg/week) or at a high dose of 7.5 mg/kg every 2 weeks or 15 mg/kg every 3 weeks (dose intensity of 5 mg/kg/week).

The primary focus of this trial is to demonstrate the similarity of BI 695502 with the approved reference products, bevacizumab (Avastin®), as US and EU source.

During the treatment period, each subject will receive a single 1-mg/kg iv infusion of the drug to which they are randomized. It has been observed that the PK of bevacizumab is dose-independent, except for doses < 1 mg/kg. The PK of bevacizumab appears to be linear over the dose range 1 to 10 mg/kg (R12-1012). As bevacizumab or BI 695502 is to be administered to healthy subjects, the lowest possible dose in the linear PK range is the appropriate dose for the PK similarity comparison.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are as outlined in Table 4.1.4: 1 below:

Table 4.1.4: 1 Treatments in single administration

Treatment	Substance	Formulation	Total dose
1	BI 695502	Concentrate for solution for infusion	1 mg/kg
2	bevacizumab (Avastin®), US source	Solution for intravenous infusion	1 mg/kg
3	bevacizumab (Avastin®), EU source	Concentrate for solution for infusion	1 mg/kg

On Day 1 of Visit 2, the medication will be administered as a single dose of 1 mg/kg as a 30-minute iv infusion in the supine position under the supervision of the investigator or designee. Subjects will be kept under close medical surveillance until up to 48 hours following drug administration. Days 5 to 99 will be performed in an ambulatory fashion.

This trial is a three parallel-arm study. All subjects will be randomized to BI 695502, bevacizumab (US-origin Avastin®), or bevacizumab (EU-origin Avastin®).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This will be a single-blind study. Additionally, the trial bioanalyst as well as the trial pharmacokineticist will be blinded to the origin of PK samples to maintain objectivity.

4.1.5.2 Procedures for emergency unblinding

Not applicable.

4.1.6 Packaging, labeling, and re-supply

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

Resupply is planned once decision of the Stage 2 recruitment is made.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging under the recommended storage conditions (light protected, between +2 and +8°C) and should not be frozen or shaken.

4.1.8 Drug accountability

Drug supplies, which will be provided by the sponsor, must be kept in a secure, limited-access storage area under the storage conditions defined by the sponsor. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The site pharmacist will receive the study medications delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study CTP by the Institutional Review Board (IRB) / ethics committee;
- Availability of a signed and dated clinical trial contract between the sponsor and the head of trial center;
- Approval / notification of the regulatory authority (e.g., competent authority);
- Availability of the curriculum vitae of the investigator;
- Availability of a signed and dated CTP or immediately imminent signing of the CTP; and
- Availability of the proof of a medical license for the investigator, as necessary.

The investigator and / or delegate must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s).

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the study medication and trial subjects. The investigator / delegate will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all study medication received from the sponsor. At the time of return to the sponsor, the investigator / delegate 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 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

Primarily, no concomitant therapy will be allowed. However, in case of AEs in need of treatment, symptomatic therapy according to the judgment of the investigator will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the eCRFs.

In the case of AEs the subjects will be treated, as necessary and as appropriate kept under constant supervision in the clinical unit or transferred to a hospital until such time that all the results of the evaluations have returned to a medically-acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Primarily, no concomitant therapy will be allowed (see Section 4.2.1).

4.2.2.2 Restrictions on diet and life-style

Subjects should abstain from smoking and alcoholic beverages 48 hours prior to the study medication administration until day 8. After that smoking is allowed (< 10 cigarettes or < 3 cigars or < 3 pipes/day). No more than 2 units of alcohol and per day are allowed until the end of study.

In addition, subjects should abstain from alcoholic beverages for 24 hours prior to further study visits.

Participation in collision sport (e.g., ice-hockey, rugby etc.) should be avoided during the course of the study.

4.3 TREATMENT COMPLIANCE

Subjects who are non-compliant (e.g., they do not appear for assessments or violate the restrictions), may be withdrawn from the trial and the eCRF will be completed accordingly (for further procedures see Section 6.2).

Compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee at the investigational sites in New Zealand. The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

Efficacy measurements will not be performed.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

All safety parameters will be evaluated descriptively and based on the investigations described below.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a subject in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

An SAE is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs subject hospitalization, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

The intensity of AEs should be classified and recorded according to the Common Terminology Criteria for Adverse Events version 4 in the eCRF.

Causal relationship of adverse event

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

Yes: There is a reasonable causal relationship between the study medication administered and the AE.
No: There is no reasonable causal relationship between the study medication administered and the AE.

If an SAE is reported from a still-blinded trial, the causal relationship must be provided by the investigator for all potential trial drugs (i.e., BI 695502, bevacizumab US and EU source).

Worsening of the underlying disease or other pre-existing conditions

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

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

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

Protocol-specified significant events

The following are considered as CTP-specified significant events:

- Gastrointestinal perforation (if the grade is ≥ 3);
- Wound healing complications (if the grade is ≥ 3);
- Hemorrhage - severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, and central nervous system hemorrhage (if the grade is ≥ 3);
- Hepatic injury defined by the following alterations of liver parameters:
- For subjects with normal liver function at baseline: an elevation of aspartate aminotransferase and/or alanine transaminase ≥ 3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample; and
- Subjects showing these laboratory abnormalities need to be followed up according to Section 10.1.2 of this CTP and the "DILI checklist" provided in remote data capture (RDC).

Protocol-specified significant events are to be reported in an expedited manner similar to SAEs, even if they do not meet any of the seriousness criteria – for details see Section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All AEs, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the observational phase) will be collected, documented, and reported to the sponsor by the investigator on the appropriate eCRFs / SAE reporting forms. After the end of study evaluation all SAEs related to trial medication and/or trial design have to be reported by the investigator. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

For each AE, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

If not stipulated differently in the ISF, the investigator must report the following events using the paper SAE form via telephone / fax immediately (within 24 hours or the next business day whichever is shorter) to the sponsor: SAEs and non-serious AEs occurring at the same time as an SAE and/or which are medically related to the SAE(s), and CTP-specified significant events.

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

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

The SAE form is to be forwarded to the defined unique entry point (country-specific contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or protocol-specified significant events becomes available.

5.2.3 Vital signs

Blood pressure and pulse rate will be measured at the time points described in the Flow Chart 1.1.

Systolic and diastolic blood pressure, as well as pulse rate will be measured by means of a validated automated blood pressure monitor after subjects have rested for 5 minutes in the supine position. All recordings should be made using the same type of blood pressure recording instrument of the same arm, if possible.

5.2.4 ECG (12-lead resting ECG)

The 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded for a 10-second duration using (site will use GE Dash 3000 and site will use Marquette MAC3500) a validated ECG machine. Electrode placement will be performed according to the American Heart Association guidelines.

Electrocardiograms will be recorded at the time points indicated in the Flow Chart 1.1 after the subjects have rested for at least 5 minutes in a supine position.

The ECGs will be evaluated by the study investigator or qualified designee. The automatic algorithm analysis (built into the ECG machines) will assist in evaluating the exclusion criteria and an immediate safety assessment during the screening and course of the study. The ECGs may be repeated for quality reasons. Additional ECGs may be collected by the investigator for safety reasons. Clinically relevant abnormal findings will be reported as AEs.

5.2.5 Clinical and laboratory tests

A total amount of 125 mL blood will be taken per subject during the whole course of the study for laboratory parameters. This amount may be exceeded if unscheduled (additional) monitoring of laboratory results is warranted.

Blood samples for the laboratory parameters will be taken in the fasting state at the time points indicated in the Flow Chart 1.1.

The parameters that will be determined are listed in Tables 5.2:5: 1 and 5.2.5: 2. The respective reference ranges will be provided in the ISF, (see Flow Chart 1.1 for time points of laboratory blood sampling).

The laboratory tests listed in Tables 5.2:5: 1 and 5.2.5: 2 will be performed at the site's local laboratory in New Zealand.

Urine sediment analysis will only be performed if there is a clinically significant positive finding on the urinalysis at investigator´s discretion. The tests listed in Table 5.2.5: 2 constitute exclusionary laboratory safety tests. These tests may be repeated, as required. The results will not be included in the CTR. To encourage compliance, a standard breath alcohol test (the detailed make and model is documented in the ISF) may be performed at any time during the study at the discretion of the investigator or designee. The results will not form part of the CTR.

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

Table 5.2.5: 1 Routine laboratory tests

Category	Test name
Hematology	Hematocrit Hemoglobin Red blood cell count / Erythrocytes White blood cells / Leucocytes Platelet count / Thrombocytes
Diff automatic	Neutrophils (absolute count) Eosinophils (absolute count) Basophils (absolute count) Monocytes (absolute count) Lymphocytes (absolute count)
Coagulation (performed at screening, baseline (Day -1 to Day 1 predose), end of study, and at the investigator's discretion)	Partial thromboplastin time Prothrombin time (Quick and international normalized ratio) Fibrinogen
Enzymes	Aspartate aminotransferase Alanine aminotransferase Alkaline phosphatase Creatine kinase Creatine kinase-MB if creatine kinase is elevated Gamma-glutamyl transferase Lactic dehydrogenase Pancreatic amylase
Substrates[1,]	Glucose Creatinine Bilirubin total Bilirubin direct Protein, total Albumin, total C-Reactive protein Uric acid Cholesterol, total Triglycerides
Electrolytes[1]	Calcium Sodium Potassium
Urinalysis[1] (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine red blood cells/Erythrocyte Urine white blood cells/Leukocytes

Table 5.2.5: 1 Routine laboratory tests (continued)

Category	Test name
Urinalysis[1] (Stix)	Urine pH
Urine sediment[1] (microscopic examination) *(if urine analysis abnormal)*	Urine sediment bacteria Urine cast in sediment Urine squamous epith cells Urine sediment red blood cell /Erythrocytes Urine sediment white blood cell/Leucocytes

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

[1] Substrates, electrolytes, and urine analysis / sediment only at screening and end of study (all portions) and at baseline (Day -1 to Day 1 predose).

The following tests will be performed only at the screening examination; the results will not be part of the CTR.

Table 5.2.5: 2 Exclusionary testing

Category	Test name
Drug screening (Urine)	Cannabis Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Methadone
Infectious serology	Hep B surface antigen (qualitative) Hep B HBc antibody (qualitative) Hep C antibodies (qualitative) HIV-1 and HIV -2 antibody (qualitative)

5.2.6 Medical examination

A medical examination will be carried out within 28 days before the study (screening), at check-in on Day -1, and on Day 99 for each subject. At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics, relevant medical and surgical history, review of inclusion / exclusion criteria, review of vital signs (blood pressure and pulse rate), temperature, height, weight, and calculation of BMI, 12-lead ECG, laboratory assessments, drug and virus screening, and a physical examination. On Day -1, the medical examination will include review of inclusion / exclusion criteria, drug screening, physical examination, vital signs (blood pressure and pulse rate), laboratory assessments, 12-lead ECG, temperature, body weight,, and calculation of BMI. At the end-of-study examination, it will include review of vital signs, 12-lead ECG,

laboratory assessment, and a physical examination. Adverse events and concomitant therapies will be assessed throughout the study.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine PK parameters in an appropriate way.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

The date and exact clock time of administration as well as PK sampling times must be recorded.

Exact time points of plasma sampling will be documented in the eCRFs by the medical personnel or sent as electronic files. These actual sampling times will be used for determination of PK parameters.

5.5.1 Pharmacokinetic endpoints

PRIMARY ENDPOINT

The primary PK endpoint for assessment of PK similarity is the following:

- Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$)

SECONDARY ENDPOINTS

The following secondary PK parameters will be evaluated:

- Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the time of the last quantifiable data point (AUC_{0-tz})
- Maximum measured concentration of the analyte in plasma (C_{max})

5.5.2 Methods of sample collection

A total amount of 125-mL blood will be taken per subject during the whole course of the study for PK purposes.

For quantification of BI 695502 and bevacizumab plasma concentrations, 2.7 mL of blood will be collected from a forearm vein in a K_3-ethylendiaminetetraacetic acid (EDTA)-anticoagulant blood drawing tube at time points indicated in Appendix 10.2. For the early time points after drug administration, the PK samples should be obtained from the forearm not used in the BI 695502 or bevacizumab iv administration. Immediately after blood sampling the drawing tubes will be transferred into an ice bath until centrifugation.

The EDTA-anticoagulated blood samples will be centrifuged within 30 minutes after collection (intermittent storage in ice water or on ice). Centrifugation will last for approximately 10 minutes at 2000 to 4000 x g at 4 to 8°C. Ethylenediaminetetraacetic acid plasma will be transferred into two appropriately-labeled cryotubes (2 to 3-mL polypropylene cryovials with flat bottom and screw caps; e.g., Nunc #368632), each to contain 0.5 mL of plasma. Plasma samples will be stored at approximately -20°C or below until shipped to the analytical laboratory. Initially, only one aliquot will be shipped to the analytical laboratory.

The second aliquot will be stored at approximately -20°C or below at the investigational site and shipped only if requested by the analytical laboratory.

Plasma concentrations of BI 695502 and bevacizumab will be measured using a sandwich enzyme linked immunosorbent assay (ELISA) method.

After completion of the study, plasma samples may be used for further methodological investigations (e.g., for stability testing). However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but no later than 3 years after the final CTR has been signed.

Additional samples for bioanalytical purposes:

In order to assess the stability of BI 695502 in whole blood, one additional blood sample will be taken from the first eight subjects of each dose group.

2.7 mL of blood will be taken in a K_3-EDTA-anticoagulant blood drawing tube at the time point: 24 hours (planned time, immediately after the drawing of a regular blood sample i.e., no additional venous puncture will be necessary). The EDTA-anticoagulated blood will be split into two aliquots:

- One aliquot will be centrifuged within 30 minutes after collection. Centrifugation will last for about 10 minutes (at approximately 2000 to 4000 x g at 4 to 8°C, and the resulting plasma will be transferred into a polypropylene cryotube (e.g., Nunc #368632).

- The second aliquot will be stored for about 4 hours at room temperature and ambient light conditions (documentation of storage time necessary) and then centrifuged. Centrifugation will last for about 10 minutes (at about 2000 to 4000 x g at 4 to 8°C), and the resulting plasma will be transferred into a polypropylene cryotube (e.g., Nunc #368632).

The aliquots should be labelled with the following information: study number, subject number, planned time, “BA-sample”. Until transfer to the analytical laboratory, both aliquots will be stored at approximately -20°C or below at the clinical site. Both aliquots will be provided to the responsible bioanalyst together with the information about sample handling (i.e., storage time of “sample” at room temperature).

The results of the stability investigation will be documented in the corresponding method validation project but will not be included in the CTR.

5.5.2.1 Urine sampling for pharmacokinetic analysis

This section is not applicable.

5.5.3 Analytical determinations

Plasma concentrations of bevacizumab of US origin, bevacizumab of EU origin, and BI 695502 will be quantitated using a validated sandwich ELISA.

5.6 BIOMARKER(S)

Not applicable.

5.7 PHARMACODYNAMICS

Not applicable.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. Time windows are permitted as follows:

- General medical examination: at screening (1 to 28 days prior to the first study day) and at the end-of-study evaluation (Day 99);
- The tolerance for vital signs andECG will be ± 1 hour; and
- Study measurements and assessments scheduled to occur on Day 1 prior to drug administration have to be performed and completed within 2 hours prior to drug administration.

For planned individual plasma concentration sampling times refer to the Flow Chart 1.1. 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.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period (Day -28 to -1) - all subjects

After the subjects have been informed on the trial, all subjects will give their written informed consent in accordance with GCP and the local legislation prior to admission to the study. The subject's eligibility will be assessed and his demographic information and medical and surgical history will be recorded.

Each subject will have a physical examination, ECG, height, weight, calculation of BMI, temperature, and their vital signs will be recorded.

For the medical and laboratory examination, including drug and virus screening during the screening visit, see Sections 5.2.6 and 5.2.5.

Adverse events and concomitant mediations will start being recorded during this visit.

6.2.2 Study period

The subjects will be kept under close medical surveillance until discharge from the investigational site after formal assessment and confirmation of their fitness by the investigator or designee.

Subjects will be randomly allocated to the treatment as described in Section 4.1.2.

For details on time points for collection of plasma samples for PK analysis and all other trial procedures, see Flow Chart 1.1.

For details on time points for all other trial procedures, see Flow Chart 1.1.

Adverse events and concomitant medication will be evaluated continuously from the signing of the informed consent until the end-of-study examination.

6.2.3 End of trial

A review of vital signs, 12-lead ECG, laboratory assessments, temperature and a physical examination will be performed at the end-of-study evaluation (Day 99).

All clinically significant abnormal values (including laboratory parameters) will be followed up using the appropriate tests until a return to a medically acceptable level is achieved, as judged by the investigator and/or sponsor.

Adverse events and concomitant medication will be evaluated continuously from the signing of the informed consent until the end-of-study examination.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

7.1.1 Objectives

The objective of the current study is to establish the PK biosimilarity of BI 695502 compared to bevacizumab (Avastin®) US and EU source bevacizumab (Avastin®), US source and bevacizumab (Avastin ®), EU source, respectively, following one iv administration. A three-fold comparison will be performed (BI 695502 vs bevacizumab (Avastin®), US source, BI 695502 vs bevacizumab (Avastin ®), EU source, and bevacizumab (Avastin®), US source vs bevacizumab (Avastin ®), EU source).

7.1.2 Design

The study will be conducted according to a randomized, single-blind, single-dose, two-stage, parallel-arm, active-comparator design. Pharmacokinetic similarity will be determined by comparing BI 695502 and bevacizumab (Avastin®), US source, BI 695502 and bevacizumab (Avastin ®), EU source as well as bevacizumab (Avastin®), US source and bevacizumab (Avastin ®), EU source between subjects.

The trial will be performed in a two-stage design with Pocock boundaries for early stopping. The interim analysis will be performed when approximately 50% of the subjects are evaluable for the primary endpoint. A single treatment may be stopped at interim analysis if both comparisons where the treatment is involved in show an early significance. A stop of the whole trial based on the interim analysis results for early significance is possible.

Although a crossover design is viewed favorably for similarity trials, it was not chosen for this trial because of the long terminal half-life of the compound.

7.1.3 Endpoints

Pharmacokinetic similarity of BI 695502 and bevacizumab is to be determined on the basis of the primary PK parameter as displayed in Section 5.5.1.

The derivation of the PK parameters is given in Appendix 10.2.

Safety will be evaluated based on the investigations described in Section 5.2.

7.1.4 Model

The statistical model used for the analysis of the primary PK parameters will be an analysis of variance (ANOVA) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'treatment' and 'weight'. All effects will be considered as fixed. The model is described by the following equation:

$$y_{ij} = \mu + \tau_i + \xi_j + e_{ij},$$

where

y_{ij} logarithm of response measured on subject j receiving treatment i;

μ the overall mean;

τ_i the i^{th} treatment effect, i = 1, 2, 3;

ξ_j weight of the j^{th} subject; and

e_{ij} the random error associated with the j^{th} subject who received treatment i.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Pharmacokinetic similarity is established by using the average biosimilarity method to ensure that the ratio for treatments (of the respective PK parameter[s]) is contained within a pre-specified acceptance range (see below). This goal is accomplished by testing the below hypothesis on the log scale.

Null hypothesis H_0 (Non-similarity): $\mu_T - \mu_R \leq -\delta$ or $\mu_T - \mu_R \geq \delta$

(i.e., the difference of the means is either less than or equal to the lower bound or greater than or equal to the upper bound of the acceptance range),

Alternative hypothesis H_a (Similarity): $-\delta < \mu_T - \mu_R < \delta$

(i.e., the difference of the means is both greater than the lower bound and less than the upper bound of the acceptance range),

where

μ_T and μ_R are the means of the log-transformed measures for the two treatments (Test and Reference) under investigation,

and δ is the biosimilarity limit that defines the acceptance range for PK parameter(s) on the logarithmic scale.

In this trial, δ is taken to be ln(1.25). This translates to an acceptance range of 80% to 125% for the ratio of the geometric means for treatments on the original scale.

This hypothesis and its alternative can be decomposed into two one-sided null hypotheses, H_{01} and H_{02}, with their accompanying alternatives:

H_{01}: $\mu_T - \mu_R \leq -\delta$ vs. H_{a1}: $\mu_T - \mu_R > -\delta$

H_{02}: $\mu_T - \mu_R \geq \delta$ vs. H_{a2}: $\mu_T - \mu_R < \delta$

The test of the null hypothesis at the $\alpha = 0.05$ level is similar to carrying out two one-sided tests of the above null hypotheses each at the $\alpha = 0.05$ level of significance. The rejection of both null hypotheses H_{01} and H_{02} at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range. The α-level for the significance testing will be adjusted for considering multiple stages (i.e. looks) based on a Pocock boundary. Hence the confidence intervals considered at each analysis (interim and final) are the 93.93% confidence intervals. No adjustment for multiple comparisons will be performed due to the fact that all three comparisons (BI 695502 vs bevacizumab (Avastin®), US source, BI 695502 vs bevacizumab (Avastin ®), EU source, bevacizumab (Avastin®), US source vs bevacizumab (Avastin ®), EU source) need to be significant.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The primary PK parameters (see Section 7.1.3) will be log transformed (natural logarithm) prior to fitting the ANOVA model described in Section 7.1.4. The difference between the expected means for log(Test)-log(Reference) will be estimated by the difference in the corresponding least-squares means (point estimate), and two-sided 93.93% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator and interval estimates for the inter-subject ratio of the geometric means for treatments.

A claim of PK similarity will be made if the 93.93% confidence interval(s) of the ratio of the geometric means are contained in the pre-defined acceptance range for all three comparisons. All randomized subjects will be included in the analysis of PK similarity, if they

- Received at least one dose of study drug;
- Had no important CTP deviation relevant to the evaluation of PK similarity. (Whether a CTP deviation is relevant, will be decided no later than the combined report planning and database lock meeting, see below.); and
- Provide at least one evaluable observation of a PK endpoint. (Whether a single PK endpoint or the entire treatment period will be classified as a non-evaluable will be decided no later than the combined report planning and database lock meeting.)

Subjects with protocol deviations relevant for PK similarity should generally be excluded from PK analysis prior to start of bioanalytical determinations. Classification of a protocol deviation as “relevant” will be made by the investigator, together with the trial pharmacokineticist. Examples for relevant deviations are:

- Randomized study drug not administered or wrong trial drug administered.
- Not observing the pre-defined treatment regimen completely, i.e.: Administered dose (amount of drug) is not in compliance with the protocol, i.e. too high or too low. Note that adjustment of the infusion rate will not be considered as relevant deviation, although potential impact on C_{max} as secondary endpoint should be discussed.

7.3.2 Secondary analyses

The PK parameters $AUC_{0\text{-}tz}$ and C_{max} will statistically be assessed using the same statistical model as described for the primary endpoint. For these endpoints ($AUC_{0\text{-}tz}$ and C_{max}) the 90% confidence intervals will be computed.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables. For the presentation of the mean profiles, the arithmetic mean and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for plasma concentrations as well as for all primary and secondary PK parameters: N (sample size), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. The individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

7.3.3 Safety analyses

All subjects who receive at least one dose of study drug will be included in the safety evaluation (treated set). Safety analyses will be performed in accordance with Boehringer Ingelheim standards.

Adverse events will be coded using the most recent version of the Medical Dictionary for Drug Regulatory Activities. The analysis of AEs will be based on the concept of treatment-emergent AEs. All AEs occurring after study medication intake until the end-of-study visit will be assigned to treatment. All AEs occurring before drug intake will be assigned to ‘screening’ and all AEs occurring after the end-of-study visit will be assigned to ‘poststudy’.

Independent of this rule, the relationship of an AE to the study drug treatments will be assessed by the investigator. Adverse event information as reported in the eCRFs will be aggregated in a two-step process. First, multiple recordings (AE occurrences) of the same AE will be combined into one AE episode (collapsing). The second step will combine all of the AE episodes of an AE into one AE record as needed for by-subject summaries (condensing). The evaluation of AEs will comprise various frequency tabulations.

Descriptive statistics of laboratory values and vital signs over time and for the change from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

7.3.4 Interim analyses

After Stage 1 of the trial, an interim analysis will be performed based on the pre-specified boundaries for early PK biosimilarity. As described in Section 7.2, the α-level will be adjusted for these multiple looks based on a Pocock boundary. This leads to a 93.93% confidence interval being relevant for the actual testing of similarity. This interim analysis will be performed by a DMC which will provide a recommendation whether to stop the trial for early PK biosimilarity. Additionally, in order to get the full data picture, the DMC will look at secondary and other PK parameters. If the trial is stopped after the interim analysis a full CTR will be written. Note that it is also possible that only a single arm is stopped for early similarity at interim if for both comparisons the arm is involved in early similarity can be shown.

Additionally, a continuous monitoring of all safety data will be done by a DMC to ensure an acceptable safety profile at any time. The DMC may consider recommending stopping the trial in case that emerging data might suggest doing so.

7.3.5 Pharmacokinetic analyses

The PK parameters described in Section 5.5.1 will be determined if feasible.

The primary PK parameter will be analyzed as described in Section 7.3.1, secondary PK parameters will be analyzed using the same statistical model (see Section 7.3.2).

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Only concentrations within the validated concentration range will be used for the calculation of PK parameters.

Plasma concentrations will be plotted graphically versus time for all subjects as listed in the drug plasma concentration-time tables, if possible, with the actual sampling times. For the presentation of the mean profiles, the arithmetic mean, and the planned blood sampling times will be used.

The following descriptive statistics will be calculated for analyte concentrations as well as for all PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. The individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

7.3.6 Pharmacodynamic analyses

Not applicable.

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values other than AE start dates and times.

7.4.2 Plasma concentration - time profiles

Concentration data identified with no sample (NOS), no valid result (NOR), not analyzed (NOA), below the limit of quantification (BLQ), and no peak detectable (NOP) will be ignored and not replaced by zero at any time point (applies also to the lag phase including the predose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA, and NOP are included).

7.4.3 Pharmacokinetic parameters

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

Every effort will be made to include all concentration data in an analysis. If not possible, a case-by-case decision will be required to decide whether the value should only be excluded from half-life estimation or the complete analysis. If a concentration is only excluded from half-life determination, it will be used for all other calculations, (e.g., descriptive statistics) and for graphical presentations.

If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. The excluded concentration itself will be listed in the tables in Section 15 of the CTR associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated".

7.5 RANDOMIZATION

Subjects will be randomized to one of the three treatment groups in a 1:1:1 ratio. If after the interim analysis a single arm is stopped for early similarity the randomization ratio for the two continued arms in Stage 2 will be 1:1.

The sponsor will arrange for the randomization as well as packaging and labeling of study 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 of randomization number of medication numbers to treatment is both reproducible and non-predictable.

7.6 DETERMINATION OF SAMPLE SIZE

Different overall power for a two arm comparison based on 2x2x30 subjects in a two-stage Pocock design are given in the following tables:

Table 7.6: 1 Overall power two stage in a two-stage Pocock-design for early stopping after 50% of the subjects for two-arm comparisons with 2x60 pts and an assumed ratio of 1

Assumed CV	**Overall power**	**P(Stop) Stage 1**	**Average sample number**
0.35	89%	41%	96
0.30	97%	65%	81
0.25	> 99%	87%	68
0.20	> 99%	98%	61

CV: coefficient of variation. Simulated with Addplan version.5.0, seed=6851, n=100000.

Table 7.6: 2 Overall power two stage in a two-stage Pocock-design for early stopping after 50% of the subjects for two-arm comparisons with 2x60 pts and an assumed ratio of 0.95

Assumed CV	**Overall power**	**P(Stop) Stage 1**	**Average sample number**
0.35	77%	32%	101
0.30	88%	53%	89
0.25	96%	73%	76
0.20	> 99%	90%	66

Simulated with Addplan version 5.0, seed=6851, n=100000.

Hence for an assumed CV of 30% the overall powers are given as approx. 97% (assumed ratio of 1.0) and approximately 88% (assumed ratio of 0.95), respectively. Note that these numbers do not take into account the multiple comparisons performed as well as the different probabilities for stopping the different treatment arms (hence the average sample number has

to be regarded with caution). In a 'worst-case' scenario of total independence between the comparisons the overall power reduces to approximately 94% and 77%, respectively.

8. INFORMED CONSENT, DATA PROTECTION, AND TRIAL RECORDS

The trial will be carried out in compliance with the CTP, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, and relevant Boehringer Ingelheim Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains in the responsibility of the treating physician of the subject.

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

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

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority 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 subject must be informed that his / her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

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

8.2 DATA QUALITY ASSURANCE

The trial will be carried out in compliance with the CTP, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, in accordance with applicable regulatory requirements, and in accordance with the company's SOPs.

Electronic CRFs for individual subjects are provided by the Department of Clinical Data Management of the sponsor via remote data capture.

The eCRFs will be kept current to reflect the subject's status at each phase during the course of the trial. The subject is not to be identified on the eCRFs by name. Appropriately coded information (e.g., subject number) is given. The investigator will make a separate confidential record of these details (subject identification code list) to permit identification of all subjects enrolled in a clinical trial in case follow-up is required.

Relevant medical history prior to enrollment will be documented during the baseline visit. Thereafter, during the trial narrative statements relative to the subject's progress during the trail have to be maintained.

The investigator is responsible for retaining all records pertaining to the trial.

Refer to Section 8.3.1 for the handling of source data.

Originals or copies of ECG results and other results based on hard copies of medical machinery will be kept as source documents at the investigational site.

The investigator / institution permits trial-related monitoring, audits, IRB / IEC review, and regulatory inspection, providing direct access to all related source data / documents. Electronic CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results will be available at all times for review by the sponsor's clinical trial monitor and inspection by health authorities. The CRA / on-site monitor will review all eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

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

8.3 RECORDS

Electronic CRFs for individual subjects will be provided by the sponsor, either on paper or via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents will be filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfill the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is "listed" i.e., is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 695502 this is the current version of the Investigator's Brochure (U12-1281-01). For the bevacizumab (Avastin®) as US and EU source this is the EU SPC and US-PI respectively. The current versions of these reference documents are to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

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

8.5 STATEMENT OF CONFIDENTIALITY

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

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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R10-4862 Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov 2004; 3: 391-400.

R12-0947 Zhan P, Wang J, Lv X, Wang Q, Qiu L, Lin X, Yu L, Song Y. Prognostic value of vascular endothelial growth factor expression in patients with lung cancer: A systematic review with meta-analysis. J Thorac Oncol 2009; 4:1094-1103.

R12-0948 Llovet JM, Pena CEA, Lathia CD, Shan M, Meinhardt G, Bruix J, SHARP Investigators Study Group. Plasma biomarkers as predictive of outcome in patient with advanced hepatocellular carcinoma. Clin Cancer Res 2012.

R12-1012 European Medicines Agency. Avastin: EPAR – scientific discussion (first published 24-Jan-2006), website: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000582/WC500029262.pdf (access date: 30 January 2012).

R12-0939 Avastin 25 mg/ml concentrate for solution for infusion (Roche Registration) (summary of product characteristics; manufacturer(s) of the biological active substance and manufacturing authorisation holder(s) responsible for batch release; conditions of the marketing authorisation; labelling and package leaflet, date of latest renewal: 14 January 2010, last updated: 5/02/2012), website: ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/ human/000582/WC500029271.pdf (access date: 9 March 2012)

R12-0971 Highlights of Prescribing Information. (21-Dec-2011), website: gene.com/gene/products/information/pdf/avastin-prescribing.pdf (access date 01 March 2012).

9.2 UNPUBLISHED REFERENCES

U12-1281-01 Investigator's Brochure BI 695502 in colorectal cancer, breast cancer, non-small cell lung cancer, renal cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer and glioblastoma, Version 1, 13 March 2012

10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (CTP-Specified Significant Events), are to be further evaluated using the following procedures:

10.1.2 Procedures

Studies without central laboratory
Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours. If ALT and/or AST ≥ 3-fold ULN combined with an elevation of total bilirubin ≥ 2-fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to Boehringer Ingelheim as soon as possible.

In addition,

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

and report these via the eCRF.

Clinical chemistry
Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, and triglycerides

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

Hormones, tumormarker
TSH

Hematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology e.g., bile duct stones or neoplasm; and
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the CTP. Depending on further laboratory changes, additional parameters identified e.g., by reflex testing will be followed up based on medical judgment and GCP.

10.2 PLANNED TIME POINTS FOR SAFETY AND PHARMACOKINETICS ASSESSMENTS

Treatment period	Visit	Day	Planned time [h:min]	Approximate time (actual time) [h:min]	Event and comment	Laboratory/ Urinalysis	PK_{blood}		12-lead ECG	Temperature	Physical examination[3]	Vital signs (Blood pressure and pulse rate)	Adverse events/Con. med
	1	-28 to -2			screening (-28 to -2)	X			X	X	X	X	
		-1			admission to trial center	X			X	X	X	X	
1	2	1	-1:00	7:00			X	X		X	X	X	
			0:00	8:00	drug administration infusion start								
			0:30	8:30	PK blood draw taken just prior to end of infusion		X		X[1.]				
			1:00	9:00								X	
			2:00	10:00			X		X			X	
			3:00	11:00								X	
			4:00	12:00			X					X	
			5:00	13:00								X	
			6:00	14:00								X	
			8:00	16:00			X		X				
		2	24:00	8:00		X	X[4]		X		X	X	
		3	48:00	8:00	discharge from trial site[2]	X	X		X		X	X	
		5	96:00	8:00	ambulatory visit		X				X	X	
		8	168:00	8:00	ambulatory visit	X	X				X	X	
		15	336:00	8:00	ambulatory visit	X	X	X	X		X	X	
		22	504:00	8:00	ambulatory visit	X	X	X			X	X	
		36	840:00	8:00	ambulatory visit	X	X	X	X		X	X	
		50	1176:00	8:00	ambulatory visit	X	X	X			X	X	
		64	1512:00	8:00	ambulatory visit	X	X		X		X	X	
		78	1848:00	8:00	ambulatory visit	X	X				X	X	
	3	99	2352:00	8:00	ambulatory visit	X	X	X	X		X	X	

[1.] ECG performed at end of infusion.
[2.] All patients will remain hospitalized for 48 hours after dosing but can be discharged after 24 hours at investigator´s discretion. If discharged on Day 2, patient must return to the site on Day 3.
[3.] Symptom directed physical examination as clinically indicated on Day 2 to Day 78.
[4.] One “BA-sample” for first 8 patients to be taken at day 2 on time point 24:00 (section 5.5.2)

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

~~This is the original protocol.~~

Number of global amendment		01
Date of CTP revision		*26 November 2012*
EudraCT number		*NA*
BI Trial number		*1302.1*
BI Investigational Product(s)		*BI 695502*
Title of protocol		*Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study.*
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		
Section to be changed		*Title page: Trial Clinical Monitor*
Description of change		*The study was handed over from to on 6 September 2012*
Rationale for change		*Update to actual Clinical Project*
Section to be changed		*Flow Chart 1.1 Schedule of assessments*
Description of change		*Following note was changed from "Note: Please refer to Appendix 10.2 for specific planned time*

Number of global amendment		01
		points" to "Note: Please refer to Appendix 10.2 for specific planned time points for safety and pharmakokinetic assessments"
Rationale for change		*Clarification to Flow Chart 1.1 which specific planned time points are meant in accordance to Appendix 10.2.*
Section to be changed		*Flow Chart 1.1 Schedule of assessments*
Description of change		*Screening range was corrected from "day -28 to -1" to "day -28 to -2"*
Rationale for change		*Clarification of Screening range to day -28 to -2 with admission to trial center on day -1 with admission to trial center on day -1 and confirmation of certain assessments to be conform with Appendix 10.2.*
Section to be changed		*1.1*
Description of change		*Second paragraph first section: "secreted" was deleted*
Rationale for change		*The secreted VEGF is only one of the isoforms, therefore it was decided to delete "secreted".*
Section to be changed		*1.2*
Description of change		*At the end of the first paragraph it was added: "…, on tumor cells and autocrine and paracrine loops."*
Rationale for change		*Clarification of VEGF receptor locations.*
Section to be changed		*2.1*
Description of change		*First paragraph last sentence: Added in the apprentices "powered for".*
Rationale for change		*Clarification that demonstrated safety and immunogenicity similarity will not be powered statistical similarity*
Section to be changed		*2.3 Drug related risks and safety measures*
Description of change		1. *Added proteinuria as most frequently side effect* 2.

Number of global amendment		01
Rationale for change		*1. Clarification on most frequently side effects in this section* *2.*
Section to be changed		*3.3*
Description of change		*4th paragraph:* *1. 3rd sentence "Single-dose" replaced by "Single therapeutic dose of"* *2.*
Rationale for change		*1. Clarification that this single dose was a single and therapeutic dose (5mg/kg)* *2.*
Section to be changed		*3.3 Table 3.3: 1*
Description of change		

Number of global amendment		01
Rationale for change		
Section to be changed		*4.1.2, 7.5*
Description of change		*At end of paragraph 4.1.2 it was added: (The same applies for randomization numbers).”* *In last sentence of 7.5 it was changed:”… so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable.” to “…so that the resulting allocation of randomization number to treatment is both reproducible and non-predictable.*
Rationale for change		*Clarification that randomization numbers and not medication numbers were allocated*
Section to be changed		*4.2.2.2*
Description of change		*Restrictions on diet and life-style: Smoker “(>10 cigarettes or > 3 cigars or >3 pipes/day)“ was corrected to “(<10 cigarettes or <3 cigars or <3 pipes/day)“*
Rationale for change		*Clarification of Restrictions on diet and life-style*
Section to be changed		*5.2.1*
Description of change		*“Safety will be evaluated based on the investigations described in Section 5.2.” was corrected to “All safety parameters will be evaluated descriptively and based on the investigations described below.”*
Rationale for change		*Clarification of safety endpoints and analysis*
Section to be changed		*5.5.2.3*
Description of change		*First sentence “…5 mL of blood will be collected…” was changed to “…3 mL of blood will be collected…”*
Rationale for change		*There is an administrative error in the protocol regarding collection of neutralizing antibody samples. The sites were provided with 3 ml tubes instead of the 5 ml tubes stated in the protocol, so that only 3 ml blood was collected*

Number of global amendment		01
Section to be changed		*5.5.2.3*
Description of change		
Rationale for change		
Section to be changed		*5.5.3*
Description of change		*The following sentence was updated "Plasma concentrations of bevacizumab of US origin, bevacizumab of EU origin, and BI 695502 will be quantitated using a sandwich ELISA." To "Plasma concentrations of bevacizumab of US origin, bevacizumab of EU origin, and BI 695502 will be quantitated using a validated sandwich ELISA."And the following sentence was added*
Rationale for change		*Clarification that the assays used are certainly validated*
Section to be changed		*Appendix 10.2*
Description of change		*The following note to the table was added to PK blood column cell day 2: [4.] One "BA-sample" for first 8 patients to be taken at day 2 on time point 24:00 (section 5.5.2)*
Rationale for change		*Clarification that at this time point the BA sample is taken for first 8 patients.*
Section to be changed		*Appendix 10.2*
Description of change		

Number of global amendment		01
Rationale for change		

Number of global amendment		02
Date of CTP revision		*11 January 2013*
EudraCT number		*NA*
BI Trial number		*1302.1*
BI Investigational Product(s)		*BI 695502*
Title of protocol		*Pharmacokinetics and safety of BI 695502 in healthy subjects: a randomized, single-blind, single-dose, parallel-arm, active-comparator clinical Phase I study.*
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		*3.3*
Description of change		*First paragraph: "enrolled" replaced by "randomized"; some typos corrected*
Rationale for change		*The definition of "enrolled" is not always distinct, therefore it was replaced with "randomized" to avoid confusion*
Section to be changed		*3.3.3*
Description of change		*The exclusion criteria 21. Pre-existing proteinuria was added*
Rationale for change		*Exclusion criteria proteinuria was omitted in the initial protocol. None of the stage I subjects was*

Number of global amendment		02
		included with proteinuria. Proteinuria is one of the most common adverse reactions incidence (>10% and at least twice the control arm rate) of Avastin.
Section to be changed		*3.3.4.1*
Description of change		*Second paragraph: the brackets "(e.g., non-attendance at study assessments). " have been changed to "(e.g., non-attendance at study assessments, incomplete, missing or wrong trial drug administration). "*
Rationale for change		*In order to provide useful examples of situations that should be discussed in a timely manner with a view to their relevance for assessment.*
Section to be changed		*5.5.1*
Description of change		
Section to be changed		*7.3.1*
Description of change		*1. In second paragraph it was added in the brackets "see below": (Whether a CTP deviation is relevant, will be decided no*

Number of global amendment		02
		later than the combined report planning and database lock meeting, see below.); and *2. Third paragraph was added: "Subjects with protocol deviations relevant for PK similarity should generally be excluded from PK analysis prior to start of bioanalytical determinations. Classification of a protocol deviation as "relevant" will be made by the investigator, together with the trial pharmacokineticist. Examples for relevant deviations are:* • *Randomized study drug not administered or wrong trial drug administered.* • *Not observing the pre-defined treatment regimen completely, i.e.: Administered dose (amount of drug) is not in compliance with the protocol, i.e. too high or too low. Note that adjustment of the infusion rate will not be considered as relevant deviation, although potential impact on C_{max} as secondary endpoint should be discussed."*
Rationale for change		*1. Clarify relationship to other text part in protocol* *2. In order to facilitate the examples given in chapter 3.3.4.1. Same rationale.*
Section to be changed		*7.3.3*
Description of change		
Rationale for change		
Section to be changed		*7.6*
Description of change		*Correction of table numbering from 7.6.1:1 and 7.6.1:2 to 7.6:1 and 7.6:2*
Rationale for change		*Formatting of table number to be more logical*
Section to be changed		*Flow Chart 1.1 and 10.2*

Number of global amendment		02
Description of change		