Clinical Trial Protocol

	Document Number: c21745299-03
EudraCT No.:	2018-001074-18
BI Trial No.:	1368-0029
BI Investigational Product:	BI 655130
Title:	Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
Lay Title:	A study in healthy people to measure the amount of BI 655130 in the blood after injecting different doses into different parts of the body
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version 3.0 Date: 07 January 2019

Proprietary confidential information
© 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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: 25 June 2018	**Trial number:** 1368-0029		**Revision date:** 07 January 2019
Title of trial:	Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).		
Principal Investigator:			
Trial site:			
Clinical phase:	I		
Objectives:	- To investigate the relative bioavailability of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region compared to a single subcutaneous periumbilical injection of BI 655130 - To investigate the relative bioavailability of a single subcutaneous injection of BI 655130 into the thigh compared to a single subcutaneous periumbilical injection of BI 655130 - To investigate safety, tolerability, and pharmacokinetics of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region.		
Methodology:	Single dose, open-label in matched-group design		
No. of subjects:			
total entered:	48		
each treatment:	12		
Diagnosis:	Healthy subjects assigned to Dose Group 2 left and right periumbilical SC injection, of BI 655130), Dose group 3 left and right periumbilical SC injection, of BI 655130) and Dose Group 4 SC injection in the thigh, of BI 655130) will be matched for gender and body weight (± 10%) to subjects assigned to Dose Group 1 periumbilical SC injection, of BI 655130).		

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 25 June 2018	**Trial number:** 1368-0029		**Revision date:** 07 January 2019
Main criteria for inclusion:	Healthy male and female subjects, age of 18 to 50 years, body mass index (BMI) of 19.0 to 29.9 kg/m^2		
Test treatment: **dose:** **mode of admin.:**	BI 655130 solution for injection Subcutaneous (SC) injection: - Two single injections of periumbilical left and right (Dose Group 2) - Two single injections of periumbilical left and right (Dose Group 3) - One single injection of into the thigh (Dose Group 4)		
Reference treatment: **dose:** **mode of admin.:**	BI 655130 solution for injection One single subcutaneous (SC) injection of periumbilical (Dose Group 1)		
Duration of treatment:	One day (single dose) for each treatment		
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoints: $AUC_{0-\infty}$ Further parameters of interest as appropriate.		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, local tolerability, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR]).		
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', and 'matched pair'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART

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]	12-lead ECG	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[9]	Query regarding local tolerability[5]
1	-28 to -3			Screening[1]		X[12]	X	X		
	-5			Ambulatory visit		X[11]				
2	-1	-12:00	20:00	Admission to trial site		X[8]			X	
	1	-2:00	6:00		X[2]	X[2, 12]	X[2]	X[2]	X[2]	X
		0:00	8:00	Drug administration						
		0:30	8:30						X	X
		1:00	9:00					X		
		2:00	10:00	Light breakfast[6]	X			X		
		3:00	11:00		X					
		4:00	12:00	Lunch[6]	X			X	X	X
		6:00	14:00				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
	2	24:00	8:00	Breakfast[6]	X		X	X	X	X
		28:00	12:00	Lunch[6]						
		32:00	16:00	Snack (voluntary)[6]				X		
		34:00	18:00	Dinner[6]					X	X
	3	48:00	8:00	Breakfast[6] discharge from trial site (confirmation of fitness[7])	X	X	X	X	X	X
	4	72:00	8:00	Ambulatory visit	X				X	X
	5	96:00	8:00	Ambulatory visit	X				X	X
	6	120:00	8:00	Ambulatory visit	X				X	X
	7	144:00	8:00	Ambulatory visit	X				X	X
	8	168:00	8:00	Ambulatory visit	X	X	X	X	X	X
	15	336:00	8:00	Ambulatory visit	X	X			X	X

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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]	12-lead ECG	vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]	Query regarding local tolerability [5]
2	22	504:00	8:00	Ambulatory visit	X			X	X	X	
	29	672:00	8:00	Ambulatory visit	X		X	X	X	X	X
	36	840:00	8:00	Ambulatory visit	X					X	
	43	1008:00	8:00	Ambulatory visit	X					X	
	57 ±3	1344:00	8:00	Ambulatory visit	X					X	X
	71 ±3	1680:00	8:00	Ambulatory visit	X					X	
	92 ±3	2184:00	8:00	Ambulatory visit	X		X[12]	X		X	
	120 ±3	2856:00	8:00	Ambulatory visit	X					X	
	148 ±3	3528:00	8:00	Ambulatory visit	X					X	
3	176 ±3	4200:00	8:00	EoTrial[10]	X		X[12]	X	X	X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, alcohol breath test, 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 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.
8. Only drug screening and alcohol breath test.
9. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
10. EoTrial (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EoTrial must not be performed before last PK sampling.
11. Safety laboratory is to be taken within five days prior to study drug administration and can be omitted if the screening examination is performed between Day -5 and Day -3.
12. At these time points, a pregnancy test will be done.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

TABLE OF CONTENTS

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ABBREVIATIONS

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_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$\%AUC_{tz-\infty}$	The percentage of $AUC_{0-\infty}$ obtained by extrapolation
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CD	Crohn's Disease
CI	Confidence interval
CL	confidence limits
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Coefficient of variation
DILI	Drug induced liver impairment
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EoTrial	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
IL36R	Interleukin 36 receptor
IRB	Institutional Review Board

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ISF	Investigator site file
ITE	Indirect target engagement
IV	Intravenous
KO	Knock out
LOQ	Limit of Quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
MRD	Multiple rising dose
MRT	Mean residence time of the analyte in the body after SC administration
N	Number
NC	Not calculated
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
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
SAE	Serious adverse event
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TGF	Transforming growth factor
TMDD	Target mediated drug disposition
TMF	Trial Master File
TSAP	Trial statistical analysis plan
UC	Ulcerative colitis
ULN	Upper limit of normal
V_z	Volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White Blood Cells

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36 receptor (IL36R) signalling. Binding of BI 655130 to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and bowel diseases such as generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), and inflammatory bowel disease (IBD).

Genetic human studies established a strong link between IL36R signalling and skin inflammation, as demonstrated by the occurrence of GPP in patients with a loss of function mutation in IL36Rα, the gene encoding the endogenous inhibitor of IL36R, which resulted in uncontrolled IL36R signalling [R14-5158, R15-1421]. Mutations in other genes linked to the IL36 pathway such as CARD14 also lead to GPP [R16-0929]. IL36R signalling drives skin inflammation in several animal models, further supporting the strong link between IL36R biology and skin disorders based on human genetics [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 [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 signalling may play an important role in IBD. 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 patients with Crohn's disease (CD). Human IL36 ligands enhanced intestinal barrier permeability, a hallmark of IBD pathogenesis, in primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signalling and IBD was further strengthened by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute and chronic 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 (UC) and CD patients. Finally, IL36R signalling in disease relevant cells, such as intestinal myofibroblasts and macrophages, induces both pro-inflammatory (e.g. IL-1b, IL-8, TNF-α) and tissue remodelling related mediators (e.g. TGF-β, MMPs).

Altogether, these findings support a prominent role for IL36R in driving skin and intestinal inflammation and support anti-human IL36R antibody BI 655130 as a therapeutic agent for epithelial-mediated inflammatory diseases such as GPP, PPP, and IBD.

GPP is characterised by systemic inflammation of the skin and internal organs [R15-1421; R16-0933]. Acute GPP is difficult to treat and no approved or standard of care therapy is

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

available in the US/EU. Current treatment options aiming to control acute GPP and maintain response are cyclosporine, acitretin, and methotrexate [R16-0933]. Secukinumab, Infliximab, Brodalumab, and Ixekizumab have been approved for GPP exclusively in Japan based on small local uncontrolled studies. Treatment is commonly not effective in suppressing acute flares during induction and recurrences emerge frequently.

PPP is a form of chronic Pustular Psoriasis characterized by sterile pustules limited to palms and soles [R16-0927]. No approved or effective treatment is available.

Both UC and CD are characterised by abdominal pain, fever, bloody diarrhoea, and inflammatory lesions in the gastrointestinal mucosa. Current treatment options include aminosalicylates, glucocorticoid therapy, azathioprine, 6-mercaptopurine, and biologics (blocking TNF or integrin α4β7). 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 progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared with the current therapeutic standard.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 655130 is a humanized monoclonal antibody (mAb) of the IgG1 isotype that is directed against human IL36R. It is derived from a mouse antibody 81B4 (BI 674308) cloned into a human IgG1 Kappa backbone. The mAb uses an IgG1 that has two mutations in the Fc region (Leu234Ala and Leu235Ala) to reduce FcγR and complement binding. In addition, to reduce charge heterogeneity, the C-terminal lysine residue of the heavy chain is deleted.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-04].

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 [c03320877-04].

1.2.3 Toxicology

As BI 655130 does not demonstrate adequate pharmacological activity in common toxicology species, a surrogate antibody (BI 674304) specific for mouse IL36R was developed and used for toxicology assessments. The toxicology package includes 4, 13 and 26-week toxicity studies and reproductive/developmental toxicity studies with BI 674304 in mice. In addition, the toxicology package includes a 2-week toxicity study in mice with BI 655130 and local tolerance, in vitro cytokine release, and tissue cross-reactivity studies.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1.2.4 Nonclinical pharmacokinetics

The pharmacokinetics (PK) of BI 655130 was studied in cynomolgus monkeys. In mice, pharmacokinetic studies were performed with the mouse-specific anti-IL36R antibody, BI 674304 [c03320877-04].

1.2.5 Clinical experience

In Phase I, BI 655130 has been evaluated in three clinical trials: a first-in-human (FIH) SRD trial [c09985235-01], an MRD trial [c09105854-05], and a recently completed relative bioavailability study exploring the pharmacokinetics as well as safety and tolerability of a newly developed SC formulation (1368-0003, [c10896574-01].

FIH-Study (Trial 1368.1)

The FIH (first-in-human) trial [c09985235-01] explored safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenously administered BI 655130 in healthy male subjects. Subjects received single ascending IV doses of up 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.

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 diarrhea (BI 655130: 2/58 subjects [3.4%]; placebo: 2/20 subjects [10.0%]).

There were two AEs of moderate intensity, both considered not related to the study drug, (injection site hematoma and 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. Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No clinically relevant changes were observed in 12 lead ECGs, vital signs, physical exams, and cardio-monitoring.

MRD study (Trial 1368.2)

Trial 1368.2 [c09105854-05] explored the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising intravenous doses of BI.

In total, 40 subjects entered this trial and were treated. The study consisted of a multiple dose part with four dose groups and a single dose arm A total of 32 subjects were assigned to the MRD part. In each of the 4 dose groups 6 subjects received BI 655130 and 2 subjects received placebo. Additional 8 subjects entered the SD part of the trial with 6 subjects assigned to BI 655130 and 2 subjects assigned to placebo [c18789185-01].

Overall, a total of 3 subjects did not complete the planned observation time according to the CTP. One subject of the placebo group of the MRD part of the trial withdrew consent after having received all 4 planned doses. Two subjects of the MD BI 655130 treatment group discontinued treatment because of AEs: 1 subject after having received 1 dose of

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

BI 655130 and the other subject after having received 3 doses of BI 655130 (infusion of the third dose was stopped after 8 min).

The frequency of subjects with at least 1 drug-related treatment-emergent AE was similar for the MD placebo group and the MD BI 655130 treatment groups (ranging from 16.7% to 66.7%), and no dose-dependency was observed. The drug related AE with the highest incidence was headache, which was reported in 5 of 6 subjects in the group. Additionally, gastrointestinal disorders (abdominal discomfort, diarrhoea, and nausea) appeared to occur more often in subjects who received BI 655130 than in subjects who received placebo. Infusion related reaction, decreased appetite, and anxiety were only observed in the MD BI 655130 treatment group. In total, 2 out of the 24 subjects (8.3%) who received multiple doses of BI 655130 were reported with AEs leading to discontinuation of trial drug, 1 subject with mild pyrexia after the first infusion and 1 subject with mild and transient infusion related reactions during the third infusion. One subject of the placebo group of the MRD part of the trial withdrew consent after having received all 4 planned doses.

Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. For further details, please refer to the final study report [c18789185-01].

Trial 1368-0003

This study explored the pharmacokinetics as well as safety and tolerability of an SC formulation of BI 655130 at 2 different dose strengths of and in an open-label, sequential group design. Furthermore, the relative bioavailability of the SC dose was compared with one single IV dose of BI 655130 in an open-label, matched group design.

The study included a total of 36 healthy male and female subjects with 12 subjects per treatment group.

Based on preliminary data the SC formulation is considered to be well tolerated, the standardised assessment of injection pain, redness, induration, swelling, heat, or other findings did not reveal any noteworthy changes. There were three subjects with a transient occurrence of redness and one subject with a swelling at injection site 30 minutes after the SC injection. No further local tolerability findings were reported, in particular no injection pain and no induration at injection site during an observation period of up to 6 months.

Regarding systemic AEs, there were no AEs of severe intensity. Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. The clinical part of the study has been completed. The study report is under preparation (final safety tables available, [c18789185-01]).

Pharmacokinetics

The PK parameters of BI 655130 after a single IV infusion from Trial 1368.1 are shown in Table 1.2.5:1. BI 655130 plasma levels were first detected at a dose level of

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

$AUC_{0\text{-}inf}$ results should be considered for informational purposes only given the high %_AUC of extrapolated values (>50%) for the dose groups. Exposure in terms of $AUC_{0\text{-}tz}$ 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 1.2.5:1 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
$AUC_{0\text{-}tz}$ [µg·day/mL]	NC	NC	0.00652 (121)	2.08 (29.0)	9.57 (5.90)	25.1 (15.5)
$AUC_{0\text{-}inf}$ [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)	0.998 (15.7)	1.96 (11.9)
Dose Group#	**#6**	**#7**	**#8**	**#9**	**#10**	
Dose	N=4	N=6	N=6	N=6	N=4	
$AUC_{0\text{-}tz}$ [µg·day/mL]	113 (5.86)	420 (13.3)	1050 (7.26)	2610 (11.7)	4130 (12.1)	
$AUC_{0\text{-}inf}$ [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)	

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

In the MRD Trial 1368.2, PK data are consistent with the preceding single dose study as shown in Table 1.2.5:2.

Table 1.2.5:2 Geometric mean (geometric CV %) PK parameters of BI655130 in study 1368.2 after multiple dosing

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_{0-t} (µg·day/mL)	298 (9.26)	451 (7.96)	604 (4.77)	760 (4.21)
C_{max} (µg/mL)	77.9 (19.4)	101 (11.4)	117 (14.8)	141 (4.33)
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_{0-t} (µg·day/mL)	552 (10.4)	895 (4.45)	1140 (5.11)	1390 (4.63)
C_{max} (µg/mL)	130 (8.48)	185 (9.31)	223 (6.64)	253 (8.70)
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_{0-t} (µg·day/mL)	923 (17.3)	1610 (18.0)	2090 (16.9)	2500 (16.7)
C_{max} (µg/mL)	229 (22.9)	310 (21.9)	444 (34.1)	467 (21.4)
Dose	N=5 [Day 1] 0-168 h	N=5 [Day 8] 168-336 h	N=4 [Day 15] 336-504 h	N=4 [Day 22] 504-600 h
AUC_{0-t} (µg·day/mL)	1770 (12.5)	2900 (7.52)	3950 (16.1)	4660 (12.9)
C_{max} (µg/mL)	422 (18.5)	646 (10.7)	780 (17.1)	826 (15.8)

Exposure of both dose groups is in the linear dose range. The geometric mean t1/2 values after dose 4 were similar across dose groups and ranged from 26.5 to 33.5 days with no dose dependency.

Table 1.2.5:3 summarizes PK data of the recent completed clinical study 1368.3 conducted according to a parallel (matched) group design. Bioavailability of the SC injection was calculated to be about 50% and of the SC injection 70% using the IV group as reference.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 1.2.5:3 Geometric mean (geometric CV %) PK parameters of BI655130 in study 1368.3 after a single dose

Dose	N=11 [SC]	N=12 [SC]	N=11 [IV]
$AUC_{0\text{-}inf}$ (µg·day/mL)	574 (40.1)	1600 (29.5)	2280 (16.0)
C_{max} (µg/mL)	12.2 (44.5)	33.4 (32.7)	114 (18.0)
T_{max} [1] (day)	0.3 - 14 7.0	4 - 21 6.0	0.02-0.3 0.13
t½ (day)	20.6 (26.7)	25.6 (23.5)	27.1 (17.1)

[1]min – max, median

The geometric mean t1/2 values after subcutaneous administration ranged from 20.6 to 25.6

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 dose groups as compared to placebo. This demonstrates that BI 655130 is on-target for the time points analyzed.

Residual Effect Period

The Residual Effect Period (REP) of BI 655130 is up to 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-04].

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 II development.

In Phase I studies BI 655130 was mainly administered as intravenous infusion. However, the subcutaneous injection route is considered to be required to enable in upcoming therapeutic studies the self-administration of BI 655130 by patients. For this reason a subcutaneous injection formulation is undergoing clinical development.

Recently, the clinical part of a Phase 1 study (Study 1368-0003) has been completed exploring the characteristics of a subcutaneous formulation of BI 655130 with particular focus on relative bioavailability compared to an intravenous formulation. A further objective was the assessment of local tolerability. In this study, the relative bioavailability of a single SC injection containing of BI 655130 was in a range of about 50% while relative bioavailability increased to 70% for a single SC injection of of BI 655130

To further elucidate the origin of the observed potentially dose dependent increasing bioavailability, the current study will compare the pharmacokinetics (PK) of a single SC injection of of BI 655130 with the PK of two SC injections of of BI 655130 This design will investigate the impact of local factors at the SC injection site on the overall exposure of BI 655130 which may contribute to the lower bioavailability observed in the preceding clinical study.

The current study will also investigate the impact on relative bioavailability regarding the site of injection (abdomen and thigh) to enable the switch of injection site if needed.

To widen the SC dose range the current study will also investigate a subcutaneous dose of of BI 655130 corresponding to two single periumbilical SC injections of (i.e. total injection volume

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the relative bioavailability of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region compared to a single subcutaneous periumbilical injection of BI 655130

The secondary objective is to investigate the relative bioavailability of a single subcutaneous injection of BI 655130 into the thigh compared to a single subcutaneous periumbilical injection of BI 655130.

A further objective is to investigate safety, tolerability, and pharmacokinetics of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to optimize treatment regimen of the subcutaneous formulation for potential use as maintenance therapy 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. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture 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

The toxicology package conducted in mice with a mouse-specific antibody (BI 674304) includes 4, 13 and 26-week toxicity studies and reproductive/developmental toxicity studies without any findings which would preclude clinical studies in humans (see IB [c03320877-04]).

The clinical safety and tolerability profile of BI 655130 was comparable to placebo in male subjects following once weekly intravenous doses of up to body weight administered over 4 weeks. There were no deaths or other serious adverse events. 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.

Recently the clinical part of an initial with a subcutaneous formulation has been completed. The maximum tested SC dose was of BI 655130 (injection volume). The study did not reveal systemic or local AEs which would preclude further clinical studies with the SC formulation. The observed exposure at following SC injection was about 6 fold lower compared to the maximum exposure in completed clinical studies with an IV infusion of up to of BI 655130. Therefore even the planned maximum SC dose of of BI 655130 is not expected to exceed exposure limits already tested in humans.

Based on studies in healthy subjects, 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:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- The study will start with Dose Group 1 and 2 (periumbilical SC dose of of BI 655130). Provided no dose limiting AEs occurred as 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 up to Day 10 (see Section 3.1), the study will pursue with Dose Group 3 (periumbilical SC dose of of BI 655130) and Dose Group 4 (SC dose of of BI 655130 in the thigh). Dose Group 3 will be divided into 2 cohorts. In the first week, 6 subjects will be treated. There will be an interval of at least 1 week after start of dosing in the first cohort before start of dosing of the second cohort of Dose Group 3.
- 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.
- Monitoring of ECG, vital signs, and extensive safety laboratory testing (Table 5.2.3:1) is conducted throughout the study.
- After dosing, the subjects will stay at the site for at least 48 hours.
- 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 for both expected and unexpected adverse events.

Currently there are no data available to suggest interactions of BI 655130 [c03320877-04].

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 laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.2.1, adverse events of special interest.

Based on the preclinical and 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 IBD and GPP, the benefit of this trial is considered to outweigh the potential risks and justifies the exposure of healthy subjects.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will explore the relative bioavailability, safety, and tolerability following a subcutaneous (SC) injection of BI 655130 at different dose strengths, injection volumes, and injection sites:

- One SC injection of periumbilical (Dose Group 1)
- Two SC injections of each periumbilical left and right (Dose Group 2)
- Two SC injections of each periumbilical left and right (Dose Group 3)
- One SC injection of in the thigh (Dose Group 4)

The total dose in Dose Group 1, 2, and 4 is of BI 655130 and the total dose in Dose Group 3 is of BI 655130.

The study will be conducted in a single-dose, open-label, matched-group design. The exposure in Dose Group 1 will be used as reference to assess the relative bioavailability of Dose groups 2 - 4. For details refer to Section 4.1.

The study will start with Dose Group 1 and 2. After completion of treatment of the first two dose groups, the study will continue with Dose Group 3 and 4. 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).

The Dose Group 3 will follow a staggered administration with treatment of 6 subjects (cohort A) in the first week and the remaining subjects (cohort B) from Week 2.

A documented Safety Review of Dose Group 1 and 2 at least 10 days after last dosing in Dose Group 2 must take place prior to continue the study with Dose Groups 3 and 4. 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. Continuation of the study 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 8 evaluable subjects in each of the Dose Group 1 and 2 are required to decide about continuation with the remaining dose groups.

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)
- Vital signs
- Clinical laboratory tests
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 or a delegate 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

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.

The plasma analyses of BI 655130 concentrations will be performed at

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

The study will be conducted according to a single-dose, open-label design with matched groups.

The resulting group sizes (see Section 7.6) are considered to be sufficient for the exploratory evaluation of pharmacokinetics. The assignment of matched healthy volunteers is a useful method to control for other factors which may influence the pharmacokinetics of BI 1467335 in a renal impaired population.

The open-label treatment is not expected to bias results, since the primary endpoints are derived from measurement of plasma concentrations of the analytes provided by a bioanalytical laboratory. It is also considered sufficiently accurate as the trial observations are objective (PK, laboratory) and over-reporting of AEs is unlikely.

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 tolerability of BI 655130 has already been evaluated up to MRD, resulting in a far higher exposure compared to the expected exposure of the current study.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male and female subjects (12 in each dose group) will enter the study. They will be recruited from the volunteers' pool of the trial site. Healthy subjects assigned to Dose Groups 2 - 4 will be matched on an individual level for gender and body weight (± 10%) to subjects assigned to Dose Group 1 periumbilical injection).

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 19.0 to 29.9 kg/m^2 (incl.)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4. Signed and dated written informed consent prior to admission to the study in accordance with ICH-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 IU/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 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections
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)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 up to 4 weeks after administration
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 up to study completion
23. Lactation

In addition, the following trial-specific exclusion criterion applies:

24. Previous use of the trial medication

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

This study is a single dose study, therefore removal of subjects from study medication after dosing is not applicable.

An individual subject is to be removed from further assessments 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 from further assessments. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

>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.

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 administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (i.e., 16 weeks, see Section 1.2.5), 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 overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable
2. The expected enrolment goals 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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5. Further dosing will be stopped if at least 2 subjects in one dose group 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. Replacement of subjects should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment and matching criteria as the subject he or she replaces.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

The characteristics of the 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 or thigh)
Duration of use:	Single dose

At the time of use, the 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 Dose Group 1, matching subjects will be allocated to the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population matched for gender and body weight, relevant imbalances between the dose groups are not expected.

The allocation of subjects will be performed prior to the administration of trial medication. Once a subject number has been assigned to a treatment group, it cannot be reassigned to any other treatment group.

4.1.3 Selection of doses in the trial

The dose of of BI 655130 selected for this trial has been selected to correspond to the potential dose for maintenance treatment in clinical trials in patients. The highest dose tested in this trial of BI 655130) will be included to widen the SC dose range.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 solutions are provided in the ISF.

Table 4.1.4: 1 Dosage and treatment schedule

Dose Group	Total dose	Route of administration	Concentration of application solution	Application volume	Injection site
1		SC			Periumbilical
2		SC			Periumbilical (left and right)
3		SC			Periumbilical (left and right
4		SC			Thigh

Following an overnight fast of at least 10 hours, the medication will be administered. Trial drug will be injected subcutaneously in the abdominal region or into the thigh. 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.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed. 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. Emergency envelopes will not be provided, since the treatments of all subjects are known in this open-label trial.

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- Storage conditions
- Use-by date
- Batch number
- Investigator
- Subject number

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

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 special emergency procedures 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 2 h after administration of the study drug.

From 1 h before until 2 h after SC injection, fluid intake is not allowed.

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

Alcoholic beverages are not permitted starting 7 days before the administration of trial medication until Day 15. From Day 15 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.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during the in-house confinement.

Poppy-seed containing products are not allowed starting 2 days before screening and 2 days before admission to trial site (Day -1) to avoid false positive drug screening results.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the administration of trial medication up to 4 weeks after administration.

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
- Vital signs (blood pressure, pulse rate)
- Local tolerability

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.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Chances 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- 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 time since 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, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

Adverse events of special interest

The term adverse event of special interest (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 Section 5.2.2.2.

The AESI in this trial is hepatic injury, as defined by the following alterations of hepatic laboratory parameters:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, 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 that 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 judged 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 judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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

AE 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 carefully 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, intensity of the event, and 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 any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) 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 the initial information.

Information required

All (S)AEs, including those persisting after the 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 Part B) as well as non-trial specific information and consent for the pregnant partner.

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]
Haematology	Haematocrit Haemoglobin Red Blood Cell count (RBC) Reticulocytes count White Blood Cells count (WBC) Platelet Count
Automatic WBC differential (relative and absolute count possible)	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 (International Normalization Ratio)
Enzymes	AST [Aspartate transaminase] /GOT, SGOT ALT [Alanine transaminase] /GPT, SGPT Alkaline Phosphatase Gamma-Glutamyl Transferase (GGT) Creatine Kinase [CK] Creatine Kinase Isoenzyme MB [CK-MB, only if CK is elevated] Lactate Dehydrogenase (LDH) Serum tryptase[1]
Hormones[1]	Thyroid Stimulating Hormone (TSH)
Substrates	Glucose (Plasma) Creatinine Bilirubin, Total Bilirubin, Direct Bilirubin, Indirect Protein, Total Protein electrophoresis [1] Albumin Alpha-1-Globulin Alpha-2-Globulin Beta-Globulin Gamma-Globulin C-Reactive Protein (CRP) Uric Acid Cholesterol, total Triglyceride
Electrolytes	Sodium Potassium Chloride Calcium Phosphate (as Phosphorus, Inorganic)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH
Urine sediment (microscopic examination if urine analysis abnormal)	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, on Day 92, 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 (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Dräger Alcotest® 6510 and Alcotest® 510, Belgium) will be performed at screening and on Day -1, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed 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 Alere® –HCG urine, respectively.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. MAC 5500, GE Healthcare) at the time points given in the Flow Chart.

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 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.

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.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

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 (including drug screen and pregnancy test), and a physical examination. The end of trial examination will include review of vital signs, 12-lead ECG, laboratory tests, recording of AEs and concomitant therapy and a physical examination with determination of weight.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5.2.5.3 Local tolerability

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

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

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 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 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:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

5.5.1.3 Further parameters of interest

The following additional endpoints will be evaluated for BI 655130:

Further pharmacokinetic parameters might be calculated as appropriate.

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, approximately of blood will be taken from an antecubital or forearm vein into a K_2-EDTA (dipotassium 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 K_2-EDTA-anticoagulated blood samples will be mixed gently and placed on ice until centrifugation for about 10 min 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 min 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 -70°C or below at the clinical site until shipment to the analytical laboratory.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 in plasma will be determined by a validated immunoassay.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

The acceptable deviation from the scheduled time for vital signs, ECG and safety laboratory 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 15
- ± 72h from >Day 15 up to the last assessments

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Study participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 48 h following drug administration. The subjects will

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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, 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 prematurely the study before the end of the planned treatment period (i.e., Day 176 ±3) 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The trial objectives are stated in Section 2.2.

For the purpose of defining reference and test treatments, the following terminology will be used. The reference treatment (R) will refer to dose group 1, test treatment 1 (T1) refers to dose group 2, test treatment 2 (T2) refers to dose group 4 and test treatment 3 (T3) refers to dose group 3.

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 analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘treatment’ and ‘matched pair’. For each matched pair in the study a pair number will be assigned for analysis purpose. The resulting variable ‘matched pair’ will be considered as random effect.

The model is described by the following equation:

$y_{kjm} = \mu + \tau_k + p_j + e_{ijkm}$, where

y_{kjm} = logarithm of response (endpoint) measured on subject m in pair j receiving treatment k

μ = the overall mean,

τ_k = the kth treatment effect, k=1,..,4,

p_j = the jth matched pair effect,

e_{ijkm} = the random error associated with the mth subject in sequence i who received treatment k in period j.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

where $p_j \sim N(0,\sigma_B^2)$ i.i.d., $e_{ijk} \sim N(0, \sigma_W^2)$ i.i.d. and p_j, e_{ijk} are independent random variables (note that the indices 'B' and 'W' correspond to 'between' pairs and 'within' pairs variability, respectively).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of the different dose groups 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 the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the clinical trial report.

Relevant protocol violations may be:

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

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

- The subject experiences emesis that occurred at or before 2 times median tmax of the respective treatment (median tmax is to be determined excluding the subjects experiencing emesis)
- A predose concentration is >5% Cmax value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The following analysis sets will be defined for this trial:

- Treated set (TS):
  This subject set includes all subjects from the RS who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9
- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the 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/she contributes only one PK parameter value for one period to the statistical assessment

Point estimates of the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see Sections 5.5.1.1 and 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 (Least Squares 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.

The comparisons of interest will be T1 vs. R, T2 vs. R, and T3 vs. R. Further comparisons may be investigated if appropriate (e.g. T1 vs. T2) and will be described in the TSAP.

7.3.2 Secondary analyses

The same statistical model as stated in Section 7.1.3 will be repeated for the primary and secondary endpoints but with all sources of variation considered as fixed effects.

Additionally, the pharmacokinetic parameters listed in Section 5.5.1.3 will be calculated and analysed descriptively, if feasible.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see Section 1.2.5) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as 'follow-up'. The follow-up will be summarised according to previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. AEs occurring after the last per-protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

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.

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 drug BI 655130 will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-472].

Individual plasma concentration data and the pharmacokinetic parameters will be tabulated, graphically displayed and summarized by descriptive statistics. The analysis of PK endpoints will be based on PKS.

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 RANDOMISATION

The study will not be randomised as individually matched subjects will be used. Thus, this section is not applicable.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 4*12 = 48 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The observed inter-individual geometric coefficient of variation (gCV) in a previous trial (1368.3) was roughly 30% for C_{max} and for AUC. For various assumptions on the gCV, Table 7.6: 1 provides an overview of the precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.6: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a parallel trial (for one comparison based on 2 arms)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
25	1.24	90	72.64	111.51
25	1.24	100	80.71	123.90
25	1.24	110	88.78	136.29
30	1.29	90	69.70	116.21
30	1.29	100	77.45	129.12
30	1.29	110	85.19	142.03
35	1.34	90	66.95	120.99
35	1.34	100	74.38	134.44
35	1.34	110	81.82	147.88

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

The 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 Julious [R11-5230, Chapter 8] using R Version 3.4.2.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

8.2 DATA QUALITY ASSURANCE

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9. REFERENCES

9.1 PUBLISHED REFERENCES

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R14-4037 Towne JE, Renshaw BR, Douangpanya J, Lipsky BP, Shen M, Gabel CA, Sims JE. Interleukin-36 (IL-36) ligands require processing for full agonist (IL-36alpha, IL-36beta, and IL-36gamma) or antagonist (IL-36Ra) activity. J Biol Chem 2011;286(49):42594-42602.

R14-5158 Marrakchi S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 201; 365(7):620-628.

R15-1399 Blumberg H, Dinh H, Dean C, Trueblood ES, Beiley K, Shows D, Bhagavathula N, Aslam MN, Varani J, Towne JE, Sims JE. IL-1RL2 and its ligands contribute to the cytokine network in psoriasis. J Immunol 2010;185(7):4354-4362.

R15-1421 Onouofriadis A, Simpson MA, Pink AE, Meglio P di, Smith CH, Pullabhatla V, Knight J, Spain SL, Nestle FO, Burden AD, Capon F, Trembath RC, Barker JN. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89(3):432-437.

R15-1432 Blumberg H, Dinh H, Trueblood ES, Pretorius J, Kugler D, Weng N, Kanaly ST, Towne JE, Willis CR, Kuechle MK, Sims JE, Peschon JJ. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J Exp Med 2007;204(11):2603-2614.

R15-1447 Tortola L, Rosenwald E, Abel B, Blumberg H, Schaefer M, Coyle AJ, Renauld JC, Werner S, Kisielow J, Kopf M. Psoriasiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. J Clin Invest 2012;122(11):3965-3976.

R16-0927 Waal AC de, Kerkhof PCM van de; Pustulosis palmoplantaris is a disease distinct from psoriasis; J Dermatol Treat 22 (2), 102 - 105 (2011)

R16-0929 Berki DM, Liu L, Choon SE, Burden AD, Griffiths CEM, Navarini AA, Tan ES, Irvine AD, Ranki A, Ogo T, Petrol G, Mahil SK, Duckworth M, Allen MH, Vito P, Trembath RC, McGrath J, Smith CH, Capon F, Barker JN; Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis

R16-0933 Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF; Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia; Int J Dermatol 53, 676 - 684 (2014)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9.2 UNPUBLISHED REFERENCES

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

c03320877-04 Investigator´s Brochure BI 655130 for IL36R antibody in Ulcerative Colitis, Palmoplantar Pustulosis and Pustular Psoriasis. 10 Oct 2017

c09105854-05 , Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects, 1368.2, 02 Aug 2017

c09985235-01 Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers, 1368.1, 07 Apr 2017

c10896574-01 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). 1368.3. 08 Mar 2017

c18789185-01 Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (singleblind, partially randomised, placebo-controlled) in healthy male subjects. 1368.2. 29 May 2018

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10. APPENDICES

10.1 PREPARATION AND HANDLING OF BI 655130 SOLUTION FOR INJECTION

10.1.1 Preparation Instructions SC (Dose group 1, injection left or right periumbilical)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

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

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

½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile ½" needle to the syringe, adjust the volume to and gently inject the complete content of the syringe at the left or right periumbilical region.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.2 Preparation Instructions SC dose (Dose Group 2, injection left and right periumbilical)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

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

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

2 x ½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

1. Take a vial filled with of 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 syringe closure (e.g. B.Braun Combi-Stopper).
6. Attach a sterile ½" needle to the syringe, adjust the volume to (=syringe 1).
7. Repeat steps 1 to 6 with the second vial to prepare a second, separate syringe ready for injection (=syringe 2).
8. Gently inject the complete content of the first syringe containing solution for injection at the left or right periumbilical region.
9. Gently inject the complete content of the second syringe containing solution for injection periumbilical contralateral to the injection site of the first injection.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.3 Preparation Instructions SC dose (Dose group 3, injection left and right periumbilical)

Necessary materials:

4 Vials BI 655130 Solution for Injection

Consumables:

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

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

½” needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile ½” needle to the syringe, adjust the volume to (=syringe 1)
8. Repeat steps 1 to 7 with the second vial to prepare a second, separate syringe ready for injection (=syringe 2).
9. Gently inject the complete content of the first syringe containing solution for injection at the left or right periumbilical region .
10. Gently inject the complete content of the second syringe containing solution for injection periumbilical contralateral to the injection site of the first injection.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.4 Preparation Instructions SC dose (Dose group 4, injection in the thigh)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

sterile syringe (material: polypropylene) - 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: 305770)

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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile needle to the syringe, adjust the volume to and gently inject the complete content of the syringe in the left or right thigh.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		20 September 2018
EudraCT number		2018-001074-18
BI Trial number		1368-0029
BI Investigational Product(s)		BI 655130
Title of protocol		Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		5.5.2 Methods of sample collection
Description of change		Temperature for storage of clinical samples was changed to -70°C.
Rationale for change		Update on storage temperature.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Number of global amendment		2
Date of CTP revision		07 Jan 2019
EudraCT number		2018-001074-18
BI Trial number		1368-0029
BI Investigational Product(s)		BI 655130
Title of protocol		Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2.5 Clinical experience 3.3.4,1 Removal of individual subjects
Description of change		Residual effect period (REP) changed from 176±3 to 16 weeks.
Rationale for change		Residual effect period in ongoing patient studies 16 weeks, change was required to assure consistency across clinical studies with BI 655130.

APPROVAL / SIGNATURE PAGE

Document Number: c21745299 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		07 Jan 2019 13:49 CET
Author-Trial Clinical Pharmacokineticist		07 Jan 2019 14:53 CET
Approval-Therapeutic Area		07 Jan 2019 15:46 CET
Verification-Paper Signature Completion		08 Jan 2019 12:51 CET
Approval-Team Member Medicine		08 Jan 2019 18:24 CET
Author-Trial Statistician		08 Jan 2019 19:52 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

Clinical Trial Protocol

	Document Number: c21745299-03
EudraCT No.:	2018-001074-18
BI Trial No.:	1368-0029
BI Investigational Product:	BI 655130
Title:	Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
Lay Title:	A study in healthy people to measure the amount of BI 655130 in the blood after injecting different doses into different parts of the body
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 2))
Version and Date:	Version 3.0 Date: 07 January 2019

Proprietary confidential information
© 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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: 25 June 2018	**Trial number:** 1368-0029		**Revision date:** 07 January 2019
Title of trial:	Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).		
Principal Investigator:			
Trial site:			
Clinical phase:	I		
Objectives:	- To investigate the relative bioavailability of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region compared to a single subcutaneous periumbilical injection of BI 655130 - To investigate the relative bioavailability of a single subcutaneous injection of BI 655130 into the thigh compared to a single subcutaneous periumbilical injection of BI 655130 - To investigate safety, tolerability, and pharmacokinetics of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region.		
Methodology:	Single dose, open-label in matched-group design		
No. of subjects:			
total entered:	48		
each treatment:	12		
Diagnosis:	Healthy subjects assigned to Dose Group 2 left and right periumbilical SC injection, of BI 655130), Dose group 3 left and right periumbilical SC injection, of BI 655130) and Dose Group 4 SC injection in the thigh, of BI 655130) will be matched for gender and body weight (± 10%) to subjects assigned to Dose Group 1 , periumbilical SC injection, of BI 655130).		

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 25 June 2018	**Trial number:** 1368-0029		**Revision date:** 07 January 2019
Main criteria for inclusion:	Healthy male and female subjects, age of 18 to 50 years, body mass index (BMI) of 19.0 to 29.9 kg/m^2		
Test treatment: **dose:** **mode of admin.:**	BI 655130 solution for injection Subcutaneous (SC) injection: - Two single injections of periumbilical left and right (Dose Group 2) - Two single injections of periumbilical left and right (Dose Group 3) - One single injection of into the thigh (Dose Group 4)		
Reference treatment: **dose:** **mode of admin.:**	BI 655130 solution for injection One single subcutaneous (SC) injection of periumbilical (Dose Group 1)		
Duration of treatment:	One day (single dose) for each treatment		
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-tz} and C_{max} Secondary endpoints: $AUC_{0-\infty}$ Further parameters of interest as appropriate.		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, local tolerability, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR]).		
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', and 'matched pair'. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.		

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	Plasma ADA	Laboratory/ Urinalysis [3]	12-lead ECG	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[9]	Query regarding local tolerability[5]
1	-28 to -3			Screening[1]			X[12]	X	X		
	-5			Ambulatory visit			X[11]				
2	-1	-12:00	20:00	Admission to trial site			X[8]			X	
	1	-2:00	6:00		X[2]	X[2]	X[2, 12]	X[2]	X[2]	X[2]	X
		0:00	8:00	Drug administration							
		0:30	8:30							X	X
		1:00	9:00						X		
		2:00	10:00	Light breakfast[6]	X				X		
		3:00	11:00		X						
		4:00	12:00	Lunch[6]	X				X	X	X
		6:00	14:00					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
	2	24:00	8:00	Breakfast[6]	X			X	X	X	X
		28:00	12:00	Lunch[6]							
		32:00	16:00	Snack (voluntary)[6]					X		
		34:00	18:00	Dinner[6]						X	X
	3	48:00	8:00	Breakfast[6] discharge from trial site (confirmation of fitness[7])	X		X	X	X	X	X
	4	72:00	8:00	Ambulatory visit	X					X	X
	5	96:00	8:00	Ambulatory visit	X					X	X
	6	120:00	8:00	Ambulatory visit	X					X	X
	7	144:00	8:00	Ambulatory visit	X					X	X
	8	168:00	8:00	Ambulatory visit	X		X	X	X	X	X
	15	336:00	8:00	Ambulatory visit	X	X	X			X	X

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]	Plasma ADA	Laboratory/ Urinalysis [3]	12-lead ECG	vital signs (BP, PR)	Query on adverse events, concomitant therapies [9]	Query regarding local tolerability [5]
2	22	504:00	8:00	Ambulatory visit	X			X	X	X	
	29	672:00	8:00	Ambulatory visit	X	X	X	X	X	X	X
	36	840:00	8:00	Ambulatory visit	X					X	
	43	1008:00	8:00	Ambulatory visit	X	X				X	
	57 ±3	1344:00	8:00	Ambulatory visit	X	X				X	X
	71 ±3	1680:00	8:00	Ambulatory visit	X	X				X	
	92 ±3	2184:00	8:00	Ambulatory visit	X	X	X[12]	X		X	
	120 ±3	2856:00	8:00	Ambulatory visit	X	X				X	
	148 ±3	3528:00	8:00	Ambulatory visit	X	X				X	
3	176 ±3	4200:00	8:00	EoTrial[10]	X	X	X[12]	X	X	X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, alcohol breath test, 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 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.
8. Only drug screening and alcohol breath test.
9. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
10. EoTrial (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EoTrial must not be performed before last PK and ADA sampling.
11. Safety laboratory is to be taken within five days prior to study drug administration and can be omitted if the screening examination is performed between Day -5 and Day -3.
12. At these time points, a pregnancy test will be done.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

TABLE OF CONTENTS

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ABBREVIATIONS

ADA	Anti-drug antibodies
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
CA	Competent authority
CD	Crohn's Disease
CI	Confidence interval
CL	confidence limits
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Coefficient of variation
DILI	Drug induced liver impairment
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EoTrial	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
IL36R	Interleukin 36 receptor
IRB	Institutional Review Board

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ISF	Investigator site file
ITE	Indirect target engagement
IV	Intravenous
KO	Knock out
LOQ	Limit of Quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
MRD	Multiple rising dose
N	Number
NC	Not calculated
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
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
SAE	Serious adverse event
SOP	Standard Operating Procedure
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
V_z	Volume of distribution during the terminal phase after intravascular administration
WBC	White Blood Cells

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36 receptor (IL36R) signalling. Binding of BI 655130 to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and bowel diseases such as generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), and inflammatory bowel disease (IBD).

Genetic human studies established a strong link between IL36R signalling and skin inflammation, as demonstrated by the occurrence of GPP in patients with a loss of function mutation in IL36Rα, the gene encoding the endogenous inhibitor of IL36R, which resulted in uncontrolled IL36R signalling [R14-5158, R15-1421]. Mutations in other genes linked to the IL36 pathway such as CARD14 also lead to GPP [R16-0929]. IL36R signalling drives skin inflammation in several animal models, further supporting the strong link between IL36R biology and skin disorders based on human genetics [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 [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 signalling may play an important role in IBD. 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 patients with Crohn's disease (CD). Human IL36 ligands enhanced intestinal barrier permeability, a hallmark of IBD pathogenesis, in primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signalling and IBD was further strengthened by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute and chronic 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 (UC) and CD patients. Finally, IL36R signalling in disease relevant cells, such as intestinal myofibroblasts and macrophages, induces both pro-inflammatory (e.g. IL-1b, IL-8, TNF-α) and tissue remodelling related mediators (e.g. TGF-β, MMPs).

Altogether, these findings support a prominent role for IL36R in driving skin and intestinal inflammation and support anti-human IL36R antibody BI 655130 as a therapeutic agent for epithelial-mediated inflammatory diseases such as GPP, PPP, and IBD.

GPP is characterised by systemic inflammation of the skin and internal organs [R15-1421; R16-0933]. Acute GPP is difficult to treat and no approved or standard of care therapy is

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

available in the US/EU. Current treatment options aiming to control acute GPP and maintain response are cyclosporine, acitretin, and methotrexate [R16-0933]. Secukinumab, Infliximab, Brodalumab, and Ixekizumab have been approved for GPP exclusively in Japan based on small local uncontrolled studies. Treatment is commonly not effective in suppressing acute flares during induction and recurrences emerge frequently.

PPP is a form of chronic Pustular Psoriasis characterized by sterile pustules limited to palms and soles [R16-0927]. No approved or effective treatment is available.

Both UC and CD are characterised by abdominal pain, fever, bloody diarrhoea, and inflammatory lesions in the gastrointestinal mucosa. Current treatment options include aminosalicylates, glucocorticoid therapy, azathioprine, 6-mercaptopurine, and biologics (blocking TNF or integrin α4β7). 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 progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared with the current therapeutic standard.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 655130 is a humanized monoclonal antibody (mAb) of the IgG1 isotype that is directed against human IL36R. It is derived from a mouse antibody 81B4 (BI 674308) cloned into a human IgG1 Kappa backbone. The mAb uses an IgG1 that has two mutations in the Fc region (Leu234Ala and Leu235Ala) to reduce FcγR and complement binding. In addition, to reduce charge heterogeneity, the C-terminal lysine residue of the heavy chain is deleted.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-04].

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 [c03320877-04].

1.2.3 Toxicology

As BI 655130 does not demonstrate adequate pharmacological activity in common toxicology species, a surrogate antibody (BI 674304) specific for mouse IL36R was developed and used for toxicology assessments. The toxicology package includes 4, 13 and 26-week toxicity studies and reproductive/developmental toxicity studies with BI 674304 in mice. In addition, the toxicology package includes a 2-week toxicity study in mice with BI 655130 and local tolerance, in vitro cytokine release, and tissue cross-reactivity studies.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1.2.4 Nonclinical pharmacokinetics

The pharmacokinetics (PK) of BI 655130 was studied in cynomolgus monkeys. In mice, pharmacokinetic studies were performed with the mouse-specific anti-IL36R antibody, BI 674304 [c03320877-04].

1.2.5 Clinical experience

In Phase I, BI 655130 has been evaluated in three clinical trials: a first-in-human (FIH) SRD trial [c09985235-01], an MRD trial [c09105854-05], and a recently completed relative bioavailability study exploring the pharmacokinetics as well as safety and tolerability of a newly developed SC formulation (1368-0003, [c10896574-01].

FIH-Study (Trial 1368.1)

The FIH (first-in-human) trial [c09985235-01] explored safety, tolerability, pharmacokinetics, and pharmacodynamics of intravenously administered BI 655130 in healthy male subjects. Subjects received single ascending IV doses of up 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.

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 diarrhea (BI 655130: 2/58 subjects [3.4%]; placebo: 2/20 subjects [10.0%]).

There were two AEs of moderate intensity, both considered not related to the study drug, (injection site hematoma and 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. Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No clinically relevant changes were observed in 12 lead ECGs, vital signs, physical exams, and cardio-monitoring.

MRD study (Trial 1368.2)

Trial 1368.2 [c09105854-05] explored the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising intravenous doses of BI.

In total, 40 subjects entered this trial and were treated. The study consisted of a multiple dose part with four dose groups and a single dose arm A total of 32 subjects were assigned to the MRD part. In each of the 4 dose groups 6 subjects received BI 655130 and 2 subjects received placebo. Additional 8 subjects entered the SD part of the trial with 6 subjects assigned to BI 655130 and 2 subjects assigned to placebo [c18789185-01].

Overall, a total of 3 subjects did not complete the planned observation time according to the CTP. One subject of the placebo group of the MRD part of the trial withdrew consent after having received all 4 planned doses. Two subjects of the MD BI 655130 treatment group discontinued treatment because of AEs: 1 subject after having received 1 dose of

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

BI 655130 and the other subject after having received 3 doses of BI 655130 (infusion of the third dose was stopped after 8 min).

The frequency of subjects with at least 1 drug-related treatment-emergent AE was similar for the MD placebo group and the MD BI 655130 treatment groups (ranging from 16.7% to 66.7%), and no dose-dependency was observed. The drug related AE with the highest incidence was headache, which was reported in 5 of 6 subjects in the group. Additionally, gastrointestinal disorders (abdominal discomfort, diarrhoea, and nausea) appeared to occur more often in subjects who received BI 655130 than in subjects who received placebo. Infusion related reaction, decreased appetite, and anxiety were only observed in the MD BI 655130 treatment group. In total, 2 out of the 24 subjects (8.3%) who received multiple doses of BI 655130 were reported with AEs leading to discontinuation of trial drug, 1 subject with mild pyrexia after the first infusion and 1 subject with mild and transient infusion related reactions during the third infusion. One subject of the placebo group of the MRD part of the trial withdrew consent after having received all 4 planned doses.

Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. For further details, please refer to the final study report [c18789185-01].

Trial 1368-0003

This study explored the pharmacokinetics as well as safety and tolerability of an SC formulation of BI 655130 at 2 different dose strengths of in an open-label, sequential group design. Furthermore, the relative bioavailability of the SC dose was compared with one single IV dose of BI 655130 in an open-label, matched group design.

The study included a total of 36 healthy male and female subjects with 12 subjects per treatment group.

Based on preliminary data the SC formulation is considered to be well tolerated, the standardised assessment of injection pain, redness, induration, swelling, heat, or other findings did not reveal any noteworthy changes. There were three subjects with a transient occurrence of redness and one subject with a swelling at injection site 30 minutes after the SC injection. No further local tolerability findings were reported, in particular no injection pain and no induration at injection site during an observation period of up to 6 months.

Regarding systemic AEs, there were no AEs of severe intensity. Deaths, serious AEs, and protocol-specified AEs of special interest were not reported in this trial. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. The clinical part of the study has been completed. The study report is under preparation (final safety tables available, [c18789185-01]).

Pharmacokinetics

The PK parameters of BI 655130 after a single IV infusion from Trial 1368.1 are shown in Table 1.2.5:1. BI 655130 plasma levels were first detected at a dose level of

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

$AUC_{0\text{-}inf}$ results should be considered for informational purposes only given the high %_AUC of extrapolated values (>50%) for the dose groups. Exposure in terms of $AUC_{0\text{-}tz}$ 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 1.2.5:1 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
$AUC_{0\text{-}tz}$ [µg·day/mL]	NC	NC	0.00652 (121)	2.08 (29.0)	9.57 (5.90)	25.1 (15.5)
$AUC_{0\text{-}inf}$ [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)	0.998 (15.7)	1.96 (11.9)
Dose Group#	**#6**	**#7**	**#8**	**#9**	**#10**	
Dose	N=4	N=6	N=6	N=6	N=4	
$AUC_{0\text{-}tz}$ [µg·day/mL]	113 (5.86)	420 (13.3)	1050 (7.26)	2610 (11.7)	4130 (12.1)	
$AUC_{0\text{-}inf}$ [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)	

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

In the MRD Trial 1368.2, PK data are consistent with the preceding single dose study as shown in Table 1.2.5:2.

Table 1.2.5:2 Geometric mean (geometric CV %) PK parameters of BI655130 in study 1368.2 after multiple dosing

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_{0-t} (µg·day/mL)	298 (9.26)	451 (7.96)	604 (4.77)	760 (4.21)
C_{max} (µg/mL)	77.9 (19.4)	101 (11.4)	117 (14.8)	141 (4.33)
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_{0-t} (µg·day/mL)	552 (10.4)	895 (4.45)	1140 (5.11)	1390 (4.63)
C_{max} (µg/mL)	130 (8.48)	185 (9.31)	223 (6.64)	253 (8.70)
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_{0-t} (µg·day/mL)	923 (17.3)	1610 (18.0)	2090 (16.9)	2500 (16.7)
C_{max} (µg/mL)	229 (22.9)	310 (21.9)	444 (34.1)	467 (21.4)
Dose	N=5 [Day 1] 0-168 h	N=5 [Day 8] 168-336 h	N=4 [Day 15] 336-504 h	N=4 [Day 22] 504-600 h
AUC_{0-t} (µg·day/mL)	1770 (12.5)	2900 (7.52)	3950 (16.1)	4660 (12.9)
C_{max} (µg/mL)	422 (18.5)	646 (10.7)	780 (17.1)	826 (15.8)

Exposure of both dose groups is in the linear dose range. The geometric mean t1/2 values after dose 4 were similar across dose groups and ranged from 26.5 to 33.5 days with no dose dependency.

Table 1.2.5:3 summarizes PK data of the recent completed clinical study 1368.3 conducted according to a parallel (matched) group design. Bioavailability of the SC injection was calculated to be about 50% and of the SC injection 70% using the IV group as reference.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 1.2.5:3 Geometric mean (geometric CV %) PK parameters of BI655130 in study 1368.3 after a single dose

Dose	N=11 [SC]	N=12 [SC]	N=11 [IV]
$AUC_{0\text{-}inf}$ (µg·day/mL)	574 (40.1)	1600 (29.5)	2280 (16.0)
C_{max} (µg/mL)	12.2 (44.5)	33.4 (32.7)	114 (18.0)
T_{max} [1] (day)	0.3 - 14 7.0	4 - 21 6.0	0.02-0.3 0.13
t½ (day)	20.6 (26.7)	25.6 (23.5)	27.1 (17.1)

[1]min – max, median

The geometric mean t1/2 values after subcutaneous administration ranged from 20.6 SC) to 25.6 SC).

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 dose groups as compared to placebo. This demonstrates that BI 655130 is on-target for the time points analyzed.

Residual Effect Period

The Residual Effect Period (REP) of BI 655130 is up to 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For a more detailed description of the BI 655130 profile please refer to the current Investigator's Brochure (IB) [c03320877-04].

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 II development.

In Phase I studies BI 655130 was mainly administered as intravenous infusion. However, the subcutaneous injection route is considered to be required to enable in upcoming therapeutic studies the self-administration of BI 655130 by patients. For this reason a subcutaneous injection formulation is undergoing clinical development.

Recently, the clinical part of a Phase 1 study (Study 1368-0003) has been completed exploring the characteristics of a subcutaneous formulation of BI 655130 with particular focus on relative bioavailability compared to an intravenous formulation. A further objective was the assessment of local tolerability. In this study, the relative bioavailability of a single SC injection containing of BI 655130 was in a range of about 50% while relative bioavailability increased to 70% for a single SC injection of of BI 655130

To further elucidate the origin of the observed potentially dose dependent increasing bioavailability, the current study will compare the pharmacokinetics (PK) of a single SC injection of of BI 655130 with the PK of two SC injections of of BI 655130 This design will investigate the impact of local factors at the SC injection site on the overall exposure of BI 655130 which may contribute to the lower bioavailability observed in the preceding clinical study.

The current study will also investigate the impact on relative bioavailability regarding the site of injection (abdomen and thigh) to enable the switch of injection site if needed.

To widen the SC dose range the current study will also investigate a subcutaneous dose of of BI 655130 corresponding to two single periumbilical SC injections of (i.e. total injection volume

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the relative bioavailability of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region compared to a single subcutaneous periumbilical injection of BI 655130

The secondary objective is to investigate the relative bioavailability of a single subcutaneous injection of BI 655130 into the thigh compared to a single subcutaneous periumbilical injection of BI 655130.

A further objective is to investigate safety, tolerability, and pharmacokinetics of BI 655130 administered as two subcutaneous injections of in the left and right periumbilical region.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to optimize treatment regimen of the subcutaneous formulation for potential use as maintenance therapy 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. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to veinipuncture 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

The toxicology package conducted in mice with a mouse-specific antibody (BI 674304) includes 4, 13 and 26-week toxicity studies and reproductive/developmental toxicity studies without any findings which would preclude clinical studies in humans (see IB [c03320877-04]).

The clinical safety and tolerability profile of BI 655130 was comparable to placebo in male subjects following once weekly intravenous doses of up to body weight administered over 4 weeks. There were no deaths or other serious adverse events. 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.

Recently the clinical part of an initial with a subcutaneous formulation has been completed. The maximum tested SC dose was of BI 655130 injection volume). The study did not reveal systemic or local AEs which would preclude further clinical studies with the SC formulation. The observed exposure at following SC injection was about 6 fold lower compared to the maximum exposure in completed clinical studies with an IV infusion of up to of BI 655130. Therefore even the planned maximum SC dose of of BI 655130 is not expected to exceed exposure limits already tested in humans.

Based on studies in healthy subjects, 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:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- The study will start with Dose Group 1 and 2 (periumbilical SC dose of of BI 655130). Provided no dose limiting AEs occurred as 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 up to Day 10 (see Section 3.1), the study will pursue with Dose Group 3 (periumbilical SC dose of of BI 655130) and Dose Group 4 (SC dose of of BI 655130 in the thigh). Dose Group 3 will be divided into 2 cohorts. In the first week, 6 subjects will be treated. There will be an interval of at least 1 week after start of dosing in the first cohort before start of dosing of the second cohort of Dose Group 3.
- 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.
- Monitoring of ECG, vital signs, and extensive safety laboratory testing (Table 5.2.3:1) is conducted throughout the study.
- After dosing, the subjects will stay at the site for at least 48 hours.
- 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 for both expected and unexpected adverse events.

Currently there are no data available to suggest interactions of BI 655130 [c03320877-04].

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 laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also Section 5.2.2.1, adverse events of special interest.

Based on the preclinical and 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 IBD and GPP, the benefit of this trial is considered to outweigh the potential risks and justifies the exposure of healthy subjects.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This study will explore the relative bioavailability, safety, and tolerability following a subcutaneous (SC) injection of BI 655130 at different dose strengths, injection volumes, and injection sites:

- One SC injection of periumbilical (Dose Group 1)
- Two SC injections of each periumbilical left and right (Dose Group 2)
- Two SC injections of each periumbilical left and right (Dose Group 3)
- One SC injection of in the thigh (Dose Group 4)

The total dose in Dose Group 1, 2, and 4 is of BI 655130 and the total dose in Dose Group 3 is of BI 655130.

The study will be conducted in a single-dose, open-label, matched-group design. The exposure in Dose Group 1 will be used as reference to assess the relative bioavailability of Dose groups 2 - 4. For details refer to Section 4.1.

The study will start with Dose Group 1 and 2. After completion of treatment of the first two dose groups, the study will continue with Dose Group 3 and 4. 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).

The Dose Group 3 will follow a staggered administration with treatment of 6 subjects (cohort A) in the first week and the remaining subjects (cohort B) from Week 2.

A documented Safety Review of Dose Group 1 and 2 at least 10 days after last dosing in Dose Group 2 must take place prior to continue the study with Dose Groups 3 and 4. 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. Continuation of the study 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 8 evaluable subjects in each of the Dose Group 1 and 2 are required to decide about continuation with the remaining dose groups.

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)
- Vital signs
- Clinical laboratory tests
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 or a delegate 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 CPU Antwerpen of
under the supervision of the Principal Investigator.

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

Safety laboratory tests will be performed by ZNA Klinisch Laboratorium, Lindendreef 1, 2020 Antwerpen, Belgium.

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.

The plasma analyses of BI 655130 and ADA concentrations will be performed at

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

The study will be conducted according to a single-dose, open-label design with matched groups.

The resulting group sizes (see Section 7.6) are considered to be sufficient for the exploratory evaluation of pharmacokinetics. The assignment of matched healthy volunteers is a useful method to control for other factors which may influence the pharmacokinetics of BI 1467335 in a renal impaired population.

The open-label treatment is not expected to bias results, since the primary endpoints are derived from measurement of plasma concentrations of the analytes provided by a bioanalytical laboratory. It is also considered sufficiently accurate as the trial observations are objective (PK, laboratory) and over-reporting of AEs is unlikely.

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 tolerability of BI 655130 has already been evaluated up to MRD, resulting in a far higher exposure compared to the expected exposure of the current study.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 48 healthy male and female subjects (12 in each dose group) will enter the study. They will be recruited from the volunteers' pool of the trial site. Healthy subjects assigned to Dose Groups 2 - 4 will be matched on an individual level for gender and body weight (± 10%) to subjects assigned to Dose Group 1 , periumbilical injection).

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 19.0 to 29.9 kg/m^2 (incl.)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4. Signed and dated written informed consent prior to admission to the study in accordance with ICH-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 IU/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 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections
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)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 up to 4 weeks after administration
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 up to study completion
23. Lactation

In addition, the following trial-specific exclusion criterion applies:

24. Previous use of the trial medication

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

This study is a single dose study, therefore removal of subjects from study medication after dosing is not applicable.

An individual subject is to be removed from further assessments 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 from further assessments. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

>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.

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 administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (i.e., 16 weeks, see Section 1.2.5), 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 overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable
2. The expected enrolment goals 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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5. Further dosing will be stopped if at least 2 subjects in one dose group 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. Replacement of subjects should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment and matching criteria as the subject he or she replaces.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

The characteristics of the 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 or thigh)
Duration of use:	Single dose

At the time of use, the 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 Dose Group 1, matching subjects will be allocated to the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. As the study includes healthy subjects from a homogenous population matched for gender and body weight, relevant imbalances between the dose groups are not expected.

The allocation of subjects will be performed prior to the administration of trial medication. Once a subject number has been assigned to a treatment group, it cannot be reassigned to any other treatment group.

4.1.3 Selection of doses in the trial

The dose of of BI 655130 selected for this trial has been selected to correspond to the potential dose for maintenance treatment in clinical trials in patients. The highest dose tested in this trial of BI 655130) will be included to widen the SC dose range.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 solutions are provided in the ISF.

Table 4.1.4: 1 Dosage and treatment schedule

Dose Group	Total dose	Route of administration	Concentration of application solution	Application volume	Injection site
1		SC			Periumbilical
2		SC			Periumbilical (left and right)
3		SC			Periumbilical (left and right
4		SC			Thigh

Following an overnight fast of at least 10 hours, the medication will be administered. Trial drug will be injected subcutaneously in the abdominal region or into the thigh. 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.

4.1.5 Blinding and procedures for unblinding

No blinding will be performed. 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. Emergency envelopes will not be provided, since the treatments of all subjects are known in this open-label trial.

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- Storage conditions
- Use-by date
- Batch number
- Investigator
- Subject number

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

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 special emergency procedures 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 2 h after administration of the study drug.

From 1 h before until 2 h after SC injection, fluid intake is not allowed.

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

Alcoholic beverages are not permitted starting 7 days before the administration of trial medication until Day 15. From Day 15 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.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during the in-house confinement.

Poppy-seed containing products are not allowed starting 2 days before screening and 2 days before admission to trial site (Day -1) to avoid false positive drug screening results.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the administration of trial medication up to 4 weeks after administration.

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
- Vital signs (blood pressure, pulse rate)
- Local tolerability

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.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Chances 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- 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 time since 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, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

Adverse events of special interest

The term adverse event of special interest (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 Section 5.2.2.2.

The AESI in this trial is hepatic injury, as defined by the following alterations of hepatic laboratory parameters:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, 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 that 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 judged 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 judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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

AE 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 carefully 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, intensity of the event, and 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 any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) 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 the initial information.

Information required

All (S)AEs, including those persisting after the 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 Part B) as well as non-trial specific information and consent for the pregnant partner.

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]
Haematology	Haematocrit Haemoglobin Red Blood Cell count (RBC) Reticulocytes count White Blood Cells count (WBC) Platelet Count
Automatic WBC differential (relative and absolute count possible)	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 (International Normalization Ratio)
Enzymes	AST [Aspartate transaminase] /GOT, SGOT ALT [Alanine transaminase] /GPT, SGPT Alkaline Phosphatase Gamma-Glutamyl Transferase (GGT) Creatine Kinase [CK] Creatine Kinase Isoenzyme MB [CK-MB, only if CK is elevated] Lactate Dehydrogenase (LDH) Serum tryptase[1]
Hormones[1]	Thyroid Stimulating Hormone (TSH)
Substrates	Glucose (Plasma) Creatinine Bilirubin, Total Bilirubin, Direct Bilirubin, Indirect Protein, Total Protein electrophoresis [1] Albumin Alpha-1-Globulin Alpha-2-Globulin Beta-Globulin Gamma-Globulin C-Reactive Protein (CRP) Uric Acid Cholesterol, total Triglyceride
Electrolytes	Sodium Potassium Chloride Calcium Phosphate (as Phosphorus, Inorganic)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	BI test name [comment/abbreviation]
Urinalysis (Stix)	Urine Nitrite (qual) Urine Protein (qual) Urine Glucose (qual) Urine Ketone (qual) Urobilinogen (qual) Urine Bilirubin (qual) Urine Erythrocytes (qual) Urine WBC/Leucocytes (qual) Urine pH
Urine sediment (microscopic examination if urine analysis abnormal)	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, on Day 92, 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 (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Dräger Alcotest® 6510 and Alcotest® 510, Belgium) will be performed at screening and on Day -1, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 Alere® –HCG urine, respectively.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (e.g. MAC 5500, GE Healthcare) at the time points given in the Flow Chart.

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 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.

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.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

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

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 (including drug screen and pregnancy test), and a physical examination. The end of trial examination will include review of vital signs, 12-lead ECG, laboratory tests, recording of AEs and concomitant therapy and a physical examination with determination of weight.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5.2.5.3 Local tolerability

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

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

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 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 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:

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- $AUC_{0-\infty}$ (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 K_2-EDTA (dipotassium 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 K_2-EDTA-anticoagulated blood samples will be mixed gently and placed on ice until centrifugation for about 10 min 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 min 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 -70°C or below at the clinical site until shipment to the analytical laboratory.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

5.5.2.2 Plasma sampling for ADA assessment

For ADA assessment, approximately of blood will be taken from a forearm vein into a K_2-EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under "Plasma ADA".

The K_2-EDTA -anticoagulated blood samples will be mixed gently and placed on ice until centrifugation for about 10 min 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 min after withdrawal. Two aliquots of EDTA plasma samples will be obtained in two labelled polypropylene cryotubes (label to include: BI trial number, subject number, visit, PTM, aliquot #1 or #2, plasma, and ADA). The two aliquots should contain approximately of plasma each. The plasma samples will be stored in a freezer at about -70°C or below at the clinical site until shipment on dry ice to the analytical laboratory. Both aliquots will be shipped (in separate shipments with dry ice sufficient for 3 days transit) to the analytical laboratory for assessment of potential ADA to BI 655130. Once received at the analytical laboratory, both aliquots will be stored in a freezer at about -70°C or below.

The plasma samples may be used for further methodological investigations (e.g. for stability testing), however, only data related to the anti-drug antibodies will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 655130 plasma concentration

BI 655130 concentrations in plasma will be determined by a validated immunoassay.

5.5.3.2 Analytical determination of ADA to BI 655130

The presence of ADA to BI 655130 will be assessed via their detection using a validated immunoassay in a tiered approach (screening, confirmatory, and titration analysis as appropriate).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

The acceptable deviation from the scheduled time for vital signs, ECG and safety laboratory 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 15
- ± 72h from >Day 15 up to the last assessments

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

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

6.2.2 Treatment period

Study participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 48 h following drug administration. The subjects will

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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, 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 prematurely the study before the end of the planned treatment period (i.e., Day 176 ±3) 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The trial objectives are stated in Section 2.2.

For the purpose of defining reference and test treatments, the following terminology will be used. The reference treatment (R) will refer to dose group 1, test treatment 1 (T1) refers to dose group 2, test treatment 2 (T2) refers to dose group 4 and test treatment 3 (T3) refers to dose group 3.

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 analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘treatment’ and ‘matched pair’. For each matched pair in the study a pair number will be assigned for analysis purpose. The resulting variable ‘matched pair’ will be considered as random effect.

The model is described by the following equation:

$y_{kjm} = \mu + \tau_k + p_j + e_{ijkm}$, where

y_{kjm} = logarithm of response (endpoint) measured on subject m in pair j receiving treatment k

μ = the overall mean,

τ_k = the kth treatment effect, k=1,..,4,

p_j = the jth matched pair effect,

e_{ijkm} = the random error associated with the mth subject in sequence i who received treatment k in period j.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

where $p_j \sim N(0,\sigma_B^2)$ i.i.d., $e_{ijk} \sim N(0, \sigma_W^2)$ i.i.d. and p_j, e_{ijk} are independent random variables (note that the indices 'B' and 'W' correspond to 'between' pairs and 'within' pairs variability, respectively).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of the different dose groups 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 the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the clinical trial report.

Relevant protocol violations may be:

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

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

- The subject experiences emesis that occurred at or before 2 times median tmax of the respective treatment (median tmax is to be determined excluding the subjects experiencing emesis)
- A predose concentration is >5% Cmax value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The following analysis sets will be defined for this trial:

- Treated set (TS):
  This subject set includes all subjects from the RS who were documented to have received one dose of study drug. This is the full analysis set population in the sense of ICH-E9
- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the 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/she contributes only one PK parameter value for one period to the statistical assessment

Point estimates of the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see Sections 5.5.1.1 and 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 (Least Squares 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.

The comparisons of interest will be T1 vs. R, T2 vs. R, and T3 vs. R.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety 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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see Section 1.2.5) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as 'follow-up'. The follow-up will be summarised according to previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. AEs occurring after the last per-protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

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.

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 drug BI 655130 will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-472].

Individual plasma concentration data and the pharmacokinetic parameters will be tabulated, graphically displayed and summarized by descriptive statistics. The analysis of PK endpoints will be based on PKS.

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).

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 RANDOMISATION

The study will not be randomised as individually matched subjects will be used. Thus, this section is not applicable.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 4*12 = 48 subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The observed inter-individual geometric coefficient of variation (gCV) in a previous trial (1368.3) was roughly 30% for C_{max} and for AUC. For various assumptions on the gCV, Table 7.6: 1 provides an overview of the precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.6: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a parallel trial (for one comparison based on 2 arms)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
25	1.24	90	72.64	111.51
25	1.24	100	80.71	123.90
25	1.24	110	88.78	136.29
30	1.29	90	69.70	116.21
30	1.29	100	77.45	129.12
30	1.29	110	85.19	142.03
35	1.34	90	66.95	120.99
35	1.34	100	74.38	134.44
35	1.34	110	81.82	147.88

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

The 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 Julious [R11-5230, Chapter 8] using R Version 3.4.2.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

8.2 DATA QUALITY ASSURANCE

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

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9. REFERENCES

9.1 PUBLISHED REFERENCES

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R14-4037 Towne JE, Renshaw BR, Douangpanya J, Lipsky BP, Shen M, Gabel CA, Sims JE. Interleukin-36 (IL-36) ligands require processing for full agonist (IL-36alpha, IL-36beta, and IL-36gamma) or antagonist (IL-36Ra) activity. J Biol Chem 2011;286(49):42594-42602.

R14-5158 Marrakchi S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med 201; 365(7):620-628.

R15-1399 Blumberg H, Dinh H, Dean C, Trueblood ES, Beiley K, Shows D, Bhagavathula N, Aslam MN, Varani J, Towne JE, Sims JE. IL-1RL2 and its ligands contribute to the cytokine network in psoriasis. J Immunol 2010;185(7):4354-4362.

R15-1421 Onouofriadis A, Simpson MA, Pink AE, Meglio P di, Smith CH, Pullabhatla V, Knight J, Spain SL, Nestle FO, Burden AD, Capon F, Trembath RC, Barker JN. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet 2011;89(3):432-437.

R15-1432 Blumberg H, Dinh H, Trueblood ES, Pretorius J, Kugler D, Weng N, Kanaly ST, Towne JE, Willis CR, Kuechle MK, Sims JE, Peschon JJ. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. J Exp Med 2007;204(11):2603-2614.

R15-1447 Tortola L, Rosenwald E, Abel B, Blumberg H, Schaefer M, Coyle AJ, Renauld JC, Werner S, Kisielow J, Kopf M. Psoriasiform dermatitis is driven by IL-36-mediated DC-keratinocyte crosstalk. J Clin Invest 2012;122(11):3965-3976.

R16-0927 Waal AC de, Kerkhof PCM van de; Pustulosis palmoplantaris is a disease distinct from psoriasis; J Dermatol Treat 22 (2), 102 - 105 (2011)

R16-0929 Berki DM, Liu L, Choon SE, Burden AD, Griffiths CEM, Navarini AA, Tan ES, Irvine AD, Ranki A, Ogo T, Petrol G, Mahil SK, Duckworth M, Allen MH, Vito P, Trembath RC, McGrath J, Smith CH, Capon F, Barker JN; Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis

R16-0933 Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF; Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia; Int J Dermatol 53, 676 - 684 (2014)

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9.2 UNPUBLISHED REFERENCES

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

c03320877-04 Investigator´s Brochure BI 655130 for IL36R antibody in Ulcerative Colitis, Palmoplantar Pustulosis and Pustular Psoriasis. 10 Oct 2017

c09105854-05 , Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects, 1368.2, 02 Aug 2017

c09985235-01 Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers, 1368.1, 07 Apr 2017

c10896574-01 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). 1368.3. 08 Mar 2017

c18789185-01 Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (singleblind, partially randomised, placebo-controlled) in healthy male subjects. 1368.2. 29 May 2018

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10. APPENDICES

10.1 PREPARATION AND HANDLING OF BI 655130 SOLUTION FOR INJECTION

10.1.1 Preparation Instructions SC (Dose group 1, injection left or right periumbilical)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

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

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

½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile 27G ½" needle to the syringe, adjust the volume to and gently inject the complete content of the syringe at the left or right periumbilical region.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.2 Preparation Instructions SC dose (Dose Group 2, injection left and right periumbilical)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

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

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

½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

1. Take a vial filled with of 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 syringe closure (e.g. B.Braun Combi-Stopper).
6. Attach a sterile needle to the syringe, adjust the volume to

7. Repeat steps 1 to 6 with the second vial to prepare a second, separate syringe ready for injection
8. Gently inject the complete content of the first syringe containing solution for injection at the left or right periumbilical region.
9. Gently inject the complete content of the second syringe containing solution for injection periumbilical contralateral to the injection site of the first injection.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.3 Preparation Instructions SC dose (Dose group 3, injection left and right periumbilical)

Necessary materials:

4 Vials BI 655130 Solution for Injection

Consumables:

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

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

½” needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

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 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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile needle to the syringe, adjust the volume to (=syringe 1)
8. Repeat steps 1 to 7 with the second vial to prepare a second, separate syringe ready for injection (=syringe 2).
9. Gently inject the complete content of the first syringe containing solution for injection at the left or right periumbilical region .
10. Gently inject the complete content of the second syringe containing solution for injection periumbilical contralateral to the injection site of the first injection.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.1.4 Preparation Instructions SC dose (Dose group 4, injection in the thigh)

Necessary materials:

2 Vials BI 655130 Solution for Injection

Consumables:

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

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

½" needle for injection (material: stainless steel/ polypropylene) – e.g. BD (article no: 305770)

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 syringe closure (e.g. B.Braun Combi-Stopper).
7. Attach a sterile needle to the syringe, adjust the volume to and gently inject the complete content of the syringe in the left or right thigh.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		20 September 2018
EudraCT number		2018-001074-18
BI Trial number		1368-0029
BI Investigational Product(s)		BI 655130
Title of protocol		Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		5.5.2 Methods of sample collection
Description of change		Temperature for storage of clinical samples was changed to -70°C.
Rationale for change		Update on storage temperature.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Number of global amendment		2
Date of CTP revision		07 Jan 2019
EudraCT number		2018-001074-18
BI Trial number		1368-0029
BI Investigational Product(s)		BI 655130
Title of protocol		Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2.5 Clinical experience 3.3.4,1 Removal of individual subjects
Description of change		Residual effect period (REP) changed from 176±3 to 16 weeks.
Rationale for change		Residual effect period in ongoing patient studies 16 weeks, change was required to assure consistency across clinical studies with BI 655130.

APPROVAL / SIGNATURE PAGE

Document Number: c21745299 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-revision-02

Title: Relative bioavailability, safety, and tolerability following subcutaneous injection of different doses of BI 655130 and different injection sites in healthy male and female subjects (a single dose, mono-centric, open-label study in matched-group design).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		07 Jan 2019 13:49 CET
Author-Trial Clinical Pharmacokineticist		07 Jan 2019 14:53 CET
Approval-Therapeutic Area		07 Jan 2019 15:46 CET
Verification-Paper Signature Completion		08 Jan 2019 12:51 CET
Approval-Team Member Medicine		08 Jan 2019 18:24 CET
Author-Trial Statistician		08 Jan 2019 19:52 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed