Clinical Trial Protocol

	Document Number: c10896574-01
EudraCT No.:	2016-004557-32
BI Trial No.:	1368-0003
BI Investigational Product:	BI 655130
Title:	Safety, tolerability, and pharmacokinetics of two dose strengths of a single subcutaneous dose of BI 655130 and one single intravenous dose of BI 655130 in healthy male and female subjects (open-label, parallel group design)
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol
Version and Date:	Version: 1.0 Date: 08 March 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: 08 March 2017	**Trial number:** 1368-0003		**Revision date:** Not applicable

Title of trial:	Safety, tolerability, and pharmacokinetics of two dose strengths of a single subcutaneous dose of BI 655130 and one single intravenous dose of BI 655130 in healthy male and female subjects (open-label, parallel group design)
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics of two dose strengths of a single subcutaneous injection of BI 655130 and relative bioavailability of one strength of the subcutaneous formulation compared to an intravenous dose
Methodology:	Open-label, partially randomised design
No. of subjects:	
total entered:	36
each treatment:	12
Diagnosis:	Healthy subjects assigned to the intravenous dose will be matched for gender and body weight (± 10%) to subjects receiving the subcutaneous dose
Main criteria for inclusion:	Healthy male and female subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Test product:	BI 655130 solution for injection
dose:	and [Test]
mode of admin.:	Subcutaneous (SC) injection (periumbilical)
Comparator product:	BI 655130 solution for infusion [Reference]
dose:	
mode of admin.:	Intravenous (IV) as 30 min infusion
Duration of treatment:	One day (single dose) for each treatment

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 08 March 2017	**Trial number:** 1368-0003		**Revision date:** Not applicable
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoints: $AUC_{0-\infty}$		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, local tolerability, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]) and oral body temperature		
Statistical methods:	Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including effects for 'treatment'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

FLOW CHART

Single dose of BI 655130 as SC, SC or single IV infusion of of BI 655130 (subjects will receive only one dose)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]		Laboratory/ Urinalysis [3]	Body Temperature	Body Weight	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [11]
1	-28 to -3			screening[1]			X		X	X		X	
2	-2	-48:00	8:00	ambulatory visit			X[13]						
2	-1	-12:00	20:00	admission to trial site			X[10]						X
	1	-2:00	6:30		X[2]		X[2,9]	X[2]		X[2]		X[2]	X[2,5]
		0:00	8:00	drug administration start of infusion or SC injection							▲ |		
		0:30	8:30	▼ end of infusion[14]	X			X		X	|	X	X[5]
		1:00	9:00								|	X	
		1:30	9:30							X	|	X	
		2:00	10:00	light breakfast[6]	X			X		X	▼	X	
		2:30	10:30										
		3:00	11:00		X							X	
		4:00	12:00	Lunch[6]	X		X[9]					X	X[5]
		6:00	14:00					X		X		X	
		8:00	16:00	snack (voluntary)[6]	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[9]	X		X		X	X[5]
		28:00	12:00	Lunch[6]									
		32:00	16:00	snack (voluntary)[6]				X				X	
		34:00	18:00	Dinner[6]									X[5]
	3	48:00	8:00	Breakfast[6] 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]
	6	120:00	8:00	ambulatory visit	X								X[5]
	7	144:00	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]

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	Body Weight	12-lead ECG	ECG monitoring	vital signs (BP, PR)	Query on adverse events, concomitant therapies [11]
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[5]
	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[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
	148 ±3	3528:00	8:00	ambulatory visit	X								
3	176 ±3	4200:00	8:00	EOT[12]	X[15]		X	X	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), pregnancy test, 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; procedures are to be performed and completed within 3 h prior to drug administration. Within 3 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), and drug screening.
4. PK sampling times may be adapted based on information obtained during trial conduct.
5. Standardized assessment of local tolerability only for subcutaneous injection using the criteria swelling, induration, heat, redness, pain or other findings.
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. At baseline, cytokine (IL1β, IL6, TNF-α and IFNγ) samples will be collected together with safety lab. Additional cytokine samples IL1β, IL6, TNF-α and IFNγ will be collected at 4 h and 24 h post-dose. Cytokine samples are only to be analysed from an individual subject in case of specific adverse events in this subject that are suggestive for a cytokine release. At 4 h and 24 h post-dose no safety lab needs to be taken.
10. Only drug screening and alcohol breath test.
11. 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.
12. EOT (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EOT to be performed not before last PK and ADA sampling.
13. Safety laboratory is to be taken within two days prior to study drug administration and can be omitted if the screening examination is performed between Day -5 and Day -3.
14. First measure after completion of infusion is the collection of PK sample
15. In case plasma levels still exceed LOQ additional PK samples may be collected beyond Day 176 ±3.

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ABBREVIATIONS

5-ASA	5-aminosalicylic acid
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
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_{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
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
b.w.	Body weight
CA	Competent authority
CD	Crohn's Disease
CI	Confidence interval
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
CV	Coefficient of variation
DILI	Drug induced liver impairment
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
GMP	Good Manufacturing Practice
GPP	Generalized pustular psoriasis
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
IBD	Inflammatory bowel diseases
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IL36R	Interleukin 36 receptor
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
ITE	Indirect target engagement
IV	Intravenous
KO	Knock out
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
MMP	Matrix metalloproteinase
MRD	Multiple rising dose
N	Number
NC	Not calculated
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Subject set for the evaluation of PK endpoints
PPP	Palmoplantar pustulosis
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
RPM	Report Planning Meeting
RR	Riva Rocci
SAE	Serious adverse event

SCR	Screening
SOP	Standard Operating Procedure
SSc	systemic sclerosis
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
WBC	White Blood Cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody blocking IL36α, IL36β, and IL36γ by binding to IL36R. The IL36 pathway has been associated with the pathogenesis of several inflammatory diseases including generalized pustular psoriasis (GPP) and psoriasis vulgaris. Emerging preclinical data suggest that IL36R is a potential target for the treatment of inflammatory bowel diseases.

Genetic human studies have established a strong link between IL36R signaling and skin inflammation as demonstrated by the occurrence of generalized pustular psoriasis in patients with a loss of function mutation in IL36Rα, the gene encoding the endogenous inhibitor of IL36R, which resulted in uncontrolled IL36R signaling [R15-1421]; [R14-5158] .

IL36R has been discovered as a target for psoriasis based on (I) the abundant expression of all three stimulating ligands in human psoriatic lesional skin as reviewed by Towne and Sims [R14-4037], (II) IL36α overexpression in murine keratinocytes inducing a psoriatic-like phenotype [R15-1432], (III) IL36R KO mice protecting against Imiquimod-induced skin inflammation [R15-1447] and (IV) IL36R blockade ameliorating skin inflammation in a transplanted psoriatic skin model [R15-1399].

The link between IL36R-driven inflammation and epithelial inflammation has led to the hypothesis that IL36R signaling may play an important role in inflammatory bowel diseases. This hypothesis was tested using a series of *in vitro* and *in vivo* assays. Immunostaining studies demonstrated that both IL36R and its ligands are expressed in intestinal biopsies from Crohn's disease patients. Human IL36 ligands enhance intestinal barrier permeability, a hallmark of IBD pathogenesis, in primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signaling and IBD was further strengthen by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute chemically induced and chronic T cell driven murine colitis models.

The therapeutic rational for an IL36R antagonist in IBD is further based on the correlation of a set of IL36-induced genes upregulated in primary human intestinal myofibroblasts, a disease relevant cell type, with gene signatures observed in ulcerative colitis and Crohn´s disease patients. Finally, IL36R signaling in disease relevant cells, such as intestinal myofibroblasts and macrophages, induces both pro-inflammatory and tissue remodeling related mediators (e.g. TGF-β, MMPs), which differentiates this mechanism from TNF-α and IL23 pathways.

Altogether, these findings support a prominent role for IL36R in driving intestinal inflammation and position anti-human IL36R antibody BI 655130 as a first in class therapeutic for IBD and other epithelial-mediated inflammation such as systemic sclerosis (SSc) or idiopathic pulmonary fibrosis (IPF). The therapeutic effect on GPP and PPP is also under evaluation; detailed background is provided in the IB [c03320877-02].

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract characterised by abdominal pain, fever, and bloody or mucus-containing diarrhoea [R13-2231]. The mainstay of treatment for moderate to severe CD has been with glucocorticoid therapy, azathioprine, or 6-mercaptopurine [R13-2269]. More recently, biologics consisting of monoclonal antibodies directed at cytokines, thought to mediate the pathology, have been used extensively for this indication.

Ulcerative colitis (UC) has an estimated incidence of 1.2 to 20.3 cases per 100,000 persons per year, and a prevalence of 7.6 to 246.0 cases per 100,000 per year [R15-1343]. Like CD, UC is characterised clinically by abdominal pain, fever, and bloody or mucus-containing diarrhoea, and pathologically by inflammatory lesions in the gastrointestinal mucosa. UC differs from CD by the distribution of lesions, which in UC characteristically occur distal to the terminal ileum, and by the confinement of lesions to the mucosa and submucosa without transmural inflammation. Similar to CD, UC typically follows a relapsing and remitting course, and is associated with substantial acute and long-term morbidity and increased mortality. The mainstays of drug therapy for UC are the orally administered aminosalicylates, glucocorticoids, the oral immunomodulatory agents azathioprine and 6-mercaptopurine, and the biologic TNF antagonists. In patients with mild UC, 5-ASAs are a safe and effective therapy. Glucocorticoids, immunomodulators, TNF antagonists, and more recently vedolizumab, an integrin α4β7 blocker, are reserved for patients with moderate to severe disease, in whom the primary goals of drug therapy are to induce and subsequently to maintain remission from signs and symptoms of active disease.

Treatment of CD and UC is associated with a significant number of patients with primary and secondary non-response. In addition, treatment may be limited due to safety and tolerability issues. Therefore, despite therapeutic progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared to the current therapeutic standard.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 655130 is a humanized monoclonal IgG1 antibody (mAb) against human IL36R. To minimize Fc effector functions, leucines at position 234 and 235 of the heavy chain were mutated to alanine. The BI 655130 molecule is a heterodimer with a molecular weight of approximately 146 kDa. Each heterodimer is composed of a heavy chain (449 amino acids) and a light chain (215 amino acids). The four polypeptide chains of the antibody are linked together by disulphide bonds. Each heavy polypeptide chain contains one consensus sequence for N-linked glycosylation. BI 655130 blocks IL36α-, IL36 β- and IL36 γ-induced signaling by binding to the IL36 receptor.

The functional inhibition of IL36-stimulated NF-κB activation by BI 655130 was tested with all three potent stimulating IL36R ligands on several human cell types, notably HT29 and NCI/ADR-RES transformed epithelial cells, primary human keratinocytes, primary human dermal fibroblasts, and primary human intestinal myofibroblasts. All cell types showed IC90 values of inhibition by BI 655130 in a consistent range of 0.7 to 3.7 nM. BI 655130 also

inhibits IL8 release with identical potency in human NCI/ADR-RES cells, keratinocytes, and intestinal myofibroblasts.

BI 655130 was also evaluated in a primary human peripheral blood mononuclear cells (PBMC) assay. Isolated human PBMC stimulated with IL36α, IL36β, or IL36γ show a synergistic induction of IFNγ secretion when combined with IL12, as exemplified for IL36β (please see IB, c03320877-02). Similar findings were observed in mouse splenocytes where murine IL36 plus IL12 induced a synergistic production of IFN-γ (please see IB, c03320877-02), suggesting that the pathways utilized by IL36 to drive inflammatory cytokine production are conserved between mouse and human systems. These effects can be blocked by BI 655130 and BI 674304 in human and mouse assays, respectively (please see IB, c03320877-02). Of note, BI 655130 alone does not stimulate cytokine production in human PBMC, indicating that BI 655130 has a low potential to cause cytokine release. Neither the addition of BI 655130 directly to whole blood or pre-bound to plastic (to mimic the effects of mAb crosslinking) resulted in specific cytokine release.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-02].

1.2.2 Safety pharmacology

Specific safety pharmacology studies have not been conducted with BI 655130 as it is not pharmacologically active in common toxicology species. Instead, studies were performed with BI 674304, the mouse specific anti-IL36R monoclonal antibody and used as a surrogate for BI 655130 (please see also Section 1.2.3). There were no clinical signs of toxicity in mice after the 13-week administration [c03320877-02].

1.2.3 Toxicology

As BI 655130 does not demonstrate sufficient cross-reactivity to IL36R from common toxicology species, including non-human primates, *in vivo* toxicity studies were not conducted. Instead, the potential adverse effects of IL36R antagonism were assessed in toxicity studies in mice using a mouse specific anti-IL36R monoclonal antibody (BI 674304). In addition, a human tissue cross-reactivity study and an *in vitro* cytokine release assay have been conducted with the clinical candidate BI 655130. Finally, the local tolerance of subcutaneous injections of BI 655130 has been evaluated in rabbits.

In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL36R antagonism were seen at a dose (, twice weekly) that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In addition, in an embryo-fetal toxicity study, there was no evidence of effects on fetal growth or dysmorphogenesis (teratogenicity) in mice after administration of /dose of BI 674304 during gestation. The *in vitro* cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI 655130 stains epithelium in a variety of tissues. There were no signs of local irritation after single, injections of the subcutaneous formulation in rabbits. These preclinical data suggest that BI 655130 can be safely administered to humans for up to 13 weeks.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-02].

1.2.4 Nonclinical pharmacokinetics

The pharmacokinetics of BI 655130 was studied in cynomolgus monkeys. In mice, pharmacokinetic studies were performed with the mouse-specific anti-IL36R antibody, BI 674304 [c03320877-02].

1.2.5 Clinical experience

BI 655130 has been evaluated in two clinical trials: a first-in-human (FIH) SRD trial (1368.1, completed) and a MRD trial (1368.2, on-going).

The FIH (first-in-human) trial [c09985235-01] was conducted according to a single-blind, partially randomised, single rising dose and placebo-controlled (within dose groups) design.The study explored safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenously administered BI 655130 in healthy male subjects. Subjects received single ascending IV doses of , to body weight or placebo. Overall, the study included 78 male subjects with 58 subjects treated with BI 655130 and 20 subjects treated with placebo.

Trial 1368.2 [c09105854-04] explored the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising intravenous doses of BI 655130 in a double-blind, partially randomised within dose groups, placebo-controlled, parallel group design and of one single intravenous dose of BI 655130 in a single-blind, partially randomised, placebo-controlled design. A total of 32 healthy male subjects were randomised to 4 sequential groups comprising 8 subjects per group. The study consisted of a multiple dose part with three dose groups and and a single dose arm Within each dose group, 6 subjects received the active drug and 2 received placebo. Subjects assigned to the multiple dose part received single intravenous doses within 4 weeks (on Day 1, Day 8, Day 15, and Day 22). The study is still ongoing, though treatment of all four dose groups has been completed.

Safety and tolerability

In the FIH study [c09985235-01], 49 of 78 subjects (62.8%) reported at least 1 treatment-emergent AE (TEAE). This included 36 of 58 subjects (62.1%) following administration of BI 655130 and 13 of 20 subjects (65.0%) following administration of placebo. There was no apparent relationship between the frequency of AEs and the dose. AEs categorised as related to treatment were observed in 3/20 (15.0%) subjects in the placebo group and in 8/58 (13.8%) subjects treated with BI 655130.

Treatment-emergent AEs were reported most frequently in the system organ classes 'infections and infestations' (BI 655130: 14/58 subjects [24.1%]; placebo: 3/20 subjects [15.0%]), 'general disorders and administration site conditions' (BI 655130: 9/58 subjects

[15.5%]; placebo: 2/20 subjects [10.0%]), 'gastrointestinal disorders' (BI 655130: 7/58 subjects [12.1%]; placebo: 4/20 subjects [20.0%]), 'musculoskeletal and connective tissue disorders' (BI 655130: 5/58 subjects [8.6%]; placebo: 3/20 subjects [15.0%]), and 'nervous system disorders' (BI 655130: 5/58 subjects [8.6%]; placebo: 3/20 subjects [15.0%]).
At preferred term level, the most frequently reported treatment-emergent AEs were nasopharyngitis (BI 655130: 12/58 subjects [20.7%]; placebo: 3/20 subjects [15.0%]), headache (BI 655130: 5/58 subjects [8.6%]; placebo: 3/20 subjects [15.0%]), influenza like illness (BI 655130: 4/58 subjects [6.9%]; placebo: 2/20 subjects [10.0%]), and diarrhoea (BI 655130: 2/58 subjects [3.4%]; placebo: 2/20 subjects [10.0%]).

There were two AEs of moderate intensity, both considered non related to the study drug, (injection site hematoma, headache); all remaining AEs were of mild intensity.

There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, hematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12 lead ECGs, vital signs, physical exams and cardio-monitoring.

Based on a preliminary evaluation of Trial 1368.2, 27 of 32 subjects (84.4%) reported at least 1 TEAE. The frequency of subjects with AEs was similar in subjects treated with BI 655130 (range 66.7% to 100%) and placebo (87.5%). AEs categorised as related to treatment were observed in 11 of the 32 subjects (34.4%) overall (BI 655130 groups: 16.7% to 66.7%; placebo: 25.0%); Table 1.2.5: 1.

Table 1.2.5: 1 Frequency [N (%)] of subjects with related adverse events by treatment and preferred term (Trial 1368.2)

	Placebo	MD*	MD*	MD*	SD**
Number of subjects (%)	8 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Total with related AEs	2 (25.0)	1 (16.7)	4 (66.7)	2 (33.3)	2 (33.3)
Abdominal discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Diarrhoea	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Injection site reaction	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	1 (12.5)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Malaise	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	2 (33.3)	1 (16.7)	1 (16.7)
Dermatitis acneiform	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Rash macular	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)

* Multiple dose
** Single dose

Treatment-emergent AEs were reported most frequently in the system organ class 'general disorders and administration site conditions' (overall: 20/32 subjects [62.5%], BI 655130 groups: 50.0% to 66.7%, placebo: 75.0%). At preferred term level, the most frequently reported treatment-emergent AEs were injection site erythema (overall: 9/32 subjects [28.1%], BI 655130 groups: 0.0% to 50.0%, placebo: 25.0%), nasopharyngitis (overall: 7/32 subjects [21.9%], BI 655130 groups: 16.7% to 33.3%, placebo: 12.5%), and headache (overall: 7/32 subjects [21.9%], BI 655130 groups: 16.7% to 33.3%, placebo: 12.5%).

BI 655130 was well tolerated in Trial 1368.2. There were no AEs considered to be dose limiting, no dose dependency, and no SAEs. All subjects completed the treatment per protocol. In all cases, the AEs were of mild intensity and resolved without further measures. Based on the preliminary evaluation, there were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory, ECG, and vital signs.

Pharmacokinetics

Trial 1368.1 PK parameters of BI 655130 after a single IV infusion are shown in Table 1.2.5:2. BI 655130 levels were first detected at a dose level of . AUC_{0-inf} results should be considered for informational purposes only given the high %_AUC of extrapolated values (>50%) for the dose groups. Exposure in terms of AUC_{0-tz} and C_{max} of BI 655130 increased with increasing dose in a greater than dose-proportional manner from and in a dose-proportional manner from . In the higher dose groups with apparent linear PK characteristics the half-life ($t_{1/2}$) of BI 655130 was in the range of 20.4 to 33.9 days. However, because of the relatively short sampling time, these values should be considered an estimate only.

Overall, PK data suggest target-mediated drug disposition (TMDD) kinetics for BI 655130.

Table 1.2.5: 2 Geometric mean (geometric CV%) PK parameters of BI 655130 after a single IV infusion (Trial 1368.1)

Dose Group#	**#1**	**#2**	**#3**	**#4**	**#5A**	**#5**
Dose	N=6	N=6	N=4	N=6	N=3	N=5
AUC_{0-tz} [µg·day/mL]	NC	NC	0.00652 (121)	2.08 (29.0)	9.57 (5.90)	25.1 (15.5)
$AUC_{\mathbf{0-inf}}$ [µg·day/mL]	NC	NC	0.0234 (125)	2.35 (23.9)	13.0 (6.59)	27.7 (16.6)
C_{max} [µg/mL]	NC	NC	0.0228 (33.5)	0.413 (21.2)0.413 (21.2)	0.998 (15.7) (15.7)	1.96 (11.9)
Dose Group#	**#6**	**#7**	**#8**	**#9**	**#10**	
Dose	N=4	N=6	N=6	N=6	N=4	
AUC_{0-tz} [µg·day/mL]	113 (5.86)	420 (13.3)	1050 (7.26)	2610 (11.7)	4130 (12.1)	
$AUC_{\mathbf{0-inf}}$ [µg·day/mL]	127 (6.05)	563 (26.2)	1260 (6.81)	3380 (15.6)	5080 (18.9)	
C_{max} [µg/mL]	6.63 (3.28)	20.3 (13.6)	60.6 (7.17)	153 (12.7)	235 (2.79)	

In the MRD Trial 1368.2, preliminary PK data up to 5 weeks are available for the and dose groups (Table 1.2.5: 3). Exposure of both dose groups is in the linear dose range; PK evaluation of the remaining dose groups is on-going.

Table 1.2.5: 3 Preliminary geometric mean (geometric CV%) PK parameters of BI 655130 after multiple IV dosing on Days 1, 8, 15, and 22 (Trial 1368.2)

Dose	N=6 [Day 1] 0-168 h	N=6 [Day 8] 168-336 h	N=6 [Day 15] 336-504 h	N=6 [Day 22] 504-672 h
$AUC_{\mathbf{0-t}}$ (µg·day/mL)	311 (10.5)	563 (6.3)	742 (7.1)	865 (8.8)
C_{max} (µg/mL)	72.2 (22.0)	107 (5.9)	132 (7.2)	156 (8.2)
Dose	N=6 [Day 1] 0-168 h	N=6 [Day 8] 168-336 h	N=6 [Day 15] 336-504 h	N=6 [Day 22] 504-600 h
$AUC_{\mathbf{0-t}}$ (µg·day/mL)	652 (5.1)	919 (4.6)	1540 (5.8)	1080 (5.6)
C_{max} (µg/mL)	140 (11.3)	183 (7.0)	277 (6.1)	323 (7.3)

Pharmacodynamics

Pharmacodynamic effects in Trials 1368.1 (SRD) and 1368.2 (MRD) were assessed by indirect target engagement (ITE) of IL36R by BI 55130 using an ex-vivo whole blood stimulation assay. Whole blood was taken before and after treatment of subjects with BI 655130 or placebo and stimulated with IL36γ ligand. After preparation of plasma, the resulting production of macrophage inflammatory protein (MIP)-1β was quantified via an immunoassay as an exploratory biomarker. MIP-1β levels are expected to inversely correlate with the level of IL36R engagement by BI 655130.

In the single rising dose trial (1368.1), doses of and above showed percent inhibition of MIP-1β of at least 94% as compared to baseline during the entire time course up to 1680 h. Furthermore, in the interim analysis of ITE in the multiple rising dose trial (1368.2) for dose groups evaluated so far, the inhibition of MIP-1β was at least 91% as compared to baseline during the entire time course up to 672 h for and dose groups as compared to placebo. This demonstrates that BI 655130 is on-target for the time points analyzed.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-02].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is in development for the treatment of GPP, PPP, CD, and UC. BI 655130 is currently in Phase I development.

Recently, a FIH trial has been completed (see Section 1.2.5) that explored safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 655130 following IV infusions of single rising doses of up to body weight in a healthy male population. BI 655130 was safe and well tolerated. A second Phase I trial investigating multiple intravenous doses is ongoing (Trial 1368.2, c09105854-04).

BI 655130 was administered as intravenous infusion in the initial Phase I studies; however, a subcutaneous injection formulation is planned for upcoming studies to support self-administration by the patient. The current study is designed to examine the characteristics of the newly developed subcutaneous formulation with particular focus on relative bioavailability compared to an intravenous formulation and local tolerability.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the relative bioavailability of of BI 655130 following subcutaneous administration (Test, T) compared to of BI 655130 following intravenous infusion (Reference, R).

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between all tested treatments BI 655130 SC, BI 655130 SC, and BI 655130 IV).

The assessment of safety and tolerability, including the standardised assessment of local tolerability, will be an additional objective of this trial.

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to investigate a newly developed subcutaneous formulation which is considered crucial for long-term studies in patients. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

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

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

Drug-related risks and safety measures

BI 655130 does not bind to IL36R from common toxicology species. Therefore, the mouse reactive mAb, BI 674304, was used to characterize the potential effects of IL36R antagonism *in vitro* and *in vivo*. The decision to conduct toxicity studies with a mouse reactive monoclonal antibody was based on the ICH S6 (R1) guidance and took into account the sequence homology and *in vitro* binding and activity assays. Binding/biologic activity is insufficient in common toxicology species to adequately evaluate the potential toxicities related to IL36R antagonism with BI 655130. It is anticipated that the degree of biologic activity is more important for assessing potential toxicity related to exaggerated pharmacology than binding affinity.

The clinical safety and tolerability profile of intravenous single doses of BI 655130 was comparable to placebo in male subjects with intravenous single doses up to body weight. There were no withdrawals for adverse events or abnormal laboratory values. There were no deaths or other serious adverse events. The adverse events reported had no apparent dose or exposure relationship. There were no dose or exposure related abnormalities in safety laboratory parameters and no safety or tolerability concerns that would preclude further clinical development of BI 655130.

Nonclinical studies support repeat-dose clinical trials of up to 13 weeks duration. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL36R antagonism was seen at a dose twice weekly) that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model.

For the first trial with the new subcutaneous formulation, a maximum dose of injection volume) was selected. This dose is significantly lower than the maximum tested intravenous single dose of in the previous single rising dose study and considered to be safe (see Section 1.2.5). The same is true for the other planned doses of SC and IV.

Based on the preceding FIH study, no specific drug-related risks are anticipated. Nevertheless, the following safety measures are/will be applied in this study in order to minimize the risk for the healthy subjects:

- Careful dose selection based on data from the completed FIH study; the exposure of any dose of BI 655130 in the current study is projected to be below the highest exposure observed in the FIH study
- For safety reasons, the study will start with the lowest SC dose of of BI 655130. The dose group will be divided into 2 cohorts: on the first study day, 6 subjects will be treated, with an interval between the injections of at least 15 min. The second cohort will be treated at least 48 h apart. There will be an interval of at least 1 week after the first dosing in the SC dose group before the start of the SC or IV dose groups in a randomised sequence (in one week 6 subjects on IV and 6 subjects on SC and in the following week again 6 + 6) Nomore than 2 subjects should simultaneously receive an infusion. At any time during the ongoing study, further dosing will be stopped in case of safety and tolerability concerns based on the criteria defined in Section 3.1
- Dose escalation will be shallow (2-fold dose escalation step). In addition, a time interval of at least 7 days will be maintained between the first dosing of of BI 655130 SC and the first dosing of of BI 655130 SC or IV. An interval of one week between the dose groups is expected to cover the period of highest risk / peak effect. The decision to proceed to the next dose will be based upon the safety and tolerability of the preceding dose. The next dose will only be given if no safety concerns arise in the previous dose group (i.e. no dose-limiting events occur) and if none of the pre-specified trial-specific stopping criteria are met (see Section 3.3).
- The dose will only be escalated if previously approved by the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy) after in-depth analysis of all available safety data (see Section 3.1)
- Monitoring of ECG and vital signs is incorporated, with continuous ECG monitoring over 1.5 hour post dose after each drug administration, the anticipated period of highest drug exposure. As an additional measure, repeated single 12-lead ECGs are scheduled in the further course of the study. The rationale for the intensified ECG monitoring is not an expected increased risk of BI 655130 mediated effects on cardiac repolarization
- Extensive safety laboratory testing will be performed (Table 5.2.3:1)
- After each dosing, the subjects will stay at the site for at least 48 hours following drug administration
- While admitted to the trial site, the subjects will be under close medical observation and thoroughly monitored for both expected and unexpected adverse events
- With IV administration, treatment with BI 655130 can be immediately discontinued, should any safety concern arise (please refer to Section 4.1.4)
- BI 655130 will be administered in a hospital setting and subjects will be under close medical observation during their hospitalisation (see Section 6.2), as well as after their discharge and until the end of observation period. Safety will be closely monitored during site visits

Currently there are no data available to suggest interactions of BI 655130 [c03320877-02].

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

As an antagonist of IL36R, BI 655130 affects a target of the immune system that is ubiquitously expressed. Due to the antagonistic effect, it is considered unlikely that BI 655130 may lead to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism. In addition, preclinical investigations and the completed FIH trial did not suggest cytokine release induced by BI 655130.

Based on the preclinical and initial clinical information for BI 655130, healthy subjects are not expected to be exposed to undue risks and adverse events in relation to the information expected from this trial. Considering the medical need for the development of an effective and well tolerated drug for the therapy of inflammatory bowel disease (and GPP flares), the benefit of this trial is considered to outweigh the potential minimal risks and justifies the exposure of healthy subjects.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will explore the safety, tolerability, and pharmacokinetics of a newly developed SC formulation of BI 655130 at two different dose strengths of and in an open-label, sequential group design. Furthermore, the relative bioavailability of the SC dose (Test) will be compared with one single IV dose of BI 655130 (Reference) in an open-label, , parallel group design). For details refer to Section 4.1. Each participating subject will receive only one dose. Subjects assigned to the IV dose will be matched for gender and body weight (± 10%) to subjects receiving the SC dose.

The study will start with the lowest SC dose of of BI 655130. The dose group will be divided into 2 cohorts: on the first study day, 6 subjects will be treated, with an interval between the injections of at least 15 min. The second cohort will be treated at least 48 h apart. There will be an interval of at least 1 week after the first dosing in the SC dose group before the start of the SC or IV dose groups in a randomised sequence (in one week 6 subjects on IV and 6 subjects on SC and in the following week again 6 + 6). No more than 2 subjects should simultaneously receive an IV infusion. At any time during the ongoing study, further dosing will be stopped in case of safety and tolerability concerns based on the pre-specified trial-specific stopping criteria (Section 3.3.4.2).

A documented Safety Review must take place prior to dose escalation to Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy) and the trial clinical monitor (or an authorised deputy). In addition, at least 6 evaluable subjects per dose level are required to decide about dose escalation to the dose level.

The minimum data set for review consists of the following data:

- AEs (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG and continuous ECG monitoring
- Vital signs
- Clinical laboratory tests
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

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

face-to-face or by video/telephone conference. The trial clinical monitor is responsible for organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule 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 the
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.

Safety laboratory tests will be performed by

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

Data management and statistical evaluation will be done by BI according to BI SOPs or a contract research organisation appointed by BI.

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

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

The trial will be conducted open-label. Blinding is not possible because the treatments are distinguishable. The open-label treatment is not expected to bias results, since the relative bioavailability endpoints are derived from measurement of plasma concentrations of the analyte.

For safety reasons, the trial will be conducted in a fixed sequence; a time interval of at least 7 days will be maintained between the first dosing of of BI 655130 SC and the first dosing of of BI 655130 SC or IV.

No placebo group is included because the study is open-label with a focus on PK. Local tolerability is an additional objective and will remain relevant in case of dose limiting local AEs, whether placebo controlled or not. The systemic AEs have been evaluated up to MRD, a far higher dose than planned for the current study.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 36 healthy male and female subjects (12 subjects per treatment group) will enter the study. They will be recruited from the volunteers' pool of the trial site. Healthy subjects of the IV dose group will be matched for gender and body weight (± 10%) to subjects of the SC dose group.

A log of all subjects enrolled into the trial (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 or female subjects according to the investigator's assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
5. Male subjects, or female subjects who meet any of the following criteria starting from at least 30 days before 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: implants, injectables, combined oral or vaginal contraceptives, intrauterine device
   - Sexually abstinent
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

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 50 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
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 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
12. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
13. Inability to refrain from smoking on specified trial days
14. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males)
15. Drug abuse or positive drug screening
16. Blood donation of more than within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
18. Inability to comply with dietary regimen of trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
20. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
21. 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

Female subjects will not be allowed to participate if any of the following applies:

22. Positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion
23. Lactation

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 for trial treatment or trial participation, 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 pregnancy, 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 marked peak aminotransferase (ALT and/or AST) elevations ≥10-fold ULN and/or needs to be followed up according to the 'DILI checklist' provided in the ISF

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

Infusion reactions could 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 pause the infusion or continue with a reduced infusion rate as described for other therapeutic proteins [P16-06636]. However, the overall infusion time (including time of discontinuation) must not exceed 45 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). If a subject is removed

from or withdraws from the trial after first 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.

If it is known that a subject becomes pregnant during the trial, the subject has to be removed from the trial. The subject is to be followed until she has given birth or until the end of pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and all related events refer to Section 5.2.2.2.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial 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 are not met
3. Violation of GCP, or the CTP, or the contract with BI by the 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 if at least 2 subjects at one dose level show 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 he replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG. The BI 655130 molecule is a heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of BI investigational product and comparator product

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:	
Daily doses:	
Posology:	1-0-0
Route of administration:	SC injection (periumbilical)
Duration of use:	Single dose

The characteristics of the reference product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Daily dose:	
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose

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

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 1 of the 6 dose cohorts (2 cohorts per dose group), the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not

influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The list with study subject numbers and allocated treatments will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The subject number procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The doses selected for this trial are based on data from Study 1368.1 (see Section 1.2.5) and correspond to potential doses used in upcoming clinical trials in patients.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are as outlined in Table 4.1.4: 1. Each subject will receive one single dose of trial medication. For further details concerning timing, see the Flow Chart. Detailed instructions for the preparation of the SC injection and IV infusion solutions are provided in the ISF.

Table 4.1.4: 1 BI 655130 treatments

Total dose	Route of administration	Concentration of application solution	Application volume
	SC		
	SC		
	IV		

Subcutaneous injection

Following an overnight fast of at least 10 hours, the medication will be administered. Trial drug will be injected subcutaneously within 60 seconds in the abdominal region. Detailed handling instructions will be provided in the ISF. Subjects will be kept under close medical surveillance until 48 hours following drug administration. For restrictions with regard to diet, see Section 4.2.2.2.

Intravenous infusion

Following an overnight fast of at least 10 hours, the medication will be administered. The infusion solution will be administered intravenously over 30 minutes. Start and time of the infusion will be recorded. Detailed handling instructions for the infusion will be provided in the ISF.

In case of safety concerns, e.g. due to infusion reactions, it is at the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited slowing down the infusion rate, stopping of the infusion and, provided no further safety

concern exist, restarting at a slower rate. Further, based on his/her medical judgment the investigator 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 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, if correct dosage cannot be ensured otherwise. For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.

Subjects will be kept under close medical surveillance until 48 h following drug administration. For restrictions with regard to diet see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed because the treatments are distinguishable from each other. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations. PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

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

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

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

No 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 trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of 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 except for hormonal contraceptives or ovary hormone replacement. 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, no food is allowed for at least 10 h before and 1.5 h after administration of the study drug (= end of infusion).

From 1 h before until 1.5 h after study drug administration, fluid intake is not allowed. From breakfast until 24 hours post-dose, water intake will be within to . Total fluid intake on 24-hour in-house days is recommended to be at least and should not exceed

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during the in-house confinement. Alcoholic beverages are not permitted starting 7 days before the administration of trial medication until Day 28. From Day 28 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 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.

If female subjects of child bearing potential are included, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for adequate measures).

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

Safety and tolerability of the investigational drug will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate)
- Local tolerability
- Oral body temperature

These parameters will be evaluated in a descriptive way only, and are therefore considered to be ‘further parameters of interest’. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,

- is life-threatening, which 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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,

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

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

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in Section 5.2.2.2, subsections 'AEs collection' and 'AE reporting to sponsor and timelines'.

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 defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

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

The AESI in this trial is 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
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

Intensity (severity) of AEs

The intensity (severity) of the AE should be assessed based on the following:

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

Causal relationship of AEs

Medical judgement 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 trial drug treatment continues or remains unchanged

5.2.2.2 Adverse event collection and reporting

AEs collection

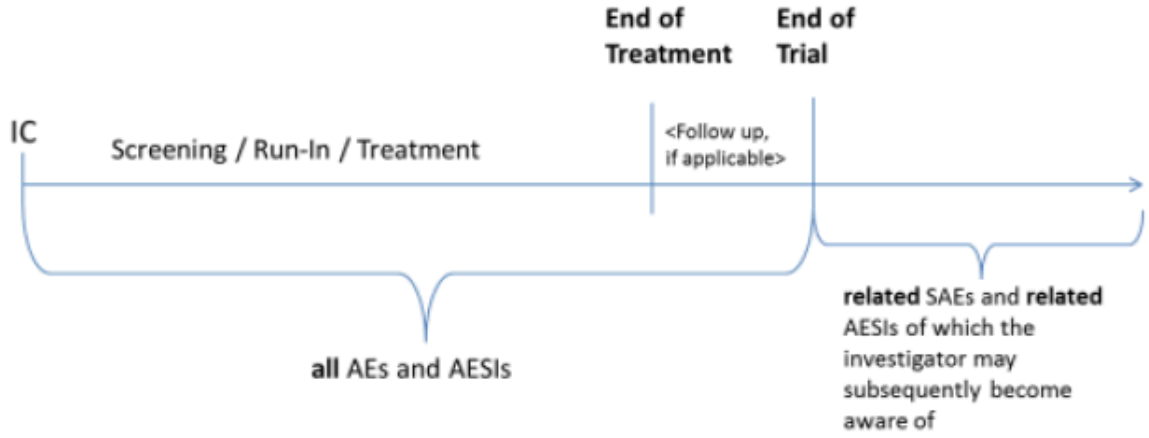
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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 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 related SAEs and related AESIs of which the investigator may become aware of by an means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.



The REP for BI 655130, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known at this early stage of development. Therefore, all AEs reported until the end of trial examination will be considered on treatment; please see Section 7.3.3.

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 BI SAE form (if applicable):

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only.

All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', 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 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 designee 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, Section 10.

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

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 (if automatic differential WBC is abnormal)	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 (AP)
	Gamma-glutamyl transferase (GGT)
	Creatine kinase (CK)
	CK-MB
	Lactate dehydrogenase (LDH)
	Serum tryptase[1]
Hormones[1]	Thyroid stimulating hormone (TSH)
	fT3, fT4
Substrates	Plasma glucose
	Creatinine
	Total bilirubin
	Direct bilirubin
	Total protein
	Protein electrophoresis (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

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 (microscopic examination if urine analysis abnormal)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Only at screening

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy test and drug screening, it is planned to perform these tests during screening only. Pregnancy testing in women will be performed at screening, prior to treatment, and as part of the end of trial examination. Drug screening will be performed at screening and at admission to the trial site the day prior to treatment.

Table 5.2.3: 2 Exclusionary laboratory tests

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

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

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 Table 5.2.3: 1 and 5.2.3: 2 will be performed ZNA Klinisch Laboratorium, Antwerpen, Belgium with the exception of the drug screening and pregnancy

tests. These tests will be performed at the trial site using 'Alere Triage TOX Drug Screen' and MAHSAN® –HCG rapid test or equivalent, respectively.

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

Samples for cytokine analysis (cytokines IL1β, IL6, TNF-α, and IFNγ) will be collected at baseline, 4h, and 24h postdose. The cytokine samples will be only analysed in case of specific adverse events suggestive for cytokine release.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (MAC 5500, GE Healthcare) 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.

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

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis.

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 and oxygen monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 2-lead ECG recording for at least 15 min before (for baseline assessment) and 2 h following the start of IV infusion or SC injection using the Dräger Telemetry monitoring system, Infinity M300. Oxygen saturation will be monitored by pulse oximetry using either Type NT1 handheld pulse oximeter from Newtech or Oxytrue A from Bluepoint Medical.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

5.2.5.2 Medical examinations

At screening, the medical examination will include 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

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

5.2.5.4 Oral body temperature

Oral body temperature will be measured at the times indicated in the Flow Chart using a standard device.

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

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

Exact time points of plasma sampling will be derived from the electronic data capturing system LabPas and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for BI 655130:

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

5.5.1.2 Secondary endpoint

The following secondary endpoint will be evaluated for BI 655130:

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

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, approximately of blood will be taken from an antecubital or forearm vein into a K2EDTA (ethylenediaminetetraacetic acid) anticoagulant blood drawing tube at the times indicated 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.

The K2EDTA-anticoagulated blood samples will be mixed gently and placed on ice until centrifugation for about 10 minutes at about 2000 g to 4000 g and at approximately 4°C. The blood should be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Two aliquots of EDTA plasma sample will be obtained in two labelled polypropylene cryotubes. At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, PTM, aliquot #1 or #2, plasma, and PK.

The two aliquots should contain approximately of plasma each. The plasma samples will be stored in a freezer at about -20°C or below at the clinical site until shipment to the analytical laboratory.

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

5.5.3.1 Analytical determination of BI 655130 plasma concentration

BI 655130 concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the 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
- ±120 min from 48 h up to Day 8
- ±48h from Day 9 up to Day 14
- ±72h from >Day 14 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 the determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

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. On all other study days, the study will be performed in an ambulatory fashion.

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 samples for PK analysis, refer to Flow Chart and Section 5.5.2.

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

6.2.3 End of trial period

For AE assessment, laboratory tests, collection of PK 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. (S)AEs persisting after subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

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 relative bioavailability of of BI 655130 following subcutaneous administration (Test, T) compared to of BI 655130 following intravenous infusion (Reference, R). This will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between all tested treatments. The secondary objective will be assessed by descriptive statistics.

The assessment of safety and tolerability is an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the inter-individual comparison of the primary and secondary endpoints following SC versus IV administration of of BI 655130 will be an ANOVA (analysis of variance) model on the logarithmic scale, accounting for the treatment group as a source of variation. The effect 'treatment group' will be considered as fixed. The model is described by the following equation:

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

y_{ij} = logarithm of response (endpoint, see Section 7.1.3) measured on subject j receiving treatment i

μ = overall treatment mean,

τ_i: effect of treatment i

e_{ij} = the random error associated with the subject j who received treatment ,

where $e_{ij} \sim N(0,\sigma^2)$ where σ^2 is the total variability

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 655130 following SC compared to IV administration will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

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

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in 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.

A PK concentration or parameter will be considered as non-evaluable if, for example, the subject did not receive the complete assigned infusion or injection volume.

Relevant protocol violations may be

- Study drug not administered or wrong trial drug administered
- Incorrect dose of trial medication taken
- Missed/missing PK samples at important phases of PK disposition curve

The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one primary or secondary PK parameter that was not excluded according to the description above. Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value to the statistical assessment.

Relative bioavailability will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see 5.5.1.1, 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (LeastSquares Means), and a two-sided 90% confidence interval based on the

t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.3.2 Secondary analyses

The secondary parameter (refer to Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will statistically be assessed using the same methods as described for the primary endpoints.

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 one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'treatment at onset'.

Treatments will be compared 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 ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to administration of trial medication will be assigned to 'screening', those between trial medication administration until the end of trial visit will be assigned to the treatment period, and those after the end of trial examination will be assigned to 'post-study'. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, 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 as well as values defined as clinically relevant will be highlighted in the listings. Additionally, differences from baseline will be evaluated. Measurements taken immediately prior to drug administration on Day 1 will be considered as baseline values.

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

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for BI 655130 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

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

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

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

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (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 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 36 subjects in the trial (12 subjects per treatment group) because this sample size is considered sufficient to achieve the aims of this exploratory trial.

With this sample size, the following precision of the ratio of geometric means (test/reference) can be expected. Precision is defined as the ratio of upper to lower confidence interval limit. Note that the precision is independent of the actual ratio of geometric means. Table 7.5: 1 provides an overview on the achievable precision for estimating the ratio of geometric means (test/reference) covering the range of gCVs estimated for the PK endpoints from the results obtained from the first-in-human SRD study for BI 655130. For illustrative purposes, the expected 90% confidence intervals with 95% coverage probability are displayed for different values of geometric means ratios T/R in the parallel design.

Table 7.5.1 Expected two-sided 90% confidence intervals for different gCVs and ratios T/R (N=12)

		90% CI for respective gMean ratio (T/R)				
gCV	Precision	80%	100%	125%	150%	200%
15.6%	1.31	(69.90, 91.56)	(87.37, 114.45)	(109.22, 143.06)	(131.06, 171.68)	(174.75, 228.90)
12.7%	1.25	(71.66, 89.31)	(89.57, 111.64)	(111.97, 139.55)	(134.36, 167.46)	(179.15, 223.28)
7.17%	1.13	(75.17, 85.15)	(93.96, 106.43)	(117.45, 133.04)	(140.94, 159.65)	(187.91, 212.86)

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper, lower}} = \exp(\ln(\theta) \pm \omega)$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by [R12-0972] using R Version 3.0.3.

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.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

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

9. REFERENCES

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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, tumor marker
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).

10.2 PREPARATION AND HANDLING OF BI 655130 SOLUTION FOR INFUSION AND BI 655130 SOLUTION FOR INJECTION

10.2.1 Preparation Instructions for BI 655130 dose (concentration

Necessary Materials:

Drug Product and Dilution Media:

3 vials BI 655130 Solution for Infusion (correlates to BI 655130)

1 bottle 0.9% sodium chloride solution (e.g. B.Braun, 401734)

Consumables:

1 x Blunt Fill needle 18 G (material: stainless steel/ Polypropylene - e.g. BD, 305180)

syringe (material: Polycarbonate/ Polypropylene – e.g. BD, 309628)

syringe (material: Polypropylene - e.g. BD, 300912)

syringe (material: Polypropylene - e.g. BD, 300629)

syringe (material: Polypropylene - e.g. Omnifix B.Braun, 4617509F)

7 x syringe closure (material: Polyethylene - e.g. Combi-Stopper B.Braun, 4495101)

4 x Spike (material: Polyolefine - e.g. Mini-Spike, 0.45 µm Air Filter B.Braun, 4550242)

Empty EVA (Ethylene vinyl acetate) infusion bag:

e.g. Freka Mix Monolayer (Fresenius-Kabi, F2859061)

In case that a material is not available it can be replaced by a one which is comparable with regard to qualitative composition and dimension.

Preparation overview:

Dilution: of BI 655130 Solution for Infusion 0.9% sodium chloride → BI 655130 (in infusion bag)

1) Put a Mini-Spike on a bottle containing 0.9% sodium chloride solution
2) Attach a syringe to the Mini-Spike, withdraw of the 0.9% sodium chloride Solution and disconnect the filled syringe. Close it with a Combi-Stopper.
3) Attach a syringe to the Mini-Spike, withdraw of the 0.9% sodium chloride Solution and disconnect the filled syringe. Close it with a Combi-Stopper.
4) Attach a syringe to the Mini- Spike, withdraw of the sodium chloride Solution and disconnect the filled syringe. Close it with a Combi-Stopper.
5) Put a Mini-Spike on each of two vials containing BI 655130 Solution for Infusion and connect one syringe to the Mini-Spike.
6) Withdraw of BI 655130 Solution for Infusion from each of the two so the total volume in the syringe is BI 655130).

7) Disconnect the syringe and lock the syringe with a Combi-Stopper.
8) Put a Mini-Spike on the third vial containing BI 655130 Solution for Infusion and connect one syringe to the Mini-Spike.
9) Withdraw of BI 655130 Solution for Infusion from the vial (= 140 mg BI 655130)
10) Disconnect the syringe and lock the syringe with a Combi-Stopper.
11) Attach a 1 mL syringe to the Mini-Spike, withdraw of the BI 655130 Solution for Infusion from the vial BI 655130) and disconnect the filled syringe. Close it with a Combi-Stopper.
12) Lock the fill port of the empty infusion bag close to the bag. Open the injection port of the bag.
13) Remove the Combi-Stopper from the syringe obtained in step 6, attach an 18 G needle and transfer the complete contents of the syringe into the infusion bag via the injection port.
14) Disconnect the empty syringe from the needle and close the needle using a Combi-Stopper. Keep bag in an upright position to prevent leakage
15) Connect consecutively the second syringe containing BI 655130 Solution for Infusion (step 9) to the needle of the infusion bag containing BI 655130 Solution for Infusion and transfer the content of the syringes completely into the infusion bag. Disconnect the empty syringe.
16) Connect the third syringe containing BI 655130 Solution for Infusion (step 11) to the needle of the infusion bag containing BI 655130 Solution for Infusion and transfer the content of the syringes completely into the infusion bag. Disconnect the empty syringe.
17) Connect consecutively the syringes containing 0.9% sodium chloride solution (step 2,3 and 4) to the needle of the infusion bag containing BI 655130 Solution for Infusion and transfer the contents of the syringes completely into the infusion bag. Disconnect the empty syringe.
18) Remove the needle and mix solution in the bag by gently kneading and turning it.

10.2.2 Infusion instructions

In all patients, the infusion solution may be intravenously administered over a period of 1 hour. Infusion time can be extended up to 4 hours provided that the maximum time between the preparation and completion of administration of the solution to the patient does not exceed the 4 hours.

10.2.3 Preparation Instructions SC dose

Necessary materials:

1 Vial BI 655130 Solution for Injection

Consumables:

sterile polypropylene syringe - e.g. B. Braun Injekt F (article no: 9166017V)

1 x 21G 1½"needle (material: stainless steel/ polypropylene) – e.g. B. Braun (article no 4657527)

1 x 30G ½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 304000)

1. Take a vial filled with of BI 655130 Solution for Injection to BI 655130 Solution for Injection out of the refrigerator and let it reach room temperature for 30 minutes.
2. Gently invert the vial five times to homogenize prior to use. Check the vial content for visible particles. The solution should be colorless to slightly brownish-yellow and clear to slightly opalescent. If discoloration or visual particles are seen discard the vial.
3. Remove the protective cap from the vial.
4. Using appropriate aseptic technique, insert a sterile 21G needle through the center of the stopper and withdraw the complete content of the vial. using a sterile syringe
5. In case the medication will not be injected immediately close the syringe with a Combi-Stopper.
6. Attach a sterile 30G ½" needle to the syringe, adjust the volume to and gently inject the complete content of the syringe.

10.2.4 Preparation Instructions SC Dose

Necessary materials:

2 Vials BI655130 Solution for Injection

Consumables:

sterile polypropylene syringe - e.g. B. Braun Injekt Solo (article no: 4606027)

needle (material: stainless steel/ polypropylene) – e.g. B. Braun (article no 4657527)

needle for injection (material: stainless steel/ polypropylene) –

e.g. BD (article no: 304000)

1. Take two vials filled with of BI 655130 Solution for Injection out of the refrigerator and let it reach room temperature for 30 minutes.
2. Take the first vial and gently invert the vial five times to homogenize prior to use. Check the vial content for visible particles. The solution should be colorless to slightly brownish-yellow and clear to slightly opalescent. If discoloration or visual particles are seen discard the vial.
3. Remove the protective cap from this vial.
4. Using appropriate aseptic technique, insert a sterile 21G needle through the center of the stopper and withdraw the complete content of this vial using a sterile syringe.
5. Repeat steps 1 to 4 with the second vial using the syringe already filled with
6. In case the medication will not be injected immediately close the syringe with a Combi-Stopper.
7. Attach a sterile needle to the syringe, adjust the volume to and gently inject the complete content of the syringe.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

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

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		08 Mar 2017 10:14 CET
Author-Trial Statistician		08 Mar 2017 10:23 CET
Author-Trial Clinical Pharmacokineticist		08 Mar 2017 15:28 CET
Approval-Therapeutic Area		09 Mar 2017 14:13 CET
Verification-Paper Signature Completion		13 Mar 2017 11:39 CET
Approval-Team Member Medicine		13 Mar 2017 12:11 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed