Boehringer Ingelheim

Clinical Trial Protocol

Document Number:	**c38438177-03**
Eu CT No.	**2022-502327-22-00**
BI Trial No.	1434-0016
BI Investigational Medicinal Product	BI 764198
Title	A phase I, open-label, two-arm, non-randomised trial to investigate the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution using two different approaches in healthy male volunteers
Lay Title	A study in healthy men to test how BI 764198 is processed in the body
Clinical Phase	I
Clinical Trial Leader	[redacted]
Principal Investigator	[redacted]
Current Version, Date	Version 3.0, 10 Aug 2023
Original Protocol Date	10 Jan 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	10 Jan 2023
Revision date	10 Aug 2023
BI trial number	1434-0016
Title of trial	A phase I, open-label, two-arm, non-randomised trial to investigate the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution using two different approaches in healthy male volunteers
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The trial is intended to investigate the basic pharmacokinetics, mass balance, excretion pathways, and metabolism of BI 764198 and its metabolites using a classical hADME approach (^{14}C-labelled [redacted]) and a microtracer approach (^{14}C-labelled [redacted])
Trial objectives	To investigate pharmacokinetics of BI 764198 and its metabolites, total radioactivity including mass balance, excretion pathways and metabolism including [redacted] following oral administration to healthy male subjects either as a single oral dose of (i) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME approach) or (ii) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME with a microtracer approach).

Trial endpoints	Primary endpoints: Mass balance and recoveries of total [^{14}C]-radioactivity in urine and faeces: - $fe_{urine,0-tz}$ (fraction of [^{14}C]-radioactivity excreted in urine expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) - $fe_{faeces,\ 0-tz}$ (fraction of [^{14}C]-radioactivity excreted in faeces expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point) Secondary endpoints: The following endpoints will be determined for [^{14}C]- radioactivity and for BI 764198: - C_{max} (maximum measured concentration of the analyte) in plasma - AUC_{0-tz} (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point) in plasma Further assessments: Additional pharmacokinetic parameters of BI 764198 and [redacted] and [redacted] may be determined as appropriate.
Trial design	Open-label, single dose, two-arm, non-randomised
Number of subjects **total entered** **on each treatment**	 24 8 on treatment 1, 16 on treatment 2
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product(s) **dose** **mode of administration**	BI 764198 (C-14) oral solution, [redacted] Treatment 1: Classical hADME approach with BI 764198 ([^{14}C]-labelled [redacted]): [redacted] containing a radioactive dose of 3.7 MBq Treatment 2: Microtracer approach hADME with BI 764198 ([^{14}C]-labelled [redacted] containing a radioactive dose of 0.1 MBq Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	single oral dose for: (i) hADME approach and (ii) hADME microtracer approach, respectively
Statistical methods	Descriptive statistics will be calculated for all endpoints

FLOW CHART 1 (CLASSICAL HUMAN ADME)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Blood sampling for PK and total radioactivity blood/plasma [2, 9]	PK urine [5]	PK faeces [4]	Blood sampling for metabolic profiling [18]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	A[13]			x[14]		x	x	
2	-1	-18:00	14:00	Admission to trial site	B[13,17]		x[3]					x
	1	-2:00	06:00			x[3]			x[3]	x[3]	x[3]	▲
		0:00	08:00	Drug administration [redacted] BI 764198 (C-14) ([^{14}C]-labelled [redacted] (treatment 1)[8]			▲	▲				│
		0:30	08:30			x	│	│				│
		1:00	09:00			x	│	│	x			│
		1:30	09:30		x[16]	x	│	│		x	x	│
		2:00	10:00	240 mL water intake		x	│	│	x			│
		3:00	11:00			x	│	│				│
		4:00	12:00	Lunch, 240 mL water intake[6]		x	┼	│	x	x	x	│
		6:00	14:00			x	│	│				│
		8:00	16:00		x[16]	x	┼	│	x			│
		10:00	18:00	Dinner[6]		x	│	│				│
		12:00	20:00	Snack[6]		x	┼	│	x	x	x	│
	2	24:00	08:00		x[16,17]	x	┼	┼	x	x	x	│
		36:00	20:00			x	│	│	x			│
	3	48:00	08:00			x	┼	┼	x			│
	4	72:00	08:00			x	┼	┼	x			│
	5	96:00	08:00			x	┼	┼	x			│
	6	120:00	08:00			x	┼	┼				│
	7	144:00	08:00			x	┼	┼				│
	8	168:00	08:00		B	x	┼	┼				│
	9	192:00	08:00			x	┼	┼				│
	10	216:00	08:00	Discharge from trial site[15]		x	▼	▼		x	x	│
	15	341:00	13:00	Start home collection[10, 11]				▲				│
	16	365:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				│
	17	389:00	13:00	Discharge from trial site[10]			▼	▼		x	x	│
	22	509:00	13:00	Start home collection[10, 11]				▲				│
	23	533:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				│
	24	557:00	13:00	Discharge from trial site[10]			▼	▼		x	x	│
	29	677:00	13:00	Start home collection[10, 11]				▲				│
	30	701:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				│
	31	725:00	13:00	Discharge from trial site[10]			▼	▼				▼
3	11-31			End of study (EoS) examination[7,12]	B					x	x	x

A, B: safety laboratory sets (see Section 5 of the CTP; Table 5.2.3: 1)

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 virus 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. At all time points indicated in the Flow Chart, PK blood samples will be taken for [^{14}C]-radioactivity assessment in whole blood and plasma, and for PK assessment of cold BI 764198 and [redacted] in plasma. PK sampling will continue as long as radioactivity in plasma is above LLOQ.
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration (or earlier if indicated or for logistical reasons).
4. All stools (for [^{14}C]-radioactivity assessment and metabolic profiling) will be collected quantitatively from Day 1 in sampling intervals as defined in the Flow Chart after intake of radiolabelled drug. Thereafter, if warranted, 24 h collections at trial site are to be performed on days 16-17, 23-24, and 30-31. A blank sample will be collected before drug administration on Day 1. Collection of the pre-dose faeces sample will start from approximately -48 h before drug administration. Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 10). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity.
5. Urine collection intervals (for PK (cold BI 764198 and metabolites)//[^{14}C]-radioactivity assessment and metabolic profiling (planned time): on Day -1 or Day 1 pre-dose (blank) sample, on Day 1 voiding of the bladder prior to start of urine collection, and at the intervals defined in the Flow Chart up to 216 h after drug administration. Thereafter, if warranted, 24 h collections are to be performed on days 16-17, 23-24, and 30-31. Urine sampling for PK will be stopped when release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 10). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity, BI 764198 and its metabolites. Urine samples of collection intervals at least up to 96 h will also be used for metabolic profiling.
6. If several procedures are performed at the same time point, the intake of meals will be the last action.
7. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, body weight, ECG, safety laboratory, recording of AEs and concomitant therapies. The EoS examination to be performed within 1 to 7 days after last discharge from the trial site, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 31.
8. Subjects are to be fasted for at least 10 h.
9. Blood sampling for an individual subject can be stopped if [^{14}C]-radioactivity in plasma is below the limit of quantification at two consecutive sampling time points for this subject.
10. The planned times for admission, discharge, as well as start and end of the collection intervals for urine and faeces are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.
11. Subjects are to collect faeces at home within 24 h intervals before being admitted to trial site for once-weekly in-house collection intervals. Home collection intervals: Day 15-16, 22-23, 29-30. If faeces are collected in the subsequent in-house collection interval, the faeces previously collected at home will be discarded. If no faeces are collected in the subsequent in-house collection interval (no defaecation) at the trial site, the faeces collected at home will be used instead for analysis.
12. For definition of the individual subject's end of trial see Section 6.2.3
13. Drug and alcohol screening will be done at this time point.
14. Based on specific instructions provided, subjects will collect a pre-dose faeces sample at home in specific containers provided by the clinical trial site approximately 48 h before trial drug administration.
15. Confirmation of fitness includes physical examination, vital signs, ECG, recordings of AEs and concomitant therapies as well as evaluation of safety laboratory assessed on Day 8.
16. At this time point, only a sample for haematocrit measurement is taken.
17. PCR testing for SARS-CoV-2 will be performed at admission on Day – 1, Day 2 and at each admission to the trial site for the 24-h visits. Polymerase chain reaction testing for SARS-CoV-2 will be performed as needed based on the current status of the pandemic. SARS-CoV-2 testing on Day 2 may take place at any time during this day.
18. Metabolite profiling sampling times may be adapted based on information obtained during trial conduct (e.g., levels of radioactivity in each urine and/or plasma sample) as long as the overall blood volume stays the same.

FLOW CHART 2A (MICROTRACER HUMAN ADME)*

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Blood sampling for PK and total radioactivity blood/plasma [2, 9]	PK urine [5]	PK faeces [4]	Blood sampling for metabolic profiling [18]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	A[13]			x[14]		x	x	
2	-1	-18:00	14:00	Admission to trial site	B[13,17]		x[3]					x
	1	-2:00	06:00			x[3]			x[3]	x[3]	x[3]	
		0:00	08:00	Drug administration [redacted] BI 764198 (C-14) ([^{14}C]-labelled [redacted] (treatment 2)[8]			▲	▲				
		0:30	08:30			x	|	|				
		1:00	09:00			x	|	|	x			
		1:30	09:30		x[16]	x	|	|		x	x	
		2:00	10:00	240 mL water intake		x	|	|	x			
		3:00	11:00			x	|	|				
		4:00	12:00	Lunch, 240 mL water intake[6]		x	┼	|	x	x	x	
		6:00	14:00			x	|	|				
		8:00	16:00		x[16]	x	┼	|	x			
		10:00	18:00	Dinner[6]		x	|	|				
		12:00	20:00	Snack[6]		x	┼	|	x	x	x	
	2	24:00	08:00		x[16,17]	x	┼	┼	x	x	x	
		36:00	20:00			x	|	|	x			
	3	48:00	08:00			x	┼	┼	x			
	4	72:00	08:00			x	┼	┼	x			
	5	96:00	08:00			x	┼	┼	x			
	6	120:00	08:00			x	┼	┼				
	7	144:00	08:00			x	┼	┼				
	8	168:00	08:00		B	x	┼	┼				
	9	192:00	08:00			x	┼	┼				
	10	216:00	08:00	Discharge from trial site[15]		x	▼	▼		x	x	
	15	341:00	13:00	Start home collection[10, 11]				▲				
	16	365:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				
	17	389:00	13:00	Discharge from trial site[10]			▼	▼		x	x	
	22	509:00	13:00	Start home collection[10, 11]				▲				
	23	533:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				
	24	557:00	13:00	Discharge from trial site[10]			▼	▼		x	x	
	29	677:00	13:00	Start home collection[10, 11]				▲				
	30	701:00	13:00	Admission to trial site[10]	x[17]	x[9]	▲	┼				
	31	725:00	13:00	Discharge from trial site[10]			▼	▼				
3	11-31			End of study (EoS) examination[7,12]	B					x	x	x

*for the assessment of main endpoints

A, B: safety laboratory sets (see Section 5 of the CTP; Table 5.2.3: 1)

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 virus 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. At all time points indicated in the Flow Chart PK blood samples will be taken for [^{14}C]-radioactivity assessment in whole blood and plasma, and for PK assessment of cold BI 764198 in plasma. PK sampling will continue as long as radioactivity in plasma is above LLOQ.
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration (or earlier if indicated or for logistical reasons).
4. All stools (for [^{14}C]-radioactivity assessment and metabolic profiling) will be collected quantitatively from Day 1 in sampling intervals as defined in the Flow Chart after intake of radiolabelled drug. Thereafter, if warranted, 24 h collections at trial site are to be performed on days 16-17, 23-24, and 30-31. A blank sample will be collected before drug administration on Day 1. Collection of the pre-dose faeces sample will start from approximately -48 h before drug administration. Faeces sampling for [^{14}C]-radioactivity assessment will be stopped when the release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 10). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity.
5. Urine collection intervals (for PK (cold BI 764198 and metabolites)/[^{14}C]-radioactivity assessment and metabolic profiling (planned time): on Day -1 or Day 1 pre-dose (blank) sample, on Day 1 voiding of the bladder prior to start of urine collection, and at the intervals defined in the Flow Chart up to 216 h after drug administration. Thereafter, if warranted, 24 h collections are to be performed on days 16-17, 23-24, and 30-31. Urine sampling for PK will be stopped when release criteria for radioactivity recovery (Section 3.1) have been met (earliest stopping on day 10). "┼" means end of last collection interval, start of following collection interval. All samples: planned for determination of [^{14}C]-radioactivity, BI 764198 and its metabolites. Urine samples of collection interval at least up to 96 h will also be used for metabolic profiling.
6. If several procedures are performed at the same time point, the intake of meals will be the last action.
7. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, body weight, ECG, safety laboratory, recording of AEs and concomitant therapies. The EoS examination to be performed within 1 to 7 days after last discharge from the trial site, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 31.
8. Subjects are to be fasted for at least 10 h.
9. Blood sampling for an individual subject can be stopped if [^{14}C]-radioactivity in plasma is below the limit of quantification at two consecutive sampling time points for this subject.
10. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.
11. Subjects are to collect faeces at home within 24 h intervals before being admitted to trial site for once-weekly in-house collection, respectively. Home collection intervals: Day 15-16, 22-23, 29-30. If faeces are collected in the subsequent in-house collection interval, the faeces previously collected at home will be discarded. If no faeces are collected in the subsequent in-house collection interval (no defecation), the faeces collected at home will be used instead for analysis.
12. For definition of the individual subject's end of trial see Section 6.2.3
13. Drug and alcohol screening will be done at this time point.
14. Subjects will collect a pre-dose faeces sample at home in specific containers provided by the clinical trial site approximately 48 h before trial drug administration.
15. Confirmation of fitness includes physical examination, vital signs, ECG, recordings of AEs and concomitant therapies as well as evaluation of safety laboratory assessed on Day 8.
16. At this time point, only a sample for haematocrit measurement is taken.
17. PCR testing for SARS-CoV-2 will be performed at admission on Day – 1, Day 2 and at each admission to the trial site for the 24-h visits. Polymerase chain reaction testing for SARS-CoV-2 will be performed as needed based on the current status of the pandemic. SARS-CoV-2 testing on Day 2 may take place at any time during this day.
18. Metabolite profiling sampling times may be adapted based on information obtained during trial conduct (e.g., levels of radioactivity in each urine and/or plasma sample) as long as the overall blood volume stays the same.

FLOW CHART 2B (MICROTRACER HUMAN ADME)*

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory	Blood sampling for PK and total radioactivity[2]	Blood sampling for metabolic profiling[10]	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy
1	-21 to -2			Screening (SCR)[1]	A[7]			x	x	
2	-1	-18:00	14:00	Admission to trial site	B[7,9]					x
	1	-2:00	06:00			x[3]	x[3]	x[3]	x[3]	↕
		0:00	08:00	Drug administration [redacted] BI 764198 (C-14) ([^{14}C]-labelled [redacted] (treatment 2)[6]						
		0:30	08:30			x				
		1:00	09:00			x	x			
		1:30	09:30			x		x	x	
		2:00	10:00	240 mL water intake		x	x			
		3:00	11:00			x				
		4:00	12:00	Lunch, 240 mL water intake[4]		x	x	x	x	
		6:00	14:00			x				
		8:00	16:00			x	x			
		10:00	18:00	Dinner[4]		x				
		12:00	20:00	Snack[4]		x	x	x	x	
	2	24:00	08:00		x[10]	x	x	x	x	
		36:00	20:00			x	x			
	3	48:00	08:00			x	x			
	4	72:00	08:00			x	x			
	5	96:00	08:00			x	x			
	6	120:00	08:00			x				
	7	144:00	08:00			x				
	8	168:00	08:00		B	x				
	9	192:00	08:00			x				
	10	216:00	08:00	Discharge from trial site[8]		x		x	x	
3	11-17			End of study (EoS) examination[5]	B			x	x	x

*to repeat assessments for objectives related to [redacted] and some secondary endpoints

A, B: safety laboratory sets (see Section 5 of the CTP; Table 5.2.3: 1)

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 virus 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. At all time points indicated in the Flow Chart PK blood samples will be taken for [^{14}C]-radioactivity assessment in plasma, and for PK assessment of cold BI 764198 in plasma.
3. The time is approximate; the procedure is to be performed within a time window of 3 h prior to drug administration (or earlier if indicated or for logistical reasons).
4. If several procedures are performed at the same time point, the intake of meals will be the last action.

5. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, body weight, ECG, safety laboratory, recording of AEs and concomitant therapies. The EoS examination is to be performed within 1 to 7 days after discharge from the trial site.
6. Subjects are to be fasted for at least 10 h.
7. Drug and alcohol screening will be done at this time point.
8. Confirmation of fitness includes physical examination, vital signs, ECG, recordings of AEs and concomitant therapies as well as evaluation of safety laboratory assessed on Day 8.
9. PCR testing for SARS-CoV-2 will be performed at admission on Day – 1, Day 2 and at each admission to the trial site for the 24-h visits. Polymerase chain reaction testing for SARS-CoV-2 will be performed as needed based on the current status of the pandemic. SARS-CoV-2 testing on Day 2 may take place at any time during this day.
10. Metabolite profiling sampling time points may be adapted based on information obtained during trial conduct (e.g., levels of radioactivity in each plasma sample) as long as the overall blood volume stays the same.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACEi	Angiotension converting enzyme inhibitor
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
$Ae_{urine, 0\text{-}tz}$	Amount of analyte that is eliminated in urine from the time interval t_0 to t_z
$Ae_{urine, t1\text{-}t2}$	Amount of analyte that is eliminated in urine from the time interval t_1 to t_2
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$AUC_{0\text{-}24hr}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24hr
$\%AUC_{tz\text{-}\infty}$	Percentage of $AUC_{0\text{-}\infty}$ obtained by extrapolation
$AUC_{t1\text{-}t2}$	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
C_{blood}	Concentration of [^{14}C]-radioactivity in whole blood
$C_{blood\ cells}$	Concentration of [^{14}C]-radioactivity in blood cells
C_{plasma}	Concentration of [^{14}C]-radioactivity in plasma
CI	Confidence interval
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease - Epidemiology Collaboration
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
$CL_{R, t1\text{-}t2}$	Renal clearance of the analyte in plasma from the time point t_1 to t_2

C_{max}	Maximum measured concentration of the analyte in plasma
COVID-19	Corona virus disease 2019
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DILI	Drug induced liver injury
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
ESKD	End Stage Kidney Disease
EuCT	European Clinical Trials Database
F	Absolute bioavailability factor
$fe_{faeces,0\text{-}tz}$	fraction of [^{14}C]-radioactivity excreted in faeces expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$fe_{urine,0\text{-}tz}$	Fraction of [^{14}C]-radioactivity excreted in urine expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point
$Fe_{urine,\ 0\text{-}tz}$	Fraction of administered drug excreted unchanged in urine from time point t_1 to t_2
$Fe_{urine,\ t1\text{-}t2}$	Fraction of administered drug excreted unchanged in urine from time point t_1 to t_2
FSGS	Focal segmental glomerulosclerosis
FU	Follow-up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
gMean	Geometric mean
hADME	Human ADME (absorption, distribution, metabolism, and excretion)
HC	Haematocrit in decimal
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
ICRP	International Commission on Radiological Protection

IEC	Independent Ethics Committee
INR	International Normalized Ratio
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LOAEL	Lowest observed adverse effect level
MATE1	Multidrug and toxin extrusion
MATE2-K	Splice variant of multidrug and toxin extrusion 2 transporter
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NOAEL	No observed adverse effect level
OCT1	Organic cation transporter 1
OCT2	Organic cation transporter 2
PCR	Polymerase chain reaction
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
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)
$RAUC_{0-\infty,\ M/P}$	Ratio of $AUC_{0-\infty}$ of metabolite and $AUC_{0-\infty}$ of parent compound after oral administration
$RAUC_{0-\infty,M/Rad}$	Ratio of $AUC_{0-\infty}$ of metabolite and $AUC_{0-\infty}$ of [^{14}C] radioactivity in plasma after oral administration
$RAUC_{0-\infty,P/Rad}$	Ratio of $AUC_{0-\infty}$ of parent compound and $AUC_{0-\infty}$ of [^{14}C] radioactivity in plasma after oral administration
[redacted]	[redacted]
SAE	Serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose

$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TRPC6	Transient receptor potential cation channel 6
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
UGT1A4	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
[redacted]	[redacted]

1. INTRODUCTION

With Clinical Trial Protocol (CTP) version 3.0 an additional cohort (cohort 2b) is introduced for the following reason. During trial conduct, due to processing errors of plasma samples taken for metabolite profiling from the first 8 subjects receiving the microtracer approach (cohort 2a), an appropriate and reliable metabolite profiling for plasma samples could not be done. Subjects in cohort 2b will receive the same treatment as cohort 2a, i.e., a single dose of BI 764198 (C-14) using the microtracer approach, mainly to enable metabolic profiling for plasma samples of this approach. Furthermore, preliminary data of the ongoing trial show that the release criteria were met at discharge on Day 10 in most subjects in the previous cohorts (microtracer and classical hADME) on the main study endpoints.
Therefore:

- an abbreviated assessment schedule is applied to cohort 2b (see Flow Chart 2b), which enables bridging of the results measured in cohort 2a and 2b
- the release criteria in excreta and blood described for cohort 1 and cohort 2a (see Section 3.1) do not apply to cohort 2b
- primary endpoints are determined for cohort 1 and cohort 2a only
- data from cohort 2a and cohort 2b will be pooled for the statistical analysis, where applicable
- the sample size assessing the microtracer approach is doubled compared to the classical human ADME approach for certain applicable measurements.

Refer to the applicable protocol sections for further details.

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 764198, an oral, small-molecule inhibitor of the transient receptor potential cation channel 6 (TRPC6), in Chronic Kidney Disease (CKD) and specifically for the treatment of focal segmental glomerulosclerosis (FSGS), a proteinuric glomerular disease, on top of standard of care.

TRPC6 is a tetrameric, non-selective cation channel expressed in several renal cell types including podocytes, which are crucial cells for the glomerular filtration function of the kidney. Gain of function mutations in TRPC6 have been demonstrated to cause hereditary FSGS based on its role in regulating intracellular calcium concentration in podocytes and inducing cytoskeletal rearrangements. These effects have been linked to podocyte foot process detachment and loss, and consequently disruption of the glomerular filtration barrier.

FSGS is a leading glomerular cause of End Stage Kidney Disease (ESKD) in the United States. FSGS refers to a histologic pattern that is a characteristic of perhaps distinct underlying aetiologies sharing a common theme of podocyte injury and depletion [P17-08386].
FSGS is characterised by histologic lesions as opposed to a specific disease. FSGS is a pathophysiological entity which commonly explains the onset of nephrotic syndrome in adult or paediatric patients. Histological abnormalities contain sclerosis in segmental (parts) of focal (some) glomeruli as assessed by microscopic investigation of kidney biopsies.

FSGS is a frequently found histopathologic lesion in adults with nephrotic syndrome within the United States accounting for 35% of all cases and >50% among African Americans [R20-3949 and R20-3978].

It is hypothesised that increased TRPC6 activity could be a principal mechanism in proteinuric kidney disease driving progression to ESKD. Therefore, BI 764198 as TRPC6 inhibitor may be a novel treatment option by limiting TRPC6 channel activity in case of pathological Ca^{2+} entry which should result in preserved podocyte function and reduced podocyte loss.

TRPC6 is expressed in several renal cell types, including podocytes which are key cells for glomerular filtration function of the kidney. Multiple gain of function mutations in TRPC6 have been demonstrated to cause FSGS by elevating intracellular calcium concentration in podocytes and inducing cytoskeletal rearrangements. This has been linked to podocyte apoptosis, foot process detachment and loss of podocytes, leading to disruption of the glomerular filtration barrier. The modulation of TRPC6 activity should therefore have the potential to improve both podocyte function and survival in proteinuric glomerular diseases and specifically in FSGS.

1.2 DRUG PROFILE

1.2.1 BI 764198

BI 764198 is an oral, small-molecule inhibitor of TRPC6. It is being developed for the treatment of advanced chronic kidney disease on top of standard of care.

Mode of action:
BI 764198 is a potent inhibitor of human TRPC6 [redacted], rat TRPC6 [redacted], mouse TRPC6 [redacted], dog TRPC6 [redacted] and cynomolgus monkey TRPC6 [redacted] in *in vitro* manual patch clamp assays using human HEK293 cells with inducible TRPC6 expression.

[redacted]

[redacted]

[redacted]

For a more detailed description of the drug profile of BI 764198, please refer to the current Investigator's Brochure (IB) [c23359245].

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 764198 as well as the resulting PK parameters and [^{14}C]-radioactivity in blood, plasma, urine and faeces both via a classical hADME and a microtracer hADME approach in healthy male volunteers. [redacted]

The investigation of these processes, including the quantitative assessment of elimination pathways and drug metabolites, is necessary for an in-depth understanding of the pharmacokinetics of BI 764198 and further development of the compound. In addition, the

quantitative determination of elimination pathways and data on drug metabolites are required for application to regulatory authorities. [R22-3641]

1.3.1 Nomenclature

In this clinical trial protocol, the following nomenclature is used:

- [^{14}C]-radioactivity: Radioactivity measured by [^{14}C]
- BI 764198 (C-14): [^{14}C]-labelled [redacted] mixture of "hot" and "cold" drug substance for treatment 1
- [C-14] BI 764198: [^{14}C]-labelled [redacted] BI 764198 compound labelled with ^{14}C ("hot" drug substance) for treatment 2
- BI 764198: non-radioactive compound ("cold" drug substance)
- BI 764198 (C-14) [^{14}C]-labelled [redacted]: Final drug product, mixture of "hot" and "cold" drug substance for treatment 1
- BI 764198 (C-14) [^{14}C]-labelled [redacted] Final drug product, mixture of "hot" and "cold" drug substance for treatment 2

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 764198, as a novel treatment which may have the potential to improve both podocyte function and survival in proteinuric glomerular diseases and specifically in FSGS.

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 764198		
[redacted]	[redacted]	[redacted]
[redacted]	[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
Radioburden Exposure to radioactivity, due to [^{14}C]-labelling of BI 764198 for the purposes of this trial. Refer to Section 1.3, 4.1, and Appendix 10.1.	The effective dose that each subject receives from one administration of 3.7 MBq in the hADME arm is approximately 0.51 mSv. This effective dose is within the limit proposed by ICRP Category 2a, (<1 mSv – risk defined as minor). For hADME studies an effective dose of 0.1 – 1.0 mSv is considered acceptable [R18-1836; R18-2184]. For details on the radiation burden calculation for the classical hADME please refer to Appendix 10.1. In the microdose arm, subjects will receive a much lower dose of 0.1 MBq (37x below the dose of the classical hADME arm).	To minimize any risks resulting from exposure to ionizing radiation in this trial female subjects will be excluded from study participation as well as subjects with previously high exposure to radiation. In addition, a conservative approach will be adopted. Male subjects will be required to maintain the contraception and to refrain from donating sperm for 90 days (i.e., the duration of one spermatogenic cycle and residence time for unejaculated sperm), in case a potential harm to the germ cell occurs due to the exposure to the radioactive tracers (Section 3.3.3 and Section 4.2.2.3).
[redacted]	[redacted]	[redacted]
[redacted]	[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
Trial procedures		
Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain	General risk by venipuncture or by in-dwelling venous catheter for blood sampling, is considered acceptable in the context of trial participation.	Medical expertise of the trial site
Loss of blood due to blood samples	The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.	Close monitoring and follow-up of trial subjects for any adverse events
Other risks		
Pandemic situations (i.e. SARS-CoV-2)	Travelling to site, being at site for assessments (standard risk in the current pandemic situation).	•Travel is reduced to a minimum. •Appropriate testing and infection control during the study. •For possible additional modifications in pandemic situation see Flow chart and site-specific risk management procedure.

Risks associated with administration of BI 764198 during SARS-CoV-2 pandemic:

Based on its mode of action, BI 764198 is not expected to have any relevant impact on the susceptibility to an infective agent (including SARS-CoV-2) or the course of an infection. For a more detailed, COVID-19 related information, please refer to the current IB [c23359245]

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 764198 are well understood.

The results of this trial are necessary for further development of BI 764198.

Based on Phase I clinical trial data, BI 764198 was overall well tolerated up to a single dose of [redacted] and daily doses of [redacted] for up to 14 days in healthy volunteers. BI 764198 is not considered a high-risk compound for clinical studies.

The dose to be administered in both treatments is a single dose of [redacted]

The risks to healthy male volunteers in this single-dose hADME / microtracer trial are considered acceptable. Appropriate measures will be taken to minimize the risks and potential side effects for participants. The risks of the participating volunteers are considered justified when compared to the potential benefits of this trial.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with kidney disease characterized by significant proteinuria, the expected benefit of a successful clinical development of BI 764198 outweighs any potential risks.

Appropriate measures will be applied to minimize the risk for trial participants in the context of the SARS-CoV-2 pandemic. The expected benefit of a successful clinical development of BI 764198 outweighs any potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the basic pharmacokinetics of BI 764198 and [redacted], total radioactivity including mass balance, excretion pathways and metabolism including [redacted] following a single oral dose of (i) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME classical approach), and (ii) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME microtracer approach) given to healthy male subjects.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 764198 for each respective approach (classical hADME and microtracer hADME):

Mass balance recoveries of total radioactivity in urine and faeces:

- $fe_{urine,0\text{-}tz}$ (fraction of [^{14}C]-radioactivity excreted in urine expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)
- $fe_{faeces,0\text{-}tz}$ (fraction of [^{14}C]-radioactivity excreted in faeces expressed as percentage of the administered dose over the time interval from 0 to the last quantifiable time point)

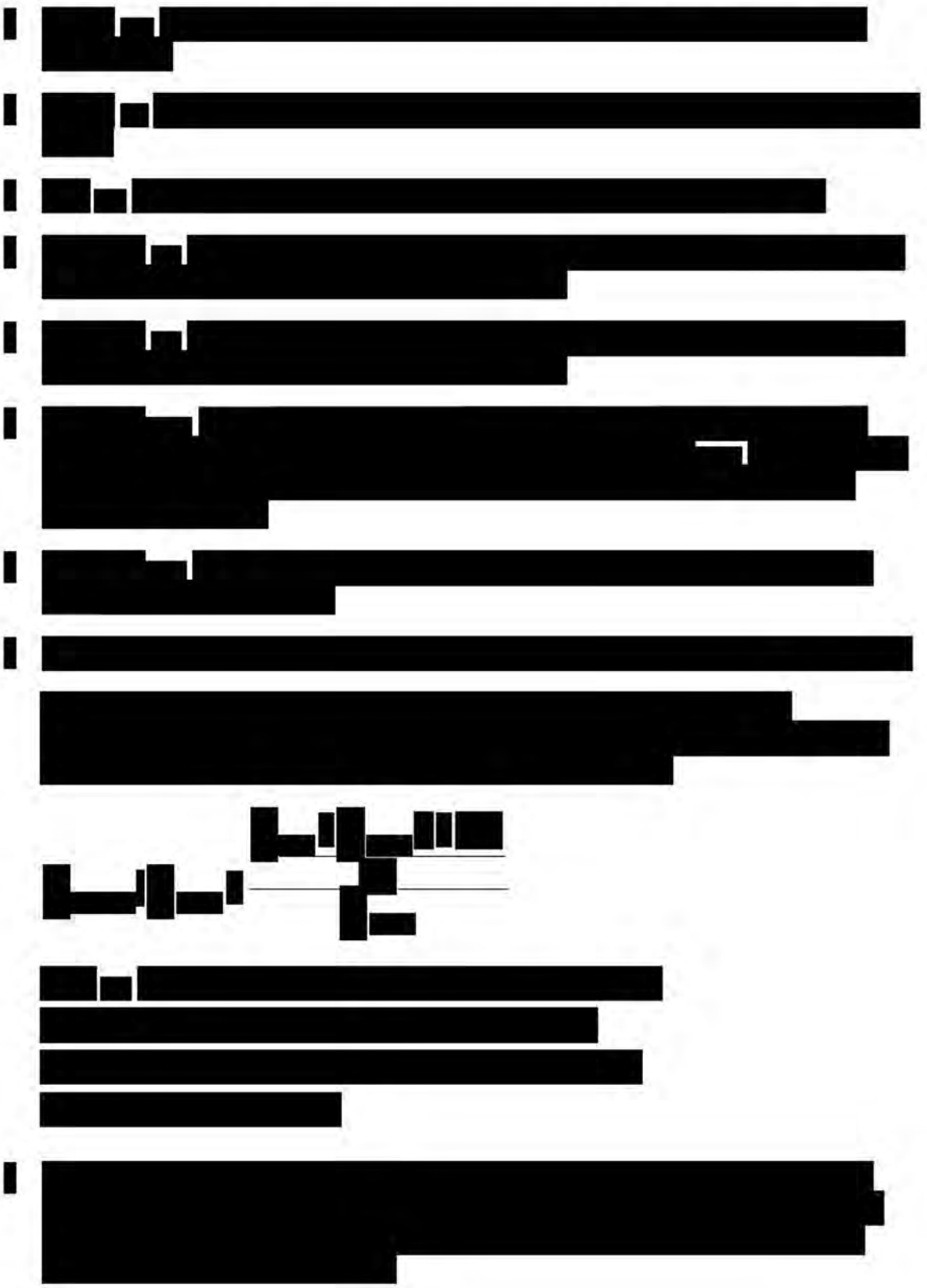
2.1.3 Secondary endpoints

The following endpoints will be determined for [^{14}C]-radioactivity and for BI 764198:

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

[redacted]

[redacted]



[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial will be performed as an open-label, non-randomised, single-dose, single-period, two-arm phase I trial in healthy male subjects in order to investigate the mass balance of excretion as well as the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution.

The difference between the two study arms is the approach used to assess the trial objectives (refer to Section 1.3 for rationale). Study arm 1 uses a classical hADME and study arm 2 uses a microtracer approach. With CTP version 3.0 an additional cohort assessing the microtracer approach was introduced, see Section 1. Thus, study arm 2 consists of 2 cohorts: cohort 2a and cohort 2b. Subjects are assigned to study arms using a 1:2 allocation ratio and based on their actual temporal availability, see Section 4.1.3.

For details on the investigational treatment, please refer to Section 4.1.

The planned radioactive dose per subject for the classical hADME cohort is 3.7 MBq (approximately 0.51 mSv).
Please refer to Appendix 10.1. for further details on radioactive dose calculation.
The planned radioactive dose per subject for the microtracer hADME cohort is 0.1 MBq.

The trial will consist of 3 visits: screening (visit 1), treatment and sampling phase (visit 2) and end of study (visit 3). For details refer to individual Flow Charts and section 6.2.2.

Subjects' individual study duration may vary depending on the time the release criteria are reached (see below). End of study may be reached on Day 10 at the earliest but is not expected to occur later than Day 31.

Following an ambulant screening phase of up to 20 days, subjects will stay at the trial site for 11 days, from admission on Day -1 (the afternoon before they will receive trial medication BI 764198 (C-14) on Day 1) until Day 10. During the in-house period, blood samples for PK assessment as well as urine and faeces will be collected for [^{14}C]-radioactivity assessment, pharmacokinetics and metabolic profiling as described in the Flow Chart. Sampling of faeces and urine will be stopped when release criteria for radioactivity recovery have been met (at the earliest on Day 10). If release criteria have not been met at the time of initial discharge, subjects will be readmitted to site up to three times for additional 24 h in-house collection of urine and faeces, respectively.

For the assessment of release criteria 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.

Based on available data, additional 24 h in-house sampling after Day 10 will not be performed any longer/will be stopped, once the following release criteria are met:

- Greater than or equal to 90% of the administered dose has been recovered in urine and faeces combined over the investigational period

and

- If <1% of the [^{14}C] dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h intervals

Note, for calculation of release criteria the fraction of administered [^{14}C] dose in urine will be rather underestimated as it will be based on the available samples, only. For the final analysis, the total excreted [^{14}C]-radioactivity in urine and faeces will be derived including an interpolation method to account for the time periods without samples taken (see Section 7.2.2).

Irrespective of whether the release criteria have been met or not on Day 31, no further sample collection is planned.

Refer to Section 5.3.2.1.1 for stopping criteria for blood samples used analysis of [^{14}C]-radioactivity and quantification of BI 764198 and its metabolites.

For the additional microtracer cohort (cohort 2b) the above-stated release criteria do not apply, see Section 1 for reasoning and Flow Chart 2b for timing of planned assessments. Discharge will take place on Day 10 and the end-of-study visit 1 to 7 days thereafter. No additional 24 h in-house sampling is required.

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

An open-label, non-randomised, single-dose treatment is a standard design for hADME trials. Including a separate control group is not required for this investigation as non-radioactive (blank) samples will be obtained from each subject prior to the administration of the radio-labelled drug.

As described above, two separate study arms will be used for the classical hADME and the microtracer approach,

Blinding is not required as all subjects per arm will receive the same treatment, respectively. Furthermore, the main endpoints cannot be subjectively influenced as they are determined in urine, faecal and blood samples.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 24 healthy male subjects enter the trial (8 subjects in study arm 1, 16 subjects in study arm 2) to get at least 6 evaluable subjects per cohort in line with current

guidelines for hADME trials [R22-3641] for the main endpoints. Refer to Section 1 for reasoning of the greater sample size for study arm 2.

They will be recruited from the volunteers' pool of the trial site, or, if necessary, recruited via external databases and advertisements.

Only male subjects will be entered into the trial.

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 at screening or the applicable time points indicated below:

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 65 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 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

[redacted]

9. History of relevant orthostatic hypotension, fainting spells, or blackouts
10. Relevant chronic or acute infections
11. 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
12. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
13. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation); as well as vaccination of any kind with or without re-vaccination required during the course of the trial
14. 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
15. Smoker (more than 5 cigarettes or 1 cigar or 1 pipe per day)
16. Inability to refrain from smoking on specified trial days
17. 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)
18. Drug abuse or positive drug screening
19. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
20. Intention to perform excessive physical activities within 4 days prior to the administration of trial medication or during the trial
21. Inability to comply with the dietary regimen of the trial site

[redacted]

24. 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

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 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 1.2.2, the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer.

2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events (AEs), or diseases)
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 early discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if more than two subjects have drug-related severe non-serious adverse events, or if at least one drug-related serious adverse event is reported. In this case, the collection of pharmacokinetic samples and other scheduled activities should continue, if possible, without undue risk to already dosed volunteer(s).

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 a subject does not complete the trial (including subjects non-evaluable for PK analysis), they may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from assessments because of a drug-related adverse event will not be replaced.

The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide in mutual agreement with the principal investigator, if and how many subjects will be replaced, i.e., how many subjects will be additionally recruited and considered in the analysis. The total number of replacements may not exceed 1/3 of the total number of evaluable subjects anticipated to complete the trial. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment cohort as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 764198 (C-14) is administered as oral solution. The oral solution contains a mixture of [^{14}C]-BI 764198 and non-radiolabelled BI 764198 and is manufactured by [redacted]

Refer to Section 1.3.1 for nomenclature.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Treatment 1:

Name:	BI 764198 (C-14) oral solution Containing [redacted] [^{14}C]-radiolabelled BI 764198 corresponding to a radioactive dose of 3.7 MBq (0.51 mSv)
Substance:	BI 764198 mixed with [^{14}C]-BI 764198 ([redacted]-labelled)
Pharmaceutical formulation:	oral solution
Source:	[redacted]
Unit strength:	[redacted]
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	single dose

Treatment 2:

Name:	BI 764198 (C-14) oral solution Containing a radioactive dose of approximately 0.1 MBq (< 0.1 mSv) Containing [redacted] [^{14}C]-radiolabelled BI 764198
Substance:	BI 764198 mixed with [^{14}C]-BI 764198 ([redacted]-labelled)
Pharmaceutical formulation:	oral solution
Source:	[redacted]
Unit strength:	[redacted]
Posology:	1-0-0
Mode of administration:	Oral

Duration of use: single dose

4.1.2 Selection of doses in the trial

[redacted]

Treatment 1: The final oral solution is characterized by a radioactivity of approximately 3.7 MBq / [redacted], corresponding to an effective radiation burden of about 0.51 mSv (see Appendix 10.1). To trace the [redacted]-labelled compound a radioactive dose of about 3.7 MBq is considered necessary to provide an adequate analytical sensitivity to enable metabolite quantification in a sufficiently low range.

Treatment 2: In this treatment arm a microtracer approach is used. To trace the [redacted]-labelled compound a radioactive dose of approximately 0.1 MBq is considered sufficient. This radioactive dose is considered sufficient to allow the detection of all expected metabolites for this label at all time points in plasma without falling below the LLOQ of an AMS setup.

4.1.3 Method of assigning subjects to treatment groups

The hADME and microtracer approach will be investigated using separate cohorts. The microtracer approach will consist of two cohorts (both receiving Treatment 2), as described in Section 1 and 3.1. Treatment of all subjects per cohort on the same calendar day is acceptable (for discussion of trial-associated risks and safety measures, see Section 1.4). In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several sub-cohorts as required.

Prior to the screening visit, subjects will be informed about the planned visit dates. The subjects willing to participate will be assigned to the cohort, i.e. planned treatment, according to their temporal availability. Therefore, the allocation of subjects to treatments is not influenced by trial personnel, but only by the subjects' actual availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the treatment groups are not expected.

The study subject numbers will be allocated to the subjects in a consecutive order on the morning of Day 1, prior to dosing. 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

This is an open-label, two-arm, single-period trial. Subjects will receive either Treatment (T) 1 or Treatment 2, depending on the cohort they are assigned to. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
Treatment 1 (hADME)	BI 764198 (C-14) with [^{14}C]-[redacted]-labelled compound	Oral solution	[redacted]	[redacted]	[redacted]
Treatment 2 (microtracer)	BI 764198 (C-14) with [^{14}C][redacted]-labelled compound	Oral solution	[redacted]	[redacted]	[redacted]

Both treatments will be administered in a similar fashion. Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. 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 sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g., reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture) except for medical examination or if necessary for any medical reasons (e.g., AEs).

For subjects in cohorts (1 and 2a) with urine and faeces sampling: In case release criteria for radioactivity recovery have not been met on Day 10, subjects will come back to the unit for up to 3 once-weekly 24 h sampling periods until release criteria are met or after the last collection interval Day 29-31 was completed (see Section 3.1).

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 Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany will provide radiolabelled [C-14] BI 764198, BI 764198 (C-14)

as well as non-[^{14}C]-labelled BI 764198 to [redacted] manufacturing of the oral solutions of BI 764198 (C-14) for each of the cohorts and their provision to the trial site.

Drug product manufacturing is done by [redacted] The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The trial medication will be dispensed in [redacted] Investigational Drug Products and labelled according to EU GMP guideline and local drug law.

The final clinical trial supply consists of [redacted] containing [redacted] for treatment 1.
The final clinical trial supply consists of [redacted] containing [redacted] for treatment 2.

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 EuCT 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 delivered from the manufacturing site (cf. Section 4.1.6) 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
- Availability of licence for clinical research using radioactive isotopes

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. However, in case of adverse events necessitating treatment, the required concomitant therapy and medical treatment will be permitted. [redacted]

All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

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

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

Alcoholic beverages are not allowed within 48 h before the screening visit and before first admission to and during in-house confinement at the trial site. During ambulatory phases alcohol consumption is restricted to 2 units per day.

[redacted]

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 24 h before first admission to and during in-house confinement at the trial site.

Consumption of poppy-seed containing products is not permitted from 72 h prior to drug screening (at Screening visit and on Day -1).

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sport) should be avoided from 4 days before the administration of trial medication until the end of study examination.

[redacted]

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication at the trial site under the supervision of the investigating physician or a designee. The measured plasma concentrations

as well as 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-study examination, medical examination will include the review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including body weight.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (Dinamap CareScape VC150, GE Medical Systems) 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 at screening, Day -1 and at EOS visit (with the exception of blood sampling for haematocrit, only, where no fasting is required). At the discretion of the investigator or designee, overnight fasting is not required for drug screening, for infectious serology and for re-tests.

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.

SARS-CoV-2 testing will be done as specified in the Flow Chart.

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
	Reticulocytes, absol.	X	X
	Reticulocytes/Erythrocyte	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leucocytes; Eosinophils/Leucocytes; Basophils/ Leucocytes; Monocytes/Leucocytes; Lymphocytes/Leucocytes	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 [redacted]	Neut. Poly (segs)/Leucocytes [%]; Eosinophils/Leucocytes [%]; Basophils/ Leucocytes [%]; Monocytes/Leucocytes [%]; Lymphocytes/Leucocytes [%];	(X)	(X)
Manual differential red blood cell count (if there is an abnormality in the blood cell count in accordance [redacted]	Only positive findings will be reported (for instance the presence of microcytes)	(X)	(X)
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time – INR (International Normalized Ratio)	X	X
	Fibrinogen	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
	Glutamate Dehydrogenase (GLDH)	X	X
	Creatine Kinase [CK]	X	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	(X)	(X)
	Lactic Dehydrogenase	X	X
	Lipase	X	X
	Amylase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Serum)	X	X
	Creatinine	X	X
	GFR/ CKD-EPI	X	X
	Cystatin C	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	Protein, Total	X	X
	Albumin	X	X
	C-Reactive Protein (Quant)	X	X
	Uric Acid	X	X
	Cholesterol, total	X	X
	Triglyceride	X	X

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B
Electrolytes	Sodium	X	X
	Potassium	X	X
	Chloride	X	X
	Calcium	X	X
	Phosphate (as Phosphorus, Inorganic)	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine RBC/Erythrocytes (qual)	X	X
	Urine WBC/Leucocytes (qual)	X	X
	Urine pH	X	X
Urine sediment (Urine sediment examinations will only be performed if there is an abnormality in urinalysis in accordance with Clinical Laboratory, standard procedures)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	(X)	(X)

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 and Visit 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. It is planned to perform these tests during screening only. However, drug screening will also be performed at admission to trial site on Day -1.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, an alcohol test in urine will be performed at screening and on Day -1 of the treatment period; the test 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 [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 (Mortara Eli 250 C) at the times provided in the Flow Chart.

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

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

All ECGs will be stored electronically on the ELI Link ECG System. 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 will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will not be entered or be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered ‘Always Serious’

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which, by their nature, can always be

considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. A copy of the latest list of 'Always Serious AEs' will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - 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 eDC. 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.

5.2.6.1.5 Intensity (severity) of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Sufficient discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

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

In rare cases, pregnancy might occur in a clinical trial. Once male subject has been enrolled in the clinical trial and has taken trial medication, the investigator must report any potential drug exposure during pregnancy if a partner of the 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.

The investigator must report any drug exposure during pregnancy immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form for Clinical Studies 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).

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. If there is an SAE and/or AESI associated with the pregnancy, an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood (whole blood and plasma), 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.

5.3.2 Methods of sample collection

5.3.2.1 Sampling of whole blood and plasma

Whole blood and plasma will be collected at time points indicated in the Flow Chart:

- To determine total [^{14}C]-radioactivity concentrations in whole blood and plasma [redacted]
- To identify additional metabolites of BI 764198 in plasma (to be reported separately)
- To determine the blood cell/plasma and blood/plasma ratios of [^{14}C]-radioactivity

5.3.2.1.1 Sampling of whole blood and plasma for [^{14}C]-radioactivity

For quantification [^{14}C]-radioactivity in whole blood and plasma, blood will be drawn by means of two separate blood collection tubes from an antecubital or forearm vein into an K2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Afterwards, separate aliquots of whole blood and plasma will be prepared for total radioactivity analysis.

Whole blood and plasma for [^{14}C]-radioactivity analysis in the classical hADME part:

For quantification of [^{14}C]-radioactivity in whole blood, 1 mL of blood will be drawn at the times indicated in the Flow Chart.
For quantification of [^{14}C]-radioactivity in plasma, 2 mL of whole blood will be drawn at the times indicated in the Flow Chart.

Whole blood and plasma for [^{14}C]-radioactivity analysis in the microtracer hADME part:

For quantification of [^{14}C]-radioactivity in whole blood (cohort 2a), 1 mL of blood (only at baseline:
5 mL of blood) will be drawn at the times indicated in the Flow Chart.
For quantification of [^{14}C]-radioactivity in plasma (cohort 2a and 2b), 2 mL of blood (only at baseline:
9 mL of blood) will be drawn at the times indicated in the Flow Chart.

Premature stopping of blood sampling

In case [^{14}C]-radioactivity in plasma samples is not detectable (< LLOQ) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the 216 hrs (day 10) sample have to be collected in any case. After day 10 (discharge), further blood samples for [^{14}C]-radioactivity will only be collected from subjects returning to trial site for additional 24 h collection of urine and faeces (cohorts 1 and 2a, as applicable).

5.3.2.1.2 Sampling for quantification of BI 764198 and [redacted]

For quantification of BI 764198 and [redacted], 2 mL of blood will be drawn at the time points indicated in the Flow Chart of the classical hADME arm.

For quantification of BI 764198 in plasma, 1 mL of blood will be drawn at the time points indicated in the Flow Chart of the microtracer hADME arm.

[redacted]

5.3.2.1.3 Sampling of plasma for metabolic profiling and [redacted]

Additional plasma samples will be obtained for the identification of drug metabolites. At each time point listed in the Flow Chart for metabolite profiling samples, blood will be withdrawn from a forearm vein. Predose 10 mL blood for the [redacted]-labeled microtracer study and predose 5 mL blood from the [redacted]-labeled classical hADME study will be taken. In the classical hADME part, blood samples will be taken at 1, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after drug intake, at the respective blood volume of 8 mL, 12 mL, 18 mL, 22 mL 45 mL, 70 mL, 70 mL, 40 mL 10 mL and 10 mL.
In the microtracer hADME part, blood samples will be taken at 1, 2, 4, 8, 12, 24, 36, 48, 72, and 96 hours after drug intake, at the respective blood volume of 10 mL, 20 mL, 25 mL, 25 mL, 40 mL, 55 mL, 55 mL, 35 mL, 10 mL and 10 mL.

[redacted]

For a detailed description of blood sampling, sample volume, sample handling, sample preparation, sample storage, tube labelling and sample shipment, refer to the laboratory manual.

5.3.2.1.4 Sampling of blood for haematocrit for blood cell/plasma ratio

At the time points listed in the Flow Chart, a blood sample of approximately 3 mL will be drawn for measuring haematocrit, which is needed for determination of blood cell/plasma ratio of [^{14}C]-radioactivity (see Section 2.2.2.1).

5.3.2.2 Urine sampling for pharmacokinetic analysis and metabolite profiling

During the trial urine for PK analysis and metabolite profiling will be collected from subjects of the applicable cohorts (1 and 2a) in defined containers at time points or in intervals as indicated in the Flow Chart.

- To determine [^{14}C]-radioactivity concentrations in urine
- To determine concentrations of BI 764198, and [redacted] in urine, if applicable
- To investigate the metabolite profiling of BI 764198 in urine

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. Subjects are told to empty their bladders at the end of each sampling interval.

The weight of the containers has to be determined prior to (empty containers) and at the end of the collection interval. The urine volume (weight will be set equal to volume, i.e., 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented. The exact start and end times of the urine collection intervals will be recorded in the CRF.

[redacted] Details about urine sample collection, required tubes, labelling of tubes, storage, and shipment (addresses) will be provided in the Laboratory Manual. At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned collection time.

All urine samples collected after the administration of trial medication are planned to be used for the determination of [^{14}C]-radioactivity and quantification of BI 764198 and [redacted] whenever appropriate. Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each urine sampling interval.
All urine samples will be collected quantitatively in portions up to Day 31 after the administration of trial medication. Refer to section 3.1 and 6.2.2 for sampling periods.

5.3.2.3 Sampling of faeces

Faeces will be collected from subjects of the applicable cohorts (1 and 2a) for the analysis of [^{14}C]-radioactivity and for metabolic profiling in the intervals indicated in the Flow Chart. A blank sample will be taken prior to administration of trial medication.

- To determine [^{14}C]-radioactivity concentrations in faeces
- To investigate the metabolite profiling of BI 764198 in faeces

All faeces samples collected after the administration of trial medication are planned to be used for the determination of [^{14}C]-radioactivity.
Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sampling interval.
All stools will be collected quantitatively in portions up to Day 31 after the administration of trial medication. Refer to section 3.1 and 6.2.2 for sampling periods.
The weight of the faeces and the exact times of faeces collection will be recorded in the eCRF.
For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the Laboratory Manual.

5.3.2.4 Handling of vomit

If vomiting occurs in a volunteer earlier than 2-fold the median [redacted] the administration of trial medication, the vomit will be collected for the determination of weight and [^{14}C]-radioactivity.

5.3.2.5 Further investigations

Back-up and left-over samples (blood, plasma, urine, faeces) not needed for their primary purpose may be used for other assessments within this trial or for further investigations as described below.
After analysis of the trial, the blood, plasma, urine, and faeces samples may be used for further methodological investigations (e.g., for stability testing, assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations.

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

5.3.3.1 Analytical determination of BI 764198 and its metabolites concentration in plasma

[redacted]

5.3.3.2 Analytical determination of BI 764198 and its metabolites concentration in urine

[redacted]

5.3.3.3 Metabolite profiling for plasma, urine, and faecal samples

[redacted]

[redacted]

5.3.3.4 Pharmacokinetics of Total Radioactivity and Excretion Balance

Classical hADME:
Determination of [^{14}C]-radioactivity concentrations in plasma, whole blood, urine, and faeces (and vomit, if applicable) [redacted]

Microtracer hADME:
Determination of [^{14}C]-radioactivity concentrations in plasma, whole blood will be [redacted]
Determination of [^{14}C]-radioactivity concentrations in urine, and faeces (and vomit, if applicable) [redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters and 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 administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (unless indicated differently in the Flow Chart).

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time up to 1 h post-dose ± 1 min.

After 1 h post-dose there is a 10% time window (for safety assessments) and a 5% time window (for PK blood/plasma sampling, metabolic profiling) of elapsed time since drug administration.

The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 h to the planned time.

If scheduled in the Flow Chart at the same time as a meal, 12-lead ECG recordings, followed by vital signs and blood sampling have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, 12-lead ECG recordings should be done prior to vital signs, and 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 and 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 beginning or end of a urine/faeces collection interval and a blood sample are scheduled for the same time point, urine/faeces collection should be done first, with withdrawal of the blood sample as closely to the planned time point as possible.

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

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.

Re-screening of individual subjects is allowed during the screening period as per the investigator's discretion. In such a case only the final re-screening results will be recorded in the eCRF. Initial screening results will be recorded in the subject's medical file.

6.2.2 Treatment period

Each subject will participate in one of the two treatment periods.

On Day -1, trial participants will be admitted to the trial site and kept under close medical surveillance for 24 h following the administration of trial medication in the morning of Day 1. The subjects will continue to stay on site and have further samples taken until discharge on Day 10 as indicated in the Flow Chart. Then they will be allowed to leave the trial site.

Note: For subjects in the additional microtracer cohort (2b) aimed at repeating blood sampling for plasma metabolite profiling and secondary endpoints, the following release criteria do not apply.

In those cohorts assessing release criteria (cohort 1 and 2a), a subject's individual end of study will vary depending on when the release criteria for radioactive recovery are met.

If release criteria have not been met (refer to section 3.1 for definition) at Day 10 (initial discharge), subjects will be readmitted to the trial site for up to three additional 24 h in-house periods for the collection of urine and faeces, 1, 2 and 3 weeks after the initial discharge, respectively. Within 24 h prior to each of these once-weekly in-house sampling periods, subjects are to collect faeces at home. These home collections will be used as a back-up option for analysis in case no defaecation occurs in the subsequent 24 h in-house collection period. If faeces are collected in the subsequent in-house collection period, the faeces previously collected at home will be discarded.

Once release criteria are met, the home collections of faeces and additional in-house sampling of urine and faeces will be stopped. If a subject is unable to attend one of these additional in-house sampling visits, they may be allowed to reschedule the visit, if needed.

Irrespective of whether release criteria have been met or not at the end of the last collection period on Day 31, no further sampling is planned.

For details on time points and procedures for the collection of blood, plasma, urine, and faeces samples, 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 the subject's written informed consent until the end of study examination.

For details on times of all of the 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 the study before the planned end 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

No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Subjects in cohort 2b receive the same treatment, using the same approach as for subjects in cohort 2a. However, for subjects in cohort 2b fewer endpoints are determined compared with cohort 2a, see Table 7.2.1 below.

Table 7.2.1: Overview of endpoints determined per cohort

Endpoints	Cohort 1	Cohort 2a	Cohort 2b
Primary endpoints	yes	yes	no
Secondary endpoints	yes	yes	yes
Further endpoints regarding			
Pharmacokinetic	yes	yes	yes*
Safety	yes	yes	yes

* Further PK endpoints for cohort 2b will be calculated as appropriate based on the available assessments.

In general, the descriptive analysis will be done by cohort: cohort 1, cohort 2a, cohort 2b and in addition for a general assessment of the microtracer approach, based on pooled data from cohorts 2a and 2b.

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 analyses of PK parameters will be based on the PKS.

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 764198 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}).
- Missing samples/concentration data at important phases of PK disposition curve

Plasma, urine, faeces and if applicable vomiting 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 descriptive statistics.

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

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 and based on the PKS.

To avoid underestimation of the total recovery of [^{14}C] in subjects who do not meet release criteria on Day 10, 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.

7.2.3 Secondary endpoint analyses

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

[redacted]

7.2.5 Safety analyses

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

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

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (see Section 1.2.2) 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'. 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 database lock 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.

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.

Vital signs 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 per study arm (approach) has been selected to provide at least 6 evaluable subjects, which are considered sufficient information to assess the main objectives of this trial. With CTP version 3.0 an additional cohort (cohort 2b) of 8 subjects is introduced also receiving treatment 2. Refer to Section 1 for rationale. Thus, the total sample size of the trial is planned to be 24.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator, and can be provided to the subjects upon request, 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 his 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.

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: gender, 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.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

[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 appointed by BI 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

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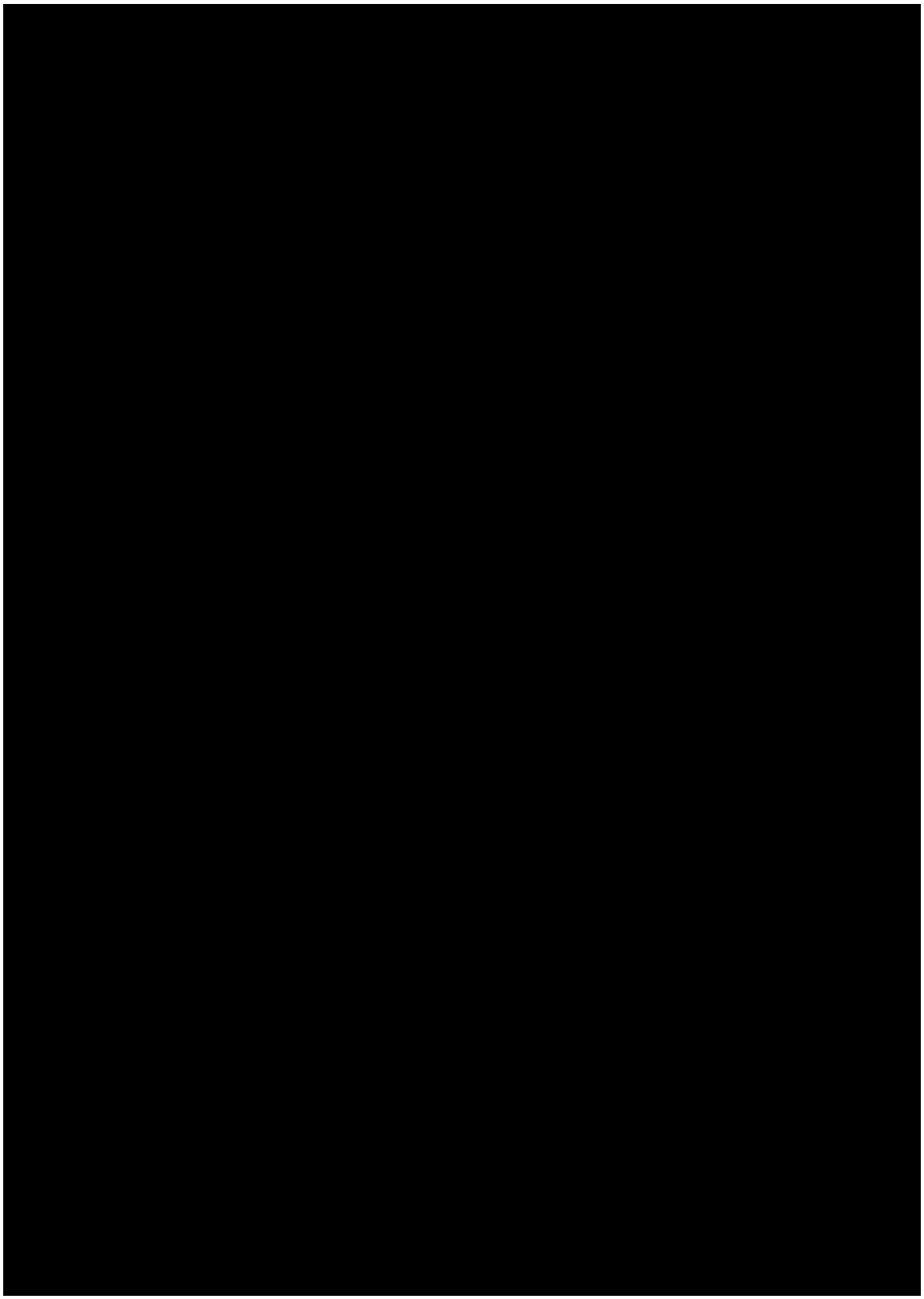
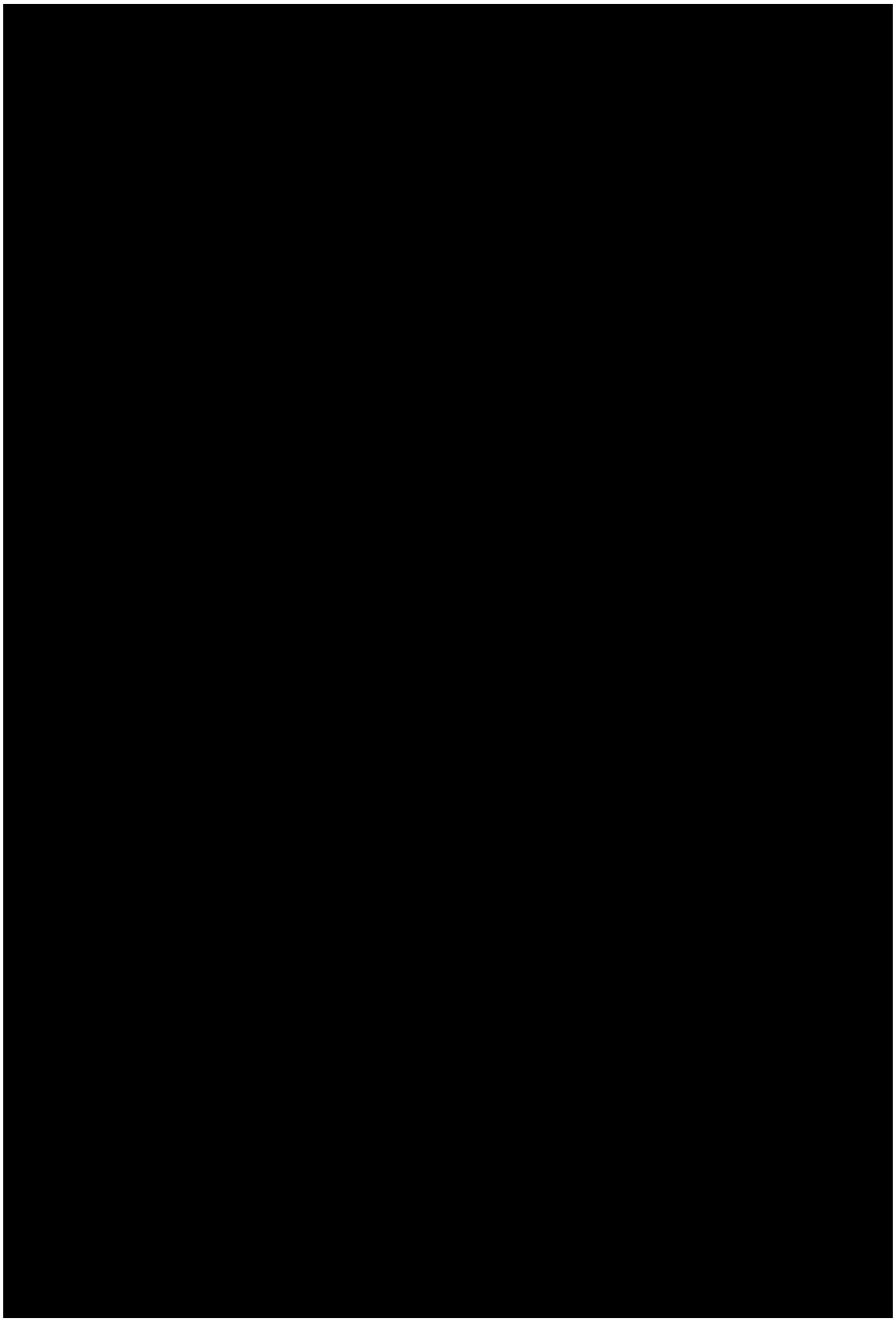
10. APPENDICES

10.1 RADIOACTIVE BURDEN CALCULATION



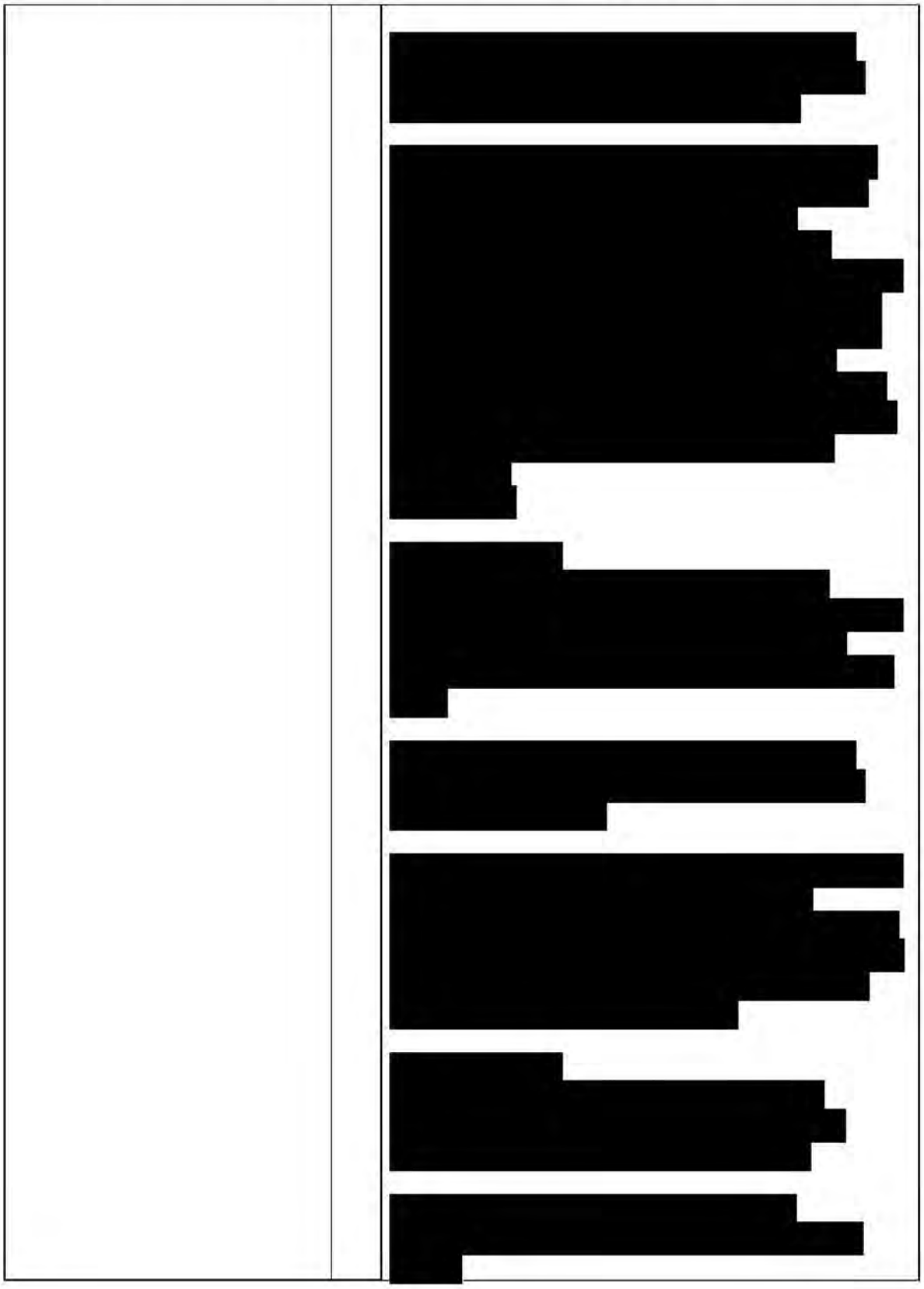


11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 May 2023
EU CT number		2022-502327-22-00
BI Trial number		1434-0016
BI Investigational Medicinal Product(s)		BI 764198
Title of protocol		A phase I, open-label, two-arm, non-randomised trial to investigate the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution using two different approaches in healthy male volunteers
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		FLOW CHART 2 (MICROTRACER HUMAN ADME)
Description of change		Column: "Blood sampling for PK and total radioactivity blood/plasma": blood sample at visit 2, day 10, planned time 216 h: respective field was not ticked as required. Respective field was ticked as required.
Rationale for change		To correct an oversight; to ensure consistency between flow chart 2 and other trial documents as well as calculation of total blood volume, in which this sample had been considered.
Section to be changed		FLOW CHART 2 (MICROTRACER HUMAN ADME)
Description of change		Column: "Safety laboratory": Footnote 13 was added to Safety Laboratory Set A at Screening
Rationale for change		To correct an oversight; to ensure consistency between Flow Chart 1 and 2 and the trial procedures described in Section 5.2.3
Section to be changed		ABBREVIATIONS AND DEFINITIONS
Description of change		- Where applicable: [14C]

		Was replaced by: [^{14}C] - Where applicable: AUC0-∞ *Was replaced by:* $AUC_{0-\infty}$
Rationale for change		Correction of formatting
Section to be changed		1.2.1 BI 764198
Description of change		Data from non-clinical toxicology studies were updated based on the most recent data in the Investigator's Brochure
Rationale for change		To provide the most current information (without any change in the overall risk profile)
Section to be changed		Table 1.4.2: 1 Overview of trial-related risks for this trial
Description of change		[redacted]



Rationale for change		[redacted]
Section to be changed		3.3.3 Exclusion criteria and 4.2.2.3 Contraception requirements
Description of change		Where applicable: patient *Was replaced by:* subject
Rationale for change		Correction of wording to match the trial population
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		5.3.2.2 Urine sampling for pharmacokinetic analysis and metabolite profiling
Description of change		[redacted]
Rationale for change		Correction of typo

Section to be changed		5.3.3.3 Metabolite profiling for plasma, urine, and faecal samples
Description of change		[redacted]
Rationale for change		Administrative change
Section to be changed		8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change		[redacted]
Rationale for change		Administrative change
Section to be changed		9.1 PUBLISHED REFERENCES
Description of change		*The following was added:* R20-3402: Recommendations related to contraception and pregnancy testing in clinical trials (version 1.1, CTFG 21/09/2020). Source: https://www.hma.eu/fileadmin/dateien/Human

		Medicines/01-About_HMA/Working_Groups/ CTFG/2020_09_HMA_CTFG _Contraception_ guidance_Version_1.1.pdf. (access date: 16 October 2020) ; Clinical Trial Facilitation Group (CTFG), Head of Medicine Agencies (HMA); 2020. R22-1956: Bowman CJ, Becourt-Lhote N, Boulifard V, et al. Science-based approach to harmonize contraception recommendations in clinical trials and pharmaceutical labels. Clin Pharmacol Ther 2022. doi:10.1002/cpt.2602
Rationale for change		To supplement further references in adapted non-clinical section

11.2 GLOBAL AMENDMENT 2

Date of amendment		10 Aug 2023
EU number		2022-502327-22-00
BI Trial number		1434-0016
BI Investigational Medicinal Product(s)		BI 764198
Title of protocol		A phase I, open-label, two-arm, non-randomised trial to investigate the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution using two different approaches in healthy male volunteers
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		Clinical Trial Protocol Synopsis and 2.1.1 Main objectives
Description of change		Trial objectives: To investigate pharmacokinetics of BI 764198 and its metabolites, total radioactivity including mass balance, excretion pathways and metabolism following oral administration to healthy male subjects either as a single oral dose of (i) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME approach) or (ii) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] group in a hADME with a microtracer approach). *Was replaced by:*

		To investigate pharmacokinetics of BI 764198 and its metabolites, total radioactivity including mass balance, excretion pathways and metabolism including [redacted] following oral administration to healthy male subjects either as a single oral dose of (i) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] in a hADME approach) or (ii) [redacted] BI 764198 (C-14) (with [^{14}C]-labelled [redacted] group in a hADME with a microtracer approach).
Rationale for change		To better reflect the further objective of metabolite profiling and [redacted]
Section to be changed		FLOW CHART 2
Description of change		Initial FLOW CHART 2 was renamed 2A and the following explanatory footnote (*) was added: *for the assessment of main endpoints
Rationale for change		To differentiate between flow chart for initial microtracer cohort and repeat cohort
Section to be changed		FLOW CHART 2
Description of change		FLOW CHART 2B was added
Rationale for change		To reflect new repeat cohort (2b) in a separate flow chart
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Number of subjects total entered: 16 on each treatment: 8 on treatment 1, 8 on treatment 2 *Was replaced by:* Number of subjects total entered: 24 on each treatment: 8 on treatment 1, 16 on treatment 2
Rationale for change		To reflect change in number of subjects due to additional microtracer cohort.
Section to be changed		1 Introduction
Description of change		*The following text was added:*

		With Clinical Trial Protocol (CTP) version 3.0 an additional cohort (cohort 2b) is introduced for the following reason. During trial conduct, due to processing errors of plasma samples taken for metabolite profiling from the first 8 subjects receiving the microtracer approach (cohort 2a), an appropriate and reliable metabolite profiling for plasma samples could not be done. Subjects in cohort 2b will receive the same treatment as cohort 2a, i.e., a single dose of BI 764198 (C-14) using the microtracer approach, mainly to enable metabolic profiling for plasma samples of this approach. Furthermore, preliminary data of the ongoing trial show that the release criteria were met at discharge on Day 10 in most subjects in the previous cohorts (microtracer and classical hADME) on the main study endpoints. Therefore: • an abbreviated assessment schedule is applied to cohort 2b (see Flow Chart 2b), which enables bridging of the results measured in cohort 2a and 2b • the release criteria in excreta and blood described for cohort 1 and cohort 2a (see Section 3.1) do not apply to cohort 2b • primary endpoints are determined for cohort 1 and cohort 2a only • data from cohort 2a and cohort 2b will be pooled for the statistical analysis, where applicable • the sample size assessing the microtracer approach is doubled compared to the classical human ADME approach for certain applicable measurements. Refer to the applicable protocol sections for further details.
Rationale for change		To provide a rationale for this protocol revision
Section to be changed		3.1 Overall trial design
Description of change		*The following text was added:* With CTP version 3.0 an additional cohort assessing the microtracer approach was introduced, see Section 1. Thus, study arm 2 consists of 2 cohorts: cohort 2a and cohort 2b. (…)

		For the additional microtracer cohort (cohort 2b) the above- stated release criteria do not apply, see Section 1 for reasoning and Flow Chart 2b for timing of planned assessments. Discharge will take place on Day 10 and the end-of-study visit 1 to 7 days thereafter. No additional 24 h in-house sampling is required.
Rationale for change		To add information on study arm (cohort) 2b
Section to be changed		3.1 Overall trial design
Description of change		Subjects are assigned to study arms using a 1:1 allocation ratio and based on their actual availability, see Section 4.1.3. *Was replaced by:* Subjects are assigned to study arms using a 1:2 allocation ratio and based on their actual temporal availability, see Section 4.1.3.
Rationale for change		To take account of new study arm (cohort) 2b
Section to be changed		3.3 Selection of trial population
Description of change		It is planned that 16 healthy male subjects enter the trial (8 subjects per arm) to get at least 6 evaluable subjects per cohort in line with current guidelines for hADME trials [R22-3641]. *Was replaced by:* It is planned that 24 healthy male subjects enter the trial (8 subjects in study arm 1, 16 subjects in study arm 2) to get at least 6 evaluable subjects per cohort in line with current guidelines for hADME trials [R22-3641] for the main endpoints. Refer to Section 1 for reasoning of the greater sample size for study arm 2.
Rationale for change		To take account of new study arm (cohort) 2b
Section to be changed		4.1.3 Method of assigning subjects to treatment groups
Description of change		*The following text was added:* The microtracer approach will consist of two cohorts (both receiving Treatment 2), as described in Section 1 and 3.1.
Rationale for change		To take account of new study arm (cohort) 2b

Section to be changed		4.1.4 Drug assignment and administration of doses for each subject
Description of change		*The following text was added in front of the last paragraph:* For subjects in cohorts (1 and 2a) with urine and faeces sampling:
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		5.3.2.1. Sampling of whole blood and plasma for [^{14}C]-radioactivity
Description of change		Whole blood and plasma for [^{14}C]-radioactivity analysis in the microtracer hADME part: For quantification of [^{14}C]-radioactivity in whole blood, 1 mL of blood (only at baseline: 5 mL of blood) will be drawn at the times indicated in the Flow Chart. For quantification of [^{14}C]-radioactivity in plasma, 2 mL of blood (only at baseline: 9 mL of blood) will be drawn at the times indicated in the Flow Chart. *Was replaced by:* For quantification of [^{14}C]-radioactivity in whole blood (cohort 2a), 1 mL of blood (only at baseline: 5 mL of blood) will be drawn at the times indicated in the Flow Chart. For quantification of [^{14}C]-radioactivity in plasma (cohort 2a and 2b), 2 mL of blood (only at baseline: 9 mL of blood) will be drawn at the times indicated in the Flow Chart.
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		5.3.2.1. Sampling of whole blood and plasma for [^{14}C]-radioactivity
Description of change		Premature stopping of blood sampling: *The following text was added:* After day 10 (discharge), further blood samples for [^{14}C]-radioactivity will only be collected from subjects returning to trial site for additional 24 h collection of urine and faeces (cohorts 1 and 2a, as applicable).
Rationale for change		To specify cohorts concerned for clarification

Section to be changed		5.3.2.1.3 Sampling of plasma for metabolic profiling and structural elucidation
Description of change		[redacted] *Was replaced by:* [redacted]
Rationale for change		Clarification: Additional samples were/will not be required and were therefore removed. [redacted]
Section to be changed		5.3.2.3 Sampling of faeces
Description of change		Faeces will be collected for the analysis of [^{14}C]-radioactivity and for metabolic profiling in the intervals indicated in the Flow Chart. *Was replaced by:* Faeces will be collected from subjects of the applicable cohorts (1 and 2a) for the analysis of [^{14}C]-radioactivity and for metabolic profiling in the intervals indicated in the Flow Chart.
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		5.3.2.5 Further investigations
Description of change		*The following text was added:* Back-up and left-over samples (blood, plasma, urine, faeces) not needed for their primary purpose may be used for other assessments within this trial or for further investigations as described below.
Rationale for change		To clarify the potential use of samples
Section to be changed		5.3.3.2 Analytical determination of BI 764198 and its metabolites concentration in urine
Description of change		[redacted]

		[redacted] *Was replaced by:* [redacted]
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		5.3.3.3 Metabolite profiling for plasma, urine, and faecal samples
Description of change		Radioprofiling of metabolites in plasma, urine, and faeces of the microtracer hADME study with the [^{14}C][redacted] label will be performed at [redacted] *Was replaced by:* Radioprofiling of metabolites in plasma, urine (only if applicable), and faeces (only if applicable) of the microtracer hADME study with the [^{14}C]-[redacted] label will be performed at [redacted]
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		6.2.2 Treatment Period
Description of change		*The following paragraph was added/modified:* Note: For subjects in the additional microtracer cohort (2b) aimed at repeating blood sampling for plasma metabolite profiling and secondary endpoints, the following release criteria do not apply. In those cohorts assessing release criteria (cohort 1 and 2a), a subject's individual end of study will vary depending on when the release criteria for radioactive recovery are met.
Rationale for change		To specify cohorts concerned for clarification
Section to be changed		7.2.1 General considerations
Description of change		*The following text was added:* Subjects in cohort 2b receive the same treatment, using the same approach as for subjects in cohort 2a. However, for subjects in cohort 2b fewer

<table>
<tr><td></td><td></td><td>endpoints are determined compared with cohort 2a, see Table 7.2.1 below.

Table 7.2.1: Overview of endpoints determined per cohort
<table><tr><th>Endpoints</th><th>Cohort 1</th><th>Cohort 2a</th><th>Cohort 2b</th></tr><tr><td>Primary endpoints</td><td>yes</td><td>yes</td><td>no</td></tr><tr><td>Secondary endpoints</td><td>yes</td><td>yes</td><td>yes</td></tr><tr><td>Further endpoints regarding</td><td></td><td></td><td></td></tr><tr><td>Pharmacokinetic</td><td>yes</td><td>yes</td><td>yes*</td></tr><tr><td>Safety</td><td>yes</td><td>yes</td><td>yes</td></tr></table>* Further PK endpoints for cohort 2b will be calculated as appropriate based on the available assessments.

In general, the descriptive analysis will be done by cohort: cohort 1, cohort 2a, cohort 2b and in addition for a general assessment of the microtracer approach, based on pooled data from cohorts 2a and 2b.</td></tr>
<tr><td>Rationale for change</td><td></td><td>To describe statistical approach under consideration of new study arm (cohort) 2b account</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Section to be changed</td><td></td><td>7.5 Determination of sample size</td></tr>
<tr><td>Description of change</td><td></td><td>The total sample size of the trial is planned to be 16.

Was replaced by:
With CTP version 3.0 an additional cohort (cohort 2b) of 8 subjects is introduced also receiving treatment 2. Refer to Section 1 for reasoning. Thus, the total sample size of the trial is planned to be 24.</td></tr>
<tr><td>Rationale for change</td><td></td><td>To reflect change in number of subjects due to additional microtracer cohort.</td></tr>
</table>

APPROVAL / SIGNATURE PAGE

Document Number: c38438177 **Technical Version Number:3.0**

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

Title: A phase I, open-label, two-arm, non-randomised trial to investigate the metabolism and pharmacokinetics of a single dose of BI 764198 (C-14) administered as oral solution using two different approaches in healthy male volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	10 Aug 2023 15:16 CEST
Approval-Clinical Program Leaders	[redacted]	10 Aug 2023 15:36 CEST
Author-Trial Statistician	[redacted]	10 Aug 2023 15:53 CEST
Verification-Paper Signature Completion	[redacted]	10 Aug 2023 16:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed