Clinical Trial Protocol

	Document Number: c02155664-05
EudraCT No.:	2014-002413-29
BI Trial No.:	1339.1
BI Investigational Product:	BI 655088
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 3))
Version and Date:	Version: 4.0 Date: 22 November 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655088			
Protocol date: 03 December 2015	**Trial number:** 1339.1		**Revision date:** 22 Nov 2017

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics and pharmacodynamics following single rising doses of BI 655088 administered as intravenous (IV) infusion
Methodology:	Single-blind, partially randomised within dose groups, placebo-controlled, parallel-group design
No. of subjects:	
total entered:	48*
each treatment:	8 per dose group (6 on active drug and 2 on placebo)
	* Additional subjects may be entered to allow for testing of additional intermediate doses within the planned dose range on the basis of experience gained during the trial conduct (e.g. safety or preliminary PK/PD data), i.e. the actual number of subjects entered may exceed 48
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 655088
dose:	
mode of admin.:	IV infusion for 120 minutes
Comparator product:	Matching placebo (buffer solution)
dose:	Not applicable
mode of admin.:	IV infusion for 120 minutes
Duration of treatment:	Single dose

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655088			
Protocol date: 03 December 2015	**Trial number:** 1339.1		**Revision date:** 22 Nov 2017
Criteria for pharmacokinetics:	Secondary endpoints: C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$		
Criteria for pharmacodynamics:			
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 655088 is the number [N (%)] of subjects with drug-related adverse events (AEs). Further criteria of interest: AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR], oral body temperature), oral glucose tolerance test (oGTT), bleeding time, anti-drug antibodies (ADA).		
Statistical methods:	Descriptive statistics will be calculated for all endpoints.		

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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
ApoE	Apolipoprotein E
$AUC_{0-\infty}$	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 the last quantifiable data point
β	Slope parameter associated with the power model used to evaluate dose proportionality
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BSA	Bovine serum albumin
CA	Competent authority
CI	Confidence interval
$C_{max(,ss)}$	Maximum measured concentration of the analyte in plasma (at steady state)
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Coefficient of variation
DILI	Drug induced liver impairment
DP	Drug product
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
(e)GFR	(Estimated) glomerular filtration rate
ELISA	Enzyme linked immunosorbent assay
HR	Heart rate
IB	Investigator's brochure
IC_{50}	Half-maximal inhibitory concentration

IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator site file
IV	Intravenous
Ki	Inhibition constant
KI	Knock-in
LC-MS/MS	Liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MoE	Multiple of exposure
NC	Not calculated
NK	Natural killer
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NSTEMI	Non-ST segment elevation myocardial infarction
oGTT	Oral glucose tolerance test
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference product or treatment
REP	Residual effect period
SAE	Serious adverse event
SC	Subcutaneous
SCR	Screening
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
TE	Thromboembolism
TGF	Transforming growth factor
$t_{1/2}$	Terminal half-life of the analyte in plasma

TDMAP	Trial Data Management and Analysis Plan
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
UACR	Urinary albumin / creatinine ratio
ULN	Upper limit of normal

1. INTRODUCTION

1.2 DRUG PROFILE

1.2.4 Clinical experience in humans

This is the first clinical trial with single intravenous administration of BI 655088 in man. The trial was started in March 2016 at a dose level of to the first cohort of healthy male volunteers (5 on active, 2 on placebo). Three days after receiving a dose of BI 655088 a serious adverse event (non-ST segment elevation myocardial infarction (NSTEMI) with coronary artery occlusion (thrombus)) occurred in a 47 year old male subject. A coronarography was performed and identified a 90% stenosis of the right coronary artery; the subject underwent insertion of a drug-eluting stent, leading to a successful angioplasty. Beside smoking, the subject had no other coronary risk factors, no known history of cardiovascular disease nor any finding during the screening examinations indicating coronary artery disease.

The investigator assessed this SAE as being not related to the study medication. Based on the clinical course and the time-to-onset BI has assessed that there is not a reasonable possibility of a causal association between the event NSTEMI and the study medication. A thorough review of the ECGs, vital signs and relevant laboratory parameters of the whole dosing group did not show clinically relevant changes and, more specifically, did not reveal relevant changes involving the cardiac system or the coagulation profile.

Despite the above, as a precautionary measure BI decided to temporarily put the trial on hold to allow sufficient time for further investigation of this observation before any further subjects will be dosed with the study medication.

Except for the subject with the myocardial infarction who decided to stop participating, the remaining 6 subjects treated with BI 655088 or placebo continued the trial as planned.

For these subjects, no clinically relevant changes in vital signs, ECG and clinical laboratory parameters including oGTT were observed throughout the approx. 3 months post-dose observation period, except an intermittent, transient but marked increase in lipase and

amylase of subject This increased amylase/lipase was not associated with any clinical symptoms.

A total of 4 baseline AEs and 18 postdose (treatment emergent) AEs were reported by 7 out of 7 subjects. Two AEs each were of moderate and severe intensity; all remaining AEs were of mild intensity. AEs categorized as related to treatment were observed in 1 subject each treated with BI 655088 and placebo, respectively. An overall summary on adverse events reported by the subjects treated in the first dose group is given in Table 1.2.4: 1 below.

Table 1.2.4: 1 Overall summary of adverse events in dose group

	BI 655088, N (%)	Placebo N (%)
Number of subjects	5 (100.0)	2 (100.0)
Subjects with any AE	5 (100.0)	2 (100.0)
Subjects with moderate AEs	2 (40.0) subject # indigestion subject # dyspnoea	0 (0.0)
Subjects with severe AEs	1 (20.0) subject # acute myocardial infarction, thoracic pain	0 (0.0)
Subjects with investigator defined drug related AEs	1 (20.0) subject # sleepiness	1 (50.0) subject # headache
Subjects with serious AEs	1 (20.0) subject # acute myocardial infarction	0 (0.0)

From these data, it is concluded that of BI 655088 or Placebo is safe and well tolerated.

The preliminary PK analysis (based on planned times) confirmed the predicted PK profile, which was based on preclinical data. The geometric mean C_{max} was 0.59 µg/ml (15.2 nM, n=5) with a range of 0.53 to 0.65 µg/ml.

The PK and PD profile of the subject experiencing the SAE did not differ from the profiles of the other four subjects receiving active drug within the first dose group.

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

As a transition from preclinical investigations to clinical development in this first-in-man trial, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 655088 will be assessed in healthy male volunteers using single rising intravenous doses in order to provide the basis for a potential ongoing clinical development of BI 655088 in the indication of

The administration of the study drug as IV infusion is considered advantageous since the administration of BI 655088 can be immediately stopped in case safety concerns arise during the running infusion. A further advantage of the IV route is the possibility to investigate supratherapeutic exposure unbiased from individual variability in bioavailability. The study will be conducted in healthy volunteers, since healthy volunteers provide a relatively stable physiological, biochemical and hormonal basis for studying drug effects, without an impact by underlying disease or concomitant medication. Healthy volunteers are easy to recruit, easy to select for age and sex, and can be tested under standardized conditions. Therefore, the study population of the planned SRD trial will consist of healthy male subjects aged 18 - 50 years.

Within each dose group, all actively treated individuals will receive the same BI 655088 dose. The next higher dose will only be administered to the next group if the treatment in the preceding dose group was safe and well tolerated (see Section 3.1). The background for dose selection and escalation steps is described below.

Based on EMA's Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (R09-6036), BI 655088 can be regarded as a risk compound for the first-in-man trial. EMA identifies 3 main criteria for risk assessment:

- the mode of action
- the nature of the target
- the relevance of animal models

Although BI 655088 is not considered as being a risk compound, a conservative approach in calculating the starting dose has been chosen and safety of participants will be enhanced by appropriate safety measures in the first-in-man trial.

2.1.1 Starting dose

Using the criteria that are described in the EMA Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (R09-6036) it would be justified to use a NOAEL approach to select the Maximum Recommended Starting Dose (MRSD) for the first application in humans.

A very similar safe starting dose was defined by PK/PD modeling.

For the first in human trial, g has been chosen as the starting dose. Taken all data together, is expected to be safe and well tolerated.

2.1.2 Maximum dose and dose escalation

Following the initial dose of , it is planned to continue the trial with intravenous doses of . Dose escalation will not exceed factor 3 and from onwards factor 2. This escalation approach is considered to be safe in the clinical setting where only one single dose will be administered. The selected doses are expected to cover the range of subtherapeutic, lowest to highest anticipated therapeutic as well as supratherapeutic doses (for corresponding exposure values, see Table 2.1.2: 1). The IV doses will be administered by infusion over 120 minutes.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 655088 in healthy male subjects following intravenous infusion of single rising doses.

Secondary objective is the exploration of the pharmacokinetics and pharmacodynamics of BI 655088 after single dosing.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

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 a new treatment modality to the current insufficient therapeutic armamentarium of . The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

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

The total volume of blood drawn during the entire study per subject might slightly exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from this blood withdrawal considering that this amount is taken over a period of 3 months.

Drug-related risks and safety measures

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

The following safety measures will be applied in this study in order to minimize the risks for trial participants:

- Careful dose selection as described in Section 2.1.1 and 2.1.2 with large safety margins up to the maximum dose, and based on a sound preclinical data package including 6 week repeat dose toxicity studies.

- The use of the IV administration has been included in this trial because IV infusions can be stopped should any safety concern arise during administration. The dose will be infused slowly over a period of 2 hours.

- For safety reasons, each dose group is divided into 3 cohorts. On the first study day of each dose level, only 2 subjects (first cohort) will be treated: one will receive active treatment, the other subject will receive placebo. If BI 655088 treatment is safe and tolerated in this first cohort, the following 2 subjects on active will be treated in the second cohort. The second subject on active will be treated at least 2 days after the administration of the first subject. The remaining 4 subjects (either active or placebo) are the third cohort and will be treated no sooner than 2 days following the 2nd cohort. A time interval of at least 10 min will be maintained between each administration of the study drug (start of infusion) to the individual subjects of the 2nd and 3rd cohort. This design ensures that between first and second active dose of each dose level there is a time interval of at least 2 days, which is expected to be sufficient to cover the period of highest risk/peak effect.

- Dose escalation will be shallow. In addition, a time interval of at least 21 days will be maintained between first administration of study drug in the actual dose level and first administration in the next dose level, which is expected to cover the period of highest risk / peak effect. The decision to proceed to the next dose will be based upon the safety and tolerability of the preceding dose. The next dose will only be given if no safety concerns arise in the previous dose group (i.e. no dose-limiting events occur) and if none of the pre-specified trial-specific stopping criteria are met (Section 3.3.4).

- Doses will only be escalated if previously approved by the principal investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) during its regular Safety Review meetings that will take place prior to each dose escalation (see Section 3.1).

- Extensive monitoring of ECG and vital signs is incorporated, with continuous ECG monitoring over 4 hours post infusion start to cover the anticipated period of highest drug exposure and additional repeated single 12-lead ECGs following drug administration.

- Extensive safety laboratory testing, determination of bleeding time, and oral glucose tolerance testing will be performed.

- The subjects will stay at the clinical site for at least 48 hours following study drug administration at each dose level. During in-house-confinement the subjects will be under close medical observation and thoroughly monitored for both expected and unexpected adverse events.

- Measurement of BI 655088 plasma concentrations and preliminary determination of pharmacokinetic parameters will be done as described in Section 7.3.4. For precautionary reasons, in a first place maximum drug plasma concentrations of and drug exposure levels , respectively, will be considered as a preliminary threshold (see Section 2.1.1). Further dose progression would only be allowed after a safety interim analysis and filing and approval of a pertinent protocol amendment.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-rising dose trial is designed as single-blind, partially randomised, and placebo-controlled within parallel dose groups. “Partially” means that randomisation is done only in the second half of subjects of each dose level. For safety reasons the first half of subjects within each dose group will be administered study drug in a fixed sequence which is unknown to the volunteers: first subject active, second placebo, third active, fourth active.

A total of 48 healthy male subjects is planned to participate in the trial, according to 6 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 48. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 3 cohorts which will be treated subsequently for safety reasons (see also Section 2.3).

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups

Dose Group	1	2	3	4	5	6
Dose (mg)						
Number of subjects	8	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2	2
Subjects receiving active drug	6	6	6	6	6	6
Subject numbers						
Replacement numbers						

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 21 days between the first drug administration in the previous dose group and treatment of a subject in the subsequent dose group. The decision to proceed to the next dose group will be based upon the safety and tolerability data of the preceding dose groups. The next dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

A documented Safety Review must take place prior to each dose escalation, but not earlier than 7 days after administration of last subject of a given dose level. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the

Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy).

The minimum data set for review consists of the following data (for the current dose group, safety data of at least 6 subjects having completed Day 8 will be required):

- AEs in the current and preceding dose groups (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead EGG and continuous ECG monitoring in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Preliminary PK/PD data for selected dose groups and time points as per Section 7.3.4
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant).

Safety Reviews can be conducted face-to-face or by video/telephone conference. The investigator or project management team at the clinical site will be responsible for organization and minutes of the review meetings. Safety data will be provided and presented by the Principal Investigator (or an authorised deputy). Preliminary PK/PD will be provided by the sponsor as per Section 7.3.4. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and the Trial Clinical Monitor (or an authorised deputy) and filed in the ISF and TMF.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add an intermediate dose level) within the planned dose range on the basis of experience gained during the study. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

3.1.1 Administrative structure of the trial

The trial will be conducted at the Clinical Pharmacology Unit (CPU) of , under the supervision of the Principal Investigator.

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

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Safety laboratory tests will be performed by local laboratories of the trial site (e.g.

).

The analyses of BI 655088 concentrations in plasma will be performed by the Department of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim, Ridgefield, USA.

The analyses of ADA will be performed in the Bioanalytical Laboratories of ,
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The analyses of exploratory biomarkers in blood will be performed at the Department of TMCP/TMBT, BI Pharma GmbH & Co. KG, Biberach, Germany.

The digitally recorded 12-lead ECGs may be sent to a specialised contract research organisation (e.g.) for additional central evaluation.

The trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

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

For single-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 655088.

With the rising dose design, single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

The single-blind conditions may introduce additional observer bias, e.g. when assessing AEs in this first-in human trial. Thus every effort will be made to enhance the objectivity of investigator's observations. The same applies especially to the second subject of each dose level who is administered placebo treatment by defined study procedure.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacodynamic effects. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for exploratory evaluations.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male will enter the study. The actual number of subjects entered may exceed the total of 48 if additional intermediate doses will be tested (see Section 3.1). Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

A log of all subjects enrolled into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included into the trial, if they meet the following criteria:

1. Healthy male subjects according to the investigator’s assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

3.3.3 Exclusion criteria

Subjects will not be allowed to participate if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), migraine, and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections

9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Use of drugs (including any biological agent) with a long half-life (more than 24 h) within 30 days or less than 10 half-lives of the respective drug (whichever is greater) prior to administration of trial medication
11. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTc interval
12. Participation in another trial where an investigational drug has been administered within 60 days or 10 half-lives (whichever is greater) prior to planned administration of trial medication
13. Smoker
14. Ex-smoker who has stopped smoking less than one year prior to enrolment and/or who has a history of equal or more than 10 pack years
15. Alcohol abuse (consumption of more 30 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

23. History of tuberculosis infection and/or a confirmed positive Quantiferon TB-Gold test
24. Subjects who in the investigator's judgement are perceived as having an excessive risk of thromboembolism (TE) for example because of a personal history and/or a first degree relative with a personal history with onset under the age of 55 of significant TE, including but not limited to deep vein thrombosis, pulmonary embolism, cortical sinus thrombosis, coronary and cerebrovascular events, cardiovascular disease, and peripheral arterial insufficiency
25. Abnormal results of coagulation values indicating an increased risk for bleeding or thromboembolism or complicating the safety evaluation during the study as determined by the investigator.
26. Deficiency of antithrombin III or protein S or protein C
27. Clinically relevant abnormal result of oral glucose tolerance test at baseline
28. Estimated glomerular filtration rate (eGFR) according to CKD-EPI formula < 90 mL/ min at screening (R12-1392)

29. Urinary albumin/creatinine ratio (UACR) ≥ 30 mg albumin / g creatinine at screening

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

1. The subject withdraws consent, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.

In addition to these criteria, the physician may discontinue subjects at any time based on his or her clinical judgment.

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to the administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.

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 any of the following reasons:

1. New toxicological or clinical findings or serious adverse events invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more

than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.

2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.
6. Dose escalation will be stopped based on the preliminary PK results as per Section 7.3.4,

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

3.3.5 Replacement of subjects

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Substance:	BI 655088
Pharmaceutical formulation:	Solution for infusion (filled in 10R clear glass vials)
Source:	BI Pharma RCV GmbH & Co. KG, Austria
Unit strength:	
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo to BI 655088
Pharmaceutical formulation:	Solution for infusion (filled in 10R clear glass vials)
Source:	BI Pharma RCV GmbH & Co. KG, Austria
Unit strength:	
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose

The dilution solution (diluent), a buffer and water for injection, will be provided in 20R clear glass vials.

4.1.2 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups and cohorts according to their temporal availability. As soon as enough subjects have been allocated to a dose cohort, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomisation list with study subject numbers and allocated treatments will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the administration of trial medication in ascending order (e.g. in dose group 1 the first subject will be the next …). Subjects will be allocated to a study subject number by the order of their subscription for the trial. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 2.1).

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The dose volume for placebo corresponds to dose volume of the respective dose level.

Table 4.1.4: 1 BI 655088 and placebo treatments, intravenous administration

Dose group	Substance	Pharmaceutical form	Concentration of active drug in reconstituted solution	Dose volume (single infusion over 2 hours)	Total dose
1	BI 655088	IV solution			
2	BI 655088	IV solution			
3	BI 655088	IV solution			
4	BI 655088	IV solution			
5	BI 655088	IV solution			
6	BI 655088	IV solution			
1-6	Placebo*	IV solution	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The solution for intravenous infusion (active drug and placebo) will be prepared according to the instruction given in Appendix 10.1 by qualified pharmacy staff members or qualified medical study personnel at the trial site under the responsibility of the investigator.

The so-called four-eye principle (two-person rule) should be applied for preparation and administration of trial medication, if correct dosage cannot be ensured otherwise. For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.

The trial medication will be administered to the subjects while in a semi-supine position under supervision of the investigating physician or an authorised designee. Subjects are requested to fast overnight for at least 10 h before the scheduled start of infusion.

Subjects will be kept under close medical surveillance until at least 48 h following start of infusion. During infusion and up to 2 h thereafter, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The treatments administered (active or placebo) will be single-blind (blinded to subjects only). However, the current dose level will be known to the subjects.

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted single-blind, the treatment information will be known to the investigator. Therefore, no emergency envelopes will be provided.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to local law as well as Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes within the clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name, address, and telephone number
- Storage conditions
- Use-by date
- Batch number
- Investigator

The vials in the box are labelled with reduced requirements.

The telephone number of the trial site is given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

Re-supply of trial medication will be done as necessary (e.g. to replace expired supplies).

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator / pharmacist / investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol

Only authorised personnel as documented in the form ‘Site Delegation Log’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorisation by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager 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 disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry (‘use-by’) dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator / pharmacist / investigational drug storage manager must verify 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 treatments

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. No food is allowed from at least 10 hours before drug administration until at least 30 minutes after end of infusion.

From drug administration until 30 min after end of infusion, no liquid intake is allowed. During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Alcoholic beverages are not allowed from five days before the administration of trial drug until after trial assessments of Day 29 have been completed. Thereafter subjects may drink up to 20 g alcohol per day, corresponding to 0.5 L beer or 0.2 L white wine.

Dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the administration of trial medication until after the end of trial examination.

During in-house confinement at the trial site, smoking and consumption of methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) is not allowed.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

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

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 655088 is the number [N (%)] of subjects with drug-related AEs.

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination and local tolerability)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate, oral body temperature)
- Oral glucose tolerance test
- Bleeding time

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

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

- results in death,

- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,

  or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered 'Always Serious'

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

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

The latest list of 'Always Serious AEs' can be found in the Remote Data Capture (RDC) system. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - o an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
  - o marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

  These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained

encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

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

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

Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.2.2.2 Adverse event collection and reporting

AEs collection

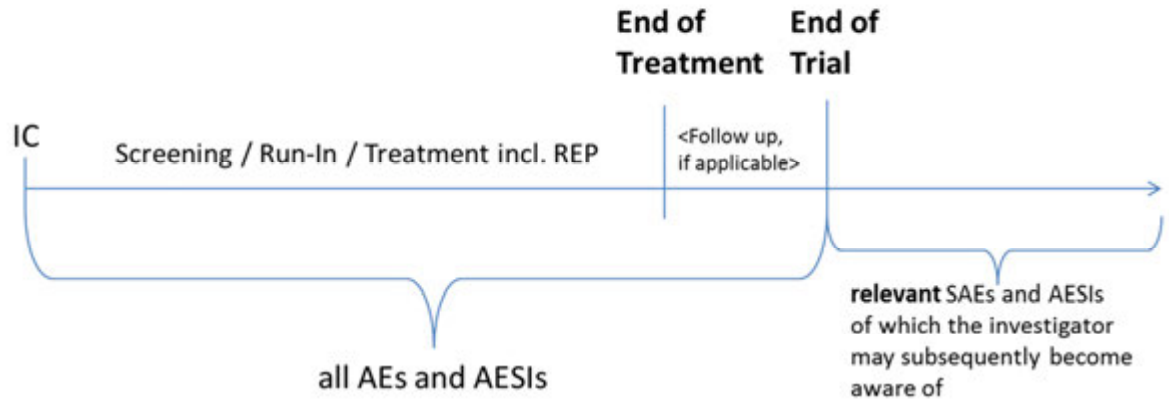
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards through the residual effect period (REP), until individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs.
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which he may become aware of.



The residual effect period (REP) for BI 655088, when measurable drug levels or PD effects are still likely to be present, is not known for this first-in-human trial. Therefore all AEs reported until the end of trial examination will be considered on treatment; please see Section 7.3.3. Events which occurred after the end of trial examination will be considered as post treatment events.

The follow-up period describes the period of time from the last administration of trial medication until the end of trial examination (last per protocol visit).

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours of awareness) to the sponsor's 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. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

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

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

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

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

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests and for time points planned to occur after a meal.

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

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

Though not necessary for clinical management, timed blood will be drawn from subjects that experience hypersensitivity or infusion reactions to help determine whether these were immune- or non-immune mediated. In accordance with clinical guidelines (R15-5401), such samples will be taken as soon as possible (without interfering with emergency treatment), preferably within 1-2 hours, but not later than 4 hours after onset of the reaction for the determination of tryptase, histamine, cytokines and complement (R15-5400). For details refer to Table 5.2.3:1. A further blood sample will be drawn 12-24 hours later after resolution of symptoms as a baseline reference.

The routine safety laboratory and exclusionary tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed at with the exception of the drug screening tests and Quantiferon analysis. Drug screening tests will be performed at the trial site using "Alere Triage TOX Drug Screen". Quantiferon TB-Gold test as well as additional laboratory tests in case of potential systemic hypersensitivity or infusion reaction or incipient albuminuria (see Table 5.2.3:1) will be done at and , respectively.

Laboratory data will be transmitted electronically from the laboratory ( ) to the trial site or via paper print-outs).

Table 5.2.3: 1 Safety laboratory tests

Functional lab group	Test name	SCR	Day -5 to -1	Within period	End-of-trial
Haematology	Haematocrit	x	x	x	x
	Haemoglobin	x	x	x	x
	Red blood cell count (RBC)	x	x	x	x
	Reticulocyte count	x	x	x	x
	White blood cell count (WBC)	x	x	x	x
	Platelet count	x	x	x	x
	Glycated haemoglobin A1c (HbA1c)	x	-	-	-
Automatic WBC differential (relative and absolute)	Neutrophils	x	x	x	x
	Eosinophils	x	x	x	x
	Basophils	x	x	x	x
	Monocytes	x	x	x	x
	Lymphocytes	x	x	x	x
Manual WBC differential (if automatic is abnormal)	Polymorphnuclear neutrophils (segs)	x	x	x	x
	Band neutrophils (stabs)	x	x	x	x
	Eosinophils	x	x	x	x
	Basophils	x	x	x	x
	Monocytes	x	x	x	x
	Lymphocytes	x	x	x	x
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x
	Prothrombin time (Quick's test and INR)	x	x	x	x
	Fibrinogen	x	x	x	x
	Antithrombin III	x	-	-	-
	Protein S	x	-	-	-
	Protein C	x	-	-	-
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x	x
	Alkaline phosphatase (AP)	x	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x	x
	Creatine kinase (CK)	x	x	x	x
	CK-MB, only if CK is elevated	x	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x	x
	Lipase	x	x	x	x
	Amylase	x	x	x	x
Hormones	Thyroid stimulating hormone (TSH)	x	-	-	-
	Insulin	-	x[1]	x[1]	-
Substrates	Plasma glucose	x	x	x	x
	Serum creatinine	x	x	x	x
	eGFR (CKD-EPI for creatinine)	x	x	x	x
	Cystatin C	x	x	x	x
	Total bilirubin	x	x	x	x
	Direct bilirubin	x	x	x	x
	Total protein	x	x	x	x
	Albumin	x	x	x	x
	C-Reactive Protein (CRP)	x	x	x	x
	Uric acid	x	-	-	x
	Total cholesterol	x	-	-	x
	Triglycerides	x	-	-	x

1 Only on study days with oral glucose tolerance test (see Flow Chart and Section 5.2.3.1)

Table 5.2.3: 1 Safety laboratory tests (cont).

Functional lab group	Test name	SCR	Day -5 to -1	Within period	End-of-trial
Electrolytes	Sodium	x	x	x	x
	Potassium	x	x	x	x
	Chloride	x	x	x	x
	Calcium	x	x	x	x
Urinalysis[1] (Stix)	Urine nitrite	x	x	x[1]	x
	Urine protein	x	x	x[1]	x
	Urine glucose	x	x	x[1]	x
	Urine ketone	x	x	x[1]	x
	Urobilinogen	x	x	x[1]	x
	Urine bilirubin	x	x	x[1]	x
	Urine erythrocytes	x	x	x[1]	x
	Urine leukocytes	x	x	x[1]	x
	Urine pH	x	x	x[1]	x
Urine sediment[1] (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	x	x	x[1]	x
Spot urine [1,2]	Creatinine	x	x	x[1]	x
	Albumin	x	x	x[1]	x
	Albumin to creatinine ratio	x	x	x[1]	x
Additional laboratory tests in case of potential systemic hypersensitivity or infusion reaction	Serum tryptase	-	-	x[3]	-
	Histamine	-	-	x[3]	-
	IL-2	-	-	x[3]	-
	IL-4	-	-	x[3]	-
	IL-6	-	-	x[3]	-
	IL-8	-	-	x[3]	-
	IL-10	-	-	x[3]	-
	IL-12	-	-	x[3]	-
	TNFα	-	-	x[3]	-
	IFNγ	-	-	x[3]	-
	C3a	-	-	x[3]	-
	C4a	-	-	x[3]	-
	C5a	-	-	x[3]	-

1 Not required at time point 4:00 on Day 1
2 Preferably 2nd morning urine
3 Only in case of a potential systemic hypersensitivity or infusion reaction; sampling as soon as possible after onset of event and approx. 12h to 24h after resolution of event

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only.

Drug screening will be performed at screening and at the start of the inhouse period prior to drug administration on Day 1.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine Barbiturates Benzodiazepine Cannabis Cocaine Opiates
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) Quantiferon TB-Gold

To encourage compliance with alcoholic restrictions, a breath alcohol test (Alcotest® 6510 and Alcotest® 5510, Dräger, Belgium) will be performed at admission to trial site on Day -1, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

5.2.3.1 Oral glucose tolerance test (oGTT)

An oGTT will be performed on the morning of Day –5 to –1 (baseline) and Day 29. After blood drawing for determination of fasting plasma glucose and serum insulin, 75 g of glucose will be dissolved in 200 mL water and swallowed by the subject. Thirty minutes, 1, 2 and 3 hours after intake of the glucose solution, further blood samples will be taken for glucose and insulin measurement. Blood samples for glucose measurements will be drawn in a 2 mL sodium fluoride (NaF) tube. Blood samples for insulin measurements will be drawn in a 2.5 mL serum tube.

5.2.3.2 Bleeding time

Bleeding time will be measured according to Duke Method at the time points given in the Flow Chart. The subject will be pricked with a lancet in the earlobe, after having been swabbed with alcohol. The prick should be about 1.5-2 mm deep. Then the blood will be wiped every 30 seconds with a filter paper. The test ceases when bleeding ceases. The usual time is about 1-3 minutes. Abnormal findings will be reported as AEs (during the trial) or baseline conditions if judged clinically relevant by the investigator.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (Cardionics SA, Brussels, Belgium) at the time points given in the Flow Chart.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for 10-sec duration after the subjects have rested for at least 5 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven. Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement on day 1 and 2.

Triple ECGs (recorded within 180 sec) will be recorded at screening, as the baseline before drug administration and up to 30 hours after start of infusion. At all other time points single ECGs will be recorded.

All locally printed ECGs will be evaluated by the investigator or a designee.

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time points with triple ECGs, all three single ECGs will be repeated. For the repeats due to quality reasons, only the repeated ECG recordings will be used for analysis provided quality was better than with the initial ECG.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths (if analysis is done).

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for external evaluation. In this case, these externally measured results would overrule any other results obtained.

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

All ECGs will be stored electronically at site in order to enable a centralised re-evaluation of all 12-lead ECGs by an independent ECG laboratory if needed.

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 2-lead ECG recording for at least 15 min before (for baseline assessment) and constantly for 4 h after start of infusion using the Dräger Telemetry monitoring system, Infinity M300.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (e.g. Welch Allyn 530TP and 530TO devices) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

Oral body temperature will be determined using a digital thermometer at the time points indicated in the Flow Chart.

5.2.5.2 Medical examinations

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.5.3 Local tolerability

Local tolerability will be assessed by the investigator according to ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or ‘other findings’.

5.3 OTHER

Not applicable.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects’ safety and to determine pharmacokinetic parameters and biomarkers in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers outlined in Section 5.6 are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 550 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

- C_{max} (maximum measured concentration of the analyte in plasma)
- AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

Further pharmacokinetic parameters might be calculated as appropriate.

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655088 plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K_3-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Within the first 6 hours following start of infusion, blood samples should be taken from the contralateral arm used for infusion.

The K_3-EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples in ice water or on ice. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 655088 plasma concentration

BI 655088 concentrations in plasma will be determined by a validated assay. All details of the analytical method will be available prior to the start of sample analysis.

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.6 BIOMARKERS

5.6.1 Biomarkers for assessment of target engagement

The pharmacodynamic (PD) assessment of this trial comprises determination of exploratory target engagement biomarkers:

5.6.2 Methods of sample collection

PD sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK/PD data), including addition of samples and visits, as long as the total blood volume taken from each subject does not exceed 550 mL. Such changes would be implemented via non-substantial CTP Amendments.

The laboratory should be contacted prior to shipment (
.

After completion of the study the samples may be used for further biomarker investigations, assay development and validation purposes, e.g. method comparison or sample stability studies. These analyses may be performed in laboratories other than Boehringer Ingelheim, Germany, if necessary. The study samples will be discarded after completion of any additional investigations but not later than 5 years after the CTR has been signed.

5.6.3 Analytical determinations

Samples will be measured at Boehringer Ingelheim, TMCP/TMBT, Biberach, Germany. Characteristics of the analytical methods will be given in the clinical study report.

Left over samples for biomarker analysis may be used for further assay development and validation purposes, e.g. method comparison or sample stability studies. These analyses may be performed in laboratories other than Boehringer Ingelheim, Germany, if necessary.

5.7 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

The PK and PD (biomarker) data from this study may be used for an exploratory investigation of PK/PD relationship of BI 655088.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the Flow Chart.

Oral glucose tolerance test at baseline may be done within 8 days prior to the drug administration, i.e. the acceptable deviation from Day -5 will be -3 days.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the start of trial drug administration (including blank values for PK and biomarkers).

The acceptable deviation from the scheduled time for vital signs (BP, PR, and body temperature) and ECG will be:

- ± 15 min up to including 12 h
- ± 30 min from after 12h up to including 48 h

The acceptable deviation from the scheduled time for laboratory samples and bleeding time:

- ± 5 min up to including 2 h
- ± 15 min from after 2h up to including 12 h
- ± 30 min from after 12h up to including 48 h
- ± 120 min from after 48 h up to Day 8
- ± 4 hours from after Day 8 up to Day 29
- ± 1, 2 or 3 days from after Day 29 up to the last measurement as indicated in the Flow Chart

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment period

Each subject will receive one dose of the respective trial medication (BI 655088 or placebo) at Visit 2.

Trial medication will be administered as IV infusion by the investigating physician or his designee. Details on treatments and procedures of administration are described in Section 4.1.4.

Study participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 48 h following the start of infusion. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion.

For details on time points and procedures for collection of blood samples for PK analysis, refer to Flow Chart and Section 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue before the end of the treatment period should undergo the end of trial visit.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The trial design and dose groups are outlined in Section 3.1 and discussed in 3.2.

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 655088 in healthy male subjects following intravenous infusion of single rising doses of
Within the parallel group design the treatment groups (dose levels and pooled placebo) will be compared by using descriptive statistics. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

The secondary objective is the exploration of the pharmacokinetics (PK) and pharmacodynamics (PD) of BI 655088. Endpoints as specified in Section 5.5.1 and 5.6.1 will be analysed by descriptive statistics. Secondary endpoints C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ as defined in Section 5.5.1.1 will be subjected to analysis of dose proportionality by use of the power model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of the different dose groups of BI 655088 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

The following analysis data sets will be used in this trial:

The Randomised set includes all randomised subjects, whether treated or not. This set will be used for Listings. Subjects not randomised will not be analysed in the CTR.

The Treated set (TS) includes all subjects who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. This set will be used for analyses of safety data, refer to Section 7.3.3.

The PK parameter analysis set (PKS) is a per protocol set with regard to PK endpoints, refer to Section 7.3.2. A full analysis set in the sense of ICH E9 will not be used in this trial.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important

protocol violations will be identified no later than in the Report Planning Meeting and provided in the TSAP.

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol violations may be:

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications.

Plasma concentrations and parameters of a subject will be considered as non-evaluable, if for example:

- Missing samples/concentration data at important phases of PK disposition curve

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS as defined in Section 7.3) who provide at least one PK parameter that was not excluded according to the description above.

Assessment of dose proportionality

Dose proportionality will be assessed using the pharmacokinetic endpoints C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ as specified in Section 5.5.1.1.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, …, j = 1, 2, …, n_i;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Graphical displays

To support the analyses of dose proportionality, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of plasma concentrations and the (geometric) mean plasma concentration time profiles as well as C_{max}, AUC_{0-tz}, and $AUC_{0-\infty}$ versus dose.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. The TS as defined in Section 7.3 will be included in the safety analyses.

Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

The analyses will be done by ‘treatment at onset’.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to administration of trial medication will be assigned to 'screening', those between start of drug administration until the end of trial visit will be assigned to the treatment period, and those after the end of trial examination will

be assigned to 'post-treatment'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated. Results of the oGTT, i.e. further plasma glucose and serum insulin measurements will be evaluated in the same way as laboratory data but presented separately. In addition, graphical representations of individual time-courses of plasma glucose and insulin measurements and the (geometric) mean time profiles will be presented.

Area under the curve will be calculated for glucose and insulin according to the linear trapezoidal rule.

Changes in AUCs for glucose and insulin (oGTT measurements) from baseline to post-treatment will be compared between BI 655088 and placebo.

Descriptive statistics of bleeding time at the time points given in the Flow Chart and for the difference from baseline will be provided.

Descriptive statistics of vital signs and for the difference from baseline will be presented per planned time. ECG data will not be listed but clinically relevant abnormal findings will be reported as adverse events.

7.3.4 Preliminary PK and PD analyses

A preliminary analysis of PK parameters (AUC_{0-168} and C_{max} of BI 655088), provided as individual values and geometric means, will be performed for

- dose levels 1, 2, 3, 4 (n) before proceeding to dose level 3, 4, 5, 6 (n+2)

In addition, exploratory analyses of pharmacodynamics
will be performed for each dose level in parallel.

In contrast to the final PK/PD calculations, the preliminary analyses will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. The preliminary analyses will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification.

The preliminary PK/PD results will be distributed to the Investigator and the trial team.

Depending on the results of available preliminary PK/PD analyses, the tolerability and safety of the compound, and changes of dosing schedule (e.g. additional intermediate doses) additional PK/PD preliminary analysis may be performed based on the request of the Trial Clinical Monitor, the investigator, or Trial Clinical Pharmacokineticist. No formal preliminary PK/PD report will be written.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for BI 655088 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.2) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

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

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

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

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or

NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo. Due to the fixed drug administration of the 4 first subjects within each dose group (1st subject active, 2nd subject placebo, 3rd and 4th subject active), the trial is called “partially-randomised”. Each dose group consists of 3 cohorts. The random numbers are assigned to the cohorts sequentially per dose group.

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

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

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 48 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics (R95-0013).

Additional subjects may be entered to allow testing of additional intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 48.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI.

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 protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The certificate of insurance cover is made available to the investigator and each subject, and is stored in the ISF.

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 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, 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 fulfil 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. Therefore a unique reference document for the evaluation of listedness needs to be provided. For BI 655088 this is the current version of the Investigator's Brochure (c02156503-03). The current version of this reference document is 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 serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

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 provided 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, i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R09-6036 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (London, 19 July 2007, doc. ref.EMEA/CHMP/SWP/28367/07). http://www.emea.europa.eu 2007.

R12-0027 European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP): ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals: step 5 (June 2011, EMA/CHMP/ICH/731268/1998). http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/ 09/WC500002828.pdf (access date: 10 January 2012); London: European Medicines Agency (EMA) 2011.

R15-5400 Brown SGA, Stone SF, Fatovich DM, Burrows SA, Holdgate A. Anaphylaxis: clinical patterns, mediator release, and severity. J Allergy Clin Immunol 2013. 132(5):1141-1149.

R15-5401 Anaphylaxis: assessment to confirm an anaphylactic episode and the decision to refer after emergency treatment for a suspected anaphylactic episode (NICE clinical guideline 134, issued: December 2011). http://www.nice.org.uk/guidance/cg134/resources/guidance-anaphylaxis-assessmentto-confirm-an-anaphylactic-episode-and-the-decision-to-refer-after-emergency-tre atment-for-a-suspected-anaphylactic-episode-pdf (access date: 16 October 2015); National Institute for Health and Clinical Excellence 2011.

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c02156503-03 Investigator's Brochure BI 655088. Version 2; 28 September 2017.

c19231668-01 Clinical Overview Statement. 18 August 2017.

10. APPENDICES

10.1 RECONSTITUTION OF IMP AND INSTRUCTION FOR USE

Preparation of trial product is a defined part of reconstitution for application of various doses. It also includes marking of various syringes with a pen in order to avoid mix-up during processing and keep single-blind status.

The preparation steps as described below in Section 10.1.2 will be carried out by experienced and adequately trained staff at the site in a four-eye principle. Training will be provided by the sponsor at the trial initiation meeting or as adequate before dosing and documented in the TMF.

If a change of dose becomes necessary a referring instruction for dilution of trial product will be drawn and filed in the ISF. In this case, an amendment is not required.

10.1.1 Equipment and material for reconstitution and administration

The following material will be used for dilution of trial product and administration:

Table 10.1.1: 1 List of material and equipment

No.	Type	Description	Supplier	Vendor Reference	Usage
	Material for IV preparation				
1	1 mL syringe	Inject F, Luer PP, latex free, PVC free 0.01 mL scale	B.Braun	9166017V	withdrawal, dilution
2	3 mL syringe	Omnifix, Luer Lock PP, latex free, PVC free 0.1 mL scale	B.Braun	4617022V	withdrawal, dilution
3	5 mL syringe	Omnifix, Luer Lock PP, latex free, PVC free 0.2 mL scale	B.Braun	4617053V	withdrawal, dilution
4	10 mL syringe	Omnifix, Luer Lock PP, latex free, PVC free 0.5 mL scale	B.Braun	4617000V	withdrawal, dilution
5	50 mL perfusor syringe	PE, DEHP free, latex free, PVC free 1.0 mL scale	B.Braun	8728844F	withdrawal; contains ready prepared IV solution; insert into perfusor pump
6	18G hypodermic needle	Latex free, needle with needle protection device	B.Braun	4658313	withdrawal
7	Combi stopper	for male and female luer lock syringes	B.Braun	4495101	lock of syringes in between dilution steps
8	Combifix adapter	Luer lock female/female	B.Braun	5206634	connection of syringes for dilution
9	Mini-spike	0.45 µm Air filter latex free, PVC free	B.Braun	4550242	withdrawal of dilution medium from vial
	Dilution medium				
10	Diluent (buffer specific for BI 655088	20R vials, 20 mL	Boehringer Ingelheim	---	dilution medium
	Material and equipment for IV application				
11	Perfusor tubing with luer lock	150 cm PE, latex free	B.Braun	8722935	connection between perfusor syringe and filter
12	Filter 0.2 µm	Posidyne ELD Filter Latex free	PALL	ELD96LLCE	connection between perfusor tubing and catheter
13	Catheter indwelling	Vasofix Safety, 20 G, 1.1x33 mm, 61 mL/min PVC free, latex free	B.Braun	4268113S-01	connection between tubing/filter and subject
14	Infusion pump	Perfusomat fm	B.Braun		syringe pump, setting of application volume and time

10.1.2 Preparation of trial product including placebo for IV infusion

The following doses of BI 655088 will be prepared for IV application:

Table 10.1.2: 1 Concentrations of BI 655088 for intravenous administration

IV dose group	Planned dose of BI 655088	Application volume	Concentration of BI 655088 in ready prepared infusion solution (perfusor syringe filled with 50 mL)

* overfill of syringe which might be necessary to pre-flush the infusion system (tubing, filter) is disregarded as the concentration per mL is still the same

Placebo will be prepared and infused in the same way as corresponding active doses.

Overall instructions for all IV doses

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		No. 1
Date of CTP revision		19 February 2016
EudraCT number		2014-002413-29
BI Trial number		1339.1
BI Investigational Product(s)		BI 655088
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)
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	1. 2. 3. 4.	Titel Page Section 3.1.1 and 5.2.3 Section 5.5.2.3 Section 6.1
Description of change	1. 2. 3. 4.	Telephone and fax number of principal investigator revised Name of additional clinical laboratory added Change of blood sampling tube for Time window for oGTT introduced
Rationale for change	1. 2. 3. 4.	New contact numbers Name specified for administrative purpose Analytical method developed for K_2 EDTA Logistic reason

Number of global amendment		No. 2
Date of CTP revision		12 October 2017
EudraCT number		2014-002413-29
BI Trial number		1339.1
BI Investigational Product(s)		BI 655088
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)
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	1. 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13.	Throughout the protocol as applicable Titel Page and Synopsis Flow Chart Section 1.2.4 Section 2.3 Section 3.1.1 and 5.2.3 Section 3.3.3 Section 3.3.4 Section 4.1.6 Section 5.2.2.1 Section 5.5 and 7.3 Section 7.3.3 Section 1, 8.4.1 and 9.2
Description of change	1. 2.	Formal corrections; adjustment of doses to be tested, number of dose groups and number of subjects Name and contact numbers of principal investigator revised

Number of global amendment		No. 2
	3.	Some of PK blood sampling timepoints on Day 1 and 2 deleted; footnote amended
	4.	Data from dose group and from additional nonclinical experiments amended.
	5.	Benefit-risk assessment for additional data added.
	6.	Name of additional clinical laboratory revised.
	7.	Exclusion criterion 13 and 14 revised to exclude current smokers or ex-smokers with a history of ≥10 pack years
	8.	Criterion for stopping dose escalation added.
	9.	Re-supply of trial medication will be planned.
	10.	Update of AE definitions.
	11.	
	12.	Deletion of erroneous text fragment.
	13.	Update of References.
Rationale for change	1.	
	2.	New principal investigator.
	3.	Timepoints not needed for PK/PD evaluation.
	4.	New data available.
	5.	New data available.
	6.	Administrative change.
	7.	To align with exclusion criterion 24.
	8.	To specify how will be considered for the decision on dose escalation.
	9.	Due to temporary hold of the trial, initial supply might expire.
	10.	Administrative change.
	11.	
	12.	Formal correction.
	13.	Updated or new references were issued.

Number of global amendment		No. 3
Date of CTP revision		22 November 2017
EudraCT number		2014-002413-29
BI Trial number		1339.1
BI Investigational Product(s)		BI 655088
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)
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	1. 2. 3.	Flow Chart and Section 5.2.4 Section 1.2.4 Section 3.3.3
Description of change	1. 2. 3.	Triplicate 12-lead ECG introduced at screening Editorial change; medical background information for subject with SAE added Exclusion criterion no. 24 amended by cardiovascular disease
Rationale for change	1. 2. 3.	Recommended by competent authority Amended for clarification To explicitly exclude personal or family history of cardiovascular disease

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 655088 administered by intravenous infusion in healthy male subjects (single-blind, partially randomised within dose groups, placebo-controlled, parallel group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		23 Nov 2017 13:18 CET
Author-Trial Clinical Monitor		23 Nov 2017 13:49 CET
Approval-Team Member Medicine		23 Nov 2017 15:28 CET
Approval-Clinical Pharmacokinetics		23 Nov 2017 17:16 CET
Approval-Therapeutic Area		23 Nov 2017 20:10 CET
Verification-Paper Signature Completion		27 Nov 2017 15:30 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed