Clinical Trial Protocol

Document Number:	**c40240667-02**
EudraCT No.	2022-003757-63
BI Trial No.	1479-0004
BI Investigational Medicinal Product	BI 1810631
Title	The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial)
Lay Title	A study in healthy men to test how itraconazole influences the amount of BI 1810631 in the blood
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 2.0, 22 Feb 2023
Original Protocol Date	27 Dec 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	27 December 2022
Revision date	22 February 2023
BI trial number	1479-0004
Title of trial	The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	[redacted] s not known. It needs to be investigated to inform concomitant treatment recommendations.
Trial objective	To investigate the effect of multiple oral doses of itraconazole, a strong inhibitor of CYP3A and a recommended inhibitor of P-gp, on the pharmacokinetics of a single dose of BI 1810631 in plasma following oral administration.
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 1810631 Secondary endpoints: AUC_{0-tz} of BI 1810631
Trial design	Open-label, two-treatment, two-period, fixed-sequence design
Number of subjects **total entered** **on each treatment**	 16 16
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product 1 **dose** **mode of administration**	BI 1810631 [redacted] mg film-coated tablets [redacted] mg single dose Oral with 240 mL of water [redacted]

Test product 2	Itraconazole oral solution (Sempera® Liquid 10 mg/mL Lösung zum Einnehmen)
dose	200 mg q.d.
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 9 h
Duration of treatment	Treatment Reference (R, BI 1810631 alone) – Period 1: - Single dose of [redacted] mg BI 1810631 in the morning of Day 1 Treatment Test (T, itraconazole + BI 1810631) – Period 2: - 14 days of itraconazole 200 mg q.d. in the mornings of Days -3 to 11 - Single dose of [redacted] mg BI 1810631 in the morning of Day 1
Statistical methods	The extent of the drug-drug interaction 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-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subject' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [4]	PK blood (BI 1810631)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A		x	x	
Period 1 (Treatment R, BI 1810631 alone) [9]	2	-1	-12:00	20:00	Admission to trial site[8]	x[5,8]				x[8]
		1	-1:30	06:30	Allocation to subject number[2]	B[2]	x[2]	x[2]	x[2]	x[2]
			0:00	08:00	**Administration of BI 1810631**					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x	x	x
			6:00	14:00			x			
			8:00	16:00	Snack[3]		x			
			10:00	18:00			x			
			11:00	19:00	Dinner					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	B	x	x	x	x
			34:00	18:00	Ambulatory visit		x			x
		3	47:00	07:00	Ambulatory visit		x			x
		4	71:00	07:00	Ambulatory visit		x			x
		6	119:00	07:00	Ambulatory visit		x			x
		8	167:00	07:00	Ambulatory visit		x			x

FLOW CHART (cont'd)

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [4]	PK blood (BI 1810631)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
Period 2 (Treatment T, itraconazole + BI 1810631) [9]	3	-3	-73:00	07:00	Ambulatory visit, **itraconazole administration**	C[10]				x[10]
		-2	-49:00	07:00	Ambulatory visit, **itraconazole administration**					x[10]
		-1	-25:00	07:00	Ambulatory visit, **itraconazole administration**	C[11]				x[10]
			-12:00	20:00	Admission to trial site[8]	x[5,8]				x[8]
		1	-1:30	06:30		B[2]	x[2]	x[2]	x[2]	x[2]
			-1:00	07:00	**Itraconazole administration**					
			0:00	08:00	**Administration of BI 1810631**					
			0:30	08:30			x			
			1:00	09:00			x			
			1:30	09:30			x			
			2:00	10:00	240 mL fluid intake		x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x	x	x	x
			6:00	14:00			x			
			8:00	16:00	Snack (voluntary)[3]		x			
			10:00	18:00			x			
			11:00	19:00	Dinner					
			12:00	20:00			x			x
		2	23:00	07:00	**Itraconazole administration**					x[10]
			24:00	08:00	Breakfast (voluntary)[3], discharge from trial site	B	x	x	x	x
			34:00	18:00	Ambulatory visit		x			x
		3	47:00	07:00	Ambulatory visit, **itraconazole administration**		x[10]			x[10]
		4	71:00	07:00	Ambulatory visit, **itraconazole administration**	C	x[10]			x[10]
		5	95:00	07:00	Ambulatory visit, **itraconazole administration**					x[10]
		6	119:00	07:00	Ambulatory visit, **itraconazole administration**	C	x[10]			x[10]
		7	143:00	07:00	Ambulatory visit, **itraconazole administration**					x[10]
		8	167:00	07:00	Ambulatory visit, **itraconazole administration**	C	x[10]			x[10]
		9	191:00	07:00	Ambulatory visit, **itraconazole administration**		x[10]			x[10]
		10	215:00	07:00	Ambulatory visit, **itraconazole administration**		x[10]			x[10]
		11	239:00	07:00	Ambulatory visit, **itraconazole administration**		x[10]			x[10]
		12	263:00	07:00	Ambulatory visit		x			x
		13	287:00	07:00	Ambulatory visit		x			x
FU	4	19-33			End of study (EoS) examination[7]	D		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to the next administration of study drug.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. A, B, C, and D designate different safety laboratory examination sets (see Section 5.2.3)
5. Urine drug screening and alcohol breath test, only
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
8. The time is approximate; procedures are to be performed and completed no later than 10 h prior to the next drug administration
9. Administration of BI 1810631 in treatment R and T will be separated by a washout interval of at least 14 days.
10. Before itraconazole dosing
11. This safety laboratory needs to be medically evaluated before administration of study drugs on Day 1 of Period 2

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
[redacted]	[redacted]
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
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
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
CRA	Clinical Research Associates
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP3A	Cytochrome P450 family 3 subfamily A
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor

EoS	End of Study (synonym for End of Trial)
EudraCT	European Clinical Trials Database
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
GMP	Good Manufacturing Practice
HER2	Human epidermal growth factor receptor 2
[redacted]	
HR	Heart rate
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
[redacted]	
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	
MTD	Month-do-Date
NF	New formulation
NSCLC	Non-small-cell lung cancer
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
RTK	Receptor tyrosine kinases
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure

ss	(at) steady state
T	Test product or treatment
TF1	Trial formulation 1
[redacted]	[redacted]
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
[redacted]	[redacted]

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR) family of homologous transmembrane receptor tyrosine kinases. The family of ErbB transmembrane receptor tyrosine kinases (RTKs) consists of the four members EGFR (ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3) and HER4 (ErbB4), which fulfil essential functions during development [R20-1872, R09-6185, R20-1990]. ErbB signalling is initiated upon binding of the extracellular domains of EGFR, HER3 or HER4 to their respective ligands and subsequent homo- or heterodimerization of ErbB family members. HER2, for which no ligand has been identified, is the preferred dimerization partner for the other ErbB members. Once an active ligand-receptor complex has been formed, the intracellular tyrosine kinase domains of EGFR, HER2 or HER4 are activated by auto- or transphosphorylation and subsequently elicit a signal transduction cascade most notably engaging the mitogen-activated protein kinase and/or the phosphoinositide 3-kinase pathways [R20-1872, R09-6185, R20-1990].

Aberrant ErbB signalling is implicated in several pathophysiological conditions including cancer or neurological diseases. In cancer, ErbB signalling is hyper-activated through mutations that render the RTK constitutively active by promoting dimerization or shifting the equilibrium towards the active conformer of the kinase and/or through amplification and consequent over-expression of the RTK. Both oncogenic mechanisms increase the net output of ErbB signalling and thereby promote cell survival, cell growth and proliferation [P15-01211].

More recently, increasing attention has been given to the emerging impact of oncogenic HER2 activation through somatic gene mutation. The majority of these HER2 mutant cancers have not been associated with concurrent HER2 gene amplification. Mutations are found across all exons of the HER2 gene including exon 20, with significant heterogeneity both between and within human cancer types. The highest prevalence of HER2 mutations is observed in prostate neuroendocrine cancer, metastatic cutaneous squamous cell carcinoma, and bladder cancer (all >10% of cases). A significant HER2 mutation prevalence is also found in more common cancers, including lung, colorectal and breast cancers, indicating a large additional patient base that could potentially be targeted with HER2-directed therapies [P19-10412].

Mutations in HER2 have been identified as oncogenic drivers and occur in 2 to 3% of non-small-cell lung cancer (NSCLC). HER2 mutations most commonly consist of a 12 base pair in-frame insertion YVMA (p.A775_G776insYVMA) in exon 20 [P19-00456, P20-09250]. There is no standard targeted treatment for NSCLC with HER2 aberrations including HER2 exon 20 insertion mutations. Clinically approved tyrosine kinase inhibitors have not been shown to be efficacious in these patients, as they are limited by EGFR wild type mediated dose limiting toxicity. Therefore there is a clear unmet medical need for new treatment options for NSCLC patients with HER2 insertion mutations.

1.2 DRUG PROFILES

1.2.1 BI 1810631

For a comprehensive description of BI 1810631 refer to the IB [c32836122]. Preliminary PK and safety data available so far from clinical studies and not included in the IB are described below in Section 1.2.1.3.

1.2.1.1 Mode of action

BI 1810631 is an EGFR wild type sparing, selective HER2 inhibitor with potent inhibitory activity on all major HER2 mutations including the HER2 YVMA insertion allele.

1.2.1.2 Potential for drug-drug interactions (DDIs) with CYP3A inhibitors

Based on *in vitro* data, CYP3A4/5 is primarily responsible for the hepatic oxidative metabolism of BI 1810631, [redacted] For more details refer to the IB [c32836122].

1.2.1.3 Data from studies in humans (data are preliminary; data on file)

Prior to the current trial, BI 1810631 was administered in the ongoing first-in-man trial in patients with cancer 1479-0001 and in one PK study in healthy volunteers (trial 1479-0003).

Short description of patient first-in-man trial 1479-0001

At the time of CTP finalization, the dose escalation part of trial 1479-0001 is ongoing. Data cut time point for the data described here is 03 Nov 2022. 1479-0001 is an open-label, Phase I dose escalation trial, with dose confirmation and expansion, of BI 1810631 as monotherapy in patients with advanced or metastatic solid tumors with HER2 aberrations. Patients are continuously treated in different dose groups with q.d. or b.i.d. dosing schemes. PK and safety data are collected. So far, 30 patients were treated with BI 1810631 either in one of the b.i.d. cohorts (17 patients - 15-30-60-100-150 mg) or the q.d. cohorts (13 patients - 60-120-180 mg).

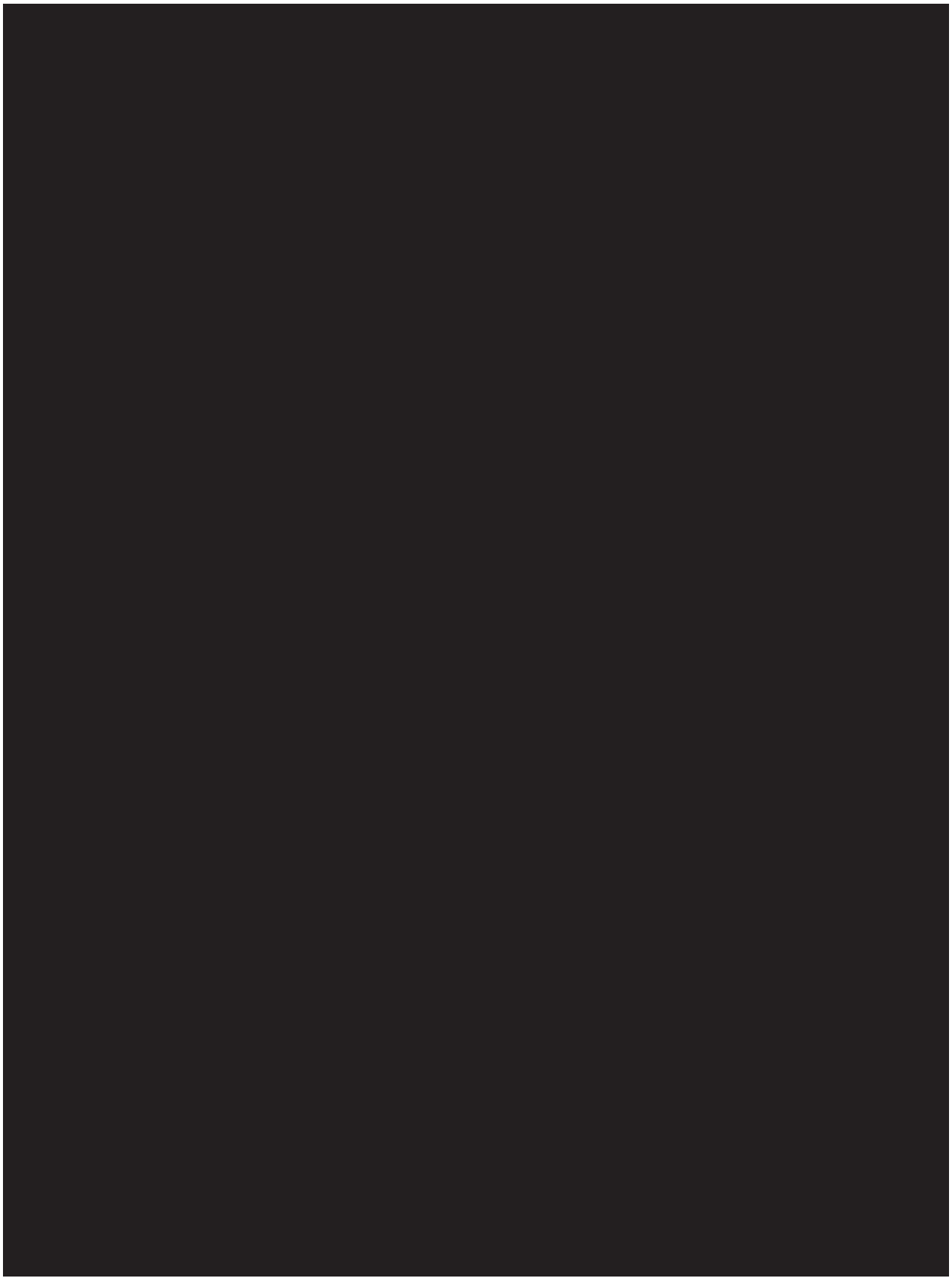
Short description of healthy volunteer trial 1479-0003

At the time of CTP finalization, trial 1479-0003 is in the analysis and reporting phase. Trial 1479-0003 was an open-label, randomized, 4-way crossover Phase I trial. The trial investigated relative bioavailability of BI 1810631 after administration as two different formulations (trial formulation 1 [TF1] and new formulation [NF]), investigated [redacted] on the pharmacokinetics of a single dose of BI 1810631. Thirteen healthy male volunteers were dosed with single doses of 30 mg BI 1810631 in 4 treatment periods in randomized order, separated by wash-out intervals of at least 14 days. The 4 treatments were:

- R: [redacted] mg BI 1810631 trial formulation 1 (TF1) [redacted]
- T1: [redacted] mg BI 1810631 new formulation (NF) [redacted]

- T2: [redacted] mg BI 1810631 NF [redacted]
- T3: [redacted] mg BI 1810631 NF [redacted]
  [redacted].

[redacted]



1.2.1.3.3 Safety and tolerability data of patient first-in-man trial 1479-0001 (preliminary data)

Among the 30 patients treated with BI 1810631 in either q.d. or b.i.d. dosing schemes,

[redacted]

1.2.1.3.4 Safety and tolerability data of healthy volunteer trial 1479-0003 (preliminary data)

In trial 1479-0003, in which oral single doses of 30 mg BI 1810631 were administered to healthy volunteers, [redacted].

1.2.2 Itraconazole

Absorption of itraconazole oral solution is fast with maximum plasma concentrations reached within 2.5 h after oral administration under fasting condition. Bioavailability of itraconazole liquid is higher by 30% when given under fasting condition compared to administration together with food [R23-0681]. Mean peak plasma concentrations were 545.7 ng/mL after a single dose of 200 mg itraconazole solution (fasting) and 1,965 ng/mL after 15 days of daily treatment with 200 mg itraconazole solution (fasting). Pharmacokinetics of itraconazole is non-linear. The half-life of itraconazole after multiple doses of 200 mg once daily with solution formulation was about 40 h [R17-3742].

In the liver, itraconazole is metabolised extensively to more than 30 metabolites [R17-3743]. Its main metabolite, hydroxy-itraconazole, accounts for about twice the concentration of plasma itraconazole at trough. It has been shown *in vitro* that CYP3A4 is mainly responsible for the formation of this metabolite [R23-0681].

FDA classifies itraconazole as strong index inhibitor of CYP3A and as clinical inhibitor of P-glycoprotein (P-gp) [R18-0241]. However, not only itraconazole contributes to the *in vivo* inhibition of CYP3A observed after itraconazole administration but also three of its metabolites (hydroxy-itraconazole, keto-itraconazole, and N desalkyl-itraconazole) [R10-1102].

For a more detailed description of itraconazole, please refer to the German Summary of Product Characteristics (SmPC) for Sempera® Liquid 10 mg/ml [R23-0681].

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of single doses of BI 1810631 is conservatively estimated as [redacted]. This is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.

The REP of itraconazole is defined as 8 days.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Based on *in vitro* data, CYP3A4/5 is primarily responsible for the hepatic oxidative metabolism of BI 1810631, [redacted] [c32836122]. Moreover, BI 1810631 is a substrate for P-gp. [redacted] It is therefore necessary to investigate the effect of an inhibitor of CYP3A and P-gp on the pharmacokinetics of BI 1810631 in plasma to inform concomitant treatment recommendations.

Itraconazole is chosen for this trial as perpetrator drug, as this drug is recommended as strong inhibitor of CYP3A by EMA and PMDA [P15-06991, P15-06298] and as strong index inhibitor of CYP3A and clinical inhibitor of P-gp by FDA [R18-0241]. Moreover, safety and tolerability of itraconazole were acceptable in several previous DDI trials.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1810631 for treatment of patients with advanced solid tumours with HER2 aberrations.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1810631		
[redacted]	[redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only two single doses with appropriate wash-out [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	• Subjects are protected from this finding by administration of only two single doses with appropriate wash-out • AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously [redacted]

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont'd)

[redacted]	[redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Physical examination of subjects at end-of-study visit • Protection of subjects by administration of only two single doses
[redacted]	[redacted]	[redacted] • Protection of subjects by administration of only two single doses with appropriate wash-out
[redacted]	[redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only two single doses with appropriate wash-out
[redacted]	[redacted]	[redacted]

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont'd)

[redacted]	[redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of BI 1810631, subjects will be in-house under close observation for at least 24 hours • Protection of subjects by administration of only two single doses with appropriate wash-out
Uncertainties due to the early stage of development	[redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Following administration of BI 1810631, subjects will be in-house under close observation for at least 24 hours • VS and ECGs after dosing (see Flow Chart) • Protection of subjects by administration of only two single doses with appropriate wash-out
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont'd)

Investigational Medicinal Product: Itraconazole		
Side effects described in the SmPC of Sempera Liquid 10 mg/ml Lösung zum Einnehmen [R23-0681]	Gastrointestinal side effects including hepatotoxicity are amongst the side effects that are most frequently reported. Other potential side effects are described in the SmPC of Sempera® Liquid 10 mg/mL. Overall, the risks associated with 14-day treatment with 200 mg/day itraconazole are considered acceptable.	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Safety laboratory at pre-defined time points during itraconazole dosings (see Flow Chart and Section 5.2.3) • Stringent in- and exclusion criteria define a relatively homogenous population and exclude subjects that might be at increased risk for AEs (see Section 3.3) • Criteria for withdrawal of individual subjects from trial treatment are defined in Section 3.3.4.1
Potential interaction between itraconazole and BI 1810631		
Perpetrator: itraconazole Victim: BI 1810631	Preclinical data (refer to IB [c32836122]) indicate a risk for increased plasma exposure of BI 1810631 when administered with itraconazole	• A low dose of BI 1810631 is used for this study (see Section 4.1.2) to ensure that BI 1810631 plasma concentrations remain within the range of concentrations that were explored in the dose escalation part of first-in-man trial 1479-0001 (see Section 1.2.1.3.1) and that showed good safety and tolerability (see Section 1.2.1.3.3). • Subjects are in-house under close observation for at least 24 hours following administration of BI 1810631 • AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • ECG, VS, and safety laboratory will be performed as scheduled in the Flow Chart

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont'd)

Trial procedures		
Blood sampling: Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site
ECG recording: Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes.
Other risks		
SARS-CoV-2 infection	• Participation in this trial may increase the risk of COVID-19 exposure due to travels to the study site and completion of protocol-defined procedures at the site. • To date there is no evidence suggesting an association between Covid-19 and HER2 inhibition targeted by BI 1810631. • Available non-clinical data have not shown an increased risk of infections due to treatment with BI 1810631 (see IB [c32836122])	• A risk management plan has been set up at the clinical site that details precautionary measures (e.g., hygiene rules, wearing of face masks, physical distancing) and screening for SARS-CoV-2 infection. • During the Covid-19 pandemic, subjects with laboratory results indicative of a SARS-CoV-2 infection are excluded from trial participation (see exclusion criterion 24 in Section 3.3.3)

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

There is significant medical need in cancer patients harbouring HER2 mutations for effective, safe and well-tolerated therapies. BI 1810631 is an EGFR wild-type sparing selective HER2 inhibitor with potent inhibitory activity on all major HER2 mutations.

It provides a unique opportunity for the treatment of NSCLC patients harbouring HER2 mutations, and data further suggest that BI 1810631 could be efficacious in all HER2-dependent cancers.

BI 1810631 has been adequately characterized in preclinical studies. [redacted] Moreover, preliminary data from two clinical trials are available (see Section 1.2.1.3) that support the two single doses of BI 1810631 (with or without itraconazole) planned for the current trial. [redacted] The observed plasma exposures of BI 1810631 in trial 1479-0001 provide a large safety window for potential exposure increases in the current trial, when BI 1810631 is given together with itraconazole.

The current study is necessary to support the development of BI 1810631: [redacted]

Considering the medical need for an effective and safe treatment of solid tumours with HER2 mutations, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objective

The main objective of this trial is to investigate the effect of multiple oral doses of the strong CYP3A inhibitor and recommended P-gp inhibitor itraconazole on the pharmacokinetics of a single dose of BI 1810631 in plasma following oral administration.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1810631:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 1810631:

- 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)

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1810631 and itraconazole will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, two-treatment, two-period, fixed-sequence crossover trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be

- Treatment T: One oral single dose of [redacted] mg BI 1810631 administered as film-coated tablet together with multiple oral doses of 200 mg itraconazole as oral solution
- Treatment R: One oral single dose of [redacted] mg BI 1810631 administered as film-coated tablet alone.

BI 1810631 and itraconazole are administered to subjects [redacted]. In the first treatment period (Period 1 = Visit 2), all subjects are planned to undergo treatment R, and in the second treatment period (Period 2 = Visit 3), all subjects are planned to undergo treatment T. For details, refer to Section 4.1.

There will be a washout interval of at least 14 days between the administrations of BI 1810631.

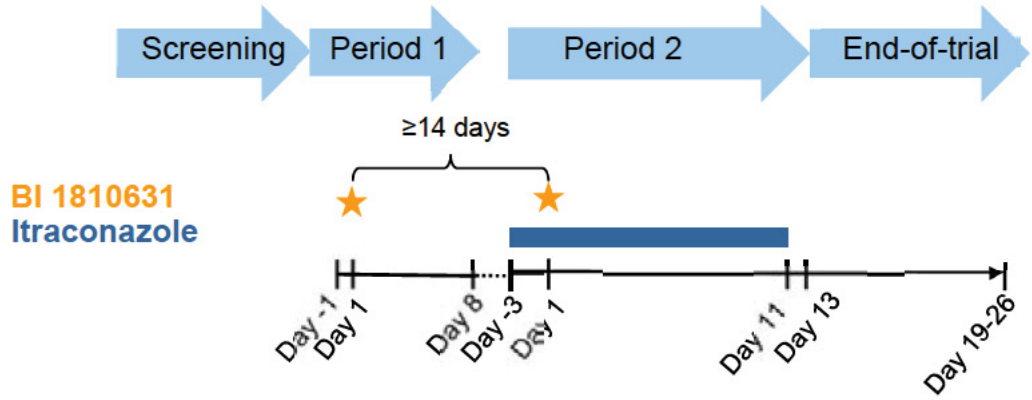


Figure 3.1: 1 Trial design

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.

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

For drug interaction trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529].

Because of the long elimination half-life (about 40 h) of itraconazole and its metabolites, a two-period fixed-sequence design was selected, with administration of itraconazole in the second study period, only.

This design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time effects are unlikely due to the short trial duration. For itraconazole studies, this design is recommended by the Innovation and Quality in Pharmaceutical Development's Clinical Pharmacology Leadership Group (CPLG) [R17-3744].

For this PK drug-drug interaction trial, open-label treatment is acceptable, because the primary and secondary endpoints of this trial are PK endpoints derived from measurement of plasma concentrations of BI 1810631. These endpoints are not expected to be affected by knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included in the trial because of the reproduction toxicity reported from nonclinical studies with itraconazole.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF, irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as 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 (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

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) deviating from normal and assessed as clinically relevant by the investigator

2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation or any kind of vaccination)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. [redacted]
15. [redacted]
16. Alcohol abuse (consumption of more than 24 g per day)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)

23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection
25. Subjects with WOCBP partner who are unwilling to use highly effective contraception from time point of first administration of BI 1810631 until 30 days after the last administration of BI 1810631. Highly effective methods of contraception are:

    - Subject is sexually abstinent

    - Subject is vasectomized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) and uses condom

    - Use of intrauterine device or intrauterine hormone-releasing system by female partner plus use of condom

    - Use of progestogen-only hormonal contraception by female partner that inhibits ovulation (injectables or implants) plus use of condom

    - Use of combined (estrogen and progestogen containing) hormonal contraception by female partner that prevents ovulation (oral, intravaginal, or transdermal) plus use of condom

    - Bilateral tubal occlusion in the female partner plus use of condom

    Sperm donation is not allowed from the time point of first administration of BI 1810631 until 30 days after the last administration of BI 1810631
26. Liver enzymes (ALT, AST, GGT) above upper limit of normal at the screening examination, confirmed by a repeat test
27. History of drug-induced liver injury, heart failure, or any evidence of ventricular dysfunction

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may withdraw consent to trial participation as a whole (‘withdrawal of consent’) with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR).

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed.

If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.3, the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases). This may include:
   - The subject has an elevation of AST and/or ALT ≥3-fold ULN
   - For the safety laboratory on Period 2, Day -1: The subject has an elevation of AST and/or ALT≥ 55 U/L
   - The subject has a serious adverse reaction or a CTCAE Grade 3 non-serious adverse reaction
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

1. Failure to meet expected enrolment goals
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of CTCAE grade 2 severity (except for grade 2 headache), or if grade 3 drug-related non-serious adverse events occur in at least two subjects, or if at least one drug-related serious adverse event is reported

3.3.5 Replacement of subjects

In case more than 4 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced if considered necessary to reach the objectives of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Clinical Pharmacologist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 4 subjects (1/3 of the total number of evaluable subjects required to complete the trial). A replacement subject will be assigned a unique trial subject number.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Test product 1:

Substance:	BI 1810631
Pharmaceutical formulation:	Film-coated tablet [redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted] mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose in treatment R and T

Test product 2:

Name:	Sempera® Liquid 10 mg/ml Lösung zum Einnehmen
Substance:	Itraconazole
Pharmaceutical formulation:	Oral solution
Source:	Public pharmacy
Holder of marketing authorisation:	Janssen-Cilag GmbH, Neuss, Germany
Unit strength:	10 mg/mL
Posology:	20 mL-0-0
Mode of administration:	Oral
Duration of use:	Once daily for 14 consecutive days in treatment T

4.1.2 Selection of doses in the trial

The dose of itraconazole selected for this trial reflects standard clinical doses, [redacted] P-gp inhibition and has been used successfully and safely in previous drug-drug interaction trials.

[redacted]

For the current trial, a dose of [redacted] mg BI 1810631 has been selected, to ensure that BI 1810631 plasma concentrations will be, even in case of a relevant increase when given with itraconazole, in the range of concentrations that were explored so far in the dose escalation part of trial 1479-0001 and that were associated with good safety and tolerability (see Section 1.2.1.3).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are summarised in Table 4.1.4: 1 below. All subjects will receive the 2 treatments in a fixed order.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	BI 1810631	Film-coated tablet	[redacted] mg	1 tablet as single dose on study day 1 of period 1	[redacted] mg
T (Test)	BI 1810631	Film-coated tablet	[redacted] mg	1 tablet (15 mg) as single dose on study day 1 of period 2	[redacted] mg
	Itraconazole	Oral solution	10 mg/mL	20 mL (200 mg) once daily for 14 days (study days -3 to 11 of period 2)	2,800 mg

Administration of trial medication will be performed after subjects have [redacted]. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

In each period, subjects will be kept under close medical surveillance until 24 h after BI 1810631 administration. During the first 4 h after BI 1810631 administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless required for medical procedures or treatment of AEs.

The BI 1810631 administrations will be separated by a wash-out interval of at least 14 days.

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal product BI 1810631 will be provided by BI. It will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided 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.

Itraconazole will be obtained by the trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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 in accordance with the recommended (labelled) storage conditions. If 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 Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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 documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee 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 medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

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, if adverse events require 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 results of medical evaluations are acceptable.

Table 4.2.1: 1 [redacted]

[redacted]		

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Drugs with a known hepatotoxic profile (e.g., paracetamol or diclofenac) or drugs that are contraindicated to be co-administered with itraconazole [R23-0681] should be avoided during the entire study.

In case of AEs requiring analgesic / antiphlogistic treatment such as headache, short-term use of ibuprofen is acceptable.

4.2.2.2 Restrictions on diet and life style

[redacted]

Day 1 (Periods 1 and 2): From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h following administration of BI 1810631, total fluid intake is restricted to 3000 mL.

[redacted] are not permitted from 7 days before the first administration of trial medication until after the last PK sample of the trial is collected.

Alcoholic beverages are forbidden from 5 days before the first administration of trial medication until after the last PK sample of the trial.

[redacted] should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug screen.

[redacted] and smoking are not allowed during in-house confinement.

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

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

4.2.2.3 Contraception requirements

Subjects whose sexual partner is a WOCBP must be sexually abstinent or use highly effective contraception starting from the first dose of BI 1810631 and for at least 30 days after the last dose of BI 1810631. See Section 3.3.3 for required contraceptive measures.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (alcohol history not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2 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 (Dinamap Pro 100, [redacted] 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.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 9 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	X	--	X
	Haemoglobin	X	X	--	X
	Red Blood Cell Count/Erythrocytes	X	X	--	X
	White Blood Cells/Leucocytes	X	X	--	X
	Platelet Count/Thrombocytes (quant)	X	X	--	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.				
Coagulation	Activated Partial Thromboplastin Time	X	X	--	X
	Prothrombin time (Quick)	X	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	X	--	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X	X
	Alkaline Phosphatase	X	X	X	X
	Gamma-Glutamyl Transferase	X	X	X	X
	Lactic Dehydrogenase	X	X	--	X
	Lipase	X	X	--	X
	Troponin T ultrasensitive	X	--	--	--
	NT-proBNP	X	--	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	X	--	X
	Creatinine	X	X	--	X
	GFR/ CKD-EPI	X	X	--	X
	Bilirubin, Total	X	X	X	X
	Bilirubin, Direct	X	X	X	X
	Protein, Total	X	X	--	X
	C-Reactive Protein (Quant)	X	X	--	X
	Cholesterol, total	X	X	--	X
Electrolytes	Sodium	X	X	--	X
	Potassium	X	X	--	X
	Calcium	X	X	--	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	--	--	X
	Urine Protein (qual)	X	--	--	X
	Urine Glucose (qual)	X	--	--	X
	Urine Ketone (qual)	X	--	--	X
	Urobilinogen (qual)	X	--	--	X
	Urine Bilirubin (qual)	X	--	--	X
	Urine HGB (qual)	X	--	--	X
	Urine leukocyte esterase (qual)	X	--	--	X
	Urine pH	X	--	--	X
Urine sediment [1]	Only positive findings will be reported [2]				

[1] microscopic examination if erythrocytes, leukocytes, nitrite, or protein are abnormal in urine
[2] e.g., the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes
A, B, C, D: different sets of safety laboratory. For time points see Flow Chart.

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and at admission to in-house stay during each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, [redacted] will be performed at admission to in-house stay during each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted], with the exception of drug screening tests. These tests will be performed at the trial site using M-10/14-PDT Surestep Multiline test, or comparable test systems.

In case of positive drug screen, confirmatory test may be done at [redacted].

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

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph ([redacted]) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 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 considered related or not.

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

- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or 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

5.2.6.1.3 AEs considered ‘Always Serious’

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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. A copy of the latest list of ‘Always Serious AEs’ will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in 5.2.6.2, subsections ‘AE Collection’ and ‘**AE reporting to sponsor and timelines’**.

5.2.6.1.4 Adverse events of special interest

The term adverse events 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 5.2.6.2.2.
The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (aspartate aminotransferase) 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 in samples drawn within 30 days of each other, or
  - o 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.

[redacted]

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [R18-1357].

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, 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)
- 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

- There is an 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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 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. 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 (the End of Study (EoS) visit):
    - 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 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 new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. as 'chronic' or 'stable'), or no further information can be obtained.

5.2.6.2.3 Pregnancy

Once the subject has been enrolled in the clinical trial and has taken BI 1810631, and if a partner of the male trial participant becomes pregnant, the investigator must report any BI 1810631 exposure during pregnancy in a partner of the male trial participant by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner. Reporting and consenting must be in line with local regulations.

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 Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and Part B).

As the female partner's pregnancy itself is not to be reported as an AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1810631 concentrations in plasma, 2.7 mL of blood will be drawn 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. Blood will

be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time.

Further use of samples

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites), to address Health Authority questions regarding the results/methodology, or to measure concentrations of itraconazole and/or its metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

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 the end of trial examination are provided 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.

In treatment period T, a time window of ± 120 min around planned time applies to itraconazole dosings in the morning of Days -3 and -2. In the morning of Day -1, a time window of ± 60 min around planned time applies to itraconazole dosing.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 60 min.

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

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

At visits 2 and 3, for PK samples, itraconazole administrations and safety laboratory tests at planned time +47 h and later, a time window of ± 120 min around planned time applies.

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 provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Days -1 to Day 8 in period 1 and Days -3 to Day 13 in period 2). At least 14 days will separate administrations of BI 1810631 in the first and second treatment periods.

In the evening of Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following BI 1810631 administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

All abnormal values (including laboratory parameters) that are assessed as 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 a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1810631 in plasma when given as a single dose together with multiple oral doses of Itraconazole (T) versus a single dose of BI 1810631 alone (R) will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the IPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1810631 will be calculated according to the relevant BI internal procedures.

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 deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration of BI 1810631 is >5% C_{max} value of that subject in the respective treatment period,
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the 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).

7.2.2 Primary endpoint analyses

Primary analyses

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subject and treatment. The effect 'subject' will be considered as random, whereas the effect ‘treatment’ will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received treatment k,

where $s_m \sim N(0, \sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and s_m, e_{km} are independent random variables.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with 'subject' considered as fixed effects.

In addition to the model based approach all parameters will be calculated and analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints.

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

For all analyses, the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the assigned treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP 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 follow-up 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 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

It is not planned to impute missing values for safety parameters.

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

The trial will not be randomised, thus this section is not applicable. All subjects will receive the same treatments in the same order.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects with the aim of at least 12 evaluable 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.

For various assumptions around the gCV of 25%, Table 7.5: 1 provides an overview of the achievable 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 7.5: 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 2-period fixed-sequence trial *(N=12)*

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]

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

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

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

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

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.1.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to finalisation of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, 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 according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

8.3 RECORDS

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

ClinBase™
In the [redacted] Phase I unit – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as database. Instead of being entered into CRFs, selected data are directly entered into the ClinBase™ system.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number,

and social security number) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents.

The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site 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.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (e.g. biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

- Samples and/or data may be transferred to third parties and other countries as specified in the ICF

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first subject in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject Completed').

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial 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 Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The BI 1810631 trial medication will be provided by the [redacted] and itraconazole oral solution will be obtained by the trial site from a pharmacy.

Safety laboratory tests will be performed by the local laboratory of the trial site ([redacted]).

Analyses of BI 1810631 concentrations in plasma will be performed at [redacted].

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 or by a contract research organization appointed by BI.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

P11-09424 [redacted]

P15-01211 Arteaga CL, Engelman JA. ERBB receptors: from oncogene discovery to basic science to mechanism-based cancer therapeutics. Cancer Cell; 2014; 25(3); 282-303. Cancer Cell 25, March 17, 2014 ª2014 Elsevier Inc. 303

P15-06298 Ministry of Health, Labour and Welfare. Drug interaction guideline for drug development and labeling recommendations (draft). http://www.solvobiotech.com/documents/Japanese_DDI_guideline_(draft)_2014Jan.pdf (access date: 22 June 2015); Ministry of Health, Labour and Welfare; 2014.

P15-06991 European Medicines Agency (EMA). Committee for Human Medicinal Products (CHMP): guideline on the investigation of drug interactions (21 June 2012, CPMP/EWP/560/95/rev. 1 corr. 2). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/0 7/WC500129606.pdf (access date: 8 July 2015); London: European Medicines Agency (EMA); 2012.

P19-00456 Wang Y, Jiang T, Qin Z, Jiang J, Wang Q, Yang S, et al. HER2 exon 20 insertions in non-small-cell lung cancer are sensitive to the irreversible pan-HER receptor tyrosine kinase inhibitor pyrotinib. Annals of Oncology. 31 December 2018. 447-455

P19-10412 Connell CM, Doherty GJ. Activating HER2 mutations as emerging targets in multiple solid cancers. ESMO Open 2017 ; 2; e000279

P20-09250 Jebbink M, Langen AJ de, Boelens MC, Monkhorst K, Smit EF. The force of HER2 - a druggable target in NSCLC?. Cancer Treat Rev 2020 ; 86; 101996

R09-6185 Hynes NE, MacDonald G. ErbB receptors and signaling pathways in cancer. Curr Opin Cell Biol; Current Opinion in Cell Biology 2009, 21:177–184

R10-1102 Templeton IE, Thummel KE, Kharasch ED, Kunze KL, Hoffer C, Nelson WL, Isoherranen N. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. Clin Pharmacol Ther 2008; 83(1):77-85. Clin Pharmacol Ther 1994. 55(5):481-485.

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

R17-3742 Barone JA, Moskovitz BL, Guarnieri J, Hassell AE, Colaizzi JL, Bierman RH, et al. Food interaction and steady-state pharmacokinetics of itraconazole oral solution in healthy volunteers. Pharmacotherapy 1998; 18(2):295-301.

R17-3743 Willems L, Geest R van der, Beule K de. Itraconazole oral solution and intravenous formulations: a review of pharmacokinetics and pharmacodynamics. J Clin Pharm Ther 2001; 26:159-169.

R17-3744 Liu L, Bello A, Dresser MJ, Heald D, Komjathy SF, O'Mara E, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. J Clin Pharmacol 2016. 56(2):143-151.

R18-0241 Guidance for industry: clinical drug interaction studies - study design, data analysis, and clinical implications (draft guidance, this guidance document is being distributed for comment purposes only) (October 2017, clinical pharmacology). https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf (access date: 19 January 2018); Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2017.

R18-1357 U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). U.S.Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2017.

R20-1872 Citri A, Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol; 2006; 7; 505-516. JULY 2006

R20-1990 Wang Z. ErbB receptors and cancer. Methods in Molecular Biology; 2017;1652; 3-35. vol. 1652, DOI 10.1007/978-1-4939-7219-7_1, © Springer Science+Business Media LLC 2017

R23-0681 Sempera Liquid 10 mg/ml, Lösung zum Einnehmen (Janssen-Cilag) (Fachinformation, Stand der Information: Dezember 2022). 2022.

R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

9.2 UNPUBLISHED REFERENCES

c32836122 [redacted] Investigator's Brochure BI 1810631 1479-P01 Version 2.0. 12 Jan 2022

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 Feb 2023
EudraCT number **EU number**		2022-003757-63
BI Trial number		1479-0004
BI Investigational Medicinal Product(s)		BI 1810631
Title of protocol		The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial)

Substantial Global Amendment due to urgent safety reasons To be implemented immediately in order to eliminate hazard – IEC / Competent Authority to be notified of change with request for approval.	☐
Substantial Global Amendment e.g. changes in safety or physical or mental integrity of trial subjects, or in inter-pretation of scientific documents/value of the trial, or in conduct/management of the trial, or change/addition of principal investigators, co-ordinating investigators, or trial sites – implementation only after IEC / Competent Authority approval.	☒
Non-substantial Global Amendment e.g. changes that involve logistical or administrative aspects, or exploratory endpoints only – can be implemented without IEC / Competent Authority approval	☐

Section to be changed		1. Flow Chart 2. Section 3.3.4.1 3. Synopsis and Section 3.3.2 4. Section 5.2.3: Table 5.2.3.1 5. Section 3.3.3 6. Section 3.3.3 7. Section 8.1 8. Section 3.3.4.3 9. Sections 1.2.2, 1.4.2 and 4.2.2.1
Description of change		1. Addition of safety laboratory C on Days -1, 4 and 6 of period 2, deletion of safety lab on Day 5 of period 2. Addition of footnote 11 to safety laboratory C on Day -1 (safety laboratory to be medically evaluated before dosing on Day 1)

		2. Addition of text "For the safety laboratory on Period 2, Day -1: The subject has an elevation of AST and/or ALT≥ 55 U/L" to individual withdrawal criterion 4 3. Reduction of upper age limit to 50 years 4. Addition of troponin t ultrasensitive and NT-proBNP to safety laboratory set A 5. Adaptation of exclusion criterion 10 so that subjects with any documented active or suspected malignancy or history of malignancy are now excluded from trial participation 6. Adaptation of exclusion criterion 2: Increase of lower acceptable pulse limit from 45 bpm to 50 bpm 7. Deletion of the subject's legally accepted representative 8. Criterion 5 has been modified so that the study needs to be stopped in case of drug-related Grade 3 events in at least two subjects 9. Replacement of reference to SmPC Sempera® Liquid 10 mg/ml Lösung zum Einnehmen by current version (December 2022)
Rationale for change		1. Request from Ethics Committee 2. Request from Ethics Committee 3. Request from Competent Authority 4. Request from Competent Authority 5. Request from Competent Authority 6. Request from Competent Authority 7. Request from Competent Authority 8. Request from Competent Authority 9. Request from Competent Authority

APPROVAL / SIGNATURE PAGE

Document Number: c40240667 **Technical Version Number:2.0**

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

Title: The effect of multiple doses of itraconazole on the pharmacokinetics of a single oral dose of BI 1810631 in healthy male subjects (an open-label, two-period, fixed-sequence trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	22 Feb 2023 14:07 CET
Approval-Clinical Program [redacted]		22 Feb 2023 15:48 CET
Author-Trial Statistician		22 Feb 2023 17:40 CET
Verification-Paper Signature Completion		23 Feb 2023 09:52 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed