	Document Number: **c41814759-02**
EU Trial No.	2023-505683-11-00
BI Trial No.	1397-0026
BI Investigational Medicinal Product	BI 1291583
Title	Investigation of pharmacokinetics and absolute [redacted] bioavailability of BI 1291583 administered as an [redacted] with an [redacted] microtracer dose of [^{14}C]-BI 1291583 in healthy male volunteers
Lay Title	A study in healthy men to test how BI 1291583 is taken up by the body
Clinical Phase	I
Clinical Trial Leader	[redacted] On behalf of Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173, 55216 Ingelheim am Rhein, Germany Phone: +49 (0)6132 77-8873, Fax: +49 (0)6132 72-8873
Principal Investigator	[redacted]
Current Version, Date	Version 2.0, 31-Oct-2023
Original Protocol Date	11-Aug-2023

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CLINICAL TRIAL PROTOCOL SYNOPSIS

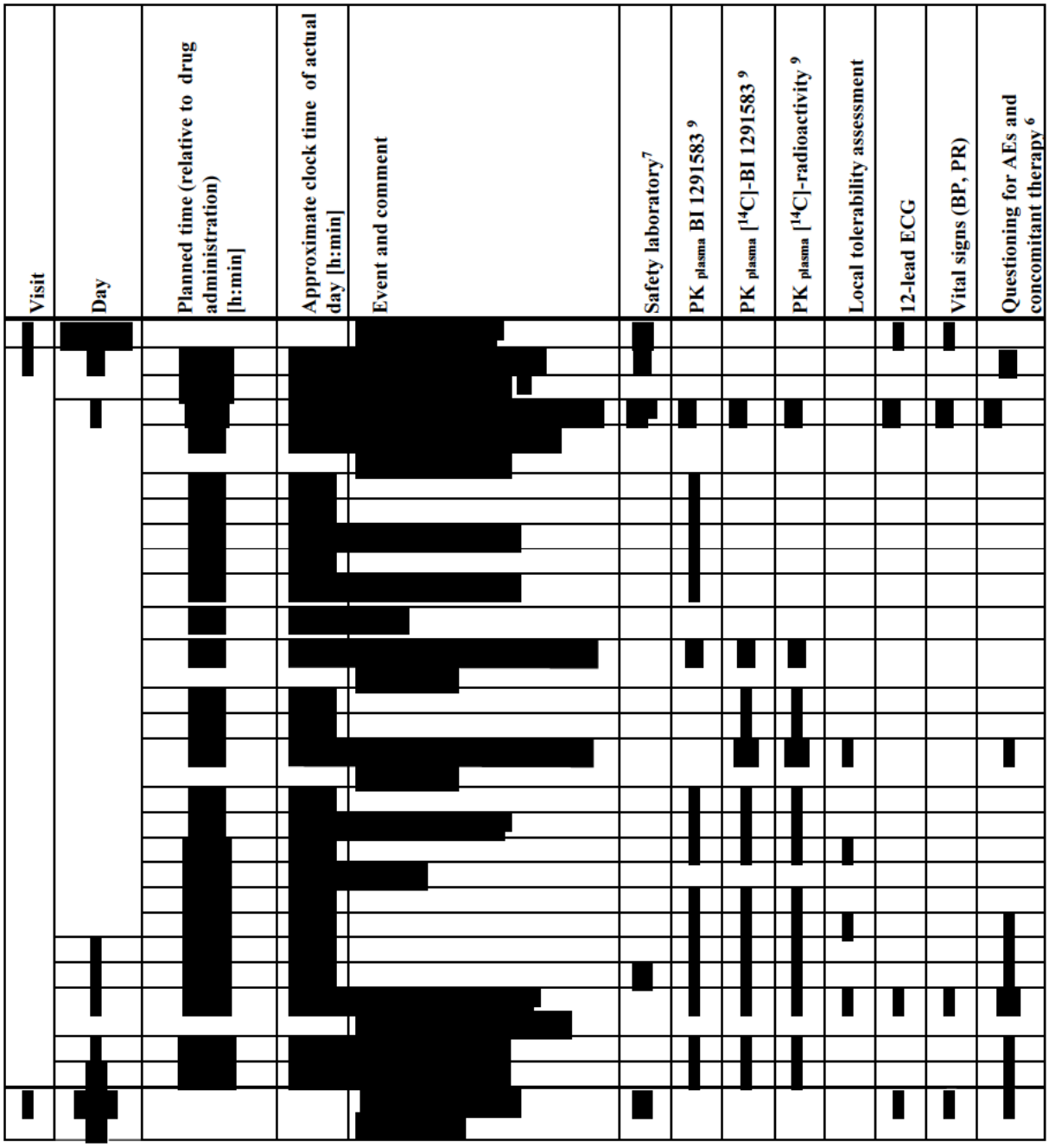
Company name	Boehringer Ingelheim
Original protocol date	11-Aug-2023
Revision date	31-Oct-2023
BI trial number	1397-0026
Title of trial	Investigation of pharmacokinetics and absolute [redacted] bioavailability of BI 1291583 administered as an [redacted] with an [redacted] microtracer dose of [^{14}C]-BI 1291583 in healthy male volunteers
Principal Investigator	[redacted]
Trial site	ICON Early Development Services
Clinical phase	I
Trial rationale	This trial is intended to examine the absolute bioavailability of BI 1291583 as [redacted] formulation for [redacted] administration ,using an [redacted] microtracer approach with [^{14}C]-labelled BI 1291583. These data are considered necessary to further support the understanding of the pharmacokinetics of BI 1291583
Trial objective	To investigate the absolute bioavailability of BI 1291583 administered as [redacted] (test treatment T in 2 doses, not radio-labelled) compared with BI 1291583 (C-14) (reference treatment R) administered as [redacted] microtracer
Trial endpoints	*Primary endpoints:* The following primary endpoint will be determined in plasma for [^{14}C]-BI 1291583 after [redacted] and for BI 1291583 after [redacted] administration • $AUC_{0-\infty}$ *Secondary endpoints:* The following secondary endpoints will be determined in plasma for [^{14}C]-BI 1291583 after [redacted] and for BI 1291583 after [redacted] administration • C_{max} • AUC_{0-tz}
Trial design	Non-Randomised, open-label, two arm, single period
Number of subjects **total entered** **on each treatment**	 14 (2 dose levels) 7
Diagnosis	Not applicable

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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	BI 1291583 [redacted] Test Treatment (T)
dose	[redacted]
mode of administration	[redacted] with 240 mL of water after an overnight fast of at least 10 h
Reference product	BI 1291583 (C-14) as [redacted] solution: Reference Treatment (R)
dose	consisting of [redacted] BI 1291583 mixed with [redacted] [^{14}C]-BI 1291583 in [redacted] ([redacted] (C-14)/[redacted]) The radioactive dose [redacted] will be ~20 kBq
mode of admin.	[redacted]
Duration of treatment	[redacted] (Treatment T): [redacted] [redacted] (Treatment R): [redacted]
Statistical methods	Absolute bioavailability (F) will be estimated for each dose group [redacted]) by the ratios of the geometric means (test/reference) for the dose normalized primary endpoint $AUC_{0-\infty}$ and secondary endpoints C_{max} and AUC_{0-tz} Additionally, their two-sided 90% confidence intervals (CI) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified. The statistical model will be an ANOVA on the logarithmic scale including the fixed effect for 'formulation' and 'subject' as a random effect. CIs will be calculated based on the residual error from ANOVA. Descriptive statistics will be calculated for all endpoints.

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FLOW CHART



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 alcohol test and drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
   The physical examination includes [redacted]
2. The time is approximate; the procedure is to be performed and completed within 3 h prior to first drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action. Standardised meals should be given at same timepoints during all in-house days.

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4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. The physical examination includes [redacted]
5. Only urine/serum drug screening and urine alcohol test as well as C-reactive protein will be done at this time.
   To be taken and evaluated within 26 hours before drug administration. Admission can be done anytime within -26 hours and -10 hours before first drug administration.
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Letters A, B and C describe different sets of safety laboratory examinations (see Table 5.2.3:1).
   SARS-CoV-2 testing will be done as needed based on the current status of the pandemic.
8. [redacted] exactly on planned time. PK samples will be taken before the [redacted]
9. For details of PK blood sampling (including samples for the quantification of BI 1291583 concentrations in plasma, [^{14}C]-BI 1291583, and total radioactivity in plasma), refer to Section 5.3.2.
   Following the administration of BI 1291583 [redacted], samples should be taken within +/- 5 min from the scheduled time up to time 6.5h timepoint; from 6.5 h post-dose (BI 1291583 [redacted]) until discharge, samples should be taken within +/- 5% of the elapsed time since BI 1291583 [redacted] were taken.
   After discharge, samples should be taken in line within the time window for ambulatory visits (cf. footnote 10).
10. Time window for ambulatory visits is +/- 4 h.
11. Time window +/- 1 h
12. Discharge after formal assessment and confirmation of the subject's fitness. Discharge may be in the time window from planned time until 4 h later
13. PK sample to be taken immediately before the [redacted].
14. Questioning for adverse events and concomitant medication includes [redacted]

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CatC	Cathepsin C
CF	Cystic Fibrosis
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic Obstructive Pulmonary Disease
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
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)

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F	Absolute bioavailability factor
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
gMean	Geometric mean
IB	Investigator's brochure
IEC	Independent Ethics Committee
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
$MRT_{,in}$	Mean residence time of the analyte in the body, intravascular
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
mSV	Milisievert
NE	Neutrophil Elastase
NSP	Neutrophil Serine Proteases
PCD	Primary Ciliary Dyskinesia
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
T	Test product or treatment

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$t_{1/2}$	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_{ss}	calculated volume of distribution at steady state after intravascularadministration, only for parent compound
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of childbearing potential

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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 heterogeneous 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.

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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.

1.2.1.2 Key pharmacokinetic characteristics from clinical studies

Following single dose administration ([redacted]) in single rising dose (SRD) trial 1397-0001 and 1397-0003 and multiple-dose administration ([redacted] in multiple rising dose (MRD) trials 1397-0002, 1397-0011, and 1397-0003 (Japanese healthy volunteers, data analyses ongoing), BI 1291583 was readily absorbed with peak plasma concentration observed 6 h to 7 h post-dose. Pharmacokinetic steady state is reached within [redacted].
Overall, exposure to BI 1291583 was slightly (less than 2-fold) higher in Japanese (data analyses ongoing) than in non-Japanese, but was below the exposure caps based on non-clinical studies.
In a relative bioavailability single [redacted] dose food effect study (1397-0008), similar BI 1291583 plasma concentration-time curves were observed under fasted and fed (high fat and high caloric) conditions. There was no food effect observed.
Initially, the following [redacted] human metabolites of BI 1291583 were identified:
[redacted]

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compound BI 1291583. [redacted] was also not pharmacologically active regarding CatC inhibition

[redacted] (for more details see Section 1.2.1.4).

[redacted]

A summary of gMean (%gCV) of relevant PK parameters ([redacted]) after [redacted] BI 1291583 from the SRD 1397-0001 [c31468932] are provided in Table 1.2.1.2: 1. [redacted].

[redacted]

Table 1.2.1.2: 1 Summary of gMean (%gCV) of relevant PK parameters after single dose administration of [redacted] BI 1291583

	BI 1291583	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*for tmax, the median and range (min, max) are given, **n.c. no descriptive data calculated, [redacted]

The pharmacodynamic effects noted with CatC in the SRD trials 1397-0002 and 1397-0011 were dose dependent. Peripheral inhibition of CatC activity was noted at [redacted] post-dose on the first day of dosing. [redacted]

Based on the clinical exposure data from the MRD trials 1397-0002 and 1397-0011, the expected human therapeutic dose is [redacted], leading to [redacted] in whole blood after zymosan stimulation.

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After administration of a [redacted] of BI 1291583, the median CatC inhibition was [redacted], respectively (ref. CTR 1397-0001).
No relevant NE inhibition is expected after administration of [redacted] BI 1291583 single dose.

1.2.1.3 Drug-drug interactions

BI 1291583 [redacted] as investigated. Study results show an approximate [redacted]
For the current trial [redacted] doses were selected. If for medical reasons a concomitant therapy is required, there are no [redacted] see Section 4.2.2.1).
For the major metabolites described above, [redacted]

1.2.1.4 Data from non-clinical studies

In the rat ADME trial, recovery was complete following [redacted] administration, with 4.8% and 10.3%, respectively, remaining in the rat 168 h after administration. Main route of [redacted] (86.6% of the [redacted] dose and 83.4% of the [redacted] dose), with more [redacted] (8.1% of the [redacted] dose and 7.9% of the [redacted] dose) [n00256437, n00258671].

The toxicology program of BI 1291583 to date includes [redacted]

In rats, the [redacted] due to differences in protein binding between rats and humans.

BI 1291583 induced findings considered to be related to [redacted]

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and rat, respectively. [redacted] therefore not considered adverse.

Findings considered [redacted]

In the 26-week study in the rat, [redacted] [c18711868].

For toxicological qualification, [redacted]

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[redacted] not observed in the embryofetal development (EFD) toxicity study in Wistar rats and New Zealand White Rabbits:

- In rats, [redacted]
- In rabbits, [redacted]

In summary, the currently available toxicology data supports the administration of BI 1291583 up to [redacted] for an indefinite time period in human with [redacted] administration.

1.2.1.5 Key safety data from clinical studies

BI 1291583 has been investigated in 6 Phase I trials in healthy subjects and was tolerated well, with no serious AEs or AEs of special interest reported.

The most commonly observed adverse events across all trials were [redacted] and [redacted] receiving BI 1291583 in the SRD trial 1397-0001.

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A safety summary of adverse events (AEs) that the investigators considered drug related are displayed in Table 1.2.1.5: 1.

The following adverse events were classified by the investigator as possibly drug related to BI 1291583: [redacted]

The following adverse events were classified as possibly drug related to BI 1291583 + [redacted]

Across all trials, most AEs were of mild or moderate intensity, [redacted]
Both were considered not related to BI 1291583.

AEs were reported for various system organ classes and preferred terms, however with no particular organ pattern emerging and no relationship with dose. One subject receiving BI 1291583 [redacted] (MRD) [redacted] both considered not drug related.

[redacted] ore frequently for subjects treated with BI 1291583 than subjects receiving placebo.

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Table 1.2.1.5: 1 Summary of AEs considered drug related by investigators across healthy volunteer trials performed (for more details refer to the current Investigator's Brochure (IB) for BI 1291583 [c18711868])

Healthy volunteer trials performed	Summary of AEs considered drug related by investigators
1397-0001, single-rising-dose. • [redacted] • 54 healthy male subjects versus placebo. 40 subjects received BI 1291583, 14 subjects received placebo.	[redacted]
1397-0008, food-effect cross-over trial • [redacted] of BI 1291583 once in the fasted state and once following a standard high-fat, high-calory meal • 12 healthy male subjects	
1397-0010, DDI trial (itraconazole) • [redacted] • 14 healthy male subjects	[redacted]
1397-0002 and 1397-0011, multiple-rising-dose. [redacted] • [redacted] • 48 healthy male and female subjects. 36 subjects received BI 1291583, 12 subjects received • [redacted]	[redacted]
1397-0003, Japanese single rising dose, multiple dose, DDI study • [redacted] 24 healthy male subjects. 18 subjects received BI 1291583, 6 subjects received placebo • [redacted] 9 subjects received BI 1291583, 3 subjects received placebo	

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No effects [redacted] were seen in the [redacted] MRD studies in healthy volunteers at exposures up to two fold higher than will be tested in the Phase II trials, suggesting that repeat-dose administration of BI 1291583 in humans is not associated with any [redacted].

For a more detailed description of the BI 1291583 profile, please refer to the current Investigator's Brochure (IB) [c18711868].

1.2.2 Residual Effect Period

The residual effect period (REP) is the period after the last dose during which measurable drug levels and/or pharmacodynamic effects are still likely to be present.
Based on PK and PD data from trial 1397-0002 and 1397-0011 ([redacted]) the REP of BI 1291583 was defined as [redacted].
However, in this trial with the administration of a [redacted] (BI 1291583 oral dose of [redacted] BI 1291583 (C-14)) no relevant pharmacodynamics effects are expected.
Considering the $t_{1/2}$ of [redacted] of BI 1291583, highest dose, a REP [redacted] appears appropriate (see Section 1.2.1.2).

1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the absolute bioavailability of BI 1291583 as [redacted] formulation for [redacted] administration ([redacted]), using an intravenous microtracer approach with [^{14}C]-labelled BI 1291583. These data are considered necessary to further support the understanding of the pharmacokinetics of BI 1291583.
Rationale for the investigation of [redacted] levels:
[redacted]

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.

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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. - Visual inspection of the skin of palms, soles, an oral cavity at specified timepoints - Exclusion of subjects having a history of hyperkeratosis in palms or soles. - Exclusion of subjects with signs of current clinically relevant gingivitis/periodontitis. - Live or live-attenuated vaccine should be avoided during the trial.
Effects on lung, liver, kidney and bone	In non-clinical studies, [redacted]	- Exclusion of subjects with a relevant concomitant disease assessed as clinically relevant by the investigator, particularly gastrointestinal, hepatic, renal, pulmonary, cardiovascular, metabolic, immunological, or hormonal disorders.

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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Effects on lung, liver, kidney and bone	The incidence and severity were low, additional degenerative changes or any changes in the clinical status of the animals were not observed. Overall, the margins to which effects were seen and the margin to the lower exposure where the effects were not seen in non-clinical studies are sufficiently high (Section 1.2.1.4).	- Laboratory testing, including blood cell count, measuring liver function, renal function, and urinalysis, as well as physical examination, will be used to monitor lungs, liver, and kidneys.
Drug-drug interactions	[redacted] (Section 1.2.1.3)	[redacted] (Section 4.2.2.1)
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)

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
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 will not exceed the volume of a normal blood donation (500 mL; see Appendix 10.1.) No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.
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 absolute bioavailability trial. Therefore, subjects will be exposed to ionizing radiation. The effective whole body dose that each subject receives from one administration of ≈ 20 kBq is approx. 0.002 mSv.	The effective whole body dose in this study is 0.002 mSv. This is lower than the limit specified by: International Commission on Radiological Protection (ICRP) Category 1, (<0.1 mSv – risk defined as trivial) [R18-1836, R18-1905]

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1.4.3 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.
Overall, the preclinical safety profile of BI 1291583 is interpreted as favourable for the intended indication and does not show evidence for genotoxicity at the doses to be tested. A dose of up to [redacted] is considered adequate for life-long treatment from a preclinical and clinical point of view.
The exposure after a [redacted], highest dose, (oral administration) and intravenous administration of [redacted] BI 1291583 (C-14) is expected to be similar to the exposure reached in the SRD (i.e. [redacted] see Table 1.2.1.2: 1).
The exposure of [redacted] is well below the exposures after [redacted] ([redacted], see Section 1.2.1.4) which is formally considered as maximum acceptable exposure in this trial. Parent compound and metabolites are covered in the general toxicity studies. An increased exposure due to DDIs is not expected in this trial due to restrictions in concomitant medication.
The results of the Phase I trials show a favourable safety profile in healthy volunteers up to the highest level assessed ([redacted]), with no serious adverse events (SAEs) or adverse events of special interest (AESI) reported. Across all trials, most AEs were of [redacted] intensity in subjects receiving BI 1291583, with the exception o [redacted] respectively. Both were considered not related to BI 1291583.
AEs were reported for various system organ classes and preferred terms, however with no particular organ pattern emerging and no relationship with dose. One subject receiving BI 1291583 was reported with AEs leading to [redacted] both assessed as not drug-related).

Summary

The nature of the target and the mechanism of action of BI 1291583 is well understood. BI 1291583 [redacted] were safe and well tolerated (Section 1.2). However, there is always the potential for subjects receiving medication to experience adverse events (AEs), and rarely also serious adverse events (SAEs).
In the current trial, healthy male volunteers will receive a [redacted] BI 1291583 and [redacted] 1291583 (C-14). The trial design is optimized to obtain data on the absolute bioavailability of BI 1291583 which is required for an in-depth understanding of the pharmacokinetics of the compound. Each participating subject will receive only one radioactive dose. The risk associated with the expected radiation burden falls in ICRP category 1 (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.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the absolute bioavailability of BI 1291583 administered as [redacted] (test treatment T, not radio-labelled, [redacted]) compared with BI 1291583 (C-14) (reference treatment R) administered as [redacted].

2.1.2 Primary endpoint

The following pharmacokinetic parameter will be determined in plasma for [^{14}C]-BI 1291583 after intravenous and for BI 1291583 after oral administration (2 dose groups: [redacted]:

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

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined in plasma for [^{14}C]-BI 1291583 after [redacted] and for BI 1291583 after [redacted] administration (2 dose groups: [redacted]):

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

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are the evaluation and comparison of additional pharmacokinetic parameters between the treatments and assessment of safety and tolerability.
More specifically further objectives are:

- Determination of further PK parameters for BI 1291583, for [^{14}C]-BI 1291583, and for [^{14}C]-radioactivity, as feasible
- Evaluation of safety and tolerability of a [redacted] BI 1291583 together with a [redacted] dose of [redacted] 1291583 (C-14)

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2.2.2 Further endpoints

2.2.2.1 Further pharmacokinetic endpoints

Further PK endpoints will be calculated as appropriate for BI 1291583 in plasma after [redacted] administration (2 dose groups: [redacted]), and may include, but are not limited to:

- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- t_{max}
- λ_z
- $t_{1/2}$
- AUC_{t1-t2}
- MRT_{ex}
- CL/F
- V_z/F

Further PK endpoints will be calculated as appropriate for [^{14}C]-BI 1291583 and [^{14}C]-radioactivity in plasma after [redacted] dose, and may include, but are not limited to:

- $AUC_{0-\infty}$ for [^{14}C]-radioactivity
- AUC_{0-tz} for [^{14}C]-radioactivity
- C_{max} for [^{14}C]-radioactivity
- $\%AUC_{tz-\infty}$
- t_{max}
- λ_z
- $t_{1/2}$
- AUC_{t1-t2}
- MRT_{in} (mean residence time of the analyte in the body after [redacted] administration)
- CL (total clearance of the analyte after [redacted] administration, only for parent compound [^{14}C]-BI 1291583)
- V_z (apparent volume of distribution during the terminal phase after [redacted] administration, only for parent compound [^{14}C]-BI 1291583)
- V_{ss} (calculated volume of distribution at steady state after [redacted] administration, only for parent compound [^{14}C]-BI 1291583)

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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 and assessment of local tolerability, including [redacted])
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a non-randomized, open-label, two-arm, single period trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be 2 dose groups, either [redacted] BI 1291583 [redacted] (T) administered in fasting state followed by [redacted] BI 1291583 (C-14) (R) administered to 7 subjects per dose group with a total of 14 subjects. The radioactive dose of the [redacted] is approximately 20 kBq (expected to result in <0.1 mSv radiation burden – which is considered negligible. For details, refer to Section 4.1.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedule and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

For absolute bioavailability trials, the cross-over design is preferred because of its efficiency: since each subject serves as his own control, the comparison between formulations is based on an intra-subject comparison, thus removing inter-subject variability from the comparison [R94-1529]. Compared to the traditional cross-over design (i.e., two trial periods separated by a wash-out period), the chosen microtracer approach is considered more favourable, because both treatments are administered on the same day (resulting in 1 trial period with overlapping intervals of PK sampling).

Fourteen volunteers are included to ensure 6 evaluable subjects per dose ([redacted]). This is considered necessary to allow an accurate determination of absolute BA. Sampling duration is up to [redacted] after BI 1291583 administration), i.e. [redacted] which is considered sufficient for accurate determination of absolute bioavailability.

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

3.3 SELECTION OF TRIAL POPULATION

It is planned that 14 healthy male subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site or, if necessary, via external databases and advertisements.

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.

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

3.3.2 Inclusion criteria

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

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)

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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 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking while admitted to the trial site
16. Alcohol abuse (consumption of more than 24 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine, or 35 mL of spirits)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. Known coronavirus disease 2019 (COVID-19) infection, persistent symptoms of known prior COVID-19 infection, and/or known positive COVID-19 test within 2 weeks prior to screening or prior to D 1
25. Known relevant immunodeficiency
26. Subjects who have received or are planned to receive live or live-attenuated vaccine within 4 weeks prior to dosing
27. C-reactive protein above upper limit of laboratory reference range at screening and/or on Day -1
28. Subjects with signs of current clinically relevant gingivitis/periodontitis. Inspection of the oral cavity will be performed by the investigator
29. Subjects with a history of hyperkeratosis or erythema in palms or soles
30. Male subjects with women of childbearing potential (WOCBP) partner who are unwilling to use male contraception (condom or sexual abstinence) or to refrain from donating sperm, from time point of administration of trial medication until at least 6 months thereafter.

For restrictions of the trial, refer to Section 4.2.2.

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3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.2 , 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

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involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of 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 more than one subject per dose group does not complete the trial (including subjects non- evaluable for PK), one subject per dose group 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 Clinical Pharmacologist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number.

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Substance:	BI 1291583
Pharmaceutical formulation:	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	[redacted]
Duration of use:	[redacted], after an overnight fast of at least 10 hours, as treatment Test (T)

Substance:	BI 1291583
Pharmaceutical formulation:	[redacted]
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	[redacted]
Duration of use:	[redacted], after an overnight fast of at least 10 hours, as treatment Test (T)

The characteristics of the reference product are given below:

Name	BI 1291583 (C14) [redacted]
Substance:	Unlabelled BI 1291583 mixed with labelled [^{14}C] BI 1291583
Pharmaceutical formulation:	[redacted]
Source:	[redacted]., Groningen, The Netherlands
Unit strength:	[redacted]
Dose:	[redacted] BI 1291583 (C-14) containing a radioactive dose of approximately 20 kBq.
Posology:	[redacted]
Mode of administration:	[redacted]

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Duration of use: [redacted]
As treatment Reference (R)

4.1.2 Selection of doses in the trial

The dose selected for this trial is the anticipated therapeutic dose. This dose is well below the highest [redacted] tested in the SRD trial and was demonstrated to be safe and well tolerated (see Section 1.2).

In this trial an [redacted] containing a microtracer of BI 1291583 (C-14) is administered. The planned dose of [redacted] is characterized by a radioactivity of approximately 20 kBq which is considered to be sufficient for PK measurements.

4.1.3 Method of assigning subjects to treatment groups

This is a fixed-sequence crossover study with a timely overlap of PK sampling intervals. All subjects receive an [redacted] dose [redacted]) followed by an [redacted] later. All subjects form one treatment group and can be treated in one cohort (i.e. may be dosed on the same day). In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into cohorts as required. The first 7 subjects will be assigned to the [redacted] group and the second 7 subjects will be assigned to the [redacted].

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

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive the first the [redacted] dose of either [redacted] BI 1291583 (treatment T) followed by an [redacted] of [redacted] BI 1291583 (C-14) (treatment R). The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1291583	[redacted]	[redacted]	[redacted]	[redacted]
T (Test)	BI 1291583	[redacted]	[redacted]	[redacted]	[redacted]
R (Reference)	BI 1291583 (C-14)	[redacted]	[redacted]	[redacted]	[redacted]

Treatment T:
Administration of the [redacted] BI 1291583 [redacted]) 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 [redacted]) together with about 240 mL of water to subjects who are in a standing or sitting position.

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Treatment R:
For administration of the BI 1291583(C-14) [redacted]. A [redacted] used for collection of blood samples will be placed [redacted] The BI 1291583(C-14) [redacted] will be administered [redacted] to subjects in semi supine position under supervision of the investigating physician or an authorised designee. The [redacted] of treatment T. [redacted] be recorded.

All treatments:
For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, if correct dosage cannot be ensured otherwise.
Subjects will be confined to bed with a bed in half-supine or sitting position for the first 4 hours after administration of treatment T. Subjects will be kept under close medical surveillance until planned discharge from the trial site in the morning of Day 2.

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

BI 1291583 [redacted] will be provided to [redacted] by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.
They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).
The label will be prepared according to regulation (EU) No 536/2014, Annex 6, omitting certain particulars with the following justification:

- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site.
- The visit number is not relevant for the label because the product will remain at the clinical site.
- The investigator name was omitted from the label because it is included on the Trial Identification Card (TIC), which will be issued to each trial participant and it can be identified by the trial reference code.

Drug product manufacturing of radiolabeled BI 1291583 (C-14) [redacted] is done by [redacted] B.V.. The final clinical trial supply consists of vials containing the [redacted] GMP.
For details of packing and the description of the label, refer to the ISF.
The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EU CT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.
No re-supply is planned.

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4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs (BI 1291583 [redacted]) delivered from the sponsor when the following requirements are fulfilled:

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

[redacted] will provide the investigational drugs manufactured by [redacted], i.e. BI 1291583 (C-14) [redacted] upon availability of a valid prescription from the investigator. The investigator will order the drugs after the following requirements are fulfilled:

Approval of the clinical trial protocol by the IRB / ethics committee

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

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

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the

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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.
If for medical reasons a concomitant therapy is required, the following restrictions have to be taken into account:

[redacted]

Live or live-attenuated vaccine should be avoided during the trial.

Paracetamol or ibuprofen may be used as analgetic drugs at the discretion of the investigator.

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

4.2.2.2 Restrictions on diet and life style

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

From 1 h before drug intake (BI 1291583 [redacted]) until lunch, fluid intake is restricted to, [redacted] an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

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Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample is collected.

Poppy-seeds containing products should not be consumed starting 2 days before trial drug administration until discharge from the site.

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

Methylxanthine-containing drinks or foods (such as coffee, tea (green tea is not allowed 7 days before first administration in until the last PK sample is taken), cola, energy drinks, or chocolate) are not allowed from 24 h before until discharge from trial site.

Smoking is not allowed during in-house confinement.

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

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial (from 24 h before first drug intake until end of trial).

4.2.2.3 Contraception requirements

Male subjects with WOCBP partner are required to use male contraception (condom or sexual abstinence) and to refrain from donating sperm, from time point of administration of trial medication until at least 6 months thereafter. This is based on the recently identified metabolite for which a genotoxicity assessment is not yet available.

4.3 TREATMENT COMPLIANCE

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

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

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5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

At time points specified in the Flow Chart, visual inspection of the skin of palms and soles and oral cavity is performed. Clinically relevant skin or oral cavity findings will be documented as adverse event.

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 laboratory parameters (profile A, B, C), blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

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

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

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Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal and in accordance with Clinical laboratory ICON standard procedures)	Neut. Poly (segs)/Leukocytes [%]; Eosinophils/Leukocytes [%]; Basophils/ Leukocytes [%]; Monocytes/Leukocytes [%]; Lymphocytes/Leukocytes [%]			
Manual differential red blood cell count (if automatic differential WBC is abnormal and in accordance with Clinical laboratory ICON 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
	Total Amylase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--

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Table 5.2.3: 1 Routine laboratory tests (cont'd)

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Substrates	Glucose (Serum)	X	X	X
	Creatinine	X	X	X
	GFR/ CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Uric Acid	X	X	X
	Cholesterol, total	X	--	--
	Triglyceride	X	--	--
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X		X
	Urine Protein (qual)	X		X
	Urine Glucose (qual)	X		X
	Urine Ketone (qual)	X		X
	Urobilinogen (qual)	X		X
	Urine Bilirubin (qual)	X		X
	Urine RBC/Erythrocytes (qual)	X		X
	Urine WBC/Leucocytes (qual)	X		X
	Urine pH	X		X
Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 2 on Day 1 and 3 (for time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (end of trial 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.

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Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, an urine alcohol test will be performed at screening and on Day -1, 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] (see Section 8.7)

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

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abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

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

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of swelling, induration, heat, redness, pain, and other findings. Local findings assessed as clinically relevant by the investigator must be recorded as AE.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation, or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect

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

5.2.6.1.3 AEs considered 'Always Serious'

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

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

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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

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5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
  - All AEs (serious and non-serious) and all AESIs
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.
- After the individual subject's end of trial:
  - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial,

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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 the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 1291583 concentrations 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 with a metal needle.

For blood volumes see Appendix 10.1.

Details about blood sample collection, plasma preparation, required tubes, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the Laboratory Manual.

5.3.2.2 Blood sampling for [^{14}C] BI 1291583 analysis in plasma

For quantification of [^{14}C] BI 1291583 concentrations 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

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

For blood volumes see Appendix 10.1.

Details about blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the Laboratory Manual.

5.3.2.3 Blood sampling for [^{14}C] radioactivity analysis in plasma

For quantification of [^{14}C] radioactivity 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 blood volumes see Appendix 10.1.

Details about blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the Laboratory Manual.

5.3.2.4 Further investigations

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

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 1291583 concentrations in plasma

Plasma concentrations of BI 1291583 will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis. For the name and address of the laboratory refer to Section 8.7.

5.3.3.2 Analytical determination of [^{14}C]-BI 1291583 concentrations in plasma

Plasma concentrations of [^{14}C]-BI 1291583will be determined by means of accelerator mass spectrometry (AMS). For the name and address of the laboratory refer to Section 8.7.

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

Total [^{14}C]-radioactivity in plasma will be determined by means of accelerator mass spectrometry (AMS). For the name and address of the laboratory refer to Section 8.7.

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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 or intravenously 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.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, local tolerability, AE questioning and laboratory tests will be ± 30 min.

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

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

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

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

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed

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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.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The absolute bioavailability of either [redacted] BI 1291583 administered as [redacted] (test treatment T) compared with [redacted] BI 1291583 (C-14) (reference treatment R) administered as [redacted] will be estimated by the ratio of the geometric means (test/reference) for primary and secondary dose-normalized PK endpoints, and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

$$F\ (\%) = (AUC_{0-\infty} / Dose)_{[redacted]} / (AUC_{0-\infty} / Dose_{[redacted]} * 100$$

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 [^{14}C]-BI 1291583 will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning

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Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

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

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

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

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.
Descriptive and inferential statistics of PK parameters will be based on the PKS.
Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

Primary analyses

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

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

y_{km} = logarithm of response measured on subject m receiving treatment k,
μ = the overall mean,
s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n,
τ_k = the k^{th} treatment effect, k = 1, 2,
e_{km} = the random error associated with the m^{th} subject who received treatment k

where $s_m \sim N(0, \sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and s_m, e_{km} are independent random variables.
Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

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For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('subjects', 'treatment') considered as fixed effects.

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

7.2.3 Secondary endpoint analyses

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

7.2.4 Further endpoint analyses

7.2.4.1 Pharmacokinetic analyses

Further PK endpoints will be analysed descriptively.

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. 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 administration of treatment will be discussed in 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 end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that

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AEs occurring after the last per protocol contact will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

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

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

7.4 RANDOMISATION

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

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7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 14 subjects with 2 dose groups ([redacted]) of each 7 subjects in the trial with the aim of 6 evaluable subjects per dose group, which are considered sufficient information to assess the main objectives of this trial.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as 'protocol deviation'.
Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.
The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to a subject's participation in the trial, written informed consent must be obtained from each subject (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.

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

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

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

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8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

Before providing any copy of subjects' source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure subject confidentiality.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)

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

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

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8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.
A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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

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

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

8.6 TRIAL MILESTONES

The 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').

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
The trial will be conducted a [redacted], [redacted] The Netherlands, under the supervision of the Principal Investigator.
Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.
BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

Trial medication:

- BI 1291583 [redacted] will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany.
- BI 1291583 (C14) [redacted], The Netherlands

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

Bioanalytical analyses will be performed at:

- For BI 1291583in [redacted]
- For [^{14}C]-BI 1291583in plasma: [redacted], The Netherlands

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- For total [^{14}C]radioactivity in plasma: [redacted]
  The Netherlands

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.

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9. REFERENCES

9.1 PUBLISHED REFERENCES

P13-15562 Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomised controlled trial. JAMA 2013 ; 309(12); 1260-1267

R12-0355 Chahoud I, et al, Classification terms in developmental toxicology: need for harmonisation: report of the second workshop on the terminology in developmental toxicology Berlin, 27 - 28 August 1998. Reprod Toxicol; 1999; 13(1); 77-82

R17-2915 Adkison AM, Raptis SZ, Kelley DG, Pham CTN.
Dipeptidyl peptidase I activates neutrophil-derived serine proteases and regulates the development of acute experimental arthritis. J Clin Invest; 2002; 109(3); 363-371.

R17-3100 Dhanrajani PJ. Papillon-Lefevre syndrome: clinical presentation and a brief review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod; 108(1), p. e1-e7; 2009.

R17-3101 Sorensen OE Clemmensen SN Dahl SL Ostergaard O Heegaard NH Glenthoj A et al. Papillon-Lefevre syndrome patient reveals species-dependent requirements for neutrophil defenses. J Clin Invest; 124(10), p. 4539-4548; 2014.

R18-1836 Valentin J. The 2007 recommendations of the International Commission on Radiological Protection: ICRP publication 103.
Ann ICRP; 2007; 37(2 - 4); 1-332.

R18-1905 International Commission on Radiological Protection (ICRP).
Factors related to project evaluation.
Ann ICRP; 1992; 22(3); 11-13.

R18-3384 Torphy TJ, Allen J, Cantin AM, Konstan MW, Accurso FJ, Joseloff E, et al, Antiinflammatory Therapy Working Group. Considerations for the conduct of clinical trials with antiinflammatory agents in cystic fibrosis: a Cystic Fibrosis Foundation workshop report. Ann Am Thorac Soc; 2015; 12(9); 1398-1406.

R18-3357 Hartl D, Latzin P, Hordijk P, Marcos V, Rudolph C, Woischnik M, et al Cleavage of CXCR1 on neutrophils disables bacterial killing in cystic fibrosis lung disease. Nature Med 2007 ; 13(12); 1423-1430.

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R21-3309 Ringshausen FC, Roux A de, Pletz MW, Hamalainen N, Welte T, Rademacher J Bronchiectasis-associated hospitalizations in Germany, 2005 - 2011: a population-based study of disease burden and trends. Plos One 2013; 8(8); e71109.

R21-3311 Kwak HJ, Moon JY, Choi YW, Kim TH, Sohn JW, Yoon JH, Shin DH, Park SS, Kim SH. High prevalence of bronchiectasis in adults: analysis of CT findings in a health screening program. Tohoku J Exp Med 2010; 222(4) 237-242.

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

9.2 UNPUBLISHED REFERENCES

c18711868 Lotz R,da Costa A,Sarubbi D,Sauter W,She F,Zadow B. Investigator's Brochure BI 1291583. Current Version.

c31468932 Voelk C, Hauel E, Wong D, Kaiser A, Diefenbach C. Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 1291583 (single-blind, partially randomised, placebo-controlled parallel group design) in healthy male subjects. 1397-0001.Clinical Trial Report 07-Sep-2021

n00256437 Blattner S. Excretion of radioactivity in urine, faeces and bile after oral and intravenous administration of [^{14}C]-BI 1291583 to rats. A135/17SMB, B5993, 12 May 2017.

n00258671 Fuchs H. Pharmacokinetics of radioactivity and parent compound after oral and intravenous administration of [^{14}C]-BI 1291583 to rats. A136/17SMB, B6052, 02 Nov 2017.

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10. APPENDICES

10.1 BLOOD VOLUME

For analysis of BI 1291583 in plasma, 2 mL blood (K_2-EDTA) is collected per time point, i.e. 34 mL blood in total
For analysis of [^{14}C]-BI 1291583 in plasma, 2 ml blood (K_2-EDTA) is collected per time point, i.e. 30 mL blood in total.
For analysis of total [^{14}C]-radioactivity in plasma, 2 mL blood (K_2-EDTA) is collected per time point (only at baseline: 9 mL of blood), i.e. 37 mL blood in total.

Table 10.1: 1 Blood volumes for safety assessments

Assessment	**Maximum # Samples**	**Volume of Blood per Sample (mL)**	**Total Volume of Blood (mL)**
Clinical chemistry	4	3.5	14
Hematology	4	3	12
Coagulation	1	2.7	2.7
Serology	1	5	5
PK BI 1291583	17	2	34
PK [^{14}C]-BI 1291583	15	2	30
total [^{14}C]-radioactivity	1 + 14	9 + 2	37
Total volume of blood drawn for safety			

The total blood volume to be collected from each subject app. 170 mL in total.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		31-Oct-2023
EU number		2023-505683-11-00
BI Trial number		1397-0026
BI Investigational Medicinal Product(s)		BI 1291583
Title of protocol		Investigation of pharmacokinetics and absolute [redacted] bioavailability of BI 1291583 administered as an [redacted] of [14C]-BI 1291583 in healthy male volunteers
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☒
Non-substantial Global Amendment		☐
Section to be changed		1) Synopsis 2) 3.1: Trial design 3) 3.3.3: exclusion criteria 4) 4.1.3: Method of assigning subjects to treatment groups 5) 4.2.2: Restrictions 6) Table 5.2.3: 1: Routine laboratory tests
Description of change		1) Correcting the dose of unlabelled BI 1291583 and harmonizing the dose as per section 4.1.2. Updating trial design to 2-arm design ([redacted] 2) Updating trial design to 2-arm design ([redacted]) 3) Added exclusion criteria on contraception for men 4) As per request from Dutch health authorities, adding the sequence of assignment of subjects to the doses 5) Adding restrictions on contraceptives requirements 6) Removing Fibrinogen as not needed
Rationale for change		As we have 2 dose groups the design was updated accordingly to have a two-arm design Contraception requirements for participants with WOCBP partner were updated. This is based on the newly identified sixth metabolite for which a genotoxicity assessment is not yet available. The assignment of subjects to the dose groups are added.