Clinical Trial Protocol

	Document Number: c08998695-04
BI Trial No.:	1368-0009
BI Investigational Product:	BI 655130
Title:	Safety, tolerability and pharmacokinetics of single rising intravenous dose and single subcutaneous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled design)
Lay title:	This study is done in healthy Japanese volunteers. It looks at how BI 655130 is taken up in the body and how well it is tolerated.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol(based on global amendment3))
Version and Date:	Version: 4.0 Date: 01 Aug 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 18 Jan 2017	**Trial number:** 1368-0009		**Revision date:** 01 Aug 2017

Title of trial:	Safety, tolerability and pharmacokinetics of single rising intravenous dose and single subcutaneous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability and pharmacokinetics following single rising intravenous dose and single subcutaneous does of BI 655130
Methodology:	double-blind, randomised, placebo-controlled within dose group
No. of subjects:	
total entered:	32 Japanese
each treatment:	8 subjects per dose group (6 on active drug and 2 on placebo)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male Japanese subjects Age ≥20 and ≤45 years BMI range: ≥18.5 and ≤25.0 kg/m^2
Test product 1:	BI 655130 [redacted]) solution for infusion
dose:	Single dose of [redacted] and [redacted] mg
mode of admin.:	Intravenous as 90 min infusion
Test product 2:	BI 655130 [redacted]) solution for injection
dose:	Single dose of [redacted]
mode of admin.:	Subcutaneous injection
Comparator product 1:	Matching placebo for BI 655130 ([redacted]L) solution for infusion
dose:	Not applicable

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mode of admin.:	Intravenous as 90 min infusion
Comparator product 2:	Matching placebo for BI 655130 ([redacted] solution for injection
dose:	Not applicable
mode of admin.:	Subcutaneous injection
Duration of treatment:	One day (single dose) for each treatment
Criteria for pharmacokinetics:	(iv) single rising dose group Secondary endpoints: $AUC_{0-\infty}$, C_{max}, CL and V_{ss} (sc) single dose group Secondary endpoints: $AUC_{0-\infty}$ and C_{max}
Criteria for pharmacodynamics:	Not applicable
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of subjects with drug-related adverse events (AEs).
Statistical methods:	Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 655130 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed.

FLOW CHART

(iv) Single rising dose group

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]		Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]
1	-28 to -3			screening[1]			X		X		X	
2	-3 to -1	-72:00	8:00	ambulatory visit			X[11]					
	-1	-12:00	20:00	admission to trial site								X
	1	-2:00	6:00	randomization and pre-dose[2]	X		X	X	X		X	X[5]
		0:00	8:00	drug administration start of infusion						▲		
		0:30	8:30	↓						↓	X	
		1:00	9:00	↓						↓	X	
		1:30	9:30	▼ end of infusion[12]	X			X	X	↓	X	X[5]
		2:00	10:00		X			X	X	▼	X	
		3:00	11:00		X						X	
		4:00	12:00	Lunch[6]	X		X				X	X[5]
		6:00	14:00					X	X		X	
		8:00	16:00		X						X	
		10:00	18:00	Dinner[6]								
		12:00	20:00		X			X	X		X	X[5]
	2	24:00	8:00	Breakfast[6]	X		X	X	X		X	X[5]
		28:00	12:00	Lunch[6]								
		32:00	16:00					X			X	
		34:00	18:00	Dinner[6]								X
	3	48:00	8:00	Discharge from trial site (confirmation of fitness[7])	X				X		X	X
	4	72:00	8:00	ambulatory visit	X		X					X
	5	96:00	8:00	ambulatory visit	X							X
	8	168:00	8:00	ambulatory visit	X		X		X		X	X
	15	336:00	8:00	ambulatory visit	X							X

FLOW CHART (cont.)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]		Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]
2	22	504:00	8:00	ambulatory visit	X		X		X		X	X
	29	672:00	8:00	ambulatory visit	X		X		X		X	X
	36	840:00	8:00	ambulatory visit	X							X
	43	1008:00	8:00	ambulatory visit	X							X
	57	1344:00	8:00	ambulatory visit	X							X
	71	1680:00	8:00	ambulatory visit	X							X
	92±2	2184:00	8:00	ambulatory visit	X							X
	120±3	2856:00	8:00	ambulatory visit	X							X
3	148±3	3528:00	8:00	EOT [10]	X [13]		X		X		X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate: blood sampling is to be performed and completed within 30 minutes prior to drug administration; all other procedures are to be performed and completed within 2 h prior to drug administration. Within 2 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV, QuantiFERON), and drug screening.
4. PK sampling times may be adapted based on information obtained during trial conduct.
5. Local tolerability test inclusive.
6. If several actions are indicated at the same time point, the intake of meals will be the last action.
7. Confirmation of fitness includes physical examination.

9. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.

11. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.
12. First measure after completion of infusion collection of PK sample

FLOW CHART

(sc) Single dose group

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]		Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]
1	-28 to -3			screening[1]			X		X		X	
2	-3 to -1	-72:00	8:00	ambulatory visit			X[11]					
	-1	-12:00	20:00	admission to trial site								X
	1	-2:00	6:00	randomisation and pre-does[2]	X		X	X	X		X	X[5]
		0:00	8:00	drug administration						▲		
		0:30	8:30		X			X		|	X	X[5]
		1:00	9:00							|	X	
		1:30	9:30		X					|	X	
		2:00	10:00		X			X	X	▼	X	
		3:00	11:00		X						X	
		4:00	12:00	Lunch[6]	X		X				X	X[5]
		6:00	14:00					X	X		X	
		8:00	16:00		X						X	
		10:00	18:00	Dinner[6]								
		12:00	20:00		X			X	X		X	X[5]
	2	24:00	8:00	Breakfast[6]	X		X	X	X		X	X[5]
		28:00	12:00	Lunch[6]								
		32:00	16:00					X			X	
		34:00	18:00	Dinner[6]								X[5]
	3	48:00	8:00	Discharge from trial site (confirmation of fitness[7])	X				X		X	X[5]
	4	72:00	8:00	ambulatory visit	X		X					X[5]
	5	96:00	8:00	ambulatory visit	X							X[5]
	8	168:00	8:00	ambulatory visit	X		X		X		X	X[5]
	15	336:00	8:00	ambulatory visit	X							X[5]

FLOW CHART (cont.)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]		Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]
	22	504:00	8:00	ambulatory visit	X		X		X		X	X[5]
	29	672:00	8:00	ambulatory visit	X		X		X		X	X[5]
	36	840:00	8:00	ambulatory visit	X							X[5]
	43	1008:00	8:00	ambulatory visit	X							X[5]
2	57	1344:00	8:00	ambulatory visit	X							X[5]
	71	1680:00	8:00	ambulatory visit	X							X
	92±2	2184:00	8:00	ambulatory visit	X							X
	120±3	2856:00	8:00	ambulatory visit	X							X
3	148±3	3528:00	8:00	EOT[10]	X[12]		X		X		X	X[5]

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate: blood sampling is to be performed and completed within 30 minutes prior to drug administration; all other procedures are to be performed and completed within 2 h prior to drug administration. Within 2 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV, QuantiFERON), and drug screening.
4. PK sampling times may be adapted based on information obtained during trial conduct.
5. Local tolerability test inclusive.
6. If several actions are indicated at the same time point, the intake of meals will be the last action.
7. Confirmation of fitness includes physical examination.

9. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.

11. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.

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ABBREVIATIONS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
AST	Aspartate amino transferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
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
$\%AUC_{tz-\infty}$	the percentage of $AUC_{0-\infty}$ obtained by extrapolation
β	Slope parameter associated with the power model used to evaluate dose proportionality
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravenous administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CRO	Clinical Research Organization
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supply Unit
DILI	Drug induced liver impairment
DP	Drug product
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Linked Immunosorbent Assay
EOT	End of trial
FDA	Food and Drug Administration
FIH	First in Human
GCP	Good Clinical Practice

HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IPV	Important protocol violations
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant in plasma
kDA	Kilodalton
LI	linearity index
LOQ	Limit of Quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters Mercury
MMP	Matrix metalloproteinase
MRD	Multiple Rising Dose
MRT	Mean residence time of the analyte in the body after intravenous administration
N	Number
NC	Not calculated
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
pM	Picomolar
PR	Pulse rate
PTM	Planned Time
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)
REP	Residual Effect Period
RR	Respiratory Rate
SAE	Serious adverse event
SOP	Standard Operating Procedure
SRD	Single-rising dose
ss	(at) steady state

$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TGF	Transforming growth factor
TMDD	Target mediated drug disposition
TMF	Trial Master File
TSAP	Trial statistical analysis plan
UC	Ulcerative colitis
ULN	Upper limit of normal
USP	United States Pharmacopeia
V_{ss}	Volume of distribution at steady state after intravenous administration
V_z	Volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White Blood Cells

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 655130 following administration of single rising intravenous doses and single subcutaneous dose in healthy Japanese male volunteers.

Secondary objective is the exploration of the pharmacokinetics including dose proportionality of BI 655130 in healthy Japanese male volunteers.

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.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The single rising intravenous dose part of the trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups. The single subcutaneous dose part of the trial is designed as double blind, randomised, and placebo-controlled.

A total of 32 healthy male subjects is planned to participate in the trial, according to 4 dose groups comprising 8 subjects per group. Within each dose group 6 subjects will receive the active drug and 2 subjects will receive placebo.

Only single dose is tested within each dose group. 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**
Dose	intravenous			subcutaneous
	[redacted]	[redacted]	[redacted]	[redacted]
No. of subjects	8	8	8	8
Subjects receiving placebo	2	2	2	2
Subjects receiving active	6	6	6	6

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 14 days between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group in single rising dose part. (Dose groups 1-3) 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).

The investigator is allowed to interrupt the further dose escalation in case the safety evaluation leads to concerns until alignment with sponsor.

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 is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial will be conducted at in 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 under the responsibility of Clinical Operations in BI Korea.

Safety laboratory tests will be performed by the local laboratory of the trial site or/and at a CRO designated by the sponsor.

The analyses of BI 655130 concentrations in plasma and ADAs will be performed at .

Data management and statistical evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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

For single rising dose part, 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 655130.

With the rising dose design, double-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 and investigators. 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 subcutaneous part (will start at least 1 week after the first drug administration of the first dose group (of the single-rising intravenous dose part.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. 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 the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 32 healthy male subjects will enter the study. 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 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. Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who were all born in Japan
3. Age of 20 to 45 years (incl.)
4. BMI of 18.5 to 25.0 kg/m^2 (incl.)
5. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
6. Male subjects who agree to minimize the risk of female partners being pregnant by fulfilling any of the following criteria starting from the first administration of trial medication and until 30 days after trial completion:
   - Use of adequate contraception, e.g. any of the following methods *plus* condom: combined oral contraceptives, intrauterine device
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy) female partner

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), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections including active tuberculosis, HIV or viral hepatitis; QuantiFERON TB test will be performed at screening.
9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
11. Participation in another trial where an investigational drug has been administered within 5 half-lives prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug.

13. Administered live vaccine within 6 weeks prior to randomisation or Have plans for administration of live vaccines during the study period.
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 30 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than [redacted] within 30 days prior to administration of trial medication or intended donation during the trial
19. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
20. Inability to comply with dietary regimen of trial site
21. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
22. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
23. 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

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 Section 10.1 of this clinical trial protocol and 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.

Infusion reactions should also lead to the removal of an individual subject. However, in mild transient cases of infusion reactions (with clinical symptoms such as dizziness, headache, nausea) requiring no treatment the clinical investigator may continue [P16-06636]. However, the overall infusion time must not exceed 90 minutes.

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 first 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). The only exception to this rule is when the subject had an AESI and/or SAE that the investigator considers related to the screening procedure. 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. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. 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 findings or serious adverse events invalidate 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.

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 replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator products

For intravenous administration

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	(per [redacted] vial)
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose [redacted]

At the time of use, the IV solution for dosing will be prepared as detailed in the instruction given in ISF.

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

Substance:	
Pharmaceutical formulation:	solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	not applicable
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose [redacted]

For subcutaneous administration

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	solution for injection
Source:	BI Pharma GmbH & Co. KG, Germany

Unit strength:	(per [redacted] vial)
Posology:	1-0-0
Route of administration:	SC injection
Duration of use:	Single dose ([redacted]

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

Substance:	
Pharmaceutical formulation:	solution for injection
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	not applicable
Posology:	1-0-0
Route of administration:	SC injection
Duration of use:	Single dose ([redacted]

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 according to their temporal availability. As soon as enough subjects have been allocated to one of the 4 dose groups, the following subjects will be allocated to one of the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population in each ethnicity, relevant imbalances between the dose groups are not expected.

The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. 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

Three dose strengths for intravenous administration and one dose strength for subcutaneous administration are to be investigated in this trial. These three doses for IV will cover potential therapeutic dose ranges and provide a safety margin for future development. The number of doses will also allow for evaluation of dose proportionality.

This trial is designed to evaluate the safety, tolerability and pharmacokinetics of BI 655130 in Asian healthy young male volunteers using a safe and tolerable dose achieved in previous trials.

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. Each subject will receive one single dose of trial medication. The dose volume for placebo corresponds to the dose volume of the respective dose level. For further details concerning timing see Flow Chart. Detailed instructions for the preparation are provided in ISF.

Table 4.1.4: 1 Final dose of BI 655130 in solution containing active drug

Dose group	Final dose of BI 655130 [redacted]
1	[redacted] (intravenous infusion)
2	[redacted] (intravenous infusion)
3	[redacted] (intravenous infusion)
4	[redacted] subcutaneous injection)

For intravenous administration

The detailed instructions for the dilution of the trial product, the preparation of the infusion solution and the volume to be administered is provided in ISF. In all subjects the infusion solution will be intravenously administered over 90 minutes approximately between 8:00 and 10:00 of the respective study day. Start and end time of the infusion will be recorded.

In case of safety concerns, e.g. due to infusion reactions, the investigator or his/her designee should stop of the infusion. Further based on medical judgment he/she will provide medications such as steroids, etc. as needed.

For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

The administration of the trial medication on all study days will be done under supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.

Water is allowed except for 1 hour before start of infusion and 1.5 h after end of infusion.

For subcutaneous administration

Following an overnight fast of at least 10 hours, the medication will be administered. Trial drug will be injected subcutaneously in the abdominal region. The skin is sanitized before injection. Combi-stopper is removed from syringe containing trial drug. Syringe is connected to hypodermic needle for injection. Needle is placed subcutaneously and solution with trial drug is injected within 60 seconds. Detailed handling instructions will be provided in the ISF.

For all dose groups standardised meals will be served as outlined in the Flow Chart. Subjects will be kept under close medical surveillance until 48 h following drug administration. Thereafter subjects will be discharged and further assessments will be conducted in an ambulatory fashion. For restrictions with regard to diet see also Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators. The trial will only be unblinded to the subjects, investigators and trial site staffs after locking of the database.Sponsor staffs that have direct interaction with the investigator and site staff (e.g. CML and CRA) will not be aware of the treatment allocation (i.e. active vs placebo) as well until database lock.
Monitoring on drug accountability should be conducted by unblinded CRA.
Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

4.1.5.2 Procedures for emergency unblinding

For blinded trials, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

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 clinical trial supply containers will be labelled with:

- BI trial number
- Medication number
- Batch 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 and address
- Storage conditions

- Use-by date
- Investigator

The vials are labelled with reduced requirements.

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. Examples of the labels will be available in the ISF.

Re-supply is planned.

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. Where necessary, 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 ‘Trial Staff List’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. All used medication will be destructed locally by the trial site. Receipt, usage, return and disposal must be documented on the respective forms in ISF. 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 or partially used 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 or

return to the sponsor, 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. On Day 1 for all subjects, no food is allowed for at least 10 h before and 1.5 h after administration of the study drug (= end of infusion for intravenous dose group).

On all days of drug administration, starting from 1 hour before drug administration until 1.5 h after the completion of administration liquid intake is not allowed. Until 24 hours post-dose water intake will be within [redacted]. Total fluid intake on all 24 hours inhouse days is recommended to be at least 1.5 liters and should not exceed 3.5 liters.

Smoking is not allowed during in-house confinement at the trial site. On the ambulatory days it is restricted to not more than 10 cigarettes or 3 cigars or 3 pipes per day

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during inhouse confinement. Alcoholic beverages are not permitted starting 7 days before the first administration of trial medication until Day 28. From Day 29 onwards, alcohol consumption is restricted to 20 g alcohol per day corresponding to 0.5 L beer or 0.2 L of white wine per day.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first 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 655130 is the number [N (%)] of subjects with drug-related AEs.

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse)

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.

Adverse reaction

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

Serious adverse event

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

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

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

AEs considered 'Always Serious'

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 RDC system, a remote data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

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.

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:
    - 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
    - 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

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

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

5.2.2.2 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.

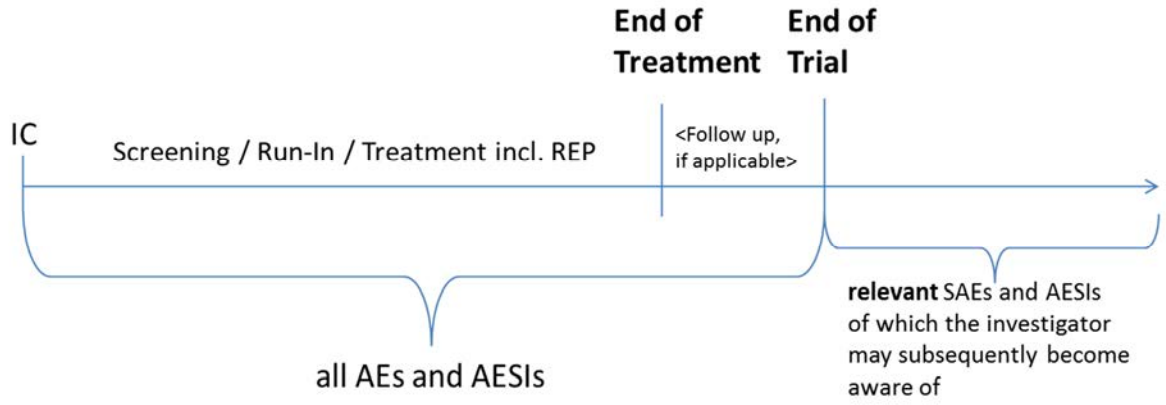
Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will 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 an 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 may become aware of.



The residual effect period (REP) for BI 655130, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment, please see section 7.3.3.

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

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). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (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.

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

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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

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

5.2.3 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 designate for retests.

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.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is a clinically relevant abnormality in the automatic blood cell count or in the urinalysis, respectively, and it is deemed clinically necessary by the investigator.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute cell count)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC[1]	Neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (ALP)) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Serum tryptase[1]
Hormones[2]	Thyroid stimulating hormone (TSH) fT3, fT4
Substrates	Serum glucose Creatinine Total bilirubin Direct bilirubin Total protein Protein electrophoresis (Protein EP) (only at screening examination)[1] Albumin Alpha-1-Globulin Alpha-2-Globulin Beta-Globulin Gamma-Globulin C-Reactive Protein (CRP) Uric acid Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Chloride Calcium Inorganic phosphate (IP)

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment[3]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Only if automatic differential WBC is abnormal and it is deemed clinically necessary by the investigator

[2] Only at screening

[3] Only if erythrocytes, leukocytes, nitrite or protein are abnormal in urinalysis and it is deemed clinically necessary by the investigator

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. Drug screening will be performed at screening.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Opiates
Infectious screening (blood)[1]	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV antibody (qualitative) QuantiFERON (qualitative)

[1] Only at screening

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening, and may be repeated at any time during the study at the discretion of an investigator or designate. The results will not be included in the CTR.

In case of a potential systemic allergic reaction blood samples for determination of serum tryptase will be collected 0.5 h, 2 h, 6 h and 24 h after onset of the event.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory of the trial site or/and at a CRO designated by the sponsor.

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

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 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 a 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.

At all 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). 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.

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.

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.

5.2.4.2 Continuous ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 12-lead ECG recording for at least 15 min before (for baseline assessment) and 2 h following drug administration.

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 in healthy volunteers) will be measured by a blood pressure monitor 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.

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 with determination of weight

5.2.5.3 Local tolerability test

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

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Not applicable.

5.3.2 Other endpoints

Not applicable.

5.3.3 Other assessments

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 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, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be documented in the CRFs. The actual sampling times will be used for determination of pharmacokinetic parameters.

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 [redacted]. 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

IV administration:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)
- CL (total clearance of the analyte in the plasma after intravenous administration)
- V_{ss} (Volume of distribution at steady state after intravenous administration)

SC administration:

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, approximately [redacted] of blood will be taken from a forearm vein into a K_2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Two aliquots of plasma will need to be processed from the blood volume collected at each planned time point. The detailed procedure for sample processing and handling can be found in the Lab Manual.

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing. However, only data related to the analyte 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 after the final study report has been signed.

5.5.3 Analytical determinations

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

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, observation visit, and end of trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration (including blank values for PK).

The acceptable deviation from the scheduled time for vital signs and ECG will be:
- ±15 min up to including 12 h
- ±30 min from 12h up to including 48 h
- ±60 min from 48 h up to Day 8
- ±24h from Day 15 up to Day 71
- ±48h on Day 92
- ±72h from Day 120 up to the last measurements

The tolerance for pharmacokinetic/ADA/laboratory parameters will be:
- ±1 min up to including 1 h
- ±5 min up to including 12 h
- ±15 min up to including 48 h
- ±60 min from 48 h up to Day 8
- ±24h from Day 15 up to Day 71
- ±48h on Day 92
- ±72h from Day 120 up to the last measurements

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.

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

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 drug administration. 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.

Trial medication will be administered as intravenous infusion or subcutaneous injection according to each dose group by the investigating physician or designee. Details on treatments and procedures of administration are described in Section 4.1.4.

For details on time points and procedures for collection of plasma 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 and follow-up period

For AE assessment, laboratory tests, collection of PK and ADA samples, 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 treatment before the end of the planned 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

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 655130 by using descriptive statistics for all endpoints comparing active dose groups to placebo. 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) of BI 655130. Endpoints as specified in 5.5.1 will be analysed by descriptive statistics. $AUC_{0-\infty}$ and C_{max} for intravenous doses will be subjected to analysis of dose proportionality by use of the power model.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 4 different dose groups of BI 655130 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

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 (IPVs) 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). Analyses will be performed for parent drug.

Plasma concentration data and parameters of a subject will be included in the statistical PK

analysis 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 violation may be:

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

Plasma concentrations and/or 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 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 for $AUC_{0-\infty}$ and C_{max} in intravenous doses.

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 number of dose groups i = 1, 2, 3, and j = 1, 2, …, N where N is the number of subjects per dose group;
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.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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.

Measurements (such as vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the concept of treatment emergent AEs. Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake 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-study’. 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 highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial examination will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.4 Interim analyses

A preliminary analysis of available safety, tolerability and/or PK data will be performed in order to provide the results for the interaction with regulatory agency.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 655130 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 7.3.1.) will be reported with their individual plasma and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma, 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/urine 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 analysed), 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.

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 32 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 in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics [R95-0013].

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 SOPs.

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.

The certificate of the insurance cover is made available to the investigator and the subjects, 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/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her 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 CTMF.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the 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.

8.3.3 Storage of records

Trial site:
The trial site must retain the source and essential documents (including ISF) for 15 years based on the site's Trial Close-Out Visit date.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P16-06636 Denis Choquette, Rafat Faraawi et al., J Rheumatol 2015;42;1105-1111

R09-2768 Vargas HM, Bass AS, Breidenbach A, Feldman HS, Gintant GA, Harmer AR, Heath B, Hoffmann P, Lagrutta A, Leishman D, McMahon N, Mittelstadt S, Polonchuk L, Pugsley MK, Salata JJ, Valentin JP. Scientific review and recommendations on preclinical cardiovascular safety evaluation of biologics. J Pharmacol Toxicol Methods 2008;58(2):72-76.

R13-2269 Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. Dig Dis 2010;28:536-542.

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.

9.2 UNPUBLISHED REFERENCES

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

c03320877-02 Investigator’s Brochure of BI 655130

c03361085-07 Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers, 1368.1, 27 Jan 2016.

c09105854-04 Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects, 1368.2, 11 Oct 2016.

10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-specified AESIs), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 h. If it is confirmed that ALT and/or AST values ≥3 fold ULN occur in conjunction with an elevation of total bilirubin of ≥2 fold ULN, the laboratory parameters listed below (clinical chemistry, serology, hormones, haematology) must be determined and made available to the investigator and to BI as soon as possible.

In addition,

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

and report these via the CRF.

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

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

Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

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

11. DESCRIPTION OF GLOBAL AMENDMENT

Number of global amendment		1
Date of CTP revision		17 Feb 2017
EudraCT number		
BI Trial number		1368-0009
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravenous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled 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. Throughout the protocol 2. Throughout the protocol 3. Synopsis 4. Synopsis 5. Synopsis 6. Synopsis 7. Flow Chart 8. Flow Chart 9. Flow Chart 10. Flow Chart 11. Flow Chart 12. Abbreviation 13. Abbreviation 14. Abbreviation 15. Abbreviation 16. Section 1.2 17. Section 2.1 18. Section 2.2

Number of global amendment		1
		19. Section 2.3 20. Section 2.3 21. Section 3.1 22. Section 3.1.1 23. Section 3.2 24. Section 3.3 25. Section 3.3.3 26. Section 4.1.1 27. Section 4.1.2 28. Section 4.1.2 29. Section 4.1.2 30. Section 4.1.3 31. Section 4.1.4 32. Section 4.1.8 33. Section 4.1.8 34. Section 4.2.2.2 35. Section 4.2.2.2 36. Section 5.2.2.2 37. Section 5.2.3 38. Section 5.2.3 39. Section 5.2.5.3 40. Section 5.5.1.1 41. Section 5.5.1.1 42. Section 5.5.1.2 43. Section 6.2.2 44. Section 7.2 45. Section 7.3.4 46. Section 7.6 47. Section 9.2
Description of change		1. 1368.0009 -> 1368-0009 2. Deletion of single subcutaneous dose group in title 3. Insert of ‘Lay title’ 4. Number of subjects 32 -> 24 5. Deletion of Test product 2 and Comparator pruduct 2 6. Deletion of sc dose group in Criteria for PK 7. Deletion of sc dose group 8. Pkplasma -> pkblood 9. Remove '9' on Laboratory/Urinalysis 10. Remove 'Breakfast' 11. Local telerability test inclusite in Note 5 12. Remove bolus in MRT 13. REP: Residual Effect Period 14. RR: Respiratory Rate

Number of global amendment		1
		15. Remove single in Vss 16. Update the result of 1368-0002 in Clinical PK/PD studies 17. Update the reference of 1368-0002 18. Deletion of sc dose group 19. Deletion of sc dose group in Drug-related risks and safety measures 20. Deletion of continuous ECG monitoring interval 21. Deletion of sc dose group 22. -> 23. Deletion of sc dose group 24. Number of subjects 32 -> 24 25. Update the exclusion criteria 13 26. Deletion of sc IMP 27. One of the 8 dose groups -> one of the 3 dose groups 28. Add 'As the study includes healthy subjects from a homogenous population in each ethnicity, relevant imbalances between the dose groups are not expected.' 29. Remove 'For this purpose, the subjects will be allocated to a study subject number by drawing lots. ' 30. Deletion of sc dose group 31. Deletion of sc dose group and details of infusion bag 32. Disposed locally by the trial site upon written authorisation by the clinical monitor -> destructed locally by the trial site 33. Disposal of unused products -> disposal of unused or partially used products 34. Deletion of 'From breakfast' 35. From Day 28 -> From Day 29 36. Add 'Pregnancy' related paragraph 37. Deletion of 'and at admission to trial site the day prior to each treatment.' 38. Deletion of 'and at start of the inhouse period (Day -1), ' 39. Local tolerability -> Local tolerability test 40. Deletion of sc dose group 41. Deletion of 'apparent' in Vss 42. Deletion of 'total' in MRT 43. Deletion of sc dose group 44. Deletion of sc dose group

Number of global amendment		1
		45. Deletion of 'and/or PK' 46. Number of subjects 32 -> 24 47. Add reference for 1368-0002 trial
Rationale for change		1. Format change of trial name 2. Deletion of SC dose group 3. Update 4. Update due to deletion of SC dose group 5. Update due to deletion of SC dose group 6. Update due to deletion of SC dose group 7. Update due to deletion of SC dose group 8. Correction 9. Correction 10. Update 11. To clarify 12. Correction 13. Correction 14. Correction 15. Correction 16. Update 17. Update 18. Update due to deletion of SC dose group 19. Update due to deletion of SC dose group 20. Correction 21. Update due to deletion of SC dose group 22. To clarify 23. Update due to deletion of SC dose group 24. Update due to deletion of SC dose group 25. To clarify 26. Update due to deletion of SC dose group 27. Correction 28. To clarify 29. Correction 30. Update due to deletion of SC dose group 31. Update due to deletion of SC dose group and details are specified in ISF 32. Correction 33. To clarify 34. Correction 35. Correction 36. Update the process for pregnancy 37. Correction 38. Correction 39. To clarify 40. Update due to deletion of SC dose group 41. Correction

Number of global amendment		1
		42. Correction 43. Update due to deletion of SC dose group 44. Update due to deletion of SC dose group 45. Correction 46. Update due to deletion of SC dose group 47. Update of reference

Number of global amendment		2
Date of CTP revision		24 Feb 2017
EudraCT number		
BI Trial number		1368-0009
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravenous dose and single subcutaneous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled 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. Thoughout the protocol 2. Synopsis 3. Synopsis 4. Synopsis 5. Flow Chart 6. Section 2.2 7. Section 2.3 8. Section 3.1 9. Section 3.2 10. Section 3.3 11. Section 4.1.1 12. Section 4.1.2 13. Section 4.1.3 14. Section 4.1.4 15. Section 4.1.5.1 16. Section 5.5.1.1 17. Section 5.5.1.2 18. Section 6.2.2 19. Section 7.2 20. Section 7.6

Number of global amendment		2
Description of change		1. Addition of single subcutaneous dose group in title 2. Number of subjects 24 -> 32 3. Addition of Test product 2 and Comparator pruduct 2 4. Addition of sc dose group in Criteria for PK 5. Addition of sc dose group 6. Addition of sc dose group 7. Addition of sc dose group in Drug-related risks and safety measures 8. Addition of sc dose group 9. Addition of sc dose group 10. Number of subjects 24 -> 32 11. Addition of sc IMP 12. Addition of sc dose group 13. Addition of sc dose group 14. Addition of sc dose group 15. Add the unblinded CRA for drug accountability 16. Addition of sc dose group 17. Addition of sc dose group 18. Addition of sc dose group 19. Addition of sc dose group 20. Number of subjects 24 -> 32
Rationale for change		1. Addition of SC dose group 2. Update due to addition of SC dose group 3. Update due to addition of SC dose group 4. Update due to addition of SC dose group 5. Update due to addition of SC dose group 6. Update due to addition of SC dose group 7. Update due to addition of SC dose group 8. Update due to addition of SC dose group 9. Update due to addition of SC dose group 10. Update due to addition of SC dose group 11. Update due to addition of SC dose group 12. Update due to addition of SC dose group 13. Update due to addition of SC dose group 14. Update due to addition of SC dose group 15. Update due to the difference in color of sc formulation between active and placebo 16. Update due to addition of SC dose group 17. Update due to addition of SC dose group 18. Update due to addition of SC dose group 19. Update due to addition of SC dose group 20. Update due to addition of SC dose group

Number of global amendment		3
Date of CTP revision		01 Aug 2017
EudraCT number		
BI Trial number		1368-0009
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravenous dose and single subcutaneous dose of BI 655130 in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled 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. Section 3.1.1 2. Section 4.1.4 3. Section 5.2.3 4. Section 6.1
Description of change		1. The name for analytic analysis is changed to 2. Change 'For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject and closed with a mandrin.' ➔ 'For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject and will be kept patent with a saline infusion.' 3. Add the description for safety laboratory test, '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 designate for

Number of global amendment		3
		retests. 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. Manual differential white blood cell count or urine sediment examinations will only be performed if there is a clinically relevant abnormality in the automatic blood cell count or in the urinalysis, respectively.' Change 'Plasma glucose' ➔ 'Serum glucose' Remove 'microscopic examination if urine analysis abnormal' Change 'Laboratory data will be transmitted electronically from the laboratory to the trial site.' ➔ 'Laboratory data will be transmitted electronically from the trial site to BI.' 4. Change 'The tolerance for pharmacokinetic /laboratory parameters will be' ➔ 'The tolerance for pharmacokinetic/ADA/laboratory parameters will be' Change '±24h from Day 8 up to Day 71' ➔ '±24h from Day 15 up to Day 71'
Rationale for change		1. The analytic laboratory is changed 2. Mandrin is not available in this trial 3. To clarify regarding safety laboratory test (sample logistics, fasting status, condition for urine sediment test) 4. To clarify the time window for sampling

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		01 Aug 2017 14:22 CEST
Approval-Therapeutic Area		01 Aug 2017 16:10 CEST
Author-Clinical Monitor		02 Aug 2017 02:04 CEST
Approval-Clinical Pharmacokinetics		02 Aug 2017 03:04 CEST
Author-Trial Statistician		02 Aug 2017 07:42 CEST
Verification-Paper Signature Completion		02 Aug 2017 07:48 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed