Clinical Trial Protocol

Document Number:	**c37738815-04**
EU CT No.	2022-502264-20-00
BI Trial No.	1397-0016 (CRO-No BID22145-22145X)
BI Investigational Medicinal Products	BI 1291583
Title	A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects
Lay Title	A study in healthy men to test how BI 1291583 is processed in the body
Clinical Phase	I
Clinical Trial Leader	[redacted]
[redacted] **Investigator**	[redacted]
Current Version, Date	Version 4.0, 13 Jun 2023
Original Protocol Date	22 Dec 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	22 December 2022
Revision date	13 June 2023
BI trial number	1397-0016
Title of trial	A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The trial is intended to investigate the basic pharmacokinetics, excretion pathways and metabolism of BI 1291583
Trial objective	• To assess the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces following a single oral dose [redacted] BI 1291583 (C-14) • To provide plasma and urine samples for pharmacokinetic investigations • To provide plasma, urine, and faeces samples for metabolic profiling and structural identification of metabolites

Trial endpoints	**Primary endpoints:** Primary endpoints will be the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces: • $fe_{urine,\ 0\text{-}tz}$ (fraction 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) Timeframe: The timeframe for determination of these endpoints depends on individual excretion/recovery of radioactivity and may vary between 2 and 6 weeks, inclusive, after drug administration. **Secondary endpoints:** The following secondary endpoints will be evaluated for [^{14}C]-radioactivity, BI 1291583 and five metabolites (M407(1) /BI 1373234, M396(1) / CD 18507, M397(1) / CD 17849, M549(1) / CD 16785 and M141(1) / CD 16426) in plasma: • C_{max} (maximum measured concentration of the analyte) • $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte over the time interval from 0 to the last quantifiable time point)
Trial design	Open-label, non-randomized, single-dose, single-arm, single-period design
Number of subjects **total entered** **on each treatment**	 8 8
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
Test product **dose** **mode of administration**	BI 1291583 (C-14) as oral solution [redacted] [redacted] containing a radioactive dose of approximately ≈ 0.36 MBq (0.04 mSv) Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	One day (day 1), single dose of radiolabelled oral solution (Test product)
Statistical methods	Descriptive statistics will be calculated for all endpoints

FLOW CHART

Period	Visit	Day	Planned time (relative to first drug administration) h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	Blood sampling for PK and total radioactivity[8]	Blood sampling for metabolic profiling[9]	Urine sampling [10]	Faeces sampling [11]	Vomit collection (if applicable)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-28 to -2			Screening (SCR)[1]	x[A]						x	x	
	2	-1	-18:00	14:00	Admission to trial site	x[B,5,17]				x[14]				▲
			-14:00	18:00	Light supper (voluntary)[3,15]				x					
		1	-1:00	07:00			x[2]	x[2]				x[2]	x[2]	
			0:00	08:00	Drug administration				▲	▲	▲			
			1:00	09:00		x[C]	x							
			1:30	09:30			x							
			2:00	10:00	240 mL fluid intake		x							
			3:00	11:00			x							
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]	x[C]	x	x					x	
			6:00	14:00			x							
			8:00	16:00	Snack[3]	x[C]	x	x						
			10:00	18:00			x							
			11:00	19:00	Dinner									
			12:00	20:00			x							
			13:00	21:00	Snack									
			14:00	22:00			x							
		2	24:00	08:00		x[B]	x	x			▼		x	x[18]
		3	48:00	08:00		x[C]	x	x						
		4	72:00	08:00		x[C]	x	x						
		5	96:00	08:00				x						
		6	120:00	08:00			x	x						
		7	144:00	08:00										
		8	168:00	08:00		x[C]	x	x						
		9	192:00	08:00										
		10	216:00	08:00		x[C]	x							
		11	240:00	08:00										
		12	264:00	08:00			x	x						
		13	288:00	08:00										
		14	312:00	08:00										
		15	336:00	08:00	Breakfast (voluntary), discharge from trial site[3,16]	x[B]	x	x	▼	▼		x	x	x[18]

Period	Visit	Day	Planned time (relative to first drug administration) h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	Blood sampling for PK and total radioactivity[8]	Blood sampling for metabolic profiling[9]	Urine sampling[10]	Faeces sampling[11]	Vomit collection (if applicable)	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy[6]
		20	461:00	13:00	Start home collection					▲				
		21	485:00	13:00	Admission to trial site[12,13]	x[17]	x	x	▲	┼				
		22	509:00	13:00	Discharge from trial site[12,19]				▼	▼				
		27	629:00	13:00	Start home collection					▲				
		28	653:00	13:00	Admission to trial site[12,13]	x[17]	x	x	▲	┼				
		29	677:00	13:00	Discharge from trial site[12, 19]				▼	▼				
		34	797:00	13:00	Start home collection					▲				
		35	821:00	13:00	Admission to trial site[12,13]	x[17]	x	x	▲	┼				
		36	845:00	13:00	Discharge from trial site[12, 19]				▼	▼				
		41	965:00	13:00	Start home collection					▲				
		42	989:00	13:00	Admission to trial site[12,13]	x[17]	x	x	▲	┼				
		43	1013:00	13:00	Discharge from trial site[12, 19]				▼	▼				▼
FU	3	42-50			End of study (EoS) examination[4]	x[D]						x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (such as race, and ethnic origin, including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. [redacted]
2. The time is approximate; the procedure is to be performed and completed within the 4 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. [redacted]
   EoS examination to be performed earliest on day 42 with the last blood samples (PK, metabolic profiling) or prior to discharge on Day 43, if all once-weekly 24 h sampling periods are needed. To provide flexibility for EoS appointments, EoS examination is allowed up to day 50.
5. Safety laboratory, serum/urine drug and alcohol screening will be done (see Section 5.2.3). For these activities there is a time window of ±4 hours.
6. AEs and concomitant therapies will be recorded throughout the trial; during in-house days subjects will be specifically asked for at least twice daily.
7. Safety laboratory sets (A, B, C, D) see Table 5.2.3: 1

8. Pharmacokinetics (PK): BI 1291583 and its metabolites [redacted] in plasma (see Section 5.3.2); [C-14] BI 1291583 total radioactivity in whole blood and plasma (see Section 5.3.2).
[redacted]
9. Metabolite 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.
[redacted]
10. Urine collection intervals (for PK of BI 1291583, and [^{14}C] -radioactivity assessment and metabolic profiling; planned time): On Day -1 or Day 1 (within 14 hours prior to dosing) pre-dose (blank) spot sample,
on Day 1 prior to start of urine collection voiding of the bladder,
0-4 , 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216 -240, 240-264, 264-288, 288-312, 312-336 hours after administration of BI 1291583 (C14). Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on Day 21.
Urine sampling for PK/[^{14}C]-radioactivity and metabolic profiling will be stopped when release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 15).
"┼ " means: end of last collection interval, start of following collection interval.
For details on sample usage see Section 5.3.2.2).
[redacted]
11. All stools ([^{14}C]-radioactivity and metabolic profiling) will be collected quantitatively in portions up to 336 hours (sampling intervals of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, 192-216, 216 -240, 240-264, 264-288, 288-312, 312-336 hours after administration of BI 1291583 (C14). Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on Day 20.
Further details regarding home collection see footnote 13. For blank sample see footnote 14.
Faeces sampling for [^{14}C]-radioactivity and metabolic profiling will be stopped when release criteria for radioactivity recovery (see Section 3.1) have been met (earliest stopping on Day 15).
"┼ " means: end of last collection interval, start of following collection interval. For details on sample usage see Section 5.3.2.3)
[redacted]
12. 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 hours to the planned time. However, the ambulatory onsite collections should be at least over 24 hours.
13. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 20-21, 27-28, 34-35, and 41-42.
If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), last faeces collected at home in the 24 h interval before admission be used instead for analysis.
14. Subjects will collect a pre-dose (blank) faeces sample at home or at the site on Days -2 (after screening, if screening is on Day -2), -1 or 1 (prior to dosing) in specific containers provided by [redacted]. Only the last pre-dose faeces sample will be analysed (if applicable).
15. Subjects are to be fasted for at least 10 h before drug administration.
16. Prior to discharge from trial site on Day 15 confirmation of fitness will be performed including physical examination, ECG, vital signs, safety laboratory, recording of AEs and concomitant medication.
17. Testing for SARS-CoV-2 (PCR or antigen test) will be performed on Day -1 prior to admission, on Day 2, and at each admission to the trial site for 24-hours visits. Additional tests may be performed as needed based on the current status of the pandemic.
18. [redacted]
19. Formal assessment and confirmation of fitness is based on questioning for adverse events and concomitant medication and personal judgement of the investigator.

*** Release criteria:**
Greater than or equal to 90% of the administered [^{14}C] 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

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
$Ae_{faeces,\ 0\text{-}tz}$	Amount of analyte eliminated in faeces from the time interval from time 0 to the last quantifiable time point
$Ae_{faeces,\ t1\text{-}t2}$	Amount of analyte that is eliminated in faeces from the time interval t_1 to t_2
$Ae_{urine,\ 0\text{-}tz}$	Amount of analyte that is eliminated in urine from the time interval from time 0 to the last quantifiable time point
$Ae_{urine,\ t1\text{-}t2}$	Amount of analyte that is eliminated in urine from the time interval t_1 to t_2
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
AMS	Accelerator mass spectroscopy
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
$\%AUC_{tz\text{-}\infty}$	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
$AUC_{0\text{-}tz}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC0-∞	area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CatC	Cathepsin C
CatG	Cathepsin G
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
DDI	Drug-drug interaction
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
F	Absolute bioavailability factor
$fe_{faeces,t1-t2}$	Fraction of administered drug excreted unchanged in faeces over the time interval from t_1 to t_2
$fe_{faeces,\ 0-tz}$	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
$fe_{urine,t1-t2}$	Fraction of administered drug excreted unchanged in urine over the time interval from t_1 to t_2
$fe_{urine,\ 0-tz}$	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
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
MBq	Megabecquerel
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
MRT_{ex}	Mean residence time of the analyte in the body, extravascular
mSv	Millisievert

NE	Neutrophil elastase
NOAEL	no observed adverse effect level
NSP	Neutrophil serine protease
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PLS	Papillon-Lefèvre-Syndrome
PR	Pulse rate
PR3	Proteinase 3
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)
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of childbearing potential
XTC	Ecstasy

1. INTRODUCTION

BI 1291583 is an inhibitor of cathepsin C (CatC) and is being developed for the treatment of bronchiectasis.

1.1 MEDICAL BACKGROUND

Bronchiectasis is a heterogenous respiratory syndrome characterised by abnormal and irreversible dilated bronchi. Patients with bronchiectasis can have a variety of symptoms which include persistent cough, production of large volumes of sputum, dyspnea, chronic fatigue and hemoptysis. These symptoms are burdensome and are often associated with social stigmatism, urine incontinence, anxiety, depression and a reduced quality of life.
Underlying etiologies range from well characterised genetic diseases such as Cystic Fibrosis (CF) and Primary Ciliary Dyskinesia (PCD), asthma, Chronic Obstructive Pulmonary Disease (COPD), post infectious sequelae, and various autoimmune diseases such as inflammatory bowel disease or rheumatoid arthritis. However, the largest single underlying etiology is not yet determined, or idiopathic, bronchiectasis. The incidence of bronchiectasis is increasing worldwide. Previously classified as a rare or orphan disease, bronchiectasis not related to cystic fibrosis is estimated at 53 to 566 cases per 100000 inhabitants. Prevalence increases with age and female gender [R21-3309; R21-3311].
Bronchiectasis is characterised by neutrophilic bronchial inflammation. Serine proteases released by neutrophils (NSP), such as neutrophil elastase (NE), cause structural damage to the airways, mucus gland hyperplasia, impaired mucus clearance, and result in a vicious cycle of recurrent severe infections and further airway damage [P13-15562]. Free airway NE is particularly high in patients with bronchiectasis [R18-3357]. Damaged and dilated airways filled with mucus are an ideal growth medium, leading to chronic colonization with pathogens such as Pseudomonas aeruginosa (P. aeruginosa).
Irreversibly dilated airways, mucus gland hyperplasia, and impaired mucus clearance leads to recurrent acute severe pulmonary infections, referred to as an exacerbation. Exacerbations are a hallmark of bronchiectasis, leading to further airway damage and increased mortality.
Even though airway dilation is irreversible, the consequences might be mitigated.
There is no registered therapy that ameliorates the neutrophilic inflammation and tissue destruction mediated by uncontrolled NSP activity in the airways.
The current key pharmacological management option is as-needed antibiotics to treat pulmonary exacerbations. Bronchodilators and/or inhaled corticosteroids are used ‘off-label’ and dependent on underlying etiology with limited supportive evidence. Chronic antibiotic treatment, mucoactive therapies and physiotherapy (airway clearance) are also used.
Consequently, the medical need for an efficacious anti-inflammatory treatment for bronchiectasis is high.
By suppressing key effectors of airway inflammation and tissue destruction, inhibiting Cathepsin C (CatC) is expected to have anti-inflammatory and tissue-preserving effects, as well as to reduce mucus hypersecretion and to restore effective clearance of pathogenic

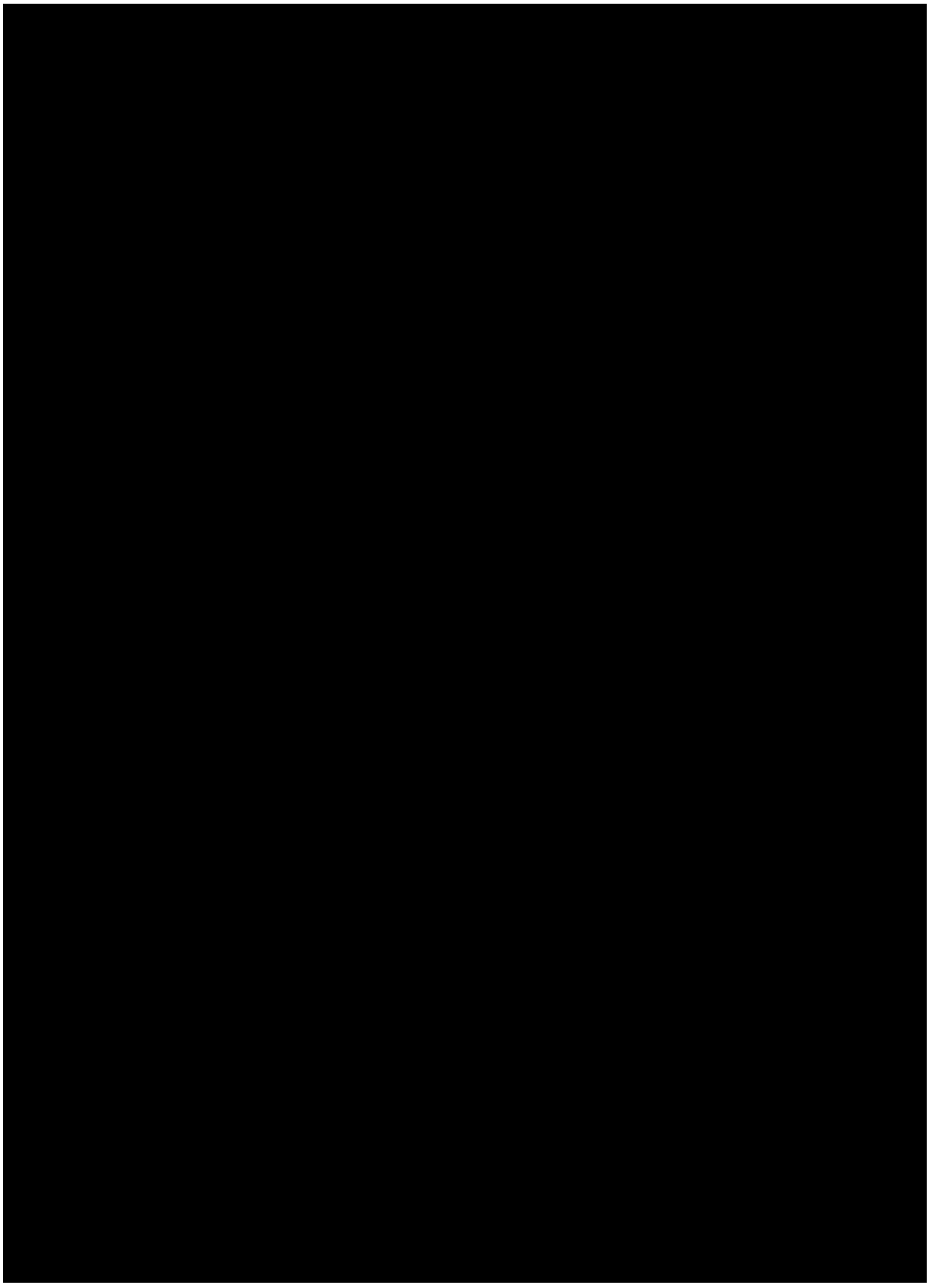
bacteria. CatC inhibition is expected to reduce the rate and severity of pulmonary exacerbations of bronchiectasis and hence reduce hospitalisations, improve symptoms of cough and sputum, and improve health-related quality of life.

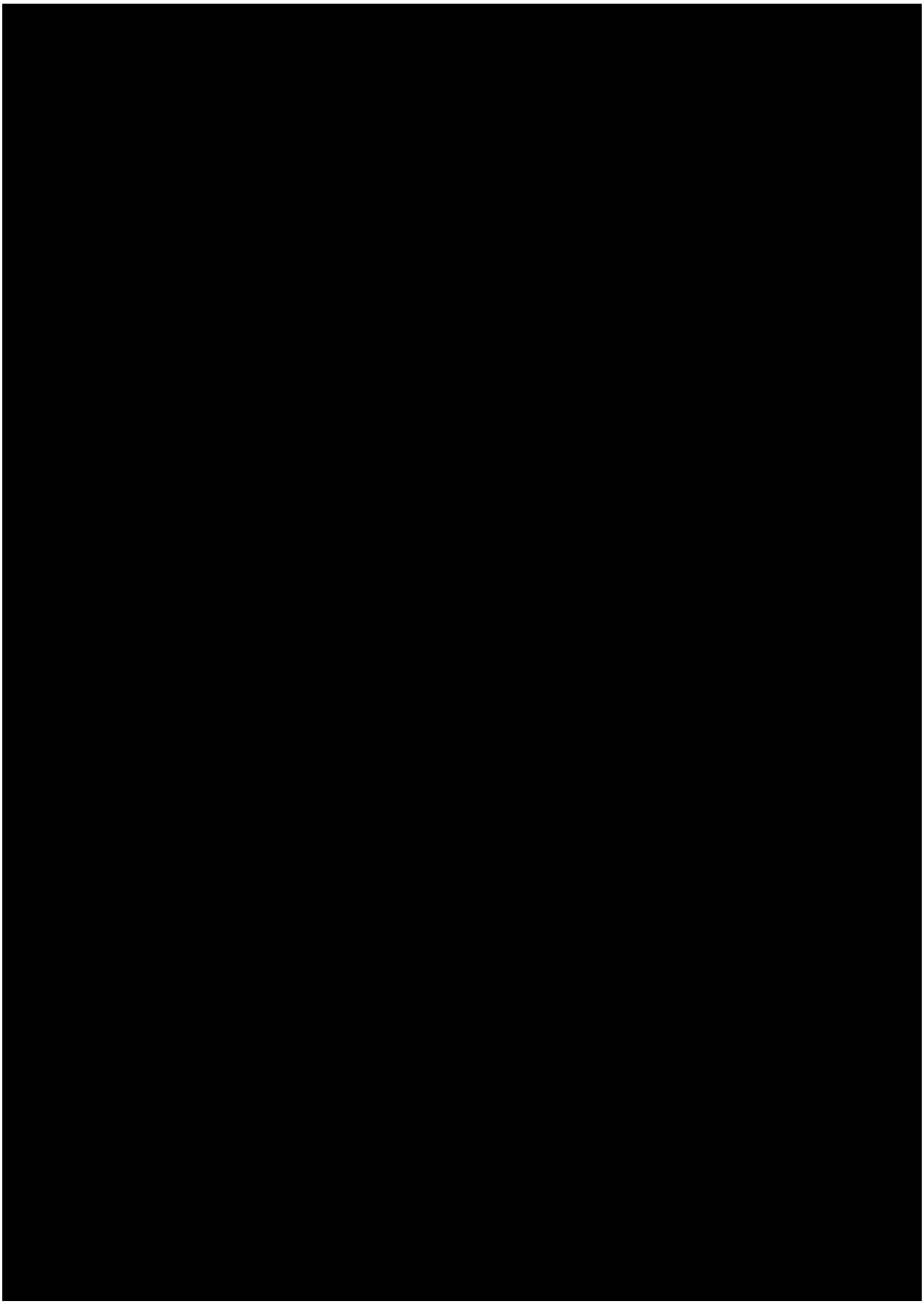
1.2 DRUG PROFILE

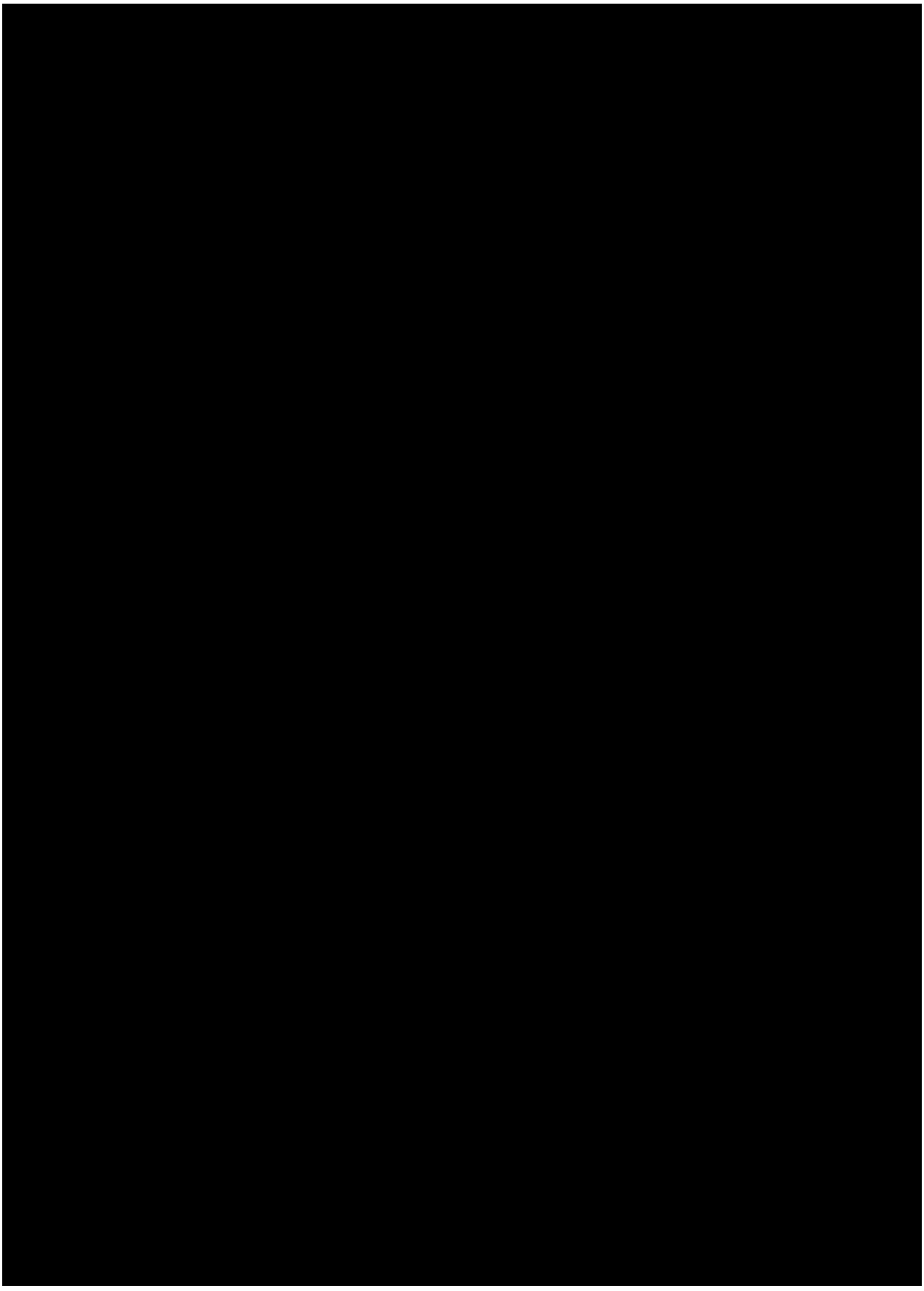
1.2.1 BI 1291583

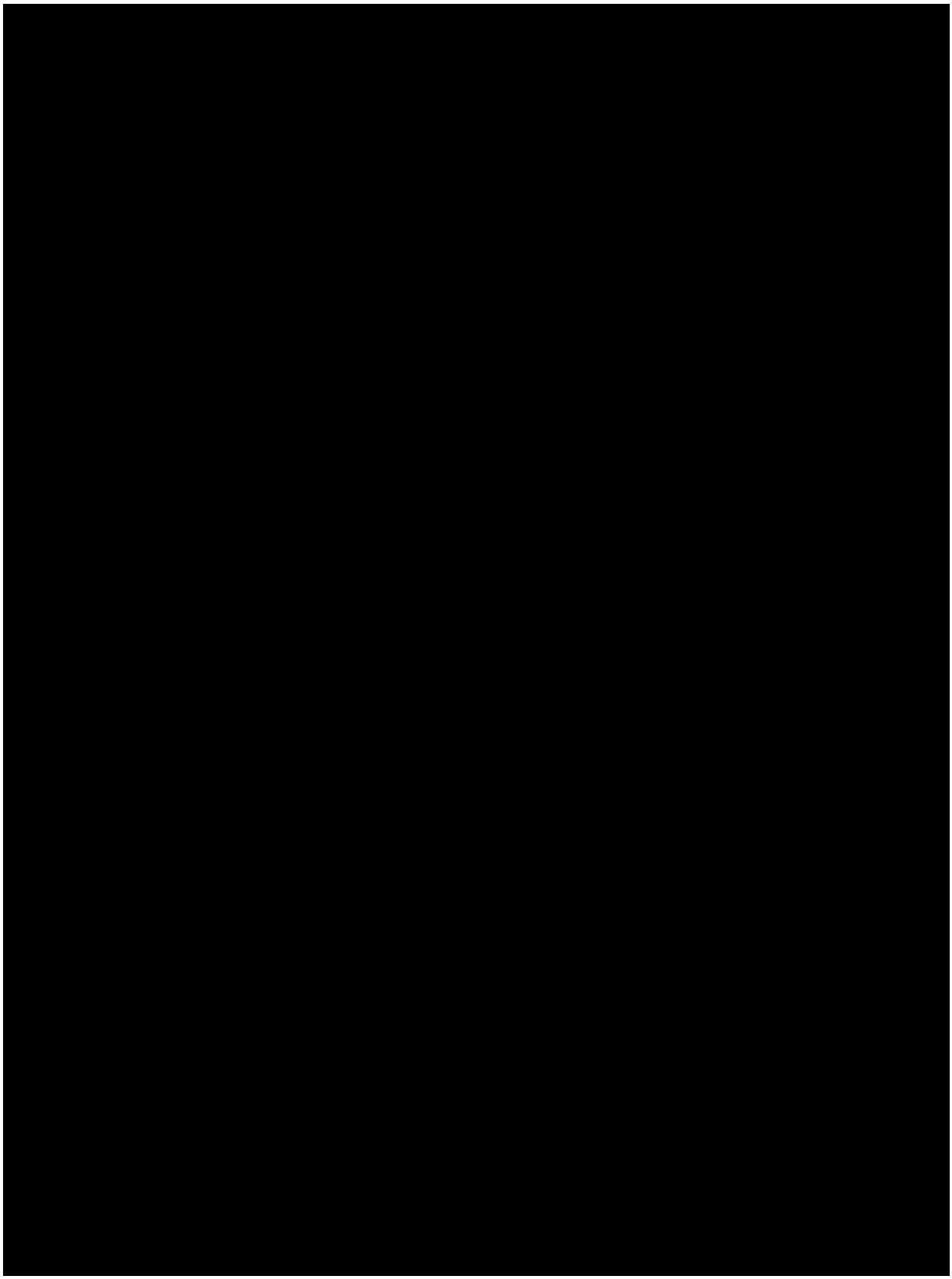
1.2.1.1 Mechanism of action

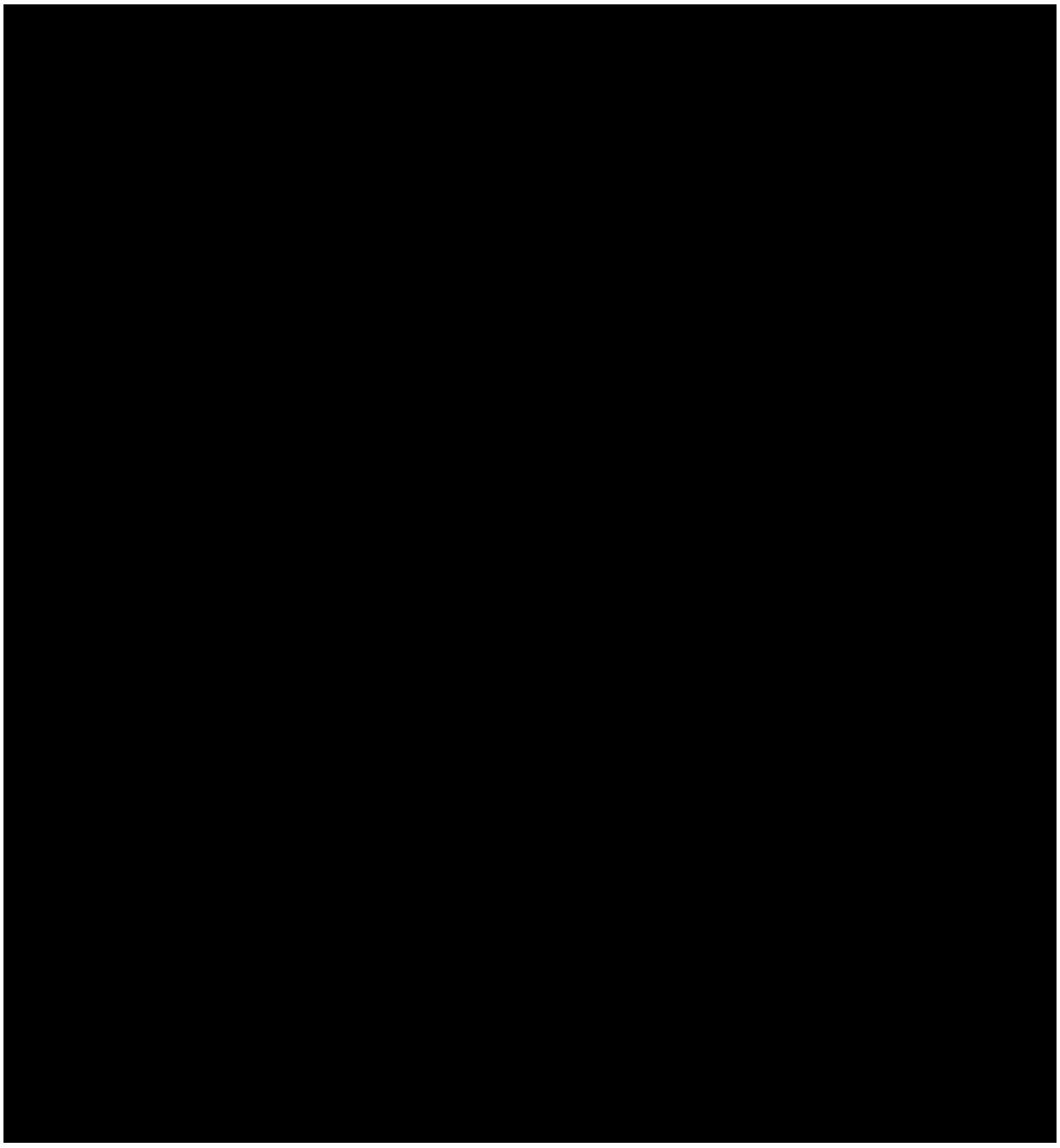
CatC is a cysteine protease which is exclusively responsible for the activation of all NSP (neutrophil elastase, Cathepsin G, Proteinase 3) during myelopoiesis of neutrophils in the bone marrow [R17-2915].
BI 1291583 is a potent, selective, and reversible CatC inhibitor. CatC inhibition leads to suppression of the three key NSPs, neutrophil elastase (NE), proteinase 3 (PR3), and Cathepsin G (CatG). All three NSPs contribute to inflammation and tissue destruction. Neutrophil elastase impairs ciliary function and promotes mucus secretion, it cleaves CXCR1, CD14, CD16 on neutrophils and thus disables bacterial killing and impairs innate immunity. By crippling normal host opsonophagocytosis, bacterial persistence is promoted. Epithelial cells, induced by NE, release IL-8, which in turn recruits even more neutrophils that are unable to kill bacteria, i.e. excessive amounts of NE induce ineffective antibacterial defense [R18-3384]. Inhibition of CatC is expected to lead to neutrophils with a decreased loading of active NE, PR3, and CatG, resulting in an improvement of the protease-antiprotease balance in the lungs of patients with bronchiectasis.

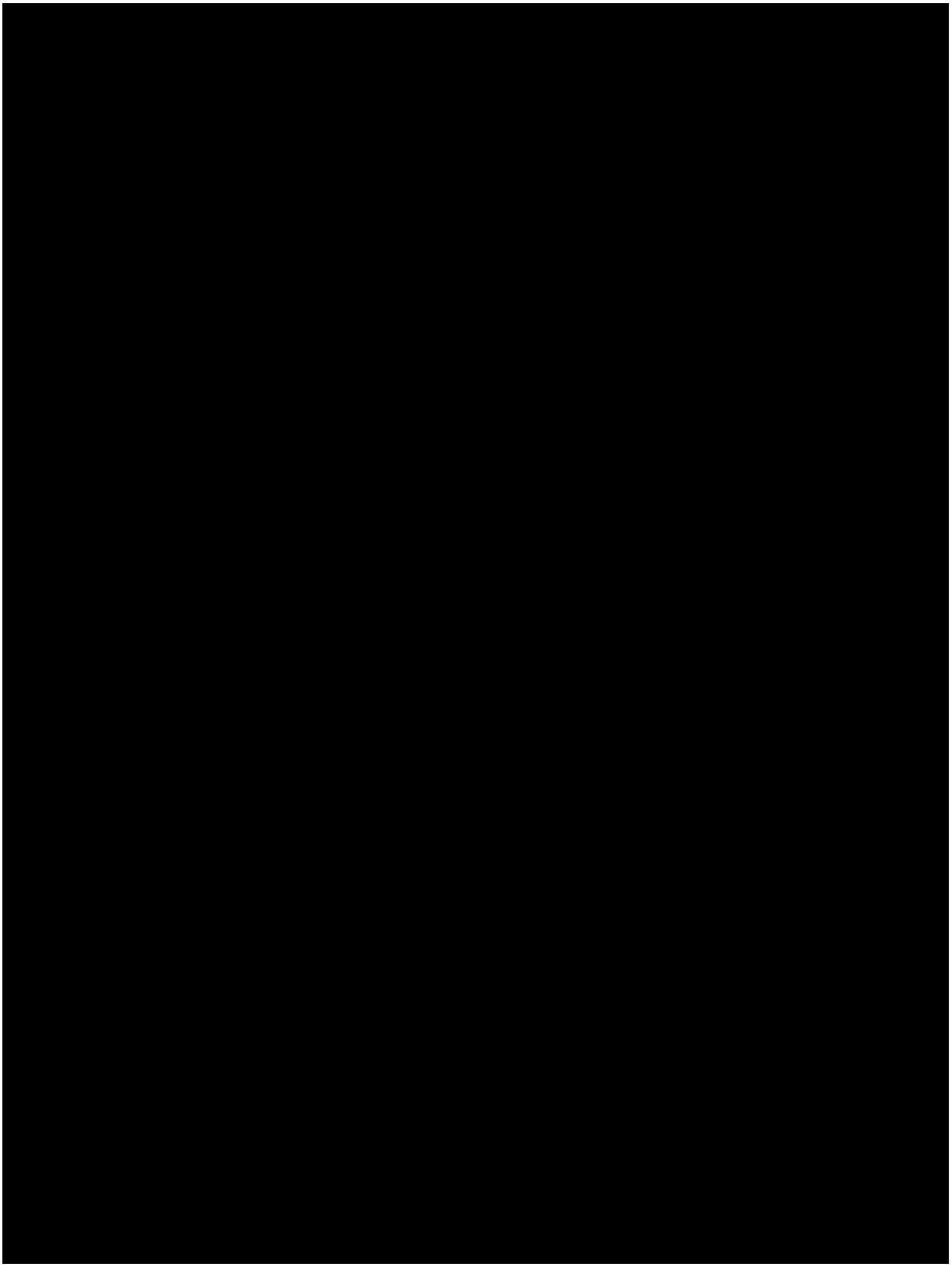












1.3 RATIONALE FOR PERFORMING THE TRIAL

The trial is intended to investigate the basic pharmacokinetics, excretion pathways and metabolism of BI 1291583.

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 1291583. In addition, the data are required for future submission to regulatory authorities.

1.3.1 Nomenclature

In this clinical trial protocol the following nomenclature applies:

- [^{14}C]-radioactivity: Radioactivity measured by [^{14}C]
- [C-14] BI 1291583: BI 1291583 labelled with ^{14}C, “hot” drug substance
- BI 1291583: non-labelled, “cold” drug substance
- BI 1291583 (C-14): Drug product, mixture of “hot” and “cold” drug substance, 1:50

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 1291583.

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 for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: BI 1291583		
Possible effects of CatC inhibition	Based on observations in patients with the rare genetic disease Papillon-Lefèvre Syndrome (PLS), clinical signs and symptoms of life-long complete absence of CatC are palmoplantar hyperkeratosis, severe periodontitis, alveolar bone resorption, loss of deciduous and permanent teeth, and an increased susceptibility to infections [R17-3100]. The immune-deficiency in PLS patients is generally mild [R17-3101].	- Such effects are not expected to occur after a single dose. - Exclusion of subjects with relevant immunodeficiency or receiving immunosuppressive medication or having an acute infection. - Regular clinical and laboratory monitoring for infection. - [redacted]
[redacted]		

Table 1.4.2: 1: Overview of trial related risks and mitigation strategy (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
[redacted]		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators. Although not specifically expected with this molecule or mechanism, monitoring for DILI is standard in drug development.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters. (see Section 5.2.6.1.4)
Trial procedures		
Blood sampling	Blood sampling is a standard clinical procedure. As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	- Close clinical monitoring for AEs - Selection of experienced sites and site staff **Blood sampling** The total volume of blood to be withdrawn per subject during the entire trial was calculated as 464.2 mL, i.e. it 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.

Table 1.4.2: 1: Overview of trial related risks and mitigation strategy (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
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 procedures.
Risk related to the administration of **BI 1291583 (C-14)**	BI 1291583 (C-14) contains the isotope [^{14}C] which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective whole body dose that each subject receives from one administration of ≈ 0.36 MBq is approx. 0.04 mSv.	The effective whole body dose in this study is 0.04 mSv. This is lower than the limit specified by: International Commission on Radiological Protection (ICRP) Category 1, (<0.1 mSv – risk defined as trivial) For details on the radiation burden calculation please refer to Appendix 10.1. For clinical investigations to study the disposition, metabolism and excretion of new pharmaceutical compounds in man an effective dose of up to 1.0 mSv is considered acceptable [R15-3219].

1.4.3 Risk related to the COVID-19-pandemic

The available evidence does not suggest an increased risk of acquiring an infection with a viral pathogen targeting the airways, including SARS-CoV-2, nor of a particularly more severe clinical presentation in case of such an infection, with suppression of CatC. Currently available evidence does also not suggest an increased risk of bacterial superinfection in case of COVID-19. CatC inhibition is not expected to reduce the efficacy of a COVID-19 vaccine to induce an immune response; and vice versa, vaccination is not expected to reduce the efficacy of the CatC inhibitor. Please also refer to the current Investigator's Brochure (IB) for BI 1291583 [c18711868].

1.4.4 Discussion

By reducing NE, PR3, and CatG activities BI 1291583 is expected to break the vicious cycle of bronchiectasis. BI 1291583 is expected to increase the time to pulmonary exacerbation, improve lung function and burdensome symptoms and, ultimately, quality of life.

[redacted]

Summary

The nature of the target and the mechanism of action of BI 1291583 is well understood.

[redacted]

In the current trial, healthy male volunteers will receive a single oral dose [redacted] BI 1291583 (C-14). Each participating subject will receive only one radioactive dose. The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 1291583 without exposing participating volunteers to undue risk.

However, there is always the potential for subjects receiving medication to experience adverse events (AEs), and rarely also serious adverse events (SAEs).
The risk associated with the expected maximal radiation burden falls in ICRP category 1 with trivial level risk. This is considered to be acceptable.

Healthy subjects are not expected to have any direct benefit from participation in this trial. Considering the medical need of the development of an effective treatment to slow the progression of bronchiectasis for patients with this disease, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers. The

benefit/risk assessment for the administration of BI 1291583 to healthy subjects remains unaltered also in face of the COVID-19 pandemic.

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

- assess the mass balance and total recovery of [^{14}C]-radioactivity in urine and faeces following a single oral dose of [redacted]BI 1291583 (C-14)
- provide plasma and urine samples for pharmacokinetic investigations
- provide plasma, urine, and faeces samples for metabolic profiling and structural identification of metabolites

2.1.2 Primary endpoints

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

- $fe_{urine,\ 0\text{-}tz}$ (fraction 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)

Timeframe: The timeframe for determination of these endpoints depends on individual excretion/ recovery of radioactivity and may vary between 2 and 6 weeks, inclusive, after drug administration.

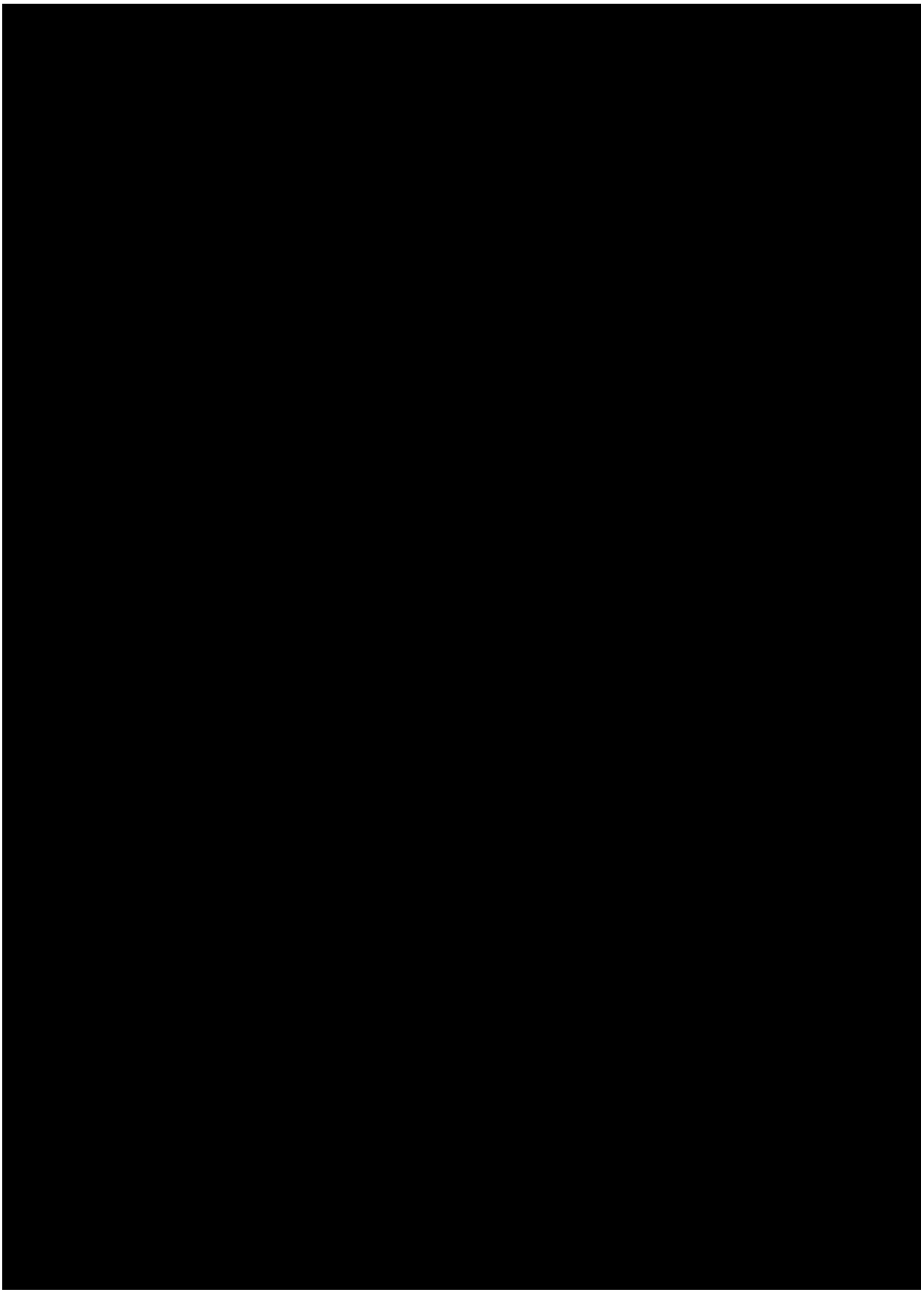
2.1.3 Secondary endpoints

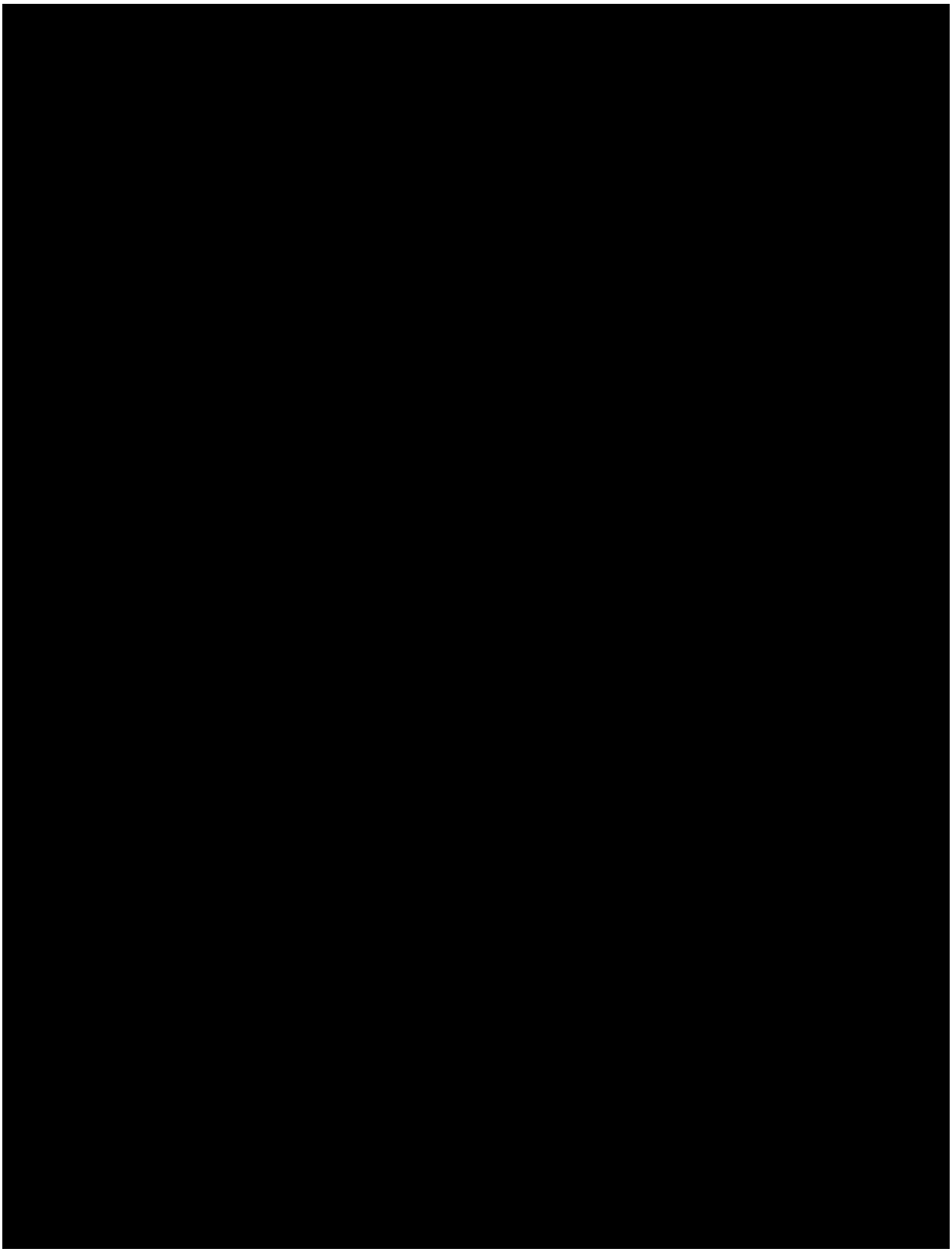
The following secondary endpoints will be evaluated for [^{14}C]-radioactivity, BI 1291583 and five metabolites (M407(1) /BI 1373234, M396(1) / CD 18507, M397(1) / CD 17849, M549(1) / CD 16785) and M141(1) / CD 16426 in plasma:

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

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

[redacted]





2.2.2.2 Safety and tolerability

Safety and tolerability of BI 1291583 will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, single-arm, single-dose trial in healthy male subjects to investigate the basic pharmacokinetics of BI 1291583, its metabolites (M407[1] / BI 1373234, M396(1) / CD 18507, M397(1] / CD 17849, M549(1] / CD 16785 and M141(1) / CD 16426) and [^{14}C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of [redacted] BI 1291583 (C-14).

A total of 8 healthy male subjects are planned to participate in the trial.

The planned radioactive dose per subject is approximately ≈ 0.36 MBq (0.04 mSv).

On Day 1, subjects will receive the drug product, i.e. [redacted] BI 1291583 (C-14) and will then stay in the study centre up to the morning of Day 15 for collection of samples of blood, urine and faeces, and if applicable for collection of vomit (within 24 hours after drug administration).

[redacted]

Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 21, 28, 35, and 42, if release criteria have not been met before. Within 24 hours before each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. Otherwise it will be discarded.

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

If the following release criteria have been met, the subsequent 24 h collection intervals after Day 15 will not be performed:

- Greater than or equal to 90% of the administered [^{14}C] 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 during clinical conduct the fraction of administered [^{14}C] dose will be rather underestimated as it will be based on the available samples, only. For the final analysis, the total excreted [^{14}C]-radioactivity will be derived including an interpolation method to account for the time periods without samples taken (see Section 7.2.2).
In this trial the term “release” does not mean that no further assessments are required and that the end of study examination can be performed. Subjects need to return for blood sampling

(PK and metabolite profiling) even if formal release criteria for the excretion of 14C-labeled drug material in excreta have been met.
If a subject is unable to attend one of the ambulatory visits, they may be allowed to reschedule the visit if needed. Irrespective of whether release criteria have been met or not, no further collections are planned after collection interval day 42-43.

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

This is a well-known design for a [^{14}C] human study for investigation of absorption, metabolism, and excretion including determination of mass balance. Inclusion of a control group is not required for this investigation. The study will use a low amount of [^{14}C]-radioactivity and accelerator mass spectrometry (AMS) for the measurement of [^{14}C] for sensitive detection, tracking and quantification of the parent drug and metabolites of mass balance.

Based on excretion data of drug-related radioactivity in the rat ADME trial [n00256437, n00258671] and the available PK data from clinical trials (see Section 1.2.1.2) a prolonged sampling duration was planned.
Following 15 days in-house excreta collection after dosing, subjects will return on a weekly basis **for in-house 24-h collection intervals (urine/faeces)** for up to 6 weeks (i.e., up to Day 43) after dosing **as long as release criteria are not met** (Section 3.1).

[redacted]

Blinding and randomisation is not necessary because all subjects receive the same treatment. 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 8 healthy male subjects will enter the trial. A sample size of 6 evaluable subjects is generally considered adequate for a human ADME study [R22-3641]. They will be recruited from the volunteers' pool of the trial site or recruited via e.g. external databases and advertisements.

Healthy male subjects are an appropriate population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 55 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

12. Use of drugs within 14 days (or 5 half-lives, whichever is longer) of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 30 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered.
14. Smoker (more than 5 cigarettes or 1 cigar or 1 pipe per day)
15. Inability to refrain from smoking during in-house confinement
16. Alcohol abuse (average intake of more than 21 units per week)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within 5 days prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study.

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 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 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 trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products, complying with local legislation
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

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 some subjects do not complete the trial, subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. 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.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The oral solution contains a mixture of pure [^{14}C]-labelled "hot" drug substance, and BI 1291583, i.e. unlabelled "cold" drug substance.

The mixture of hot and cold substance and solution for oral administration will be manufactured by the manufacturing division [redacted]

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Name:	BI 1291583 (C-14) solution for oral administration Containing a radioactive dose of approximately ≈ 0.36 MBq (0.04 mSv)
Substance:	BI 1291583 mixed with [C-14] BI 1291583
Pharmaceutical formulation:	Oral solution
Source:	[redacted]
Unit strength:	[redacted] i.e. [redacted] Containing [redacted] (2% of total dose) [^{14}C]-radiolabelled BI 1291583 corresponding to a radioactive dose of ≈ 0.36 MBq (0.04 mSv)
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	single dose

4.1.2 Selection of doses in the trial

[redacted]

This dose will include a low dose of [^{14}C]-radiolabelled BI 1291583, i.e. ≈ 0.36 MBq (0.04 mSv). This radioactive dose is considered sufficient to allow the detection of all expected metabolites at all time points in plasma without falling below the lower limit of quantification (LLOQ) of an AMS setup.

4.1.3 Method of assigning subjects to treatment groups

This is an open-label, single-arm, single-dose phase I study. All subjects will receive the same dose of BI 1291583 (C-14).

The study subject numbers will be allocated to the subjects in 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.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day, which is acceptable from a safety perspective (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 cohorts as required.

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the same treatment as 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
BI 1291583(C-14)	BI 1291583	Oral solution	[redacted]		

Administration of BI 1291583 (C-14) 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, if correct dosage cannot be ensured otherwise.
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 poster), except when instructed to do so by one of the investigators.

Water may be consumed ad libitum until 1 hour prior to drug administration. For restrictions regarding fluid consumption post-dose please refer to Section 4.2.2.2. Standardised meals will be served as outlined in the Flow Chart. For restrictions with regard to diet see Section 4.2.2.2.

After drug administration subjects will be kept under close medical surveillance until planned discharge from the unit on Day 15. In case release criteria for radioactivity recovery have not been met on Day 15, subjects will come back to the unit for up to four once-weekly 24 h sampling periods until release criteria are met or after the last collection interval Day 42-43 was completed (see Section 3.1). [redacted]

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

Non-[^{14}C]-labelled and radioactively-labelled drug substance supplies will be provided to [redacted]

Drug product manufacturing is done by the manufacturing division of [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 amber glass bottles holding the Investigational Drug Products and will be labelled according to EU GMP guideline and local drug law. For details of packing and the description of the label, refer to the ISF.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU Clinical Trial Number is indicated on the title page of this protocol.

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

[redacted]

The investigator will not order the drugs from the [redacted] before the following requirements are fulfilled:

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

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed.

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

4.2.2.2 Restrictions on diet and lifestyle

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.
On day 1, standardised meals will be served at the times indicated in the Flow Chart.
Subjects are to be fasted for at least 10 h prior to dosing. No food is allowed for at least 4 h after drug intake.
Water may be consumed ad libitum until 1 hour prior to drug administration.
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 should be at least 1.0 litres but should not exceed 3.5 litres.

On all other days (i.e. after 24 h post-dose) during in-house confinement, there are no special requirements [redacted]

When not fasting, meals and snacks (such as decaffeinated coffee, fruit, and biscuits) will be provided according to [redacted] standard operating procedures (SOPs).

Poppy-seed containing products should not be consumed within 2 days before screening and starting 2 days before first admission to trial site until last PK sampling of the trial.

Alcoholic beverages are not allowed within 2 days before screening and 2 days 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.

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

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.

Excessive physical activity (such as competitive sport) should be avoided starting 5 days before trial drug administration until the end-of-trial examination.
Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial.

[redacted]

4.3 TREATMENT COMPLIANCE

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

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

[redacted]

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured using an automated device 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 safety laboratory parameters (profile A, B, D) blood and urine samples (if applicable) will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 4 h. At the discretion of the investigator or designee, overnight fasting is not required for drug screening, for retests and safety laboratory parameters (profile C).

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Haematology	Haematocrit	X	X	X	X
	Haemoglobin	X	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X	X
	White Blood Cells/Leucocytes	X	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal and in accordance with Clinical laboratory [redacted] standard procedures)	Neut. Poly (segs)/Leukocytes [%]; Eosinophils/Leukocytes [%]; Basophils/ Leukocytes [%]; Monocytes/Leukocytes [%]; Lymphocytes/Leukocytes [%]				
Manual differential red blood cell count (if there is an abnormality in the blood cell count in accordance with Clinical laboratory [redacted] standard procedures)	Only positive findings will be reported (for instance the presence of microcytes)				
Coagulation	Activated Partial Thromboplastin Time	X	--	--	--
	Prothrombin time	X	--	--	--
	Prothrombin time – INR (International Normalization Ratio)	X	--	--	--
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	--	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	--	X
	Alkaline Phosphatase	X	X	--	X
	Gamma-Glutamyl Transferase	X	X	--	X
	Creatine Kinase [CK]	X	X	--	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	X	--	X
	Lactate dehydrogenase	X	X	--	X
	Lipase	X	X	--	X
	Amylase	X	X		X
Hormones	Thyroid Stimulating Hormone	X	--	--	--

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A	B	C	D
Substrates	Glucose (serum)	X	X	--	X
	Creatinine	X	X	--	X
	Bilirubin, Total	X	X	--	X
	Bilirubin, Direct	X	X	--	X
	Protein, Total	X	X	--	X
	C-Reactive Protein (Quant)	X	X	--	X
	Blood Urea Nitrogen	X	X	--	X
	Uric Acid	X	--	--	--
	Cholesterol, total	X	--	--	--
	Triglycerides	X	--	--	--
Electrolytes	Sodium	X	X	--	X
	Potassium	X	X	--	X
	Calcium	X	X	--	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	--	--	X
	Urine Protein (qual)	X		--	X
	Urine Glucose (qual)	X	--	--	X
	Urine Ketone (qual)	X	--	--	X
	Urobilinogen (qual)	X	--	--	X
	Urine Bilirubin (qual)	X	--	--	X
	Urine RBC/Erythrocytes (qual)	X		--	X
	Urine WBC/Leucocytes (qual)	X	--	--	X
	Urine pH	X	---	--	X
Urine sediment (Urine sediment examinations will only be performed if there is an abnormality in urinalysis in accordance with Clinical Laboratory, standard procedure)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day -1, Day 2, and Day 15 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 2 on Day 1, Day 3, Day 4, Day 8, and Day 10 (for time points refer to Flow Chart)
D: parameters to be determined at Visit 3 (end of study examination)

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

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA[1] including XTC[3] Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA[2] Opiates Phencyclidine Alcohol
Drug screening (blood)	Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV[4]-1 and HIV-2 antibody (qualitative)

[1]MDA Methylenedioxyamphetamine, [2] MDMA Methylenedioxymethamphetamine, [3] XTC Ecstasy, [4] Human Immundeficiency Virus

An alcohol test in urine will be performed at screening and on Day -1 of the treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the safety laboratory of [redacted]

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

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

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

5.2.4 Electrocardiogram

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

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

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

All ECGs will be stored electronically. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

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

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

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which, by their nature, can always be considered to be 'serious' even though they may not have met the criteria of an SAE as defined above.

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  - An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the

ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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 CRFs 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

If a partner of a male trial participant becomes pregnant, potential drug exposure during pregnancy must be reported immediately (without undue delay) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.This requires written consent of a 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 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 and urine samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Sampling of whole blood and plasma

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

- To determine total [^{14}C]-radioactivity concentrations in whole blood and plasma

- To determine concentrations of BI 1291583 and its metabolites M407(1) /BI 1373234, M396(1) / CD 18507, M397(1) / CD 17849, M549(1) / CD 16785 and M141(1) / CD 16426 in plasma
- To identify additional metabolites of BI 1291583 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 of concentrations of [^{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 K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Afterwards, separate aliquots of whole blood and plasma will be prepared for total radioactivity analysis.

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

5.3.2.1.2 Quantification of BI 1291583 and its metabolites in plasma

For quantification of concentrations BI 1291583 and its metabolites [redacted]
in plasma, blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

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

5.3.2.1.3 Sampling of plasma for metabolic profiling and structural elucidation

At each time point listed in the Flow Chart for metabolic profiling sampling, full blood will be withdrawn from an antecubital or forearm vein into two K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube. The blood samples will be processed in the same way as the PK samples (see laboratory manual). However, the obtained plasma from one of the samples will be divided into two aliquots both to be used for metabolic profiling via AMS analysis. The other plasma sample is used for further internal investigations of BI 1291583 metabolism in the drug metabolism laboratory of BI.

Evaluation of drug metabolism will be reported separately and will not be included in the CTR.

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

5.3.2.2 Sampling of urine

Urine will be collected at time points or in intervals as indicated in the Flow Chart:

- To determine total [^{14}C]-radioactivity
- To determine concentrations of BI 1291583
- To investigate the metabolic profiling of BI 1291583 (to be reported separately)

[redacted]

A blank sample will be taken within approximately 14 hours prior to drug administration.

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. Volunteers will be asked to empty their bladders at the end of each sampling interval. The exact start and end times of the urine collection intervals will be recorded in the CRF.

All urine samples after administration of BI 1291583 (C-14) until release criteria are met are planned to be used for determination of [^{14}C]-radioactivity as well as for analysis of BI 1291583. Samples for metabolic profiling will be selected according to the levels of radioactivity in each urine sample.

For a detailed description of preparation of collection containers, sample additives, sample storage, sample handling, labelling, and sample shipment refer to the laboratory manual.

5.3.2.3 Sampling of faeces

Faeces will be collected at time points or in intervals as indicated in the Flow Chart:

- To determine total [^{14}C]-radioactivity
- To investigate the metabolic profiling of BI 1291583 (to be reported separately)

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

Faeces samples collected after administration of BI 1291583 (C-14) until release criteria are met are planned to be used for determination of [^{14}C]-radioactivity. Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sample interval. For faeces samples to be discarded (see footnote 13 and 14).

All stools will be collected continuously in portions up to 336 hours after drug administration. All stool portions will be taken quantitatively at the time-points depicted in the Flow Chart. The weight of the faeces and the exact times of faeces collection will be recorded in the eCRF.

If subjects are to collect faeces during the ambulatory phase of the study (see Section 3.1 for release criteria), subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals are (if applicable): Days 20-21, 27-28, 34-35, and 41-42. All faeces samples (including home collection, if

applicable) will be shipped [redacted]. If faeces is collected during in-house collection interval, this faec sample will be used for analysis and the respective home collection faeces sample has to be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.

For a detailed description of faeces sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.3.2.4 Collection of vomit

If vomiting occurs within 24 hours after drug administration the vomit will be collected to calculate the weight and determine the [^{14}C]-radioactivity levels. For a description of vomit sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.3.2.5 Further investigation

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

[redacted]

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 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 in human mass-balance trials.

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 4 h-period prior to the trial drug administration.

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 except safety lab) and a 5% time window (for blood sampling PK, metabolic profiling, safety lab) of elapsed time since drug administration.

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

For planned blood sampling times and urine / 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 period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.
For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

6.2.2 Treatment period

Each subject is expected to participate in one treatment period (Visit 2).

On Day -1 of the treatment period study participants will be admitted to the trial site and kept under close medical surveillance until discharge from the trial site on Day 15. In the morning of Day 15, the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness.

[redacted]

Until release criteria (see Section 3.1) have been reached, subjects will take part in the 24-h collection intervals of urine and faeces. For these additional 24 h collection intervals, subjects will be admitted to the trial site on Days 21, 28, 35, and 42. One day later, on Days 22, 29, 36, and 43, respectively, subjects will be discharged from the trial site after formal assessment and confirmation of their fitness.

Within 24 h before each once-weekly in-house collection interval, subjects are to collect faeces at home (beginning of home collections on Days 20, 27, 34, and 41). Faeces collected in these 24 h home-collection intervals will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval. E.g., if no defecation occurs in in-house collection interval Day 21-22, faeces of home-collection interval Day 20-21 will be used for analysis. If, however, faeces are collected in the subsequent 24 h in-house collection interval, faeces collected at home will be discarded. Once release criteria are reached, home collections will be stopped.

Irrespective of whether release criteria have been met or not after collection interval Days 42-43, no further collections are planned. For details on time points and procedures for collection of plasma, whole blood, urine and faeces samples for PK analysis and mass balance assessment, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination. For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

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

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

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

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This is a phase I, non-randomised, open-label, single-dose, single-arm study to investigate human ADME of BI 1291583 administered to healthy male subjects. No confirmatory analysis will be conducted for this study. Data will be reported with descriptive statistics only. The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

- N number of non-missing observations
- Mean arithmetic mean
- SD standard deviation
- Min minimum
- Median median
- Max maximum

For concentration data as well as for all PK parameters the following descriptive statistics will additionally be calculated:

- CV arithmetic coefficient of variation
- gMean geometric mean
- gCV geometric coefficient of variation

For PK parameters the following descriptive statistics will additionally be calculated:

- P10 10th percentile
- Q1 1st quartile
- Q3 3rd quartile
- P90 90th percentile

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group.

Further details may be provided in the TSAP.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or

secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

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

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

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug BI 1291583 and its metabolites will be calculated according to the relevant BI internal procedures.

Plasma, urine, faeces, and vomit (as applicable) concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis). For collection of vomit see Section 5.3.2.4.
- A pre-dose concentration (in plasma) is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

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

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

7.2.2 Primary endpoint analyses

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

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 descriptive in nature.

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 treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP in order to provide summary statistics for time intervals, such as combined treatments, on-

treatment totals, or periods without treatment effects (such as screening and follow-up intervals). The final TSAP is signed/approved 10 days before database lock at the latest.

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

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

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory study, no prospective calculations of statistical power have been made. The sample size of 8 subjects has been selected to provide at least 6 evaluable subjects. This is considered sufficient information to assess the main objectives of this trial.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form 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 or the subject's legally accepted representative.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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 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 patient identification number instead of the subject's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the subject files and clinical data is strictly limited: 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 subjects 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.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

[redacted]

[redacted]

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

Data management and statistical evaluation will be done by BI and/or a contract research organisation according to BI SOPs.

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

9. REFERENCES

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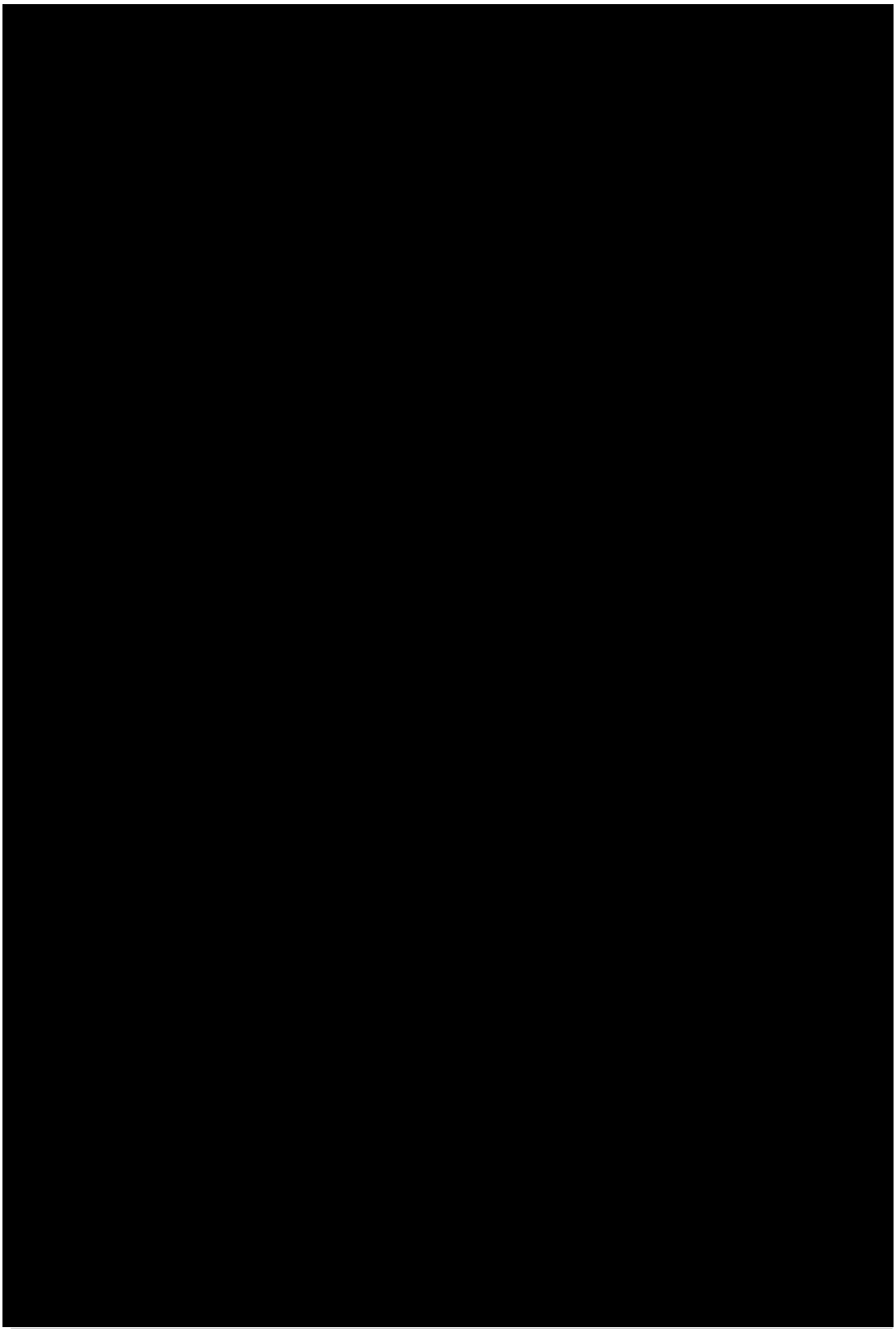

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		20 Mar 2023
EU CT number		2022-502264-20-00
BI Trial number		1397-0016
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1. Flowchart, footnote 1 2. Table 1.4.2: 1 3. Section 5.2.1 4. Section 7.1 5. Section 7.2.5
Description of change		1. ‘race and ethnic origin’ added 2. Amount of blood that is drawn was specified 3. ‘race and ethnic origin’ added 4. Information about standard descriptive statistical parameters inserted 5. Information included that TSAP is signed prior to database lock
Rationale for change		1. Request for information (RFI): Part I, Consideration #1 2. RFI: Part I, Consideration #4 3. RFI: Part I, Consideration #1 4. RFI: Part I, Consideration #2 5. RFI: Part I, Consideration #7

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Apr 2023
EU CT number		2022-502264-20-00
BI Trial number		1397-0016
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		1) Flowchart, footnote 5 2) Section 4.1.4
Description of change		1) Time window defined 2) Position of subject within 4 hours after dosing specified
Rationale for change		1) Logistical reasons 2) Clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		13 Jun 2023
EU CT number		2022-502264-20-00
BI Trial number		1397-0016
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		Title page
Description of change		Change of Clinical Trial Leader
Rationale for change		Personnel change

APPROVAL / SIGNATURE PAGE

Document Number: c37738815 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: A phase I, open-label, single dose, mass balance trial to investigate metabolism and pharmacokinetics of BI 1291583 (C-14) administered as oral solution in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	13 Jun 2023 15:35 CEST
Approval-Clinical Program Leaders		13 Jun 2023 16:08 CEST
Author-Trial Statistician		14 Jun 2023 12:01 CEST
Verification-Paper Signature Completion		14 Jun 2023 13:57 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**