Clinical Trial Protocol

Document Number:	**c40561285-03**
EUCT No.	2022-503046-50-00
BI Trial No.	1479-0011 (CRS trial number: 140/22)
BI Investigational Medicinal Product	BI 1810631
Title	The effect of multiple doses of carbamazepine 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 whether carbamazepine 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 3.0, 14 Sep 2023
Original Protocol Date	31 Mar 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	31 March 2023
Revision date	14 Sep 2023
BI trial number	1479-0011
Title of trial	The effect of multiple doses of carbamazepine 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	
Clinical phase	I
Trial rationale	BI 1810631 is a substrate for CYP3A *in vitro*. The *in vivo* effect of induction of CYP3A on BI 1810631 pharmacokinetics is not known. It needs to be investigated to inform concomitant treatment recommendations.
Trial objective	To investigate the effect of multiple oral doses of the strong CYP3A inducer carbamazepine on the pharmacokinetics of a single dose of BI 1810631 in plasma.
Trial endpoints	Primary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 1810631 Secondary endpoint: AUC_{0-tz} of BI 1810631
Trial design	Open-label, two-period, fixed-sequence crossover design
Number of subjects **total entered** **on each treatment**	 16 16
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 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 60 mg film-coated tablets 60 mg Oral with 240 mL of water after an overnight fast of at least 10 h

Test products 2 and 3	Test product 2: Carbamazepin-neuraxpharm® 400 mg retard tablets Test product 3: Carbamazepin-neuraxpharm® 600 mg retard tablets
Dose	Titration, starting with low dose 200 mg q.d., to mid dose 400 mg q.d., followed by the maximal dose 600 mg q.d.
mode of admin.	Oral with 240 mL of water after a dinner
Duration of treatment	Period 1: - BI 1810631 60 mg: 1 single dose in the morning of Day 1 Period 2: - Carbamazepine o Day -18 to -15: 200 mg q.d. in the evening o Day -14 to -8: 400 mg q.d. in the evening o Day -7 to +6: 600 mg q.d. in the evening - BI 1810631 60 mg: 1 single dose 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 [12]	Safety laboratory [10]	PK BI 1810631 (plasma)	PK carbamazepine (plasma)	4β-OH Cholesterol (plasma)	6β-OH Cortisol / cortisol ratio (urine)[7]	12-lead ECG and vital signs (BP, PR)	Neurological examination, C-SSRS[13]	Skin inspection[14]	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	A					x	x	x	
Period 1 (Treatment R = BI 1810631 alone)	2	-1	-14:00	18:00	Admission to site	x[5]								x
			-13:00	19:00	Dinner[3]									
		1	-1:00	07:00		B[2]	x[2]				x[2]			x[2]
			0:00	08:00	**Administration: BI 1810631 60 mg**									
			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
			6:00	14:00			x							
			8:00	16:00	Snack (voluntary)[3]		x							
			10:00	18:00			x							
			11:00	19:00	Dinner[3]									
			12:00	20:00			x							x
		2	24:00	08:00		B	x				x			x
			36:00	20:00			x							x
		3	48:00	08:00	Discharge from site		x							x
		4	72:00	08:00	Ambulatory visit		x							x
		6	120:00	08:00	Ambulatory visit		x							x
		8[11]	168:00	08:00	Ambulatory visit	B	x							x
Period 2 (Treatment T = carbamazepine + BI 1810631)	3	-19[11]	-446:00	18:00	Admission to site	x[5]								x
			-444:00	20:00						▲				
		-18	-432:00	08:00							x	x	x	x
			-421:00	19:00	Dinner[3]									x
			-420:00	20:00	**Administration: Carbamazepine 200 mg**			x[9]	x[9]	▼				
		-17	-408:00	08:00										x
			-397:00	19:00	Dinner[3]									x
			-396:00	20:00	**Administration: Carbamazepine 200 mg**									
		-16	-384:00	08:00										x
			-373:00	19:00	Dinner[3]									x
			-372:00	20:00	**Administration: Carbamazepine 200 mg**									
		-15	-360:00	08:00		C							x	x
			-349:00	19:00	Dinner[3]									x
			-348:00	20:00	**Administration: Carbamazepine 200 mg**									
		-14	-336:00	08:00							x			x

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [12]	Safety laboratory [10]	PK BI 1810631 (plasma)	PK carbamazepine (plasma)	4β-OH Cholesterol (plasma)	6β-OH Cortisol / cortisol ratio (urine)[7]	12-lead ECG and vital signs (BP, PR)	Neurological examination, C-SSRS[13]	Skin inspection[14]	Questioning for AEs and concomitant therapy [6]
			-325:00	19:00	Dinner[3]									x
			-324:00	20:00	**Administration: Carbamazepine 400 mg**									
		-13	-312:00	08:00										x
			-301:00	19:00	Dinner[3]									x
			-300:00	20:00	**Administration: Carbamazepine 400 mg**					▲				
		-12	-288:00	08:00		B				|	x			x
			-277:00	19:00	Dinner[3]					|				x
			-276:00	20:00	**Administration: Carbamazepine 400 mg**			x[9]	x[9]	▼				
		-11	-264:00	08:00									x	x
			-253:00	19:00	Dinner[3]									x
			-252:00	20:00	**Administration: Carbamazepine 400 mg**									
		-10	-240:00	08:00										x
			-229:00	19:00	Dinner[3]									x
			-228:00	20:00	**Administration: Carbamazepine 400 mg**									
		-9	-216:00	08:00		C								x
			-205:00	19:00	Dinner[3]									x
			-204:00	20:00	**Administration: Carbamazepine 400 mg**									
		-8	-192:00	08:00										x
			-181:00	19:00	Dinner[3]									x
			-180:00	20:00	**Administration: Carbamazepine 400 mg**					▲				
		-7	-168:00	08:00						|	x	x	x	x
			-157:00	19:00	Dinner[3]					|				x
			-156:00	20:00	**Administration: Carbamazepine 600 mg**			x[9]	x[9]	▼				
		-6	-144:00	08:00		B								x
			-133:00	19:00	Dinner[3]									x
			-132:00	20:00	**Administration: Carbamazepine 600 mg**					▲				
		-5	-120:00	08:00						|				x
			-109:00	19:00	Dinner[3]					|				x
			-108:00	20:00	**Administration: Carbamazepine 600 mg**			x[9]	x[9]	▼				
		-4	-96:00	08:00										x
			-85:00	19:00	Dinner[3]									x
			-84:00	20:00	**Administration: Carbamazepine 600 mg**					▲				
		-3	-72:00	08:00		C				|	x			x
			-61:00	19:00	Dinner[3]					|				x

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [12]	Safety laboratory [10]	PK BI 1810631 (plasma)	PK carbamazepine (plasma)	4β-OH Cholesterol (plasma)	6β-OH Cortisol / cortisol ratio (urine)[7]	12-lead ECG and vital signs (BP, PR)	Neurological examination, C-SSRS[13]	Skin inspection[14]	Questioning for AEs and concomitant therapy [6]
			-60:00	20:00	**Administration: Carbamazepine 600 mg**			x[9]	x[9]	▼				
		-2	-48:00	08:00										x
			-37:00	19:00	Dinner[3]									x
			-36:00	20:00	**Administration: Carbamazepine 600 mg**					▲				
		-1	-24:00	08:00						|		x	x	x
			-13:00	19:00	Dinner[3]					|				x
			-12:00	20:00	**Administration: Carbamazepine 600 mg**			x[9]	x[9]	▼				
		1	-1:00	07:00		B[2]	x[2]				x[2]			x[2]
			0:00	08:00	**Administration: BI 1810631 60 mg**									
			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
			6:00	14:00			x							
			8:00	16:00	Snack (voluntary)[3]		x							
			10:00	18:00			x							
			11:00	19:00	Dinner[3]									
			12:00	20:00	**Administration: Carbamazepine 600 mg**		x[8]			▲				x
		2	24:00	08:00		B	x			|	x			x
			35:00	19:00	Dinner[3]					|				x
			36:00	20:00	**Administration: Carbamazepine 600 mg**		x[9]	x[9]	x[9]	▼				
		3	48:00	08:00			x							x
			59:00	19:00	Dinner[3]									x
			60:00	20:00	**Administration: Carbamazepine 600 mg**					▲				
		4	72:00	08:00			x			|	x		x	x
			83:00	19:00	Dinner[3]					|				x
			84:00	20:00	**Administration: Carbamazepine 600 mg**			x[9]	x[9]	▼				
		5	96:00	08:00		C								x
			107:00	19:00	Dinner[3]									x
			108:00	20:00	**Administration: Carbamazepine 600 mg**									
		6	120:00	08:00			x							x
			131:00	19:00	Dinner[3]									x
			132:00	20:00	**Administration: Carbamazepine 600 mg**					▲				

Period	Visit	Day	Planned time (relative to BI 1810631 administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [12]	Safety laboratory [10]	PK BI 1810631 (plasma)	PK carbamazepine (plasma)	4β-OH Cholesterol (plasma)	6β-OH Cortisol / cortisol ratio (urine)[7]	12-lead ECG and vital signs (BP, PR)	Neurological examination, C-SSRS[13]	Skin inspection[14]	Questioning for AEs and concomitant therapy [6]
		7	144:00	08:00						▼				x
			156:00	20:00				x	x	▼				x
		8	168:00	08:00	Discharge from trial site		x							x
FU	4	15-22			End of study (EoS) examination[4]	B					x	x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, neurological examination, skin inspection, check of vital signs, ECG, safety laboratory (including drug screening test), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy, review of inclusion/exclusion criteria and suicidality assessment (C-SSRS).
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to the next drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, neurological examination, skin inspection, suicidality assessment (C-SSRS), vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies, and a determination of body weight.
5. Only urine drug screening and alcohol breath test and a nasal/oral swab for SARS-CoV-2 PCR testing (nasal/oral swab and Covid-19 test at admission or within 36 h before admission) will be done at this time
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. In period 2, urine samples are to be collected over the stated 24 h intervals (◄—►) -444 to -420, -300 to -276, -180 to -156, -132 to -108, -84 to -60, -36 to -12, +12 to +36, +60 to +84, and +132 to +156 h.
8. Blood sample on time, carbamazepine dosing immediately afterwards
9. Within 15 min before administration of carbamazepine
10. Letters A, B, and C designate different sets of safety laboratory examinations, see Section 5.2.3
11. Day 8 of period 1 is the same day as Day -19 of period 2
12. On Day 1 of both periods, only meals as described in the Flow Chart will be served. On the other days with in-house stays, food will be served as per the CRO's SOPs. Of note, a dinner will be served before all carbamazepine administrations as indicated by the Flow Chart.
13. For content of neurological examination see Section 5.2.5.1. Suicidality assessment using the Columbia-Suicide Severity Rating Scale (C-SSRS): 'Screening/Baseline' version at Visit 1, and 'since last visit' version at Visits 3 and 4 – see also Sections 5.2.5.3 and Appendix 10.1
14. See Section 5.2.5.2.

TABLE OF CONTENTS

[redacted]

ABBREVIATIONS AND DEFINITIONS

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
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Clinical Research Organisation
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
DDI	Drug Drug Interaction
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)
EUCT No.	European Clinical Trial Number

FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{po}	Mean residence time of the analyte in the body after oral administration
MTD	Month-do-Date
NF	New formulation
NSCLC	Non-small-cell lung cancer
PE	Polyethylene
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
$t_{1/2}$	Terminal half-life of the analyte in plasma

t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
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
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOBC	woman of child-bearing potential

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 PROFILE

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. It is intended to treat patients with advanced solid tumors with HER2 aberrations.

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

Based on *in vitro* data, CYP3A4/5 is primarily responsible for the hepatic oxidative metabolism of BI 1810631, [redacted]. Thus, concomitant medication with inducers of CYP3A could cause clinically relevant decreases of the plasma exposure of BI 1810631. For more details refer to the IB [c32836122].

1.2.1.3 Data from studies in humans

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

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, 42 patients were treated in the dose escalation part 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 (25 patients - 60-120-180-240-300 mg). Data cut time point for the data described here is 24 Feb 2023.

Short description of healthy volunteer trial 1479-0003

At the time of CTP 1479-0011 finalization, trial 1479-0003 is in the 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 the food effect on the pharmacokinetics of a single dose of BI 1810631 in plasma and investigated the effect of multiple-dose treatment with rabeprazole 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: 30 mg BI 1810631 trial formulation 1 (TF1) under fasted conditions
- T1: 30 mg BI 1810631 new formulation (NF) under fasted conditions

- T2: 30 mg BI 1810631 NF after a high-fat, high-calorie breakfast
- T3: 30 mg BI 1810631 NF after a 5-day pre-treatment with the proton-pump inhibitor rabeprazole.

1.2.1.3.1 Pharmacokinetic data of patient first-in-man trial 1479-0001 (preliminary data)

Table 1.2.1.3.1: 1 Single-dose BI 1810631 PK data of ongoing patient trial 1479-0001 (preliminary data)

Preliminary PK parameters: gMean (gCV%)	t_{max} [h][1]	C_{max} [nM]	AUC_{0-12} [nM*h]	AUC_{0-tz} [nM*h][2]	$AUC_{0-\infty}$ [nM*h]	$t_{1/2}$ [h]
Dose group (N)	[redacted]					
15 mg b.i.d. (3)						
30 mg b.i.d. (3)						
60 mg b.i.d. (3)						
60 mg q.d. (5)						
100 mg b.i.d. (4)						
120 mg q.d. (4)						
150 mg b.i.d. (3)						
180 mg q.d. (5)						
240 mg q.d. (4)						
300 mg q.d. (3)						

[1] median (min-max)
[2] [redacted]

Table 1.2.1.3.1: 2 Steady-state BI 1810631 PK data of ongoing patient trial 1479-0001 (preliminary data)

Preliminary PK parameters: gMean (gCV%)	$t_{max,ss}$ [h][1]	C_{max} [nM]	$AUC_{\tau,ss}$ [nM*h]	$t_{1/2,ss}$ [h]
Dose group (N)				
15 mg b.i.d. (3)	[redacted]			
30 mg b.i.d. (3)				
60 mg b.i.d. (3)				
60 mg q.d. (5)				
100 mg b.i.d. (4)				
120 mg q.d. (3)				
150 mg b.i.d. (2)				
180 mg q.d. (4)				
240 mg q.d. (4)				
300 mg q.d. (2)				

[1] median (min-max)

1.2.1.3.2 Pharmacokinetic data of healthy volunteer trial 1479-0003

Table 1.2.1.3.2: 1 Single-dose BI 1810631 PK data of healthy volunteer trial 1479-0003

Preliminary PK parameters: gMean (gCV%)	t_{max} [h][1]	C_{max} [nM]	AUC_{0-tz} [nM*h]	$AUC_{0-\infty}$ [nM*h]	$t_{1/2}$ [h]
Treatment (N)					
R = 30 mg TF1 fasted (12)	[redacted]				
T1 = 30 mg NF fasted (12)					
T2 = 30 mg NF fed (9)					
T3 = 30 mg NF fasted + rabeprazole (11)					

[1] median (min-max)

Of note, the film-coated tablets used in the current trial 1479-0011 are based on the same formulation principle as the NF used in trial 1479-0003, i.e. pharmacokinetic data of NF (fasted) are expected to be representative for current trial 1479-0011.

1.2.1.3.3 Safety and tolerability data of patient first-in-man trial 1479-0001 (preliminary data; data cut 24 Feb 2023)

Among the 42 patients treated with BI 1810631 in either q.d. or b.i.d. dosing schemes, no severe expected or serious unexpected safety findings were observed so far at data cut point (24 Feb 2023). Overall, BI 1810631 was well tolerated, and reported AEs were manageable.

B.i.d. cohorts

For all b.i.d. cohorts (17 patients treated), the most frequent treatment related reported AE was diarrhoea in 8 (47.1%) patients with CTCAE Grade 1 severity in 6 (35.3%) cases and Grade 2 severity in 2 (11.8%) cases. For 3 (17.6%) patients, anaemia was reported (related, two patients Grade 1 and one patient Grade 2). Dry skin, hypertension, rhinitis, and blood creatinine increased was reported in 2 (11.8%) patients each, all related, Grade 1.

There was one patient with related ALT increased Grade 3 during treatment with 150 mg BI 1810631. Treatment for this patient was interrupted and restarted at the same dose level. Reported AST and ALT levels decreased during continued treatment with BI 1810631.

Otherwise, single events reported of Grades 3, 4, or 5 were all assessed as not related to BI 1810631. The two fatal cases were associated to malignant neoplasm progression. No serious event was reported as related to BI 1810631.

[redacted] was observed as dose-limiting toxicity (DLT) in dose group 60 mg and [redacted]. This event caused a [redacted]. [redacted]. For another case (not yet captured in clinical database), one related AE of diarrhoea Grade 2 was observed as DLT in dose group 150 mg. [redacted] In dose group 60 mg one related AE of stomatitis Grade 1 was observed. No DLTs were reported during Cycle 1 (MTD period). No AE leading to discontinuation of BI 1810631 was reported.

Q.d. cohorts

For all q.d. cohorts (25 patients treated), the most frequent reported related AEs were diarrhoea in 5 (20.8%) patients, followed by ALT increased and blood AP increased in 4 (16.7%) patients each, followed by anaemia, AST increased, GGT increased, hyperglycaemia, and hypoalbuminaemia, each in 3 (12.5%) patients. Two related ALT increases were of CTCAE Grade 3 (180 mg, 240 mg), and one each of the related AEs AST increased (240 mg) and GGT increased (60 mg) were of Grade 3. Moreover, one related anaemia, one related lymphocyte count decreased, and one related hypocalcaemia (all at 60 mg) were of CTCAE Grade 3. Of note, the observed Grade 3 AEs of anaemia, lymphocyte count decreased and GGT increased are under re-evaluation for causality.

All other related AEs were of Grades 1 or 2. Otherwise, single events reported of Grade 3 and Grade 5 were assessed as not related to BI 1810631. There were two fatal cases, both related to underlying malignancy.

The five related diarrhoea reports were of CTCAE grade 1. In dose group 240 mg 2 related AEs of stomatitis Grade 1 were observed, and in dose group 300 mg one related AE of mouth ulceration Grade 1 was observed.

One anaemia Grade 3 (60 mg) (re-evaluation for causality pending) and one ALT / AST increased, both Grade 3, (240 mg) were reported as drug-related serious adverse events. One anaemia Grade 3 (60 mg) (re-evaluation pending) in Cycle 11 and one ALT increased Grade 3 (180 mg) in Cycle 4 were reported as DLTs. No DLTs were reported during Cycle 1 (MTD period). In one patient at 180 mg, one ALT increased Grade 3 led to dose reduction (120 mg). The AE was improving. For another patient at 240 mg, one ALT increased Grade 3 and one AST increased Grade 3 led to dose reduction (180 mg). Both AEs were improving. Follow-up data is pending for both patients who required dose reductions. One anaemia Grade 3 (re-evaluation pending) at 60 mg and one SARS-CoV-2 test positive Grade 1 at 180 mg led to treatment discontinuations.

Table 1.2.1.3.3: 1 Number (%) of patients with drug-related AEs by dose group – b.i.d. cohorts (preliminary data)

Preferred term	15 mg b.i.d. [N (%)]	30 mg b.i.d. [N (%)]	60 mg b.i.d. [N (%)]	100 mg b.i.d. [N (%)]	150 mg b.i.d. [N (%)]
Number of patients	3 (100.0)	3 (100.0)	4 (100.0)	4 (100.0)	3 (100.0)
Total with drug-related AEs	2 (66.7)	2 (66.7)	4 (100.0)	3 (75.0)	2 (66.7)
Diarrhoea	0	1 (33.3)	3 (75.0)	2 (50.0)	2 (66.7)
ALT increased	0	0	0	0	1 (33.3)
Anaemia	0	0	0	1 (25.0)	2 (66.7)
AST increased	0	0	0	0	1 (33.3)
Blood AP increased	0	0	1 (25.0)	0	0
Blood creatinine increased	0	0	0	1 (25.0)	1 (33.3)
Dyspepsia	0	1 (33.3)	0	0	0
Dry skin	0	0	0	1 (25.0)	1 (33.3)
Fatigue	0	0	1 (25.0)	0	0
Hypercholesterolaemia	1 (33.3)	0	0	0	0
Hypertension	0	1 (33.3)	0	1 (25.0)	0
Hypoalbuminaemia	0	0	0	1 (25.0)	0
Hypocalcaemia	0	0	0	1 (25.0)	0
Increased upper airway secretion	0	1 (33.3)	0	0	0
Oedema	0	0	1 (25.0)	0	0
Paronychia	0	0	0	0	1 (33.3)
Platelet count decreased	0	0	0	0	1 (33.3)
Pruritus	1 (33.3)	0	0	0	0
Rash	0	0	0	0	1 (33.3)
Rash maculo-papular	0	0	0	1 (25.0)	0
Rhinitis	0	0	1 (25.0)	1 (25.0)	0
Stomatitis	0	0	1 (25.0)	0	0
Taste disorder	0	0	0	0	1 (33.3)
Vomiting	0	0	0	1 (25.0)	0

Table 1.2.1.3.3: 2 Number (%) of patients with drug-related AEs by dose group – q.d. cohorts (preliminary data)

Preferred term	60 mg q.d. [N (%)]	120 mg q.d. [N (%)]	180 mg q.d. [N (%)]	240 mg q.d. [N (%)]	300 mg q.d. [N (%)]
Number of patients	5 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	4 (100.0)*
Total with drug-related AEs	3 (60.0)	3 (75.0)	4 (66.7)	5 (100.0)	1 (25.0)
Abdominal pain upper	0	0	1 (16.7)	0	0
ALT increased	0	1 (25.0)	2 (33.3)	1 (20.0)	0
Anaemia	1 (20.0)	1 (25.0)	1 (16.7)	0	0
Arthralgia	0	0	0	0	1 (25.0)
AST increased	0	0	2 (33.3)	1 (20.0)	0
Bilirubin conjugated increased	1 (20.0)	0	0	0	1 (25.0)
Blood AP increased	1 (20.0)	1 (25.0)	1 (16.7)	0	1 (25.0)
Blood creatinine increased	1 (20.0)	1 (25.0)	0	0	0
Blood fibrinogen increased	1 (20.0)	0	0	0	0
Blood LDH increased	0	1 (25.0)	0	0	0
Blood phosphorus decreased	0	1 (25.0)	0	0	0
Bone pain	1 (20.0)	0	0	0	0
Chest pain	0	0	0	0	1 (25.0)
Decreased appetite	1 (20.0)	0	1 (16.7)	0	0
Dermatitis acneiform	0	0	1 (16.7)	0	0
Diarrhoea	0	2 (50.0)	0	2 (40.0)	1 (25.0)
Dry eye	0	1 (25.0)	0	0	0
Dry skin	1 (20.0)	0	0	0	0
Dysgeusia	0	0	1 (16.7)	0	0
Fatigue	1 (20.0)	0	0	0	0
Flatulence	0	0	1 (16.7)	0	0
GGT increased	1 (20.0)	1 (25.0)	1 (16.7)	0	0
Glucose urine present	1 (20.0)	0	0	0	0
Hyperglycaemia	1 (20.0)	1 (25.0)	1 (16.7)	0	0
Hypermagnesaemia	0	1 (25.0)	0	0	0
Hyperphosphataemia	0	1 (25.0)	0	0	0
Hypertriglyceridaemia	1 (20.0)	1 (25.0)	0	0	0
Hyperuricaemia	1 (20.0)	0	0	1 (20.0)	0
Hypoaesthesia oral	0	0	1 (16.7)	0	0
Hypoalbuminaemia	1 (20.0)	1 (25.0)	1 (16.7)	0	0
Hypocalcaemia	1 (20.0)	1 (25.0)	0	0	0
Hypochloraemia	0	1 (25.0)	0	0	0
Hypokalaemia	1 (20.0)	1 (25.0)	0	0	0
Hypomagnesaemia	1 (20.0)	0	0	0	0
Hyponatraemia	1 (20.0)	1 (25.0)	0	0	0
Hypophosphataemia	1 (20.0)	0	0	0	0
Hypothyroidism	0	1 (25.0)	0	0	0
INR increased	1 (20.0)	0	0	0	0
Insomnia	0	0	1 (16.7)	0	0
Lymphocyte count decreased	1 (20.0)	0	0	0	0
Malaise	1 (20.0)	0	1 (16.7)	0	0
Mouth ulceration	0	0	0	0	1 (25.0)
Nausea	1 (20.0)	0	0	0	0
Paronychia	1 (20.0)	0	1 (16.7)	0	0
Peripheral sensory neuropathy	1 (20.0)	0	0	0	0
Proteinuria	1 (20.0)	1 (25.0)	0	0	0
Prothrombin time prolonged	1 (20.0)	0	0	0	0
Pruritus	0	1 (25.0)	0	0	0
Rash	0	0	1 (16.7)	0	1 (25.0)
SARS-CoV-2 test positive	0	0	1 (16.7)	1 (20.0)	0

Table 1.2.1.3.3: 2 Number (%) of patients with drug-related AEs by dose group – q.d. cohorts (preliminary data) – cont.

Preferred term	60 mg q.d. [N (%)]	120 mg q.d. [N (%)]	180 mg q.d. [N (%)]	240 mg q.d. [N (%)]	300 mg q.d. [N (%)]
Number of patients	5 (100.0)	4 (100.0)	6 (100.0)	5 (100.0)	4 (100.0)*
Total with drug-related AEs	3 (60.0)	3 (75.0)	4 (66.7)	5 (100.0)	1 (25.0)
Sinus bradycardia	0	0	0	0	1 (25.0)
Stomatitis	0	0	0	2 (40.0)	0
Vomiting	1 (20.0)	0	0	0	0
Weight increased	1 (20.0)	0	0	0	0
White blood cells urine positive	0	1 (25.0)	0	0	0

* 1 additional patient in 300 mg dose group not yet captured in clinical database

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

Table 1.2.1.3.4: 1 Frequency [N (%)] of healthy subjects with on-treatment adverse events by treatment, primary system organ class and preferred term in trial 1479-0003

System organ class / Preferred term	R – TF1 fasted [N (%)]	T1 – NF fasted [N (%)]	T2 – NF fed [N (%)]	T3 partial – Rabeprazole alone [N (%)]	T3 partial – NF fasted + rabeprazole [N (%)]	Total
Number of subjects	12 (100.0)	12 (100.0)	9 (100.0)	11 (100.0)	11 (100.0)	13 (100.0)
Total with AEs	4 (33.3)	1 (8.3)	4 (44.4)	2 (18.2)	4 (36.4)	8 (61.5)
Gastrointestinal disorders	0	1 (8.3)	2 (22.2)	0	1 (9.1)	4 (30.8)
Haemorrhoids	0	0	1 (11.1)	0	0	1 (7.7)
Nausea	0	0	1 (11.1)	0	0	1 (7.7)
Diarrhoea	0	0	0	0	1 (9.1)	1 (7.7)
Abdominal pain upper	0	1 (8.3)	0	0	0 (0.0)	1 (7.7)
Infections and infestations	3 (25.0)	1 (8.3)	0	2 (18.2)	0	6 (46.2)
COVID-19	2 (16.7)	1 (8.3)	0	0	0	3 (23.1)
Furuncle	0	0	0	1 (9.1)	0	1 (7.7)
Hordeolum	0	0	0	1 (9.1)	0	1 (7.7)
Pharyngitis	1 (8.3)	0	0	0	0	1 (7.7)
Injury, poisoning and procedural complications	0	0	1 (11.1)	0	1 (9.1)	1 (7.7)
Sunburn	0	0	1 (11.1)	0	0	1 (7.7)
Contusion	0	0	0	0	1 (9.1)	1 (7.7)
Musculoskeletal and connective tissue disorders	0	0	0	0	2 (18.2)	2 (15.4)
Arthralgia	0	0	0	0	1 (9.1)	1 (7.7)
Myalgia	0	0	0	0	1 (9.1)	1 (7.7)
Nervous system disorders	1 (8.3)	0	0	0	0	1 (7.7)
Headache	1 (8.3)	0	0	0	0	1 (7.7)
Psychiatric disorders	0	0	0	0	1 (9.1)	1 (7.7)
Insomnia	0	0	0	0	1 (9.1)	1 (7.7)
Skin and subcutaneous tissue disorders	0	0	1 (11.1)	0	1 (9.1)	2 (15.4)
Rash	0	0	1 (11.1)	0	0	1 (7.7)
Petechiae	0	0	0	0	1 (9.1)	1 (7.7)

In trial 1479-0003, in which oral single doses of 30 mg BI 1810631 were administered to healthy volunteers, there were no SAEs, no AESIs, and no other significant AEs. All AEs were of CTCAE grade 1 or 2 severity, and none of the AEs were assessed as drug-related. Available safety data including AEs, ECGs, VS, and safety laboratory indicate that single doses of 30 mg BI 1810631 were safe and well tolerated in trial 1479-0003.

1.2.2 Carbamazepine

Carbamazepine is an anticonvulsant medication indicated, amongst other indications, for the treatment of epilepsy and neuropathic pain. After oral administration, carbamazepine is slowly and nearly completely absorbed. Pharmacokinetic steady state is reached after 2 to 8 days. Plasma protein binding is between 70 and 80%. Carbamazepine is oxidated, desaminated, hydroxylated and esterified with glucuronic acid in the liver. After a single dose, carbamazepine $t_{1/2}$ is approximately 36 hours. After multiple doses, $t_{1/2}$ is reduced due to enzyme induction by about 50%. [R23-1121]

Therapeutic doses are usually given once (q.d.) or twice (b.i.d.) daily and range between 400 and 1200 mg per day. A maximal daily dose of 1600 mg should usually not be exceeded as higher doses are associated with a higher risk for side effects. It is recommended to take the extended release tablets together with or after a meal. [R23-1121]

FDA recommends carbamazepine as strong index inducer of CYP3A for clinical trials (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; accessed on 23 Jan 2023).

Stockis A et al. reported from a trial in healthy volunteers that a carbamazepine dosing regime of 200 mg/day for 4 days, followed by 400 mg/day for 7 days, followed by 600 mg/day for 21 days resulted in a maximal induction of CYP3A (based on 6β-OH cortisol/cortisol ratio) on Day 18 of this regime [R23-0228].

For a more detailed description of carbamazepine, please refer to the SmPCs for Carbamazepin-neuraxpharm® 200 mg retard / 400 mg retard [R23-1120] and Carbamazepin-neuraxpharm® 300 mg retard / 600 mg retard [R23-1121].

1.2.3 Residual Effect Period

The Residual Effect Period (REP) of single doses of BI 1810631 is conservatively estimated as 14 days. 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 carbamazepine 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]. Thus, concomitant medication with inducers of CYP3A could cause clinically relevant decreases of the plasma exposure of BI 1810631. It is therefore necessary to investigate the effect of an inducer of CYP3A on the pharmacokinetics of BI 1810631 in plasma to inform concomitant treatment recommendations.

Carbamazepine is selected because the FDA recommends carbamazepine as strong index inducer of CYP3A for clinical trials (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers; accessed on 23 Jan 2023).

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		
Mucositis	• Lesions of oral mucosa observed in dog toxicology and general pharmacology studies [c32836122] • Stomatitis / mouth ulceration observed in patients in trial 1479-0001 (Section 1.2.1.3.3)	• 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 • For recommendations for mucositis treatment see Section 4.2.1
QT prolongation	• Preclinical data indicate a low proarrhythmic potential of BI 1810631 • So far no QTc prolongations reported from patient trial 1479-0001	• Subjects with a marked QTc prolongation at baseline are excluded from participation in this trial (see exclusion criterion 20) • Subjects with a history of risk factors for Torsade de Pointes are excluded from participation in this trial (see exclusion criterion 21) • ECGs will be performed as defined in the Flow Chart

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Interstitial lung disease (ILD) and Pneumonitis	• Not observed for BI 1810631 so far, however reported from other tyrosine kinase inhibitors	• 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 • Subjects with pre-existing ILD/pneumonitis or other respiratory disorder are excluded from trial participation (see exclusion criteria 4 and 5)
Hair discoloration	• Yellow hair discoloration with indication for reversibility in rats and dogs [c32836122] • So far no hair discoloration reported from patients after multiple-dose treatment up to 150 mg b.i.d. / 300 mg q.d. BI 1810631 over at least 21 days (see Section 1.2.1.3.3)	• 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
Toxicity to adrenal glands	• Reversible changes to adrenal glands in rats after multiple dosing (increased organ weights, vacuolation, minimal single cell necrosis, hypertrophy of zona fasciculata/ reticularis) [c32836122] • Reversible changes to adrenal glands in dogs after multiple dosing (hyperplasia of zona glomerulosa) [c32836122]	• Safety laboratory (see Section 5.2.3) includes serum electrolytes • Protection of subjects by administration of only two single doses with appropriate wash-out

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Intestinal toxicity	• Reversible intestinal effects in dogs after multiple dosing (fecal alterations, Goblet cell hyperplasia) [c32836122] • Diarrhoea observed in patients in trial 1479-0001 (see Section 1.2.1.3.3)	• 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
Reproductive and developmental toxicity	• Developmental and reproductive toxicity studies have not been conducted. Teratogenicity cannot be excluded. • Through the ejaculate, BI 1810631 could potentially be transferred to a female partner of the male participant, be vaginally absorbed and could thus theoretically harm the fetus	• Only male subjects are included into this trial • Volunteers will, together with their WOCBP (woman of child-bearing potential) partner, use highly effective contraception from first dosing of BI 1810631 until 30 days after the last dosing with BI 1810631 (see also exclusion criterion 28 in Section 3.3.3)
Drug-related AEs observed in patients in trial 1479-0001	• After multiple dosing with BI 1810631, AEs assessed as drug-related were reported (see Section 1.2.1.3.3)	• 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 48 hours • Protection of subjects by administration of only two single doses with appropriate wash-out

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Uncertainties due to the early stage of development	• Comparatively very high plasma exposures were explored in humans (see Section 1.2.1.3.1) and were associated to well tolerable and manageable safety profile so far (see Section 1.2.1.3.3). However, the stage of development is still early and there may still be some yet unknown risks of treatment with BI 1810631	• 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 48 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.
Investigational Medicinal Product: Carbamazepine		
Skin reactions	• Life-threatening skin reactions (e.g., Stephens-Johnson syndrome, Toxic Epidermal Necrolysis) are very rare side effects of carbamazepine. The incidence of life-threatening skin reactions is increased in subjects of han-Chinese or Thai ancestry [R23-1121]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Skin examinations at pre-defined time points (see Flow Chart and Section 5.2.5.2) • During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • Exclusion of subjects of Asian ancestry (see exclusion criterion 25) • Withdrawal of subjects who experience clinical signs of a drug-induced Stevens-Johnson syndrome or Toxic Epidermal Necrolysis (see Section 3.3.4.1 criterion 8)

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Disorders of the haematopoietic system	• During treatment with carbamazepine, several disorders of the haematopoietic systems are observed, such as anemia, leukopenia or thrombocytopenia.	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Exclusion of subjects with relevant deviations in the safety laboratory at screening (see Section 3.3.3, exclusion criterion 3) • Exclusion of subjects with haemoglobin, leukocytes, or platelets below lower level of normal at screening (Section 3.3.3, exclusion criterion 29) • Withdrawal of subjects who, during carbamazepine treatment, develop a relevant disorder of the haematopoietic system (see Section 3.3.4.1, criterion 7) • Frequent safety laboratory during carbamazepine dosing phase (see Flow Chart)
Hypersensitivity reactions	• Various hypersensitivity reactions are reported during therapy with carbamazepine	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • Exclusion of subjects with relevant allergy or hypersensitivity including allergy to the trial medication and including allergy to drugs structurally related to carbamazepine (see Section 3.3.3 exclusion criterion 11)

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Hepatic side effects	• Rarely / very rarely, several hepatic side effects, e.g. hepatitis, can occur [R23-1121]	• Frequent safety laboratory during carbamazepine dosing phase (see Flow Chart) • Withdrawal of subjects with ALT/ AST increase ≥3x ULN during carbamazepine dosings from treatment (see Section 3.3.4.1, criterion 6)
Hyponatremia	• Carbamazepine frequently causes hyponatremia [R23-1121]	• Frequent safety laboratory during carbamazepine dosing phase (see Flow Chart) • Withdrawal in case of CTCAE grade 3 hyponatremia (see Section 3.3.4.1 criterion 9)
Suicidality	• Treatment with anticonvulsant medication has been associated with suicidal ideation and suicidal behaviour [R23-1121]	• Suicidality questionnaire implemented at screening and during the study • During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • Exclusion criterion (Section 3.3, criteria 26 and 27) and withdrawal criterion (Section 3.3.4.1, criterion 10) defined
Phototoxicity	• Photosensitivity is a very rare side effect of carbamazepine [R23-1121]	• Direct exposure to the sun or exposure to solarium radiation should be avoided starting from first carbamazepine dosing and until the end-of-trial examination (see Section 4.2.2.2)

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Risk of subjects falling	• Treatment with carbamazepine can cause ataxia, dizziness, somnolence, hypotension, confusion, and sedation. This could cause subjects to fall. [R23-1121]	• During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • Subjects who experience adverse events like dizziness or ataxia are allowed to use the lift instead of stairs during the in-house period of Visit 3 • Neurological examination at pre-defined time points (see Section 5.2.5.1 and Flow Chart)
Cardial rhythm disorders	• Carbamazepine can cause cardial conduction and rhythm disorders [R23-1121]	• Subjects with AV block, QTc prolongation or other relevant ECG finding are excluded from trial participation (see Section 3.3.3 criterion 20) • During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • ECGs will be done during the study as per Flow Chart

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Other side effects of carbamazepine	• See [R23-1121]	• Stringent in- and exclusion and individual withdrawal criteria (see Sections 3.3.2, 3.3.3 and 3.3.4.1) • During the entire phase of carbamazepine dosings, subjects are in-house at the trial site under close medical observation (see Flow Chart) • Neurological examination at pre-defined time points (see Section 5.2.5.1 and Flow Chart) • Frequent safety laboratory during carbamazepine dosing phase (see Flow Chart) • AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously
Trial procedures		
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 (see Section 3.3.3, criterion 11

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL; see Appendix 10.2 for exact blood volume). 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. Preclinically identified toxicities are addressed by appropriate mitigation (see Section 1.4.2). 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 carbamazepine) planned for the current trial. In particular, BI 1810631 has been given at multiple doses of up to 300 mg q.d. and of up to 150 mg b.i.d. over at least 21 days to patients in first-in-man trial 1479-0001, and in that study, BI 1810631 showed so far good safety and tolerability. The observed plasma exposures of BI 1810631 in trial 1479-0001 provide a large safety window for the expected exposures in the current trial.

The current study is necessary to support the development of BI 1810631: As BI 1810631 is a substrate for CYP3A, a DDI study with a CYP3A inducer is required to inform management of concomitant medications in the BI 1810631 label and for future clinical trials.

Carbamazepine is a recommended index inducer of CYP3A that has successfully been used in previous DDI studies in healthy volunteers (e.g., [R23-0228]). Relevant risks of carbamazepine are addressed by appropriate safety measures (see Section 1.4.2).

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 objectives

The main objective of this trial is to investigate the effect of multiple oral doses of the strong CYP3A inducer carbamazepine on the pharmacokinetics of a single dose of BI 1810631 in plasma.

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]

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 R: One oral single dose of 60 mg BI 1810631 administered as film-coated tablet alone
- Treatment T: One oral single dose of 60 mg BI 1810631 administered as film-coated tablet together with multiple oral doses of carbamazepine (doses titrated from 200 mg q.d. over 400 mg q.d. to 600 mg q.d.)

BI 1810631 is administered in the fasted state, and carbamazepine is administered after a dinner. 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.

Visit 3 follows immediately after Visit 2, i.e. Day 8 is the last day of Visit 2, and Day 8 of Visit 2 is the same day as Day -19 of Visit 3.

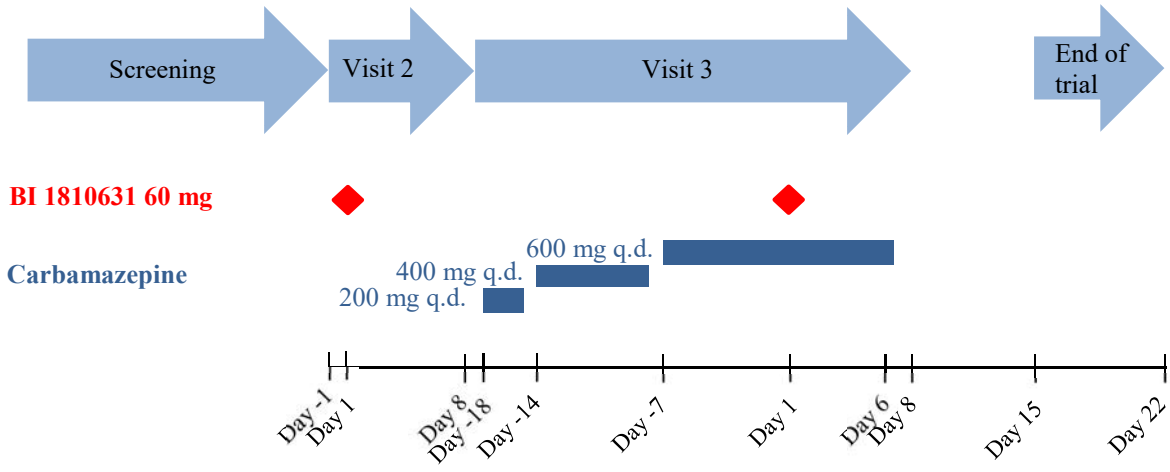

Figure 3.1: 1 Trial Design

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 potentially long-lasting CYP3A induction mediated by carbamazepine, a fixed-sequence design was selected, in which carbamazepine is administered in the second trial period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects since non-specific time-effects are unlikely due to the short trial duration.

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma and urine concentrations of the analyte, which should not be affected by knowledge of treatment administered.

Dosing duration of carbamazepine is expected to be long enough to reliably achieve maximal CYP3A induction. However, this expectation is based on one publication only [R23-0228]; therefore two biomarkers (4β-OH cholesterol in plasma and 6β-OH cortisol / cortisol ratio in urine) are sampled frequently during carbamazepine dosing to investigate the time course of induction.

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 a) no data on reproductive toxicology are available at this time for BI 1810631 and b) because of the embryotoxicity of carbamazepine [R23-1121].

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 55 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, the neurological examination, or the skin inspection) 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 within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients and including allergy to drugs structurally related to carbamazepine, such as tricyclic antidepressants)
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 or within five half-lives, whichever is longer of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (unless the subject quit smoking for at least 3 months prior to first planned administration of trial medication)
15. Alcohol abuse (consumption of more than 24 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial

18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms), atrioventricular block, or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. 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
23. History of bone marrow depression, haematologic disease, history of medication-induced haematologic reactions, or history of hepatic porphyria
24. Hyponatremia, i.e. serum sodium below lower limit of normal at screening
25. Known Asian ancestry
26. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
27. Any suicidal ideation of type 2 to 5 on the C-SSRS in the past 12 months (i.e. active suicidal thought without method, intent or plan; active suicidal thought with method but without intent or plan; active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan)
28. 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
29. White blood cell count, platelets, or blood haemoglobin below lower limit of normal (LLN) at screening

30. ALT and/or AST exceeding 10% above ULN, confirmed by a repeat test

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 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)
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
6. The subject, during treatment with carbamazepine, has an elevation of AST and/or ALT ≥3-fold ULN
7. The subject, during treatment with carbamazepine, experiences petechial or purpura bleedings, a reduction of erythrocytes in blood below 4 million/mm^3, a reduction of blood haematocrit below 32%, a reduction of blood haemoglobin below 11 g/dL, a reduction of

leukocytes below 2,000/mm^3, a reduction of neutrophil granulocytes below 1,000/mm^3, a reduction of platelets below 100,000/mm^3, or any symptomatic disorder of haematopoiesis

8. The subject, during treatment with carbamazepine, experiences signs of a drug-induced Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis (e.g., a progressive rash)
9. Hyponatremia of CTCAE grade ≥3
10. The subject exhibits serious suicidality, in the clinical judgment of the investigator or according to the following criteria:
    - Any suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
    - Any suicidal ideation of type 2 to 5 in the C-SSRS (i.e. active suicidal thought without method, intent or plan; active suicidal thought with method but without intent or plan; active suicidal thought with method and intent but without specific plan; or active suicidal thought with method, intent and plan)

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 overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI 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 or grade 3 severity (except* for benign carbamazepine-induced grade 2 side effects as follows: leukopenia; hyponatremia; neurological adverse effects such as dizziness, ataxia or headache; eye accommodation disorders; gastrointestinal disorders; and fatigue), or if at least one drug-related serious adverse event is reported

* Given the safety profile of carbamazepine, it is necessary to except certain carbamazepine-induced side effects of grade 2 severity from discontinuation criterion 5, that are acceptable as long as subjects are in-house at the study site under close medical observation, from discontinuation criterion 5; otherwise the successful conduct of the study would be jeopardized.

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

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 objective 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 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. 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:	60 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	Single dose in treatment R (Visit 2) and T (Visit 3)

Test product 2:

Name:	Carbamazepin-neuraxpharm® 400 mg retard
Substance:	Carbamazepine
Pharmaceutical formulation:	Extended release tablet
Source: Holder of marketing authorisation:	[redacted]
Unit strength:	400 mg
Posology:	Visit 3 Days -18 to -15: 200 mg (1/2 tablet) q.d., Days -14 to -8: 400 mg (1 tablet) q.d.
Mode of administration:	Oral
Duration of use:	Q.d. for 11 consecutive days in treatment T (Visit 3)

Test product 3:

Name:	Carbamazepin-neuraxpharm® 600 mg retard
Substance:	Carbamazepine
Pharmaceutical formulation:	Extended release tablet
Source: Holder of marketing authorisation:	[redacted]
Unit strength:	600 mg
Posology:	Visit 3 Days -7 to +6: 600 mg (1 tablet) q.d.
Mode of administration:	Oral
Duration of use:	Q.d. for 13 consecutive days in treatment T (Visit 3)

Note: At the time of protocol finalization, carbamazepine 200 mg retard tablets are not available on the German drug market. Therefore, a strength of 400 mg (1/2 tablet per dosing) is used for the 200 mg dose on days -18 to -15 of Visit 3.

4.1.2 Selection of doses in the trial

The doses of carbamazepine selected for this trial reflect standard clinical doses and are considered sufficient to yield significant CYP3A induction. The titration scheme has been used successfully in a previous study [R23-0228], with the modification that in the current study carbamazepine administration is q.d. instead of b.i.d. This is because a) the tolerability of carbamazepine is expected to be improved if dosed only in the evening and b) because a once-daily dosing regimen may facilitate, in future studies, that subjects are ambulatory and not in-house during large phases of the trial. This would decrease the burden to the subjects in future trials.

The dose of BI 1810631 selected for this trial, a dose of 60 mg BI 1810631, is expected to result in plasma concentrations that are in the range of concentrations that were explored so far in trial 1479-0001 and that were associated with good safety and tolerability (see Section 1.2.1.3). Moreover it is expected that the results of the study, by using a single dose of 60 mg BI 1810631, are meaningful for concomitant treatment recommendations in future trials and the label.

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 the principle “first come first serve” 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. For discussion of trial-associated risks and safety measures, see Section 1.4).

4.1.4 Drug assignment and administration of doses for each subject

This is a fixed-sequence crossover trial. All subjects will receive the 2 treatments in fixed order (R-T). The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	BI 1810631	Film-coated tablet	60 mg	1 tablet as single dose on study day 1 of period 1	60 mg
T (Test)	BI 1810631	Film-coated tablet	60 mg	1 tablet as single dose on study day 1 of period 2	60 mg
	Carbamazepine	Extended-release tablet	400 mg/ 600 mg	Period 2: • Days -18 to -15: 200 mg q.d.[a] • Days -14 to -8: 400 mg q.d.[b] • Days -7 to +6: 600 mg q.d.[c]	11,400 mg

[a] ½ tablet Carbamazepin-neuraxpharm® 400 mg retard per day
[b] 1 tablet Carbamazepin-neuraxpharm® 400 mg retard per day
[c] 1 tablet Carbamazepin-neuraxpharm® 600 mg retard per day

Administration of BI 1810631 will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

Administration of carbamazepine will be performed after a dinner. It is acceptable if the dinner is only partly consumed.

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 or sitting 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.

Subjects will be kept under close medical surveillance:

- At Visit 2: until 48 h after administration of BI 1810631
- At Visit 3: during the entire phase of carbamazepine dosings, i.e. from the evening of Day 8 of Visit 2 to the morning of Day 8 of Visit 3

During the first 4 h after administration of BI 1810631, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For measurement of vital signs and ECGs a resting time of at least 5 minutes in the supine position is permitted.

Day 8 of Visit 2 is the same day as Day -19 of Visit 3.

The administrations of BI 1810631 will be separated by a wash-out phase of 26 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).
The label will be prepared according to regulation (EU) No 536/2014, Annex 6, omitting certain particulars with the following justification:
The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.
The visit number is not relevant for the label because the product will remain at the clinical site.
The investigator name was omitted from the label because it is included on the Trial Identification Card (TIC), which will be issued to each trial participant.
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 including the name of the investigator are provided in the subject information form. The EU CT number, the Sponsor study number, and the trial site study number are indicated on the title page of this protocol as well as on the subject information and informed consent forms.

Carbamazepine will be obtained by the trial site from a public pharmacy. The drug will be dispensed out of the otherwise 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 (BI 1810631) when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated clinical trial protocol

Carbamazepine can be obtained by the trial site at any time.

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.

In case of the specific event of drug-related lesions of the oral mucosa, supportive treatment and symptom control measures are recommended. These may include atraumatic cleansing and rinsing with non-alcoholic solutions such as normal saline, diluted salt and baking soda solution (e.g. one-half teaspoonful of salt and one teaspoon of baking soda in one quart of water every four hours); avoidance of agents containing iodine, thyme derivatives and prolonged use of hydrogen peroxide; dietary manoeuvres such as promotion of soft, non-irritating foods like ice-cream, mashed/cooked vegetables, potatoes and avoidance of spicy, acidic or irritating foods such as peppers, curries, chillies, nuts, and alcohol. If the subject is unable to swallow food or liquids, parenteral fluid and/or nutritional support may be needed. Examples of some of the agents suggested in Table 4.2.1: 1 include: topical analgesics – viscous lidocaine 2%; mucosal coating agents – topical kaolin/pectin; oral antacids, maltodextrin, sucralfate; topical antifungals – nystatin suspension. (Adapted from [P11-09424]).

Table 4.2.1: 1 Grade-specific treatment recommendations of study-drug related lesions of the oral mucosa

Severity (CTCAE grading)	**Description**	**Treatment recommendations**
Mild (Grade 1)	Minimal symptoms; normal diet	Oral rinses with agents such as non-alcoholic mouth wash, normal saline, diluted salt and baking soda solution
Moderate (Grade 2)	Symptomatic, but can eat and swallow modified diet	Addition of topical analgesic mouth treatments, topical corticosteroids, antiviral therapy if herpetic infection confirmed, antifungal therapy preferably topical on a case by case basis.
Severe (Grade 3)	Symptomatic and unable to adequately aliment or hydrate orally	Same as for Grade 2; institute additional therapy (topical or systemic) as clinically indicated
Life-threatening (Grade 4)	Symptoms associated with life-threatening consequences	Same as for Grade 2; institute additional symptomatic therapy (topical or systemic) as clinically indicated

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.

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. On Day 1 of both periods, only meals as described in the Flow Chart will be served. On the other days with in-house stays, food will be served as per the CRO's SOPs. Of note, a dinner will be served before all carbamazepine administrations as indicated by the Flow Chart.

No food is allowed for at least 4 h after BI 1810631 intake.

From 1 h before BI 1810631 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 post BI 1810631, total fluid intake is restricted to 3000 mL.

Grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of BI 1810631 at Visit 2 until after the last PK sample of Visit 3 is collected.

Alcoholic beverages are not permitted from 3 days before the first administration of BI 1810631 at Visit 2 until after the last PK sample of Visit 3 is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before until 24 h after each administration of BI 1810631.

Smoking is not allowed during the trial.

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 starting from the first carbamazepine dosing until the end-of-trial examination.

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.

[redacted]

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 including a neurological examination and a skin inspection. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including a neurological examination and a skin inspection and a determination of body weight.

Demographics information includes trial participant's age on the day of informed consent, subject's sex at birth, and ethnicity and race in order to sufficiently characterize the trial population and to support possible subgroup analyses if needed.

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 10 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
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	Reticulocytes, absol.	X	X	X
	Reticulocytes/Erythrocyte	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	--
	Prothrombin time (Quick)	X	X	--
	Prothrombin time – INR (International Normalization Ratio)	X	X	--
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	X	--
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	--
	C-Reactive Protein (Quant)	X	X	--
	Iron	X	X	X
	Urea	X	X	X
	Uric Acid	X	--	--
	Cholesterol, total	X	--	--
	Triglyceride	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 RBC/Erythrocytes (qual)	X	X	--
	Urine WBC/Leucocytes (qual)	X	X	--
	Urine pH	X	X	--
Urine sediment [1]	Only positive findings will be reported			

[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
For time points of safety laboratories A, B, and C, 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. The exclusionary laboratory tests will be performed according Flow Chart.

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)
SARS-CoV-2 infection test via nasal/oral swab	SARS-CoV-2 PCR test

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. Alcotest® 6820, [redacted] will be performed prior to 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 SureStepTM Multi-Drug Test [redacted] or comparable test systems. The SARS-CoV-2 PCR test will be performed at the safety laboratory or at the trial site.

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 (CardioSoft EKG System, [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

5.2.5.1 Neurological examinations

At the time points specified in the Flow Chart, a physical neurological examination will be performed.

The neurological examination will include the following assessments:

- General level of arousal
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Reflexes
- Assessment of muscle strength
- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

Documentation, assessment, and reporting

Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator, or sub-investigator. Clinically relevant findings of the neurological examination during the trial will be reported as adverse events (AEs). Case narratives may be written if necessary. Clinically relevant findings of the

neurological examination at screening fulfil exclusion criterion 1 (see Section 3.3.3) and should lead to exclusion of the subject from trial participation.

5.2.5.2 Skin inspection

At the time points indicated by the Flow Chart, a visual inspection of the skin (subject should be in underwear) will occur to identify carbamazepine-induced skin reactions. See subject withdrawal criterion 8 in Section 3.3.4.1.

Documentation, assessment, and reporting

Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator, or sub-investigator. Clinically relevant findings of the skin inspection during the trial will be reported as adverse events (AEs). Case narratives may be written if necessary. Clinically relevant findings of the skin inspection at screening fulfil exclusion criterion 1 (see Section 3.3.3) and should lead to exclusion of the subject from trial participation.

5.2.5.3 Suicidality assessment

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the ‘screening / baseline’ version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. The life time history of suicidal ideation and behaviour will also be recorded.

For the exclusion criteria related to the C-SSRS ‘screening / baseline’ version result, see Section 3.3.3.

After the baseline visit the assessment ‘since last visit’ will be performed at the time points indicated in the Flow Chart (‘since last visit’ version).

For the withdrawal criterion related to the C-SSRS ‘since last visit’, see Section 3.3.4.1.

See Section 10.1 for the original English C-SSRS. For this trial, the paper version of the respective German translation will be used.

Positive reports are generated for any of the following findings:

Suicidal ideation

- Active suicidal ideation with method and intent but no plan (type 4)
- Active suicidal ideation with method, intent, and plan (type 5)

Suicidal behaviour

- Completed suicide
- Suicide attempt
- Interrupted attempt
- Aborted attempt
- Preparatory actions toward imminent suicidal behaviours

Negative reports of suicidal ideation are defined as reports where there are no indications of the above, i.e. suicidal ideation of type 1-3.

The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of the trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as SAEs by the investigator.

For each negative report (suicidal ideation type 1, 2, or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly. Note that BI maintains a list of AEs which are defined as "always serious" – this list includes suicidal behaviour and suicidal ideation. Consequently, if an AE relating to suicidal ideation or behaviour is reported, it will be required to be reported as SAE.

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 Section 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:
  - 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
  - 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.

- Haematologic toxicities (grades refer to CTCAE grading):
  - Grade 5
  - Grade 4 except for lymphopenia (including, but not limited to Grade 4 anaemia, Grade 4 thrombocytopenia and Grade 4 neutropenia)
  - Anaemia of any grade requiring blood transfusion
  - Febrile neutropenia
  - Grade 3 neutropenia with documented infection and/or lasting >3 days
  - Neutropenia of any grade requiring treatment with growth factors
  - Grade 3 thrombocytopenia
  - Thrombocytopenia of any grade requiring platelet transfusion
- Any ≥Grade 3 non-haematologic toxicity with the following exceptions (grades refer to CTCAE grading):
  - Grade 3 vomiting/nausea or diarrhea which persists for less than 48 hours after start of adequate treatments
  - Grade 3 fever
  - Grade 3 fatigue that persists <7 days
  - Grade 3 rash that resolves to ≤Grade 1 within 2 weeks
  - Any Grade 3 laboratory abnormality which is not considered clinically relevant by the investigator, resolves spontaneously or responds to conventional medical intervention

- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions

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.

For reporting of safety information to the Agency by the sponsor please refer to section 8.4.

5.2.6.2.3 Pregnancy

Potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner, if applicable. The investigator must report drug 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.

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), if applicable.

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies 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

BI 1810631 in plasma

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, barcode, subject number, visit, planned sampling time, and analyte 'BI 1810631'.

Carbamazepine in plasma

For quantification of carbamazepine 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 60 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, barcode, subject number, visit, planned sampling time, and analyte 'carbamazepine'.

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) or to address Health Authority questions regarding the results/methodology. 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.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

5.4 ASSESSMENT OF BIOMARKERS

5.4.1 Drug-Drug Interaction Biomarkers

5.4.1.1 Methods of sample collection

For the assessment of drug-drug interaction biomarkers, blood and urine samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.4.1.1.1 4β-OH cholesterol in plasma

For quantification of 4β-OH cholesterol 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 60 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 -70°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 -70°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, planned sampling time, and analyte ‘4β-OH cholesterol’.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. 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.

5.4.1.1.2 6β-OH cortisol and cortisol in urine

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders before the start of the sampling interval (urine to be discarded) and at the end of each sampling interval (urine to be collected).

The urine weight for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e. 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurements. If more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single polyethylene (PE)/ polypropylene (PP) or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device made of PE, PP, Teflon, or glass).

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

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -20°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After analysis, the urine samples may be used for further methodological investigations (e.g. for stability testing, assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) 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 has been archived.

5.4.2 Pharmacodynamic biomarkers

Not applicable.

5.4.3 Pharmacogenomic biomarkers

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

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 and DDI biomarker 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 orally administered drugs, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and measurements outlined in Section 5.4 are of exploratory nature only.

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' BI 1810631 administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration.

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 not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for neurological examinations and skin inspections will be ± 4 h.

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 and urine collection intervals, 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 (including for DDI biomarkers).

For activities in the mornings of Days 4, 6, and 8 of period 1, the acceptable deviation from the scheduled time will be ± 120 min.

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.

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods (Period 1: Days -1 to 8; Period 2: Days -19 to 8). Day 8 of Period 1 is the same day as Day -19 of Period 2.

On Day -1 of the first treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 48 h following administration of BI 1810631. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. This is followed by several ambulatory visits (see Flow Chart).

On Day 8 of the first treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance until at least 36 hours following the last carbamazepine dosing in the second treatment period (i.e. planned until the morning of Day 8 of the second treatment period). The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

For details on time points and procedures for collection of plasma and urine samples for PK and DDI biomarker 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 oral dose (R) or together with multiple dose of carbamazepine (T) 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.
- Biomarker parameter analysis set (BMS): This set includes all subjects in the treated set (TS) who provide at least one evaluable measure of at least one of the exploratory biomarkers without important protocol deviations (IPD) relevant to the evaluation of biomarkers (as specified in the subsection ‘Biomarkers’). Descriptive analysis of the biomarkers will be based on the BMS.

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
- 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).

7.2.1.3 Biomarkers

Exploratory biomarkers measured are outlined in Section 2.2.2.3.

Biomarker data and parameters of a subject will be included in the statistical biomarker analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of biomarkers (to be decided no later than in the Report Planning Meeting) or due to non-evaluability (as revealed during data analysis). Important protocol deviations may be similar to those listed for pharmacokinetics in Section 7.2.1.2.

Exclusion of a subject's data will be documented in the CTR. Biomarker data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

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: subjects and treatment. The effect 'subjects' will be considered as random, whereas the other effects will be considered as fixed. The model is described by the following equation:

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

ykm = logarithm of response measured on subject m in receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 16

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

e_{km} = the random error associated with the m^{th} subject 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 'subjects' 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.

[redacted]

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.

Results regarding the C-SSRS will only be listed.

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 in the trial 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.

The observed intra-individual coefficient of variation (gCV) for BI 1810631 in the previous trial 1479-0003 was roughly 31% for C_{max} and 9% for AUC for NF fed vs NF fasted, and 30.5% for C_{max} and 14.2% for AUC for NF fasted + rabeprazole vs NF fasted.

For various assumptions around the gCV of [redacted], 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 [%]
[redacted]				

*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 regulation 536/2014, 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. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. 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.

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.

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 contract or the local requirements valid at the time of the end of the trial (whatever is longer).

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 including Clinical Trial Regulation Art. 42.

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.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant'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.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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 first act of recruitment represents the start of the trial and is defined as the date when the first trial participant (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 [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 Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication BI 1810631 will be provided by the [redacted] The trial medication carbamazepine will be obtained by the trial site from a [redacted]

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]

Analyses of carbamazepine concentrations in plasma will be performed at [redacted]

Analyses of 4β-OH cholesterol concentrations in plasma will be performed at [redacted]

Analyses of 6β-OH cortisol and of cortisol concentrations in urine 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 Porta C, Osanto S, Ravaud A, Climent MA, Vaishampayan U, White DA, Creel P, Dickow B, Fischer P, Gornell SS, Meloni F, Motzer RJ. Management of adverse events associated with the use of everolimus in patients with advanced renal cell carcinoma. Eur J Cancer 2011; 47; 1287-1298.

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.

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.

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

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.

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

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.

R23-0228 Stockis A Chanteux H Rosa M Rolan P. Brivaracetam and carbamazepine interaction in healthy subjects and in vitro. Epilepsy Res; 113, p. 19-27; 2015.

R23-1120 Carbamazepin-neuraxpharm ® 200 mg retard / 400 mg retard. (Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SmPC). https://static.neuraxpharm.com/wp-content/uploads/sites/6/2021/05/06134749/fach info-carbamazepin-neuraxpharm-200-400-mg-retard-12-2021.pdf. 12/2021

R23-1121 Carbamazepin-neuraxpharm ® 300 mg retard / 600 mg retard. (Fachinformation (Zusammenfassung der Merkmale des Arzneimittels/SmPC). https://s3.eu-central-1.amazonaws.com/prod-cerebro-ifap/media_all/113537.pdf 12/2021

9.2 UNPUBLISHED REFERENCES

c32836122 [redacted]. Investigator's Brochure BI 1810631 1479-P01. Current version.

10. APPENDICES

10.1 COLUMBIA-SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact [redacted] *; inquiries and training requirements contact* [redacted]

C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past 12 Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***) Past 12 Months - ***Most Severe Ideation:*** ____ (***Type # (1-5)***) ____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 1 of 2

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past n.a. Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

 C-SSRS—Baseline/Screening (Version 1/14/09) Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by* [redacted] *in M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103-130, 2003.)*

For reprints of the C-SSRS contact [redacted] *inquiries and training requirements contact* [redacted]

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

Version 1/14.09

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts ____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____

10.2 BLOOD SAMPLING OVERVIEW

Table 10.2: 1 Blood Sampling Overview

Trial Period	Day	Number of blood samplings	Amount of blood (mL)
Safety blood samplings			
Screening	Day -21 to -1	1	14.4
Period 1	Day 1	1	11.8
	Day 2	1	11.8
	Day 8	1	11.8
Period 2	Day -15	1	7.6
	Day -12	1	11.8
	Day -9	1	7.6
	Day -6	1	11.8
	Day -3	1	7.6
	Day 1	1	11.8
	Day 2	1	11.8
	Day 5	1	7.6
End of Trial	Day 15 to 22	1	11.8
			Total number of safety blood samplings: 13 Total amount of blood for safety evaluation: 139.2 mL
PK BI 1810631 blood samplings			
Period 1	Day 1	11	29.7
	Day 2	2	5.4
	Day 3	1	2.7
	Day 4	1	2.7
	Day 6	1	2.7
	Day 8	1	2.7
Period 2	Day 1	11	29.7
	Day 2	2	5.4
	Day 3	1	2.7
	Day 4	1	2.7
	Day 6	1	2.7
	Day 8	1	2.7
			Total number of PK BI 1810631 blood samplings: 34 Total amount of blood for PK BI 1810631 blood samplings: 91.8 mL
PK carbamazepine blood samplings			
Period 2	Day -18	1	2.7
	Day -12	1	2.7
	Day -7	1	2.7
	Day -5	1	2.7
	Day -3	1	2.7
	Day -1	1	2.7
	Day 2	1	2.7
	Day 4	1	2.7
	Day 7	1	2.7

Table 10.2: 1 Blood Sampling Overview (cont)

Trial Period	Day	Number of blood samplings	Amount of blood (mL)
			Total number of PK carbamazepine blood samplings: 9 Total amount of blood for PK carbamazepine blood samplings: 24.3 mL
4β-OH cholesterol blood samplings			
Period 2	Day -18	1	2.7
	Day -12	1	2.7
	Day -7	1	2.7
	Day -5	1	2.7
	Day -3	1	2.7
	Day -1	1	2.7
	Day 2	1	2.7
	Day 4	1	2.7
	Day 7	1	2.7
			Total number of 4β-OH cholesterol blood samplings: 9 Total amount of blood for 4β-OH cholesterol blood samplings: 24.3 mL
			TOTAL BLOOD WITHDRAWN IN THE TRIAL: 279.6 mL

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		29 Jun 2023
EUCT No.		2022-503046-50-00
BI Trial number		1479-0011 (CRS trial number: 140/22)
BI Investigational Medicinal Product(s)		BI 1810631
Title of protocol		The effect of multiple doses of carbamazepine 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		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		3.3.3
Description of change		Further specification of exclusion criteria #13
Rationale for change		To exclude intake of investigational drug in another trial within 60 days or within five half-lives, whichever is longer. Request from competent authorities.
Section to be changed		5.2.6.2.2 and 8.4
Description of change		Addition of obligation of the sponsor to report safety information to the agency.
Rationale for change		Request from competent authorities

11.2 GLOBAL AMENDMENT 2

Date of amendment		12 Sep 2023
EUCT No.		2022-503046-50-00
BI Trial number		1479-0011 (CRS trial number: 140/22)
BI Investigational Medicinal Product(s)		BI 1810631
Title of protocol		The effect of multiple doses of carbamazepine 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		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		Title Page
Description of change		Clinical Trial Leader changed
Rationale for change		Change in Clinical Trial Leader
Section to be changed		4.1.4
Description of change		Clarification regarding ECG examination during the 4 h period after dosing
Rationale for change		Correction / Clarification
Section to be changed		5.2.3
Description of change		Changes due to inconsistence between Flow Chart and Section 5.2.3
Rationale for change		Correction / Clarification
Section to be changed		8.7
Description of change		Changes due to inconsistence between Flow Chart und Section 8.7
Rationale for change		Correction / Clarification

APPROVAL / SIGNATURE PAGE

Document Number: c40561285 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: The effect of multiple doses of carbamazepine 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
Approval-Clinical Program [redacted]	[redacted]	15 Sep 2023 12:14 CEST
Approval		18 Sep 2023 07:40 CEST
Verification-Paper Signature Completion		18 Sep 2023 10:46 CEST
Author-Trial Statistician		18 Sep 2023 14:20 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed