Clinical Trial Protocol

	Document Number: **c38775190-01**
EU CT No. **Universal Trial Number**	2022-503047-17-00 U1111-1291-2883
BI Trial No.	1479-0006
BI Investigational Medicinal Product	BI 1810631
Title	A phase I, open-label trial in two parallel parts to investigate mass balance, metabolism, and basic pharmacokinetics of BI 1810631 (C-14) administered as oral solution (part A) and to investigate absolute bioavailability of BI 1810631 administered as film-coated tablet together with an intravenous microtracer dose of BI 1810631 (C-14) (part B) in healthy male volunteers
Lay Title	A study in healthy men to test how BI 1810631 is taken up and processed by the body
Clinical Phase	I
Clinical Trial Leader	[redacted]
Principal Investigator	
Current Version, Date	Version 1.0, 21 Apr 2023
Original Protocol Date	21 Apr 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	21 Apr 2023
Revision date	Not applicable
BI trial number	1479-0006
Title of trial	A phase I, open-label trial in two parallel parts to investigate mass balance, metabolism, and basic pharmacokinetics of BI 1810631 (C-14) administered as oral solution (part A) and to investigate absolute bioavailability of BI 1810631 administered as film-coated tablet together with an intravenous microtracer dose of BI 1810631 (C-14) (part B) in healthy male volunteers
Principal Investigator	[redacted]
Trial site	
Clinical phase	I
Trial rationale	Part A of this clinical trial investigates the basic pharmacokinetics of BI 1810631 and total [^{14}C]-radioactivity, including mass balance, metabolism, and excretion pathways following an oral dose of BI 1810631 (C-14). Part B of this clinical trial investigates the absolute bioavailability of BI 1810631 after administration of an oral dose of unlabelled BI 1810631 and an intravenous microtracer of BI 1810631 (C-14). The data of this trial are required for an in-depth understanding of the pharmacokinetics of BI 1810631 and for submission to regulatory authorities.
Trial objectives	**Part A** – the main objectives are • To assess the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces after oral single dose administration of BI 1810631 (C-14) (test treatment T1) in healthy male subjects • To assess concentrations of BI 1810631 and [^{14}C]-radioactivity in plasma **Part B** – the main objective is: • To investigate the absolute bioavailability of BI 1810631 administered as film-coated tablet (test treatment T2, not radio-labelled) compared with BI 1810631 (C-14) (reference treatment R) administered as intravenous microtracer

Trial endpoints	**Part A - Primary endpoints:** Primary endpoints will be the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces: • $fe_{urine,0\text{-}tz}$ (fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) • $fe_{faeces,0\text{-}tz}$ (fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) **Part A – Secondary endpoints:** The following secondary endpoints will be evaluated for BI 1810631 and [^{14}C]-radioactivity (assessed by [^{14}C]BI 1810631-EQ) in plasma: • C_{max} (maximum measured concentration of the analyte) • $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point) **Part B - Primary endpoints:** The following primary endpoint will be determined in plasma for [^{14}C]BI 1810631 after intravenous administration and for BI 1810631 after oral administration: • $AUC_{0\text{-}\infty}$ (Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity) **Part B - Secondary endpoints:** The following secondary endpoints will be determined in plasma for [^{14}C]BI 1810631 after intravenous administration and for BI 1810631 after oral administration: • C_{max} • $AUC_{0\text{-}tz}$
Trial design	Non-randomized, open-label, single period design with two parallel parts
Number of subjects **total entered** **on each treatment**	15 Part A (ADME part): 8 Part B (abs. BA part): 7
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.0 to 30.0 kg/m^2 (inclusive)

Test product 1	BI 1810631 (C-14) oral solution
dose	[redacted] BI 1810631 (C-14) • In [redacted] oral solution • Concentration: [redacted] • Containing a radioactive dose of approximately 3.7 MBq
mode of administration	Oral with 240 mL of water [redacted]
Test product 2	BI 1810631 film-coated tablet, strength [redacted]
dose	[redacted]
mode of administration	Oral with 240 mL of water [redacted]
Reference product	BI 1810631 (C-14) [redacted]
dose	[redacted] BI 1810631 (C-14) • In [redacted] • Concentration: [redacted] • Containing a radioactive dose of approximately 0.03 MBq
mode of admin.	Intravenous [redacted] starting at 2:00 h after an orally administered dose of test product 2
Duration of treatment	Part A: • One single oral dose of test product 1 in the morning of Day 1 Part B: • One single oral dose of test product 2 in the morning of Day 1 • One single intravenous [redacted] of reference product [redacted] following the administration of test product 2 in the morning of Day 1
Statistical methods	Part A: Descriptive statistics will be calculated for all endpoints. Part B: Absolute bioavailability (F) will be estimated by the ratios of the geometric means (test treatment 2 [T2] / reference treatment [R]) for the primary endpoints (dose normalized) $AUC_{0-\infty}$. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including the fixed effect for 'treatment' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART PART A (ADME PART)

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [9]	Safety laboratory [15,17]	Blood sampling for PK and total radioactivity [12,14]	Urine sampling [7]	Faeces sampling [8]	Vomit collection (if applicable)	Blood sampling for metabolic profiling [12]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-28 to -2			Screening (SCR)[1]	A						x	x	
2	-2	-48:00	08:00					x					▲
	-1	-18:00	14:00	Admission to site[5]	B[5]		x						|
		-13:00	19:00	[redacted]									|
	1	-2:00	06:00		x[2,13]	x[2]	|	|		x[2]	x[2]	x[2]	|
		0:00	08:00	**Oral solution administration (BI 1810631 (C-14))**			▲	▲	▲				|
		0:30	08:30			x	|	|	|	x			|
		1:00	09:00		x[13]	x	|	|	|	x			|
		1:30	09:30			x	|	|	|				|
		2:00	10:00	240 mL fluid intake		x	|	|	|	x			|
		2:30	10:30			x	|	|	|				|
		3:00	11:00			x	|	|	|				|
		4:00	12:00	240 mL fluid intake, [redacted]	x[13]	x	|	|	|	x	x	x	|
		5:00	13:00			x	|	|	|				|
		6:00	14:00			x	|	|	|				|
		8:00	16:00	[redacted]	x[13]	x	|	|	|	x			|
		10:00	18:00			x	|	|	|				|
		11:00	19:00	[redacted]			|	|	|				|
		12:00	20:00			x	|	|	|	x			|
	2	24:00	08:00		B[13]	x	|	|	▼	x	x	x	|
		36:00	20:00			x	|	|					|
	3	48:00	08:00			x	|	|		x			|
	4	72:00	08:00			x	|	|					|
	5	96:00	08:00			x	|	|		x			|
	6	120:00	08:00		B	x	|	|					|
	7	144:00	08:00				|	|					|
	8	168:00	08:00			x	|	|		x			|
	9	192:00	08:00				|	|					|
	10	216:00	08:00			x	|	|					|
	11	240:00	08:00				|	|					|
	12	264:00	08:00			x	|	|					|
	13	288:00	08:00				|	|					|
	14	312:00	08:00				|	|					|
	15	336:00	08:00	Discharge from site[19,20]		x	▼	▼					|
	20	461:00	13:00	Start home collection[10,11]				▲					|
	21	485:00	13:00	Admission to site[11]			▲	|					|
	22	509:00	13:00	Discharge from site[11,19]			▼	▼					|
	27	629:00	13:00	Start home collection[10,11]				▲					|
	28	653:00	13:00	Admission to site[11]			▲	|					|
	29	677:00	13:00	Discharge from site[11,19]			▼	▼					|
	34	797:00	13:00	Start home collection[10,11]				▲					|
	35	821:00	13:00	Admission to site[11]			▲	|					|
	36	845:00	13:00	Discharge from site[11,19]			▼	▼					|

Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [9]	Safety laboratory [15,17]	Blood sampling for PK and total radioactivity [12,14]	Urine sampling [7]	Faeces sampling [8]	Vomit collection (if applicable)	Blood sampling for metabolic profiling [12]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
	41	965:00	13:00	Start home collection[10,11]				▲					┼
	42	989:00	13:00	Admission to site[11]			▲	┼					┼
	43	1013:00	13:00	Discharge from site[11,19]			▼	▼					▼
3	16 to 43			End of study (EoS) examination[4]	B						x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug and alcohol screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. [redacted]
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. The end of study visit is to be performed within 7 days after last discharge from the study centre, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 43.
5. Including urine/serum drug screening and urine alcohol test. To be taken and evaluated within 26 hours before drug administration. Admission can be done anytime within -26 hours and -10 hours before drug administration.
6. AEs and concomitant therapies will be recorded throughout the trial. During in-house days subjects will be specifically asked for AEs and concomitant therapies twice daily.
7. Urine collection intervals (for PK of BI 1810631, [^{14}C]-radioactivity, and for metabolic profiling): On Day -1 or Day 1 (within 18 hours prior to dosing) a predose (blank) spot sample; on Day 1 prior to start of urine collection voiding of the bladder; 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312, and 312-336 h after administration of BI 1810631 (C-14). Thereafter, if warranted, 24 h collections are to be performed every 7 days on days 21-22, 28-29, 35-36, and 42-43. Urine sampling will be stopped when release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 15). "┼" means end of last collection interval, start of following collection interval. For details on sample usage please refer to Section 5.3.2.1.3
8. Stool collection (for [^{14}C]-radioactivity assessment and metabolic profiling): A blank sample will be collected before drug administration on Day -2, Day -1 or Day 1 (at home or at the site) in specific containers provided by [redacted] Collection of this pre-dose faeces sample will start from approximately planned time -48:00 h. Following drug administration, all stools will be collected quantitatively in portions in the following sampling intervals: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216-240, 240-264, 264-288, 288-312, and 312-336 h after administration of BI 1810631 (C-14). Thereafter, if warranted, 24-h collections are to be performed every 7 days on days 21-22, 28-29, 35-36, and 42-43. Faeces sampling will be stopped when the release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on Day 15). "┼" means end of last collection interval, start of following collection interval. For details on sample usage please refer to Section 5.3.2.1.4.
9. [redacted]
10. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, and 41-42. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
11. The planned times for admission, discharge, start and end of urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time. However, the duration of each once weekly on-site collection interval should be as close to 24 h as possible.
12. Blood volumes: see Appendix 10.1
13. At this time point, a sample for hematocrit measurement is taken.
14. BI 1810631 in plasma and [^{14}C]-radioactivity in whole blood and plasma (see Section 5.3.2.1.1 and Appendix 10.1)
15. Letters A and B describe different sets of safety laboratory examinations (see Table 5.2.3: 1)
16. Time window of ± 1 hour

17. SARS-CoV-2 Polymerase chain reaction (PCR) testing will be done as needed based on the current status of the pandemic.
18. Time window of ± 2 hours
19. After formal assessment and confirmation of the subject's fitness
20. Discharge may be in the time window from planned time until 4 h later

FLOW CHART PART B (ABSOLUTE BIOAVAILABILITY PART)

Visit	Day	Planned time (relative to first drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment [8]	Safety laboratory [7,9]	PK plasma (BI 1810631)	PK plasma ([14C]BI 1810631)	PK plasma ([14C]-radioactivity)	Local tolerability assessment[12]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
1	-28 to -2			Screening (SCR)[1]	A					x	x	
2	-1	-18:00	14:00	Admission to trial site[5]	B[5]							▲
		-13:00	19:00	[redacted]								|
	1	-2:00	06:00			x[2]	x[2]	x[2]		x[2]	x[2]	|
		0:00	08:00	**Oral drug administration (BI 1810631, film-coated tablet)**								|
		0:30	08:30			x						|
		1:00	09:00			x						|
		1:30	09:30			x						|
		[redacted]										|
		2:30	10:30			x	x	x				|
		2:45	10:45				x	x				|
		3:00	11:00			x	x	x				|
		3:30	11:30				x	x				|
		4:00	12:00	240 mL fluid intake, [redacted]		x	x	x	x	x	x	|
		5:00	13:00			x	x	x				|
		6:00	14:00			x	x	x				|
		8:00	16:00	[redacted]		x	x	x				|
		10:00	18:00			x	x	x				|
		11:00	19:00	[redacted]								|
		12:00	20:00			x	x	x	x			|
	2	24:00	08:00		B	x	x	x	x	x	x	|
		36:00	20:00			x	x	x				|
	3	48:00	08:00			x	x	x				|
	4	72:00	08:00			x	x	x				|
	5	96:00	08:00			x	x	x				|
	6	120:00	08:00		B	x	x	x				|
	8	168:00	08:00	Discharge from trial site[11,13]		x	x	x				▼
3	15 to 22			End of study (EoS) examination[4]	B					x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug and alcohol screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to first drug administration.
3. [redacted]
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.

5. Including urine/serum drug screening and urine alcohol test. To be taken and evaluated within 26 hours before drug administration. Admission can be done anytime within -26 hours and -10 hours before first drug administration.
6. AEs and concomitant therapies will be recorded throughout the trial. During in-house days subjects will be specifically asked for AEs and concomitant therapies twice daily.
7. Letters A and B describe different sets of safety laboratory examinations (see Table 5.2.3: 1)
8. [redacted]
9. SARS-CoV-2 PCR testing will be done as needed based on the current status of the pandemic.
10. Time window of ± 2 hours
11. After formal assessment and confirmation of the subject's fitness
12. For details see Section 5.2.5.1
13. Discharge may be in the time window from planned time until 4 h later
14. Time window of ± 1 hour
15. PK sample to be taken before [redacted] exactly on planned time.
16. Immediately before [redacted]

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
$Ae_{urine, t1-t2}$	Amount of analyte that is eliminated in urine from time point t_1 to t_2
$Ae_{urine, 0-tz}$	Amount of analyte that is eliminated in urine from time point 0 to last quantifiable time point
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	The percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte 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	Total clearance of the analyte after intravenous administration
CL/F	Apparent clearance of the analyte after extravascular administration
$CL_{R, t1-t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2
C_{max}	Maximum measured concentration of the analyte
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
EoS	End of Study (synonym for End of Trial)

ErbB	Epidermal growth factor
EU CT number	European Union Clinical Trial number
F	Absolute bioavailability factor
$fe_{urine, t1-t2}$	Fraction excreted in urine as percentage of the administered dose over the time interval from t_1 to t_2
$fe_{urine, 0-tz}$	Fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{faeces, t1-t2}$	Fraction excreted in faeces as percentage of the administered dose over the time interval from t_1 to t_2
$fe_{faeces, 0-tz}$	Fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
HER2	Human epidermal growth factor receptor 2
hADME	Human ADME (absorption, distribution, metabolism, and excretion)
gMean	Geometric mean
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MBq	Megabecquerel
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT_{in}	Mean residence time of the analyte in the body after intravascular administration
MRT_{ex}	Mean residence time of the analyte in the body after extravascular administration
mSv	Millisievert
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
[redacted]	
SOP	Standard operating procedure
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TF1	Trial Formulation 1
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte
t_{max}	Time from dosing to maximum measured concentration of the analyte
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	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of child-bearing potential
YVMA	HER2 mutation with 12 base pair in-frame insertion YVMA (p.A775-G776insYVMA)

1. INTRODUCTION

Part A of this clinical trial investigates the basic pharmacokinetics of BI 1810631 and total [^{14}C]-radioactivity, including mass balance, metabolism, and excretion pathways following an oral dose of BI 1810631 (C-14).

Part B of this clinical trial investigates the absolute bioavailability of BI 1810631 after administration of an oral dose of unlabelled BI 1810631 and an intravenous (i.v.) microtracer of BI 1810631 (C-14).

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

For a comprehensive description of BI 1810631 refer to the IB [c32836122].

1.2.1 Mode of action

BI 1810631 is an EGFR wild type sparing, selective HER2 inhibitor with potent inhibitory activity on [redacted] HER2 mutations including the HER2 YVMA insertion allele. It is intended to treat patients with advanced solid tumors with HER2 aberrations.

1.2.2 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). A short summary of the trials and drug-related adverse events in these trials is provided here. For details on PK, safety, and efficacy refer to the IB [c32836122].

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 [redacted] dosing schemes. PK, safety, and efficacy data are collected. So far, [redacted] patients were treated in the dose escalation part with BI 1810631 either in one of the [redacted] cohorts [redacted] or the [redacted] cohorts [redacted]
Data cut time point for the data described here is 09 Mar 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 [redacted] BI 1810631 in 4 treatment periods in randomized order, separated by wash-out intervals of [redacted] The 4 treatments were:

- R: [redacted] BI 1810631 trial formulation 1 (TF1) under fasted conditions
- T1: [redacted] BI 1810631 new formulation (NF) under fasted conditions
- T2: [redacted] BI 1810631 NF after a high-fat, high-calorie breakfast

- T3: [redacted] BI 1810631 NF after a 5-day pre-treatment with the proton-pump inhibitor rabeprazole.

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

For an overview of available safety and tolerability data of trial 1479-0001 refer to the IB [c32836122]. The following text and tables in this protocol focus on drug-related AEs.

Overall, [redacted] The most common drug-related AEs were [redacted] In total, [redacted]

One [redacted]

Table 1.2.2: 1 Number (%) of patients with drug-related AEs by dose group and preferred term – on-treatment period, b.i.d. cohorts (preliminary data)

Preferred term	[redacted]				
	[N (%)]	[N (%)]	[N (%)]	[N (%)]	[N (%)]
Number of patients	[redacted]				
Total with drug-related AEs	[redacted]				

Table 1.2.2: 2 Number (%) of patients with drug-related AEs by dose group and preferred term – on-treatment period, q.d. cohorts (preliminary data)

Preferred term	[redacted]				
	[N (%)]	[N (%)]	[N (%)]	[N (%)]	[N (%)]
Number of patients	[redacted]				
Total with drug-related AEs					
[redacted]					

Safety and tolerability data of healthy volunteer trial 1479-0003

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

For more details refer to the IB [c32836122].

1.2.3 Residual Effect Period

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

1.3 RATIONALE FOR PERFORMING THE TRIAL

Part A of this clinical trial investigates the basic pharmacokinetics of BI 1810631 and total [^{14}C]-radioactivity, including mass balance, metabolism, and excretion pathways following an oral dose of BI 1810631 (C-14).

Part B of this clinical trial investigates the absolute bioavailability of BI 1810631 after administration of an oral dose of unlabelled BI 1810631 and an intravenous (i.v.) microtracer of BI 1810631 (C-14).

The data of this trial are required for an in-depth understanding of the pharmacokinetics of BI 1810631 and for submission to regulatory authorities.

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 tumors with HER2 aberrations.

1.4.2 Risks

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

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 1810631		
[redacted]	• [redacted] [c32836122] • [redacted]	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only single doses • [redacted]

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
[redacted]		
Interstitial lung disease (ILD) and Pneumonitis	• Not observed for BI 1810631 so far, however reported for other tyrosine kinase inhibitors	• Subjects are protected from this by administration of only single doses • 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)
[redacted]	• [redacted] [c32836122] • [redacted] [c32836122])	• 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 single doses

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
[redacted]	• [redacted] [c32836122] • [redacted] [c32836122]	• Safety laboratory (see Section 5.2.3) [redacted] • Protection of subjects by administration of only single doses
[redacted]	• [redacted] [c32836122] • [redacted] [c32836122])	• AE questioning (see Flow Chart) • Instruction of subjects to report AEs spontaneously • Protection of subjects by administration of only single doses
[redacted]	• [redacted] ([c32836122]). • [redacted]	• [redacted]

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
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 1.2.2)	• 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 14 days (part A) or for at least 7 days (part B) • Protection of subjects by administration of only single doses
Uncertainties due to the early stage of development	[redacted] However, BI 1810631 is currently in early development and there may be 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 14 days (part A) or for at least 7 days (part B) • VS, ECGs, and safety laboratory after dosing (see Flow Chart) • Protection of subjects by administration of only single doses
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.
Trial procedures		
Blood sampling: Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site

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
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.
<u>Other risks</u>		
Radiation burden	• In Part A of this trial a radioactive dose of approximately 3.7 MBq of 14C is administered corresponding, in a worst-case scenario, to approximately [redacted] • In Part B of this trial, a radioactive microtracer dose of approximately 0.03 MBq of 14C is administered, corresponding to [redacted]	• Part A: [redacted] [R18-1836, R18-1905] • Part B: [redacted] [R18-1836, R18-1905]

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 Appendices 10.1 and 10.2). 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 [redacted] 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, data from two clinical trials are available (see Section 1.2.2 and IB [c32836122]) that support the single doses of BI 1810631 planned for the current trial. In particular, BI 1810631 has been given at multiple doses of up to [redacted] and of up to [redacted] to patients in first-in-man trial 1479-0001, and in that study, BI 1810631 was [redacted]

The radiation burden in part A of this trial (hADME part) of approximately [redacted] (worst case) is necessary, as the respective radioactive dose of approximately 3.7 MBq of 14C is required for metabolite identification (see also Section 4.1.2). It is in the range of [redacted]

[redacted] In part B of this trial (absolute BA part), only a radioactive microtracer dose of approximately 0.03 MBq is administered corresponding to a burden of [redacted]

The current study is necessary to support the development of BI 1810631: The trial investigates the basic pharmacokinetics of BI 1810631 including mass balance, metabolism, and excretion pathways, and including investigation of absolute bioavailability. The data of this trial are required for an in-depth understanding of the pharmacokinetics of BI 1810631.

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

Part A – the primary objective is

- To assess the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces after oral single dose administration of BI 1810631 (C-14) (test treatment T1) in healthy male subjects

Part A – the secondary objective is

- To assess concentrations of BI 1810631 and [^{14}C]-radioactivity in plasma

Part B – the primary objective is:

- To investigate the absolute bioavailability of BI 1810631 administered as film-coated tablet (test treatment T2, not radio-labelled) compared with BI 1810631 (C-14) (reference treatment R) administered as intravenous microtracer

2.1.2 Primary endpoints

Part A – Primary endpoints will be the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces:

- $fe_{urine,\ 0\text{-}tz}$ (fraction excreted in urine as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)

- $fe_{faeces,\ 0\text{-}tz}$ (fraction excreted in faeces as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)

Part B – The following primary endpoint will be determined in plasma for [^{14}C]BI 1810631 after intravenous administration and for BI 1810631 after oral administration:

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

2.1.3 Secondary endpoints

Part A – The following secondary endpoints will be evaluated for BI 1810631 and for [^{14}C]-radioactivity (assessed by [^{14}C]BI 1810631-EQ) in plasma:

- C_{max} (maximum measured concentration of the analyte)

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point)

Part B – The following secondary endpoints will be determined in plasma for [^{14}C]BI 1810631 after intravenous administration and for BI 1810631 after oral administration:

- C_{max}
- $AUC_{0\text{-}tz}$

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are the evaluation of additional pharmacokinetic parameters, metabolite profiling and structural identification of metabolites, and the assessment of safety and tolerability. More specifically further objectives are:

Part A:
- Determination of further PK parameters for BI 1810631, as feasible
- Determination of further PK parameters for [^{14}C]-radioactivity in whole blood and plasma, as feasible
- Determination of routes and rates of elimination of BI 1810631 after oral administration
- Determination of the metabolic pattern of BI 1810631 in plasma, urine, and faeces, including structure elucidation of the metabolites (to be reported separately)
- Determination of blood cell/plasma and blood/plasma ratios of [^{14}C]-radioactivity
- Evaluation of safety and tolerability of a single oral dose of [redacted] BI 1810631 (C-14) oral solution

Part B:
- Determination of further PK parameters for BI 1810631, for [^{14}C]BI 1810631, and for [^{14}C]-radioactivity, as feasible
- Evaluation of safety and tolerability of a single oral dose of [redacted] BI 1810631 together with a single intravenous dose of [redacted] BI 1810631 (C-14)

2.2.2 Further endpoints

2.2.2.1 Part A - further pharmacokinetic endpoints of BI 1810631

Further PK endpoints will be calculated as appropriate for BI 1810631 in plasma or urine, and may include, but are not limited to:

- $AUC_{0\text{-}\infty}$ in plasma
- $\%AUC_{tz\text{-}\infty}$ (the percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation) in plasma
- t_{max} (time from dosing to maximum measured concentration of the analyte) in plasma
- λ_z (terminal rate constant) in plasma

- $t_{1/2}$ (terminal half-life of the analyte) in plasma
- AUC_{t1-t2} (area under the concentration-time curve of the analyte over the time interval t_1 to t_2) in plasma
- MRT_{ex} (mean residence time of the analyte in the body after extravascular administration) in plasma
- CL/F (apparent clearance of the analyte after extravascular administration) in plasma
- V_z/F (apparent volume of distribution during the terminal phase after extravascular administration) in plasma
- $Ae_{urine, t1-t2}$ (amount of analyte that is eliminated in urine from time point t_1 to t_2)
- $Ae_{urine, 0-tz}$ (amount of analyte that is eliminated in urine from time point 0 to last quantifiable time point)
- $fe_{urine, t1-t2}$ (fraction excreted in urine as percentage of the administered dose over the time interval from t_1 to t_2)
- $fe_{urine, 0-tz}$
- $CL_{R, t1-t2}$ (renal clearance of the analyte in plasma from the time point t_1 to t_2)

2.2.2.2 Part A - further pharmacokinetic endpoints of [^{14}C]-radioactivity

Further PK endpoints will be calculated as appropriate for [^{14}C]-radioactivity in plasma, whole blood, urine or faeces, and may include, but are not limited to:

- AUC_{0-tz} in whole blood
- C_{max} in whole blood
- $AUC_{0-\infty}$ in plasma and whole blood
- $\%AUC_{tz-\infty}$ in plasma and whole blood
- t_{max} in plasma and whole blood
- λ_z in plasma and whole blood
- $t_{1/2}$ in plasma and whole blood
- AUC_{t1-t2} in plasma and whole blood
- MRT_{ex} in plasma

- $Ae_{urine,\ t1\text{-}t2}$
- $Ae_{urine,\ 0\text{-}tz}$
- $fe_{urine,\ t1\text{-}t2}$
- $Ae_{faeces,\ t1\text{-}t2}$ (amount of analyte that is eliminated in faeces from time point t_1 to t_2)
- $Ae_{faeces,\ 0\text{-}tz}$ (amount of analyte that is eliminated in faeces from time point 0 to last quantifiable time point)
- $fe_{faeces,\ t1\text{-}t2}$ (fraction of administered drug excreted unchanged in faeces from time point t_1 to t_2)

2.2.2.3 Part B - further pharmacokinetic endpoints of BI 1810631

Further PK endpoints will be calculated as appropriate for BI 1810631 in plasma, and may include, but are not limited to:

- $\%AUC_{tz\text{-}\infty}$
- t_{max}
- λ_z
- $t_{1/2}$
- $AUC_{t1\text{-}t2}$
- MRT_{ex}
- CL/F
- V_z/F

2.2.2.4 Part B - further pharmacokinetic endpoints of [^{14}C]BI 1810631 and [^{14}C]-radioactivity

Further PK endpoints will be calculated as appropriate for [^{14}C]BI 1810631 and [^{14}C]-radioactivity in plasma, and may include, but are not limited to:

- $AUC_{0\text{-}\infty}$ for [^{14}C]-radioactivity
- $AUC_{0\text{-}tz}$ for [^{14}C]-radioactivity
- C_{max} for [^{14}C]-radioactivity
- $\%AUC_{tz\text{-}\infty}$

- t_{max}
- λ_z
- $t_{1/2}$
- $AUC_{t1\text{-}t2}$
- MRT_{in} (mean residence time of the analyte in the body after intravascular administration)
- CL (total clearance of the analyte after intravenous administration, only for parent compound [^{14}C]BI 1810631)
- V_z (apparent volume of distribution during the terminal phase after intravascular administration, only for parent compound [^{14}C]BI 1810631)
- V_{ss} (calculated volume of distribution at steady state after intravascular administration, only for parent compound [^{14}C]BI 1810631)

2.2.2.5 Part A: Determination of blood cell/plasma and blood/plasma ratios

The ratio of concentration of [^{14}C]-radioactivity in blood cells and plasma will be calculated at time points with haematocrit (HC) measurement (see Flow Chart) according to the formula:

$$C_{bloodcells}/C_{plasma} = \frac{\frac{C_{blood} - C_{plasma}(1-HC)}{HC}}{C_{plasma}}$$

$C_{bloodcells}$ = concentration of [^{14}C]-radioactivity in blood cells
C_{plasma} = concentration of [^{14}C]-radioactivity in plasma
C_{blood} = concentration of [^{14}C]-radioactivity in whole blood
HC = haematocrit in decimal (e.g. 0.42)

Additionally, the ratio of concentration of [^{14}C]-radioactivity in blood and plasma will be calculated at all time points (indicated in the Flow Chart) when radioactivity is above LLOQ in plasma and blood.

2.2.2.6 Safety and tolerability

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

- Adverse events (including clinically relevant findings from the physical examination and assessment of local tolerability)
- Safety laboratory tests
- 12-lead ECG

- Vital signs (blood pressure, pulse rate)
- Part B only: Local tolerability at the [redacted] site assessed by investigator or designee

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

Part A – ADME part

Part A will be performed as an open-label, single-arm, single-dose trial part in healthy male subjects in order to investigate the basic pharmacokinetics of BI 1810631 and [^{14}C]-radioactivity, including mass balance, excretion pathways, and metabolism following a single oral dose of [redacted]BI 1810631 (C-14) containing a radioactive dose of approximately 3.7 MBq. For details of the drug product refer to Section 4.1.

A total of 8 healthy male subjects is planned to participate in Part A. On Day 1, subjects will receive the [^{14}C]-labelled drug product, and will then stay in the study centre up to the morning of Day 15 for collection of samples of blood, urine, and faeces.

Release criteria (to be applied on data of individual subjects):

- Recovery of >90% of administered radioactivity in urine and faeces combined

  and

- <1% of administered radioactivity has been collected in urine and faeces within two separate, consecutive days or visits (considering a 24-h collection interval)

In case total recovery is ≤90% and <1% of administered radioactivity has been collected in urine and faeces within at least 3 separate, consecutive days or visits (considering a 24-h collection interval), investigator, Clinical Trial Leader and Trial Clinical Pharmacologist may agree to stop collection in the respective subject (considering that total recovery of >90% will not be reached).

In case total recovery of >90% is reached and, during the once-weekly sampling periods, <1% of administered radioactivity has been collected in urine and faeces in one visit, the investigator together with the Clinical Trial Leader and Trial Clinical Pharmacologist may decide to stop further sampling in this subject considering that further sampling would not be expected to contribute to the scientific objective of the study.

Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 21, 28, 35, and 42, if release criteria have not been met before. Within 24 h before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. Otherwise it will be discarded. If a subject is unable to attend one of the once-weekly collection interval visits, they may be allowed to reschedule the visit if needed. Irrespective of whether release criteria have been met or not after collection interval Day 42-43, no further collections are planned.

For determination of whether release criteria have been reached for individual subjects, [^{14}C]-radioactivity will be measured in excreta (urine and faeces). The actual recovery results will be reported as a percentage of the administered dose.

Note, for calculation of release criteria (in subjects who did not meet them up to Day 15), the fraction of administered [^{14}C]-dose will be rather underestimated as it will be based on the available samples, only. For the final analysis, the total excreted [^{14}C]-radioactivity will be

derived including an interpolation method to account for the time periods without samples taken, if applicable (see Section 7.2.2).

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.

Part B – Absolute BA part

Part B will be performed as an open-label, single-arm, single-period trial part in healthy male subjects in order to compare the test treatment (T2) to the reference treatment (R). A total of 7 healthy male subjects is planned to participate in Part B. The treatments will be [redacted] BI 1810631 administered to subjects orally [redacted] (T2) followed by [redacted] of [redacted] BI 1810631 (C-14) [redacted] later (R). The radioactive dose of the [redacted] is approximately 0.03 MBq (expected to result in [redacted] radiation burden [redacted] For details refer to Section 4.1.

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

Part A – ADME part

This is a common design for a [^{14}C] study in humans for investigation of absorption, metabolism, and excretion including determination of mass balance. Inclusion of a control group is not required for this investigation.

Eight healthy volunteers are included to ensure at least 6 evaluable subjects as requested by FDA guideline [R22-3641]. This accounts for subjects potentially vomiting within 2x t_{max}, for early drop outs or for any other reason that subjects would not be evaluable.

Shortest sampling duration is up to Day 15 (336 h post drug administration), [redacted] [c32836122]). This minimal sampling period would cover [redacted] Maximal sampling duration is up to Day 43 (1013 h post drug administration), i.e. [redacted] This maximal sampling duration would also cover [redacted]

Randomisation is not possible, because all subjects receive the same treatment. Blinding is not necessary, because the main and secondary endpoints refer to the drug's pharmacokinetics that are not influenced by the knowledge of treatment.

Part B – Absolute BA part

For absolute bioavailability trials, the cross-over design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison [R94-1529]. Compared to the traditional cross-over design (i.e., two trial periods separated by

a wash-out period), the chosen microtracer approach is considered more favourable, because both treatments are administered on the same day (resulting in 1 trial period with overlapping intervals of PK sampling).

Seven volunteers are included to ensure 6 evaluable subjects. This is considered necessary to allow an accurate determination of absolute BA. One subject less than in the hADME part is entered in this study part, in consideration of the shorter duration of the absolute BA part and thus lower risk for drop outs.

Sampling duration is up to Day 8 (168 h after BI 1810631 administration), [redacted] which is considered sufficient for accurate determination of absolute bioavailability.

Randomisation is not possible, because all subjects receive the same treatment. Blinding is not necessary, because the main and secondary endpoints refer to the drug's pharmacokinetics that are not influenced by the knowledge of treatment.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 15 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site, or, if necessary, via external databases and advertisements. Subjects who were entered (i.e. dosed) in Part A of the study are not allowed to be entered in Part B of the study and vice versa.

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 18.0 to 30.0 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

Subjects will not be allowed to participate, if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 145 mmHg, diastolic blood pressure outside the range of 45 to 90 mmHg, or pulse rate outside the range of 40 to 100 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)
12. Use of drugs (including any kind of vaccination) within 28 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation). Dietary supplements (e.g. vitamins, minerals) are allowed until 8 days before study drug administration. Paracetamol and ibuprofen are allowed before and during the study.
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. [redacted]
15. Average intake of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits)
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 4 days 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) 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. Male subjects with WOCBP partner who are unwilling to use highly effective contraception from time point of administration of study drug until 90 days afterwards. Highly effective methods of contraception are:
    - Subject is sexually abstinent if this is in line with the preferred and usual lifestyle of the subject
    - 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 administration of study drug until 90 days afterwards.
24. Participation in another ADME study with a radiation burden ≥0.1 mSv within 12 months prior to dosing
25. For Part A (ADME part) only: Exposure to radiation for diagnostic reasons in the period of 1 year prior to planned administration of study drug
26. For Part A (ADME part) only: Irregular defecation pattern (less than a mean of one bowel movement per 2 days)

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, or with the outcome of the study.
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.

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, if applicable, 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 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 CTCAE Grade 3 (except for Grade 2 headache), or if at least one drug-related serious adverse event is reported

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 2 subjects in part A and/or more than one subject in part B do not complete the trial (including subjects non- evaluable for assessment of primary and secondary endpoints), 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 in mutual agreement with the principal investigator, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Part A (ADME part): The oral solution contains a mixture of pure [^{14}C]-labelled BI 1810631 ("hot") drug substance, and BI 1810631, i.e. unlabelled ("cold") drug substance.

Part B (absolute BA part):

- The [redacted] contains a mixture of pure [^{14}C]-labelled BI 1810631 ("hot") drug substance and BI 1810631, i.e. unlabelled ("cold") drug substance.
- The oral dose will be [redacted] BI 1810631 (unlabelled).

4.1.1 Identity of the Investigational Medicinal Products

Part A (ADME part) - the characteristics of the test product 1 are given below:

Name:	BI 1810631 (C-14) oral solution
Substance:	unlabelled BI 1810631 mixed with labelled [^{14}C]BI 1810631
Pharmaceutical formulation:	Oral solution
Source:	[redacted]
Unit strength:	
Dose:	[redacted] BI 1810631 (C-14), containing a radioactive dose of approximately 3.7 MBq
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	One single dose in the morning of Part A, Visit 2, Day 1, [redacted] as treatment Test 1 (T1)

Part B (absolute BA part) – the characteristics of the reference product are given below:

Name:	BI 1810631 (C-14) [redacted]
Substance:	unlabelled BI 1810631 mixed with labelled [^{14}C]BI 1810631
Pharmaceutical formulation:	[redacted]
Source:	
Unit strength:	
Dose:	[redacted] = [redacted] BI 1810631 (C-14), containing a radioactive dose of approximately 0.03 MBq
Posology:	1-0-0
Mode of administration:	intravenous (i.v.) [redacted]
Duration of use:	One single dose in the morning of Part B, Visit 2, Day 1; [redacted] as treatment Reference (R)

Part B (absolute BA part) – the characteristics of the test product 2 are given below:

Name:	BI 1810631 film-coated tablets [redacted]
Substance:	cold BI 1810631
Pharmaceutical formulation:	Film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Dose:	
Posology:	[redacted]-0-0
Mode of administration:	oral
Duration of use:	One single dose in the morning of Part B, Visit 2, Day 1, [redacted] as treatment Test 2 (T2)

4.1.2 Selection of doses in the trial

The dose of [redacted] BI 1810631 [redacted] and using this dose in the current trial is expected to deliver results meaningful and supportive for the development of BI 1810631. Based on available data from clinical trials (see Section 1.2.2 and the IB [c32836122]), [redacted]

Part A – ADME part: The oral solution of BI 1810631 (C-14) administered in Part A is a mixture of 14C-labelled and unlabelled drug substance. The planned dose is characterized by a radioactivity of approximately 3.7 MBq, corresponding to an effective radioactive burden of approximately [redacted] (see Appendix 10.3). This radioactive dose is considered to be necessary to provide an adequate analytical sensitivity to enable metabolite quantification in a sufficiently low range.

Part B – absolute BA part: In this trial part an [redacted] containing a microtracer of BI 1810631 (C-14) is administered. The planned dose of [redacted] is characterized by a radioactivity of approximately 0.03 MBq which is considered to be sufficient for PK measurements.

The higher radioactive dose in Part A compared to Part B is due to the needs of metabolic profiling in Part A. The amount of radioactivity related to metabolites is split into a number of metabolites, i.e. each metabolite contains only a fraction of the total radioactive dose.

4.1.3 Method of assigning subjects to treatment groups

Part A (ADME part):

This is a single-period phase I trial. All subjects receive the same treatment. All subjects form one treatment group and can be treated in one cohort (i.e. may be dosed on the same 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.

Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2. Once a subject number has been assigned, it cannot be reassigned to any other subject.

Part B (absolute BA part):

This is a fixed-sequence crossover study with a timely overlap of PK sampling intervals. All subjects receive an oral single dose followed by an intravenous [redacted] All subjects form one treatment group and can be treated in one cohort (i.e. may be dosed on the same 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.

Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each subject

Part A (ADME part)

All subjects will receive the treatment as shown in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule in part A

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T1 (Test 1)	BI 1810631 (C-14)	Oral solution	[redacted]	One single dose of [redacted] (corresponding to [redacted] BI 1810631 (C-14))	[redacted]

Administration of trial medication will be performed [redacted] The investigator (or authorised designee) will administer the trial medication as an oral dose [redacted] 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, if correct dosage cannot be ensured otherwise.

Subjects will be confined to bed in half-supine or sitting position for the first 4 hours after drug administration. Subjects will be kept under close medical surveillance for at least 14 days (until Day 15), by when all subjects will be discharged from the trial site irrespective of whether the release criteria are reached. As long as release criteria are not reached, subjects will return to the site for up to four once-weekly urine and faeces sampling intervals.

Part B (absolute BA part):

All subjects will receive first the oral dose of [redacted] BI 1810631 (Test 2) followed by an intravenous [redacted] of [redacted] BI 1810631 (C-14) (Reference). Details of both treatments are given in Table 4.1.4: 2 below:

Table 4.1.4: 2 Dosage and treatment schedule in part B

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T2 (Test 2)	BI 1810631	Film-coated tablet	[redacted]	One single dose of [redacted] BI 1810631	[redacted]
R (Reference)	BI 1810631 (C-14)	[redacted]		One single dose of [redacted] (100 µg BI 1810631 (C-14))	

Treatment T2: Administration of [redacted] BI 1810631 will be performed [redacted] The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing or sitting position.

Treatment R: For administration of the BI 1810631 (C-14) [redacted] an [redacted] is placed into an arm vein of the subject. [redacted] used for collection of blood samples will be placed on the contralateral arm. The BI 1810631 (C-14) [redacted] will be administered as [redacted] under supervision of the investigating physician or an authorised designee. The [redacted] after administration of treatment T2. Start and end time of [redacted] will be recorded.

All treatments: 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, if correct dosage cannot be ensured otherwise.

Subjects will be confined to bed with a bed in half-supine or sitting position for the first 4 hours after administration of treatment T2. Subjects will be kept under close medical surveillance until planned discharge from the trial site in the morning of Day 8.

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 BI 1810631 film-coated tablets (for part B) will be provided to [redacted] by the [redacted] They 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

Drug product manufacturing of radiolabeled BI 1810631 (C-14) oral solution for Part A and of radiolabeled BI 1810631 (C-14) [redacted] for Part B is done by [redacted] The final clinical trial supply of the warm drug products consists of amber glass bottles containing oral solution (strength: [redacted] for Part A and of vials containing the [redacted] (strength: [redacted]) for Part B. The trial medication will be labelled according to GMP.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU CT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

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 (BI 1810631 tablets) delivered from the sponsor 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

[redacted] will provide the investigational drugs manufactured by [redacted] (BI 1810631 (C-14) oral solution and BI 1810631 (C-14) [redacted]) upon availability of a valid prescription from the investigator. The investigator will order the drugs after 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

Only authorised personnel documented in the form 'Site Signature Delegation Log' 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 [redacted]

[redacted]

Table 4.2.1: 1 Grade-specific treatment recommendations of [redacted]

Severity (CTCAE grading)	Description	Treatment recommendations
[redacted]		

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

In case of AEs requiring analgesic / antiphlogistic treatment such as headache, ibuprofen or paracetamol may be given.

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. [redacted]

From 1 h before intake of the oral trial medication until [redacted] fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water at planned times +2 h

and +4 h (mandatory for all subjects). From [redacted] until planned time of +24 h, total fluid intake is restricted to 3000 mL.

On days of urine collection, subjects will be advised that total fluid intake should be at least 1500 mL but should not exceed 3500 mL.

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

[redacted] should not be consumed starting 2 days before trial drug administration until discharge from the site.

Alcoholic beverages are not permitted starting 2 days before first trial drug administration until discharge from the trial site.

[redacted]

Excessive physical activity (such as competitive sport) should be avoided from 4 days before the administration of trial medication 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 dosing with BI 1810631 and for at least 90 days afterwards (see Section 3.3.3 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

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 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 4 hours. 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.

At the time points described in the Flow Chart, haematocrit measurements will be performed.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal and in accordance with Clinical laboratory [redacted] standard procedures)	Neut. Poly (segs)/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes		
Manual differential red blood count (if there is an abnormality in the blood cell count in accordance with Clinical laboratory [redacted] standard procedures)	Only positive findings will be reported (for instance, the presence of microcytes)		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Serum)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	C-Reactive Protein (Quant)	X	X
	Cholesterol, total	X	--
	Triglyceride	X	--
	Uric acid	X	--
Electrolytes	Sodium	X	X
	Potassium	X	X
	Calcium	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
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 (microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visits 2 and 3 (for time points refer to Flow Chart)

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and on Day -1 of both trial parts.

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
	Cotinine
Drug screening (serum)	Tricyclic antipressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative)
	Hepatitis B core antibody (qualitative)
	Hepatitis C antibodies (qualitative)
	HIV-1 and HIV-2 antibody (qualitative)

To encourage compliance with alcoholic restrictions, a urine alcohol test will be performed at screening and on Day -1 of each trial part, 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 the safety laboratory of [redacted]

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

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

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph 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. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings observed during the trial will be reported as AEs (during the trial), if assessed to be clinically relevant by the investigator. Of note, ECG findings at the screening visit that are assessed as clinically relevant by the investigator, lead to exclusion of the subject (see exclusion criterion 20 in Section 3.3.3). 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 Local tolerability (part B only)

In part B (absolute BA part), local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings. Local findings assessed as clinically relevant by the investigator must be recorded as AE.

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.
- [redacted]

5.2.6.1.5 Intensity (severity) of AEs

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

5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks

of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)

- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- There is an alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware

of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

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 any BI 1810631 exposure during pregnancy in a partner of the male trial participant by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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, urine, and faeces 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. More details of sample processing can be found in the laboratory manual. Changes to conditions of sample processing described in this CTP may be implemented via non-substantial amendment.

The labelled drug material corresponds to the total radioactivity measured in the different matrices and is expressed as [^{14}C]-radioactivity or [^{14}C]BI 1810631-EQ.

5.3.2 Methods of sample collection

5.3.2.1 Sample collection in Part A (ADME part)

5.3.2.1.1 Part A (ADME part) – sampling of blood for analysis of [^{14}C]-radioactivity in plasma and whole blood and for analysis of BI 1810631 in plasma

- For quantification of [^{14}C]-radioactivity in whole blood, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes at the times indicated in the Flow Chart.
- For quantification of [^{14}C]-radioactivity in plasma, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes at the times indicated in the Flow Chart.
- For quantification of BI 1810631 in plasma, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes 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.

For blood volumes see Appendix 10.1.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.1.2 Part A (ADME part) – sampling of plasma for metabolic profiling

For metabolic profiling, different volumes of blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes 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.

For blood volumes see Appendix 10.1.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.1.3 Part A (ADME part) – urine sampling for analysis of [^{14}C]-radioactivity, of BI 1810631, and for metabolic profiling

All urine samples are planned to be used for determination of [^{14}C]-radioactivity and BI 1810631 concentrations. Samples for metabolic profiling will be selected according to the levels of radioactivity in each urine sample.

A blank urine sample will be collected before administration of trial medication (see Flow Chart) to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 2 L polyethylene (PE) containers and stored at [redacted] during the sampling interval. Subjects

are told to empty their bladders before the first sampling interval and at the end of each sampling interval.

The exact start and end times of the urine collection intervals will be recorded in the CRF.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.1.4 Part A (ADME part) – faeces sampling for analysis of [^{14}C]-radioactivity and metabolic profiling

A blank sample will be taken within approximately 48 hours prior to study drug administration. If several samples are available, the sample closest to drug administration will be used for analyses.

All faeces samples are planned to be used for determination of [^{14}C]-radioactivity. Samples for metabolic profiling will be selected according to the levels of radioactivity in each faeces sampling interval.

All stools will be collected continuously and quantitatively in portions as shown in the Flow Chart. The weight of the faeces and the exact times of faeces collection will be recorded in the CRF.

If release criteria are not reached until Day 15 (see Section 3.1 for release criteria), subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. For home-collection intervals and once-weekly in-house collection intervals see the Flow Chart. If faeces is collected during an in-house collection interval, this faeces sample will be used for analysis and the prior home-collection faeces sample will be discarded. If no faeces is collected during an in-house collection interval, the prior home-collection faeces sample will be used.

For a detailed description of faeces labelling, storage and collection of faeces samples refer to the laboratory manual.

5.3.2.1.5 Part A (ADME part) – handling of vomit

If vomiting occurs within 24 hours after study drug administration, the vomit should be collected to calculate the weight and [^{14}C]-radioactivity levels.

Details of vomit sample preparation and processing, storage, labelling, and sample shipment are described in the laboratory manual.

5.3.2.2 Sample collection in Part B (absolute BA part)

5.3.2.2.1 Part B (absolute BA part) – plasma sampling for BI 1810631 analysis

For quantification of BI 1810631 in plasma, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes 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.

For blood volumes see Appendix 10.2.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.2.2 Part B (absolute BA part) – plasma sampling for [^{14}C]BI 1810631 analysis

For quantification of [^{14}C]BI 1810631 in plasma, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes 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.

For blood volumes see Appendix 10.2.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.2.3 Part B (absolute BA part) – plasma sampling for total [^{14}C]-radioactivity analysis

For quantification of total [^{14}C]-radioactivity in plasma, blood will be drawn from an antecubital or forearm vein into [redacted] blood drawing tubes 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.

For blood volumes see Appendix 10.2.

For a detailed description of sample handling / processing, sample storage, labelling, and shipment, refer to the laboratory manual.

5.3.2.3 Parts A (ADME) and B (absolute BA) – further investigations

Back-up and left-over samples (whole blood, plasma, urine, faeces) may be used for metabolic profiling if not needed for their primary purpose.

In addition, back-up and left-over samples (whole blood, plasma, urine, faeces), if not needed for their primary purpose anymore, may be used for further methodological investigations, e.g. for stability testing of drug and/or its metabolites, or for assessment of the drug or drug metabolites or to address Health Authority questions regarding the results / methodology. However, only data related to BI 1810631 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.

5.3.3 Analytical determinations in Part A (hADME part)

5.3.3.1 Determination of [^{14}C]-radioactivity in plasma, whole blood, urine, and faeces

Determination of total [^{14}C]-radioactivity in plasma, whole blood, urine, and faeces will be done by means of Liquid Scintillation Counting (LSC).

For the name and address of the laboratory refer to Section 8.7.

5.3.3.2 Analytical determination of BI 1810631 concentrations in plasma

BI 1810631 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis.

For the name and address of the laboratory refer to Section 8.7.

5.3.3.3 Analytical determination of BI 1810631 concentrations in urine

BI 1810631 concentrations in urine will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

For the name and address of the laboratory refer to Section 8.7.

5.3.3.4 Metabolic profiling in plasma, urine, and faeces

Metabolic profiling will be done by mass spectrometry analysis and by radioprofiling. For the name and address of the laboratories refer to Section 8.7.

Metabolic profiling data will be reported separately from CTR.

5.3.4 Analytical determinations in part B (absolute BA part)

5.3.4.1 Analytical determination of BI 1810631 concentrations in plasma

Plasma concentrations of BI 1810631 will be determined by a validated LC-MS/MS assay. All details of the analytical method will be available prior to the start of sample analysis.

For the name and address of the laboratory refer to Section 8.7.

5.3.4.2 Analytical determination of [^{14}C]BI 1810631 concentrations in plasma

Plasma concentrations of [^{14}C]BI 1810631 will be determined by means of accelerator mass spectrometry (AMS).

For the name and address of the laboratory refer to Section 8.7.

5.3.4.3 Analytical determination of total [14C]-radioactivity in plasma

Total [^{14}C]-radioactivity in plasma will be determined by means of accelerator mass spectrometry (AMS).

For the name and address of the laboratory refer to Section 8.7.

5.4 ASSESSMENT OF 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, to determine pharmacokinetic parameters and to perform metabolic profiling in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally (Parts A and B) or intravenously (Part B) administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the (first) 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 ± 30 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first, with blood sampling for PK and metabolite profiling to be done as closely as possible to the scheduled time point if not specified otherwise in the Flow Chart. 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/faeces 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.

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

6.2.2.1 Treatment periods in part A (ADME part)

Each subject is expected to participate in one treatment period. The subjects will be admitted to the trial site on Day -1 (start of faeces collection at home is on Day -2), and kept under close medical surveillance until discharge from the trial site on Day 15. On the day of discharge, the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness (fitness to be assessed by a physician).

If release criteria (see Section 3.1) are not met on Day 15, subjects are to return for once-weekly 24 h in-house confinements with urine and faeces sampling. In the 24 h intervals directly before each once-weekly in-house confinement, subjects are to collect faeces at home. For time intervals see the Flow Chart.

Once the release criteria are reached for an individual subject, the once-weekly collection intervals will be stopped for this subject. Irrespective of whether the criteria have been met or not after collection interval Day 42-43, no further collections are planned.

For details on time points and procedures for collection of whole blood, plasma, urine, and faeces samples for PK analysis, metabolic profiling, and mass balance assessments, 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.

6.2.2.2 Treatment periods in part B (absolute BA part)

Each subject is expected to participate in one treatment period. On Day -1 of the treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance until at least the morning of Day 8. 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 samples for PK analysis, refer to Flow Chart and Section 5.3.2.

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

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

6.2.3 Follow-up period and trial completion

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

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

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

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed

until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This is a phase I, non-randomised, open-label study to investigate human ADME and absolute bioavailability of BI 1810631 administered to healthy male subjects. No confirmatory analysis will be conducted for this study.

For Part A data will be reported with descriptive statistics only.

For Part B, the absolute bioavailability of [redacted] BI 1810631 administered [redacted] (test treatment T2) compared with [redacted] BI 1810631 (C-14) (reference treatment R) administered as intravenous microtracer will be estimated by the ratio of the geometric means (test/reference) for primary and secondary dose-normalized PK endpoints, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for BI 1810631 and [^{14}C]BI 1810631 and [^{14}C]-radioactivity will be calculated according to the relevant BI internal procedures.

Plasma, urine and faeces 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, urine and faeces 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 is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.2.2 Primary endpoint analyses

Primary analyses

Part A:

The primary endpoints (refer to Section 2.1.2) will be calculated according to the relevant BI internal procedures. The analysis will be descriptive in nature. To avoid underestimation of the total recovery of [^{14}C], the excretion during the non-sampling phase of the study will be estimated using linear interpolation between the observed 24-h sampling periods before and after the non-sampling period for urine and faeces respectively.

Part B:

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 effect 'treatment' will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., 7

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

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

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

Point estimates for the ratios of the geometric means (test/reference) for the dose-normalized 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 effect.

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

7.2.3 Secondary endpoint analyses

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

7.2.4 Further endpoint analyses

7.2.4.1 Pharmacokinetic analyses

Further PK endpoints will be analysed descriptively.

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.6. 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 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 of the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

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

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

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.
Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

The trial will not be randomised, thus this Section is not applicable.

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory study, no prospective calculations of statistical power have been made. The sample size of 8 subjects in Part A and 7 subjects in Part B has been selected to provide at least 6 evaluable subjects per trial part, which are considered sufficient information to assess the main objectives of this trial.

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 webpage: 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.

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 will be provided by:

- BI 1810631 film-coated tablets (part B): provided by [redacted]

- BI 1810631 (C-14) oral solution (part A): provided by [redacted]
- BI 1810631 (C-14) [redacted] (part B): provided by [redacted]

Safety laboratory tests and haematocrit measurements will be performed by the local laboratory of the trial site [redacted]

Bioanalytical analyses will be performed at:

- For BI 1810631 in plasma (parts A and B): [redacted]
- For BI 1810631 in urine (part A): [redacted]
- For [^{14}C]-radioactivity in whole blood, plasma, urine, and faeces (part A): [redacted]
- For metabolic profiling of BI 1810631 and its metabolites in plasma, urine, and faeces (part A):
    - Mass spectrometry analyses (plasma, urine, and faeces): [redacted]
    - Radioprofiling: [redacted]
- For [^{14}C]BI 1810631 in plasma (part B): [redacted]
- For total [^{14}C]radioactivity in plasma (part B): [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 and/or a contract research organisation according to BI SOPs.

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

[redacted]

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R18-1357	U.S. Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 5.0 (published: November 27, 2017). Website: ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v 5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 (access date: 2017-04-09); 2017
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R18-1905	International Commission on Radiological Protection (ICRP). Factors related to project evaluation. Ann ICRP; 22(3), p. 11-13; 1992.
R20-1872	Citri A Yarden Y. EGF-ERBB signalling: towards the systems level. Nat Rev Mol Cell Biol; 7, p. 505-516; 2006.
R20-1990	Wang Z. ErbB receptors and cancer. Methods Mol Biol; 1652, p. 3-35; 2017

R22-3641 Food and Drug Administration. Guidance for industry: clinical pharmacology considerations for human radiolabeled mass balance studies: draft guidance (this guidance document is being distributed for comment purposes only.) (clinical pharmacology, May 2022). Website: fda.gov/media/158178/download (access date: 2022-10-21); 2022

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

9.2 UNPUBLISHED REFERENCES

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

10. APPENDICES

10.1 BLOOD VOLUMES FOR PART A (ADME PART)

Table 10.1: 1 Blood volumes for PK in part A

Visit 2, planned time point [h]	Blood volume for [^{14}C]-radioactivity in whole blood – [redacted] [mL]	Blood volume for [^{14}C]-radioactivity in plasma – [redacted] [mL]	Blood volume for BI 1810631 in plasma – [redacted] [mL]	Blood volume for metabolic profiling in plasma – [redacted] [mL]
-2:00	[redacted]	[redacted]	[redacted]	[redacted]
0:30	[redacted]	[redacted]	[redacted]	[redacted]
1:00	[redacted]	[redacted]	[redacted]	[redacted]
1:30	[redacted]	[redacted]	[redacted]	--
2:00	[redacted]	[redacted]	[redacted]	[redacted]
2:30	[redacted]	[redacted]	[redacted]	--
3:00	[redacted]	[redacted]	[redacted]	--
4:00	[redacted]	[redacted]	[redacted]	[redacted]
5:00	[redacted]	[redacted]	[redacted]	--
6:00	[redacted]	[redacted]	[redacted]	--
8:00	[redacted]	[redacted]	[redacted]	[redacted]
10:00	[redacted]	[redacted]	[redacted]	--
12:00	[redacted]	[redacted]	[redacted]	[redacted]
24:00	[redacted]	[redacted]	[redacted]	[redacted]
36:00	[redacted]	[redacted]	[redacted]	--
48:00	[redacted]	[redacted]	[redacted]	[redacted]
72:00	[redacted]	[redacted]	[redacted]	--
96:00	[redacted]	[redacted]	[redacted]	[redacted]
120:00	[redacted]	[redacted]	[redacted]	--
168:00	[redacted]	[redacted]	[redacted]	[redacted]
216:00	[redacted]	[redacted]	[redacted]	--
264:00	[redacted]	[redacted]	[redacted]	--
336:00	[redacted]	[redacted]	[redacted]	--
TOTAL	[redacted]	[redacted]	[redacted]	[redacted]

Table 10.1: 2 Blood volumes for safety assessments in part A

Assessment	**Maximum # Samples**	**Volume of Blood per Sample (mL)**	**Total Volume of Blood (mL)**
Clinical chemistry	5	3.5	17.5
Hematology	9	3	27
Coagulation	5	2.7	13.5
Serology	1	5	5
Total volume of blood drawn			**63**

➔ The total blood volume to be collected from each subject in part A of trial 1479-0006 is [redacted] mL.

10.2 BLOOD VOLUMES FOR PART B (ABSOLUTE BA PART)

For analysis of BI 1810631 in plasma, [redacted] blood [redacted] is collected per time point, i.e. [redacted] blood in total

For analysis of [^{14}C]BI 1810631 in plasma, [redacted] blood [redacted] is collected per time point, i.e. [redacted] blood in total.

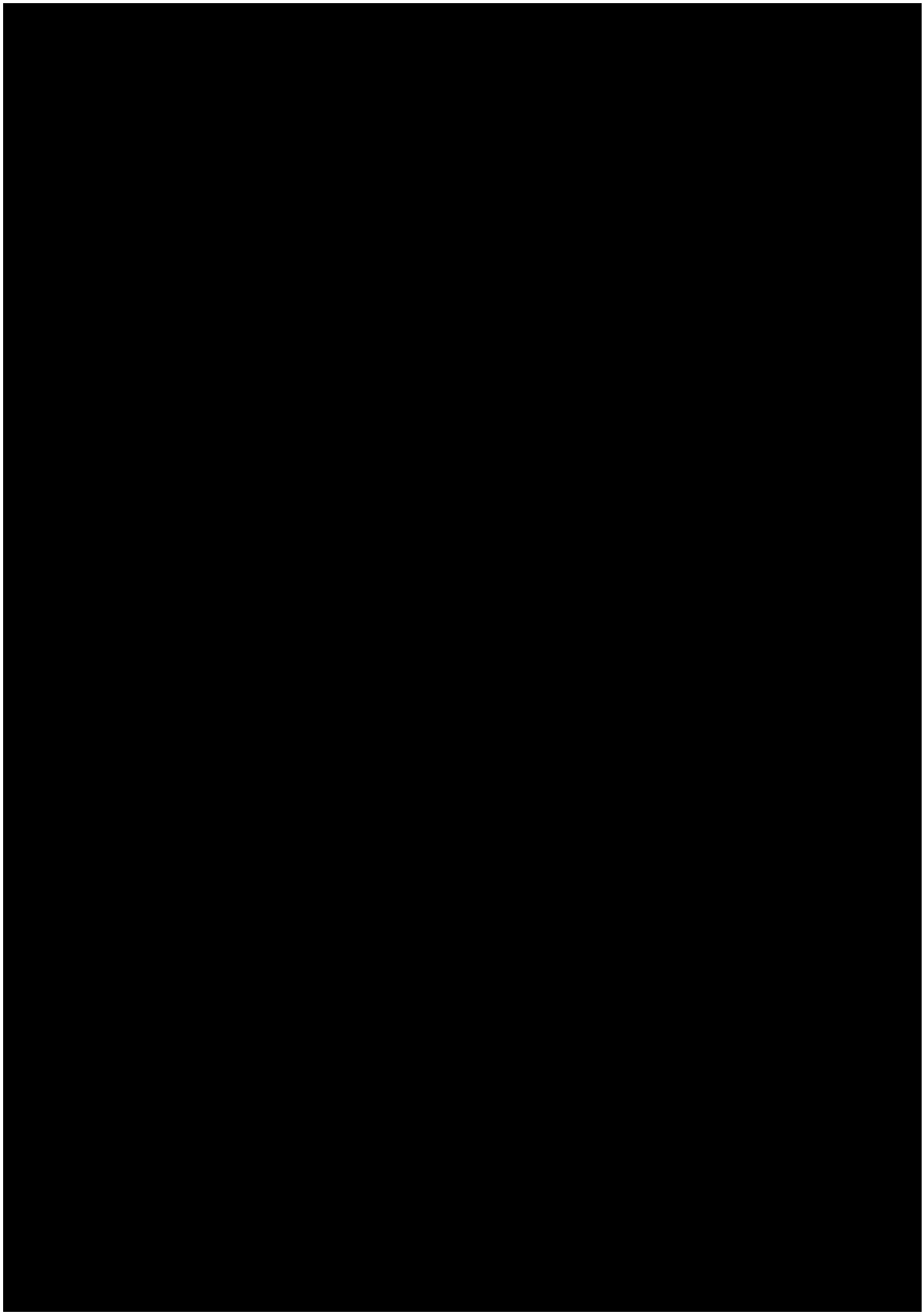
For analysis of total [^{14}C]-radioactivity in plasma, [redacted] blood [redacted] is collected per time point (only at baseline: [redacted] of blood), i.e. [redacted] blood in total.

Table 10.2: 1 Blood volumes for safety assessments in part B

Assessment	**Maximum # Samples**	**Volume of Blood per Sample (mL)**	**Total Volume of Blood (mL)**
Clinical chemistry	5	3.5	17.5
Hematology	5	3	15
Coagulation	5	2.7	13.5
Serology	1	5	5
Total volume of blood drawn			**51**

➔ The total blood volume to be collected from each subject in part B of trial 1479-0006 is [redacted]

10.3 RADIOACTIVE BURDEN CALCULATION FOR PART A (ADME PART)



11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c38775190 **Technical Version Number:1.0**

Document Name: clincial-trial-protocol-version-01

Title: A phase I, open-label trial in two parallel parts to investigate mass balance, metabolism, and basic pharmacokinetics of BI 1810631 (C-14) administered as oral solution (part A) and to investigate absolute bioavailability of BI 1810631 administered as film-coated tablet together with an intravenous microtracer dose of BI 1810631 (C-14) (part B) in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	24 Apr 2023 13:25 CEST
Approval-Clinical Program [redacted]		24 Apr 2023 14:52 CEST
Author-Trial Statistician		24 Apr 2023 18:10 CEST
Verification-Paper Signature Completion		27 Apr 2023 08:47 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed