

Clinical Trial Protocol

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EU Trial No.	2023-503542-31-00	
BI Trial No.	1484-0003	
BI Investigational Medicinal Product	BI 1584862	
Title	Effect of itraconazole on the pharmacokinetics of a single [REDACTED] dose of BI 1584862 in healthy male subjects (an open-label, two-period, fixed-sequence design study)	
Lay Title	A study in healthy men to test whether itraconazole influences the amount of BI 1584862 in the blood	
Clinical Phase	I	
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	26 April 2023
Revision date	16 August 2023
BI trial number	1484-0003
Title of trial	Effect of itraconazole on the pharmacokinetics of a single [REDACTED] dose of BI 1584862 in healthy male subjects (an open-label, two-period, fixed-sequence design study)
Principal Investigator	[REDACTED]
Trial site	
Clinical phase	I
Trial rationale	Based on <i>in vitro</i> data, [REDACTED] is involved in metabolism of BI 1584862. It is therefore necessary to investigate whether co-administration of multiple doses of itraconazole, a [REDACTED] affects single dose pharmacokinetics of BI 1584862 in healthy male subjects
Trial objective	To investigate the effect of a [REDACTED] on the pharmacokinetics of BI 1584862
Trial endpoints	Primary endpoints: AUC _{0-∞} and C _{max} of BI 1584862 Secondary endpoint: AUC _{0-tz} of BI 1584862
Trial design	Open-label, two-period fixed-sequence trial with 2 treatments (R and T)
Number of subjects total entered on each treatment	14 14
Diagnosis	Not applicable
Main inclusion criteria	Healthy male subjects, age of 18 to 50 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m ² (inclusive)
Trial product 1 dose mode of administration	BI 1584862 [REDACTED] [REDACTED] single dose [REDACTED]
Trial product 2 dose mode of admin.	Itraconazole oral solution (Sempera® Liquid 10 mg/mL) 200 mg once daily (q.d.) Oral with 240 mL of water after an overnight fast of at least 9 h

Duration of treatment	<p><u>Treatment R</u>: BI 1584862, single dose on Day 1 in Period 1 and 2</p> <p><u>Treatment T</u>: itraconazole once daily for [REDACTED] combined with a single dose of BI 1584862 on the [REDACTED] day of the itraconazole treatment (Day 1, 1 h after the itraconazole administration)</p> <p>The BI 1584862 single doses of Treatments R and T will be separated by a wash-out period of [REDACTED]</p>
Statistical methods	<p>The effect of itraconazole on the pharmacokinetics of BI 1584862 will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for subject and treatment. CIs will be calculated based on the residual error from the ANOVA.</p> <p>Descriptive statistics will be calculated for all endpoints.</p>

FLOW CHART

Treatment Reference

Visit	Period	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory ⁸	PK blood, BI 1584862	PK blood, Itraconazole	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy ⁶
1	SCR	-21 to -1			Screening (SCR) ¹	X ^A			X	X	
Visit 2 / Treatment R*	1	-3 to -1	-74:00 ⁷	06:00	Ambulatory visit	X ^{B,7}					X ⁷
		-1	-14:00	18:00	Admission to trial site ²	X ^{5,2}					X ²

*Administration of BI 1584862 in treatment R (Visit 2) and treatment T (Visit 3) separated by at least

FLOW CHART (cont.)

Treatment Test

Visit	Period	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory ⁸	PK blood, BI 1584862	PK blood, Itraconazole	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy ⁶
Visit 3 / Treatment T*	2										
4	FU				End of study (EOS) examination ⁴	x ^C			x	x	x

*Administration of BI 1584862 in treatment R (Visit 2) and treatment T (Visit 3) separated by at least

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, 12-lead ECG, safety laboratory (including drug screening and infectious serology), demographics (including determination of body height and weight, smoking status and alcohol history), medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; procedures are to be performed and completed no later than 10 h (admission on [REDACTED] and within 3 h prior to the (next) drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action. Meals will be standardised but are not mandatory to be eaten.

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. Given a subject cannot participate in the 2nd trial period (visit 3), the EoS examination can be performed starting [REDACTED] of visit 2 (1st period).
5. Urine drug screening and alcohol breath test only.
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. Safety laboratory to be taken and to be medically evaluated within 3 days prior to first administration of study drug; this assessment can be omitted if the screening examination is performed on Days -3, -2 or -1.
8. Letters A, B, and C, describe different sets of safety laboratory examinations (see Table [5.2.3: 1](#)).

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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
AST	Aspartat-Aminotransferase
AUC	Area under the concentration
AUC _{0-∞}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
%AUC _{tz-∞}	Percentage of AUC _{0-∞} obtained by extrapolation
AUC _{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t ₁ to t ₂
AUC _{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C _{max}	Maximum measured concentration of the analyte in plasma
CPLG	Clinical Pharmacology Leadership Group
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
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450 enzyme
DDI	Drug-Drug Interaction
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

EMA	European Medicines Agency
EoS	End of Study (synonym for End of Trial)
FDA	Food and Drug Administration
FE	Food effect
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GGT	Gamma-Glutamyltransferase
GLP	Good Laboratory Practice
gMean	Geometric mean
GMP	Good Manufacturing Practice
HR	Heart rate
IB	Investigator's brochure
ICH-GCP	International Conference Harmonization - Good-Clinical-Practice
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	Methylenedioxymphetamine
MDMA	Methylenedioxymphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)

R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{\max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Women of Child Bearing Potential

1. INTRODUCTION

BI 1584862 is a new molecule for [REDACTED]

1.1 MEDICAL BACKGROUND

For details on medical background refer to the Investigator's Brochure (IB) [[c38026281](#)].

1.2 DRUG PROFILE

1.2.1 BI 1584862

BI 1584862 is a new chemical entity molecule for [REDACTED]

[REDACTED] Nonclinical pharmacology, pharmacokinetics in animals and toxicology results are described in the IB [[c38026281](#)].

At the time of preparing this trial protocol, BI 1584862 has been investigated in one Phase I trial, which has completed enrolment (trial 1484-0001, in reporting phase).

In the single rising dose (SRD) part of that trial, 64 healthy male subjects were given single doses of either BI 1584862 (n=48) or placebo (n=16) [REDACTED] Doses of active test compound ranging from [REDACTED] were tested in cohorts of up to 6 subjects at each dose level and up to 2 subjects per dose level were given matching placebo [REDACTED]

An additional 13 subjects were tested with [REDACTED]

Treatments with BI 1584862 [REDACTED]

Tables [1.2.1: 1](#) and [1.2.1: 2](#) below provide an overall summary of treatment emergent AEs reported [REDACTED]

Table 1.2.1: 1 Overall summary of treatment emergent AEs in the SRD part

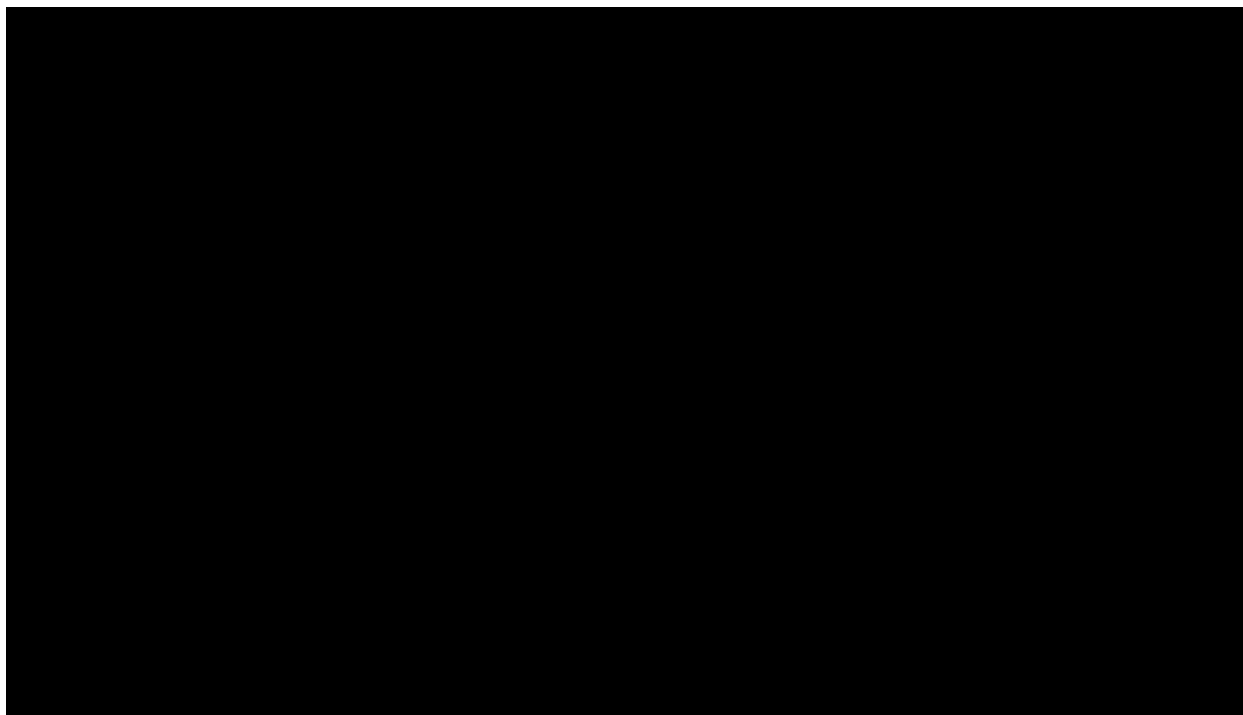

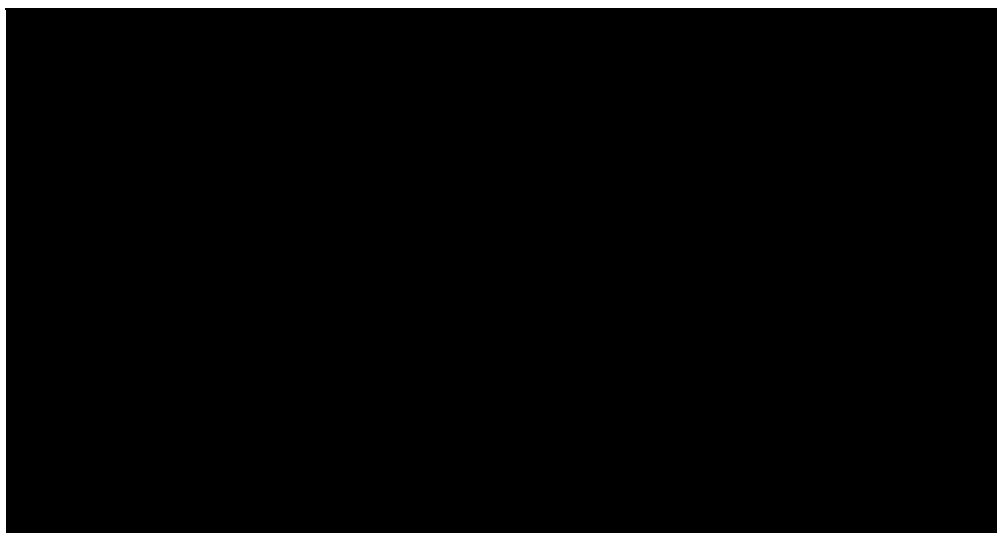




Table 1.2.1: 2 Overall summary of treatment emergent AEs in 



The most frequently reported AE defined as drug-related by the investigator was 



AEs were generally

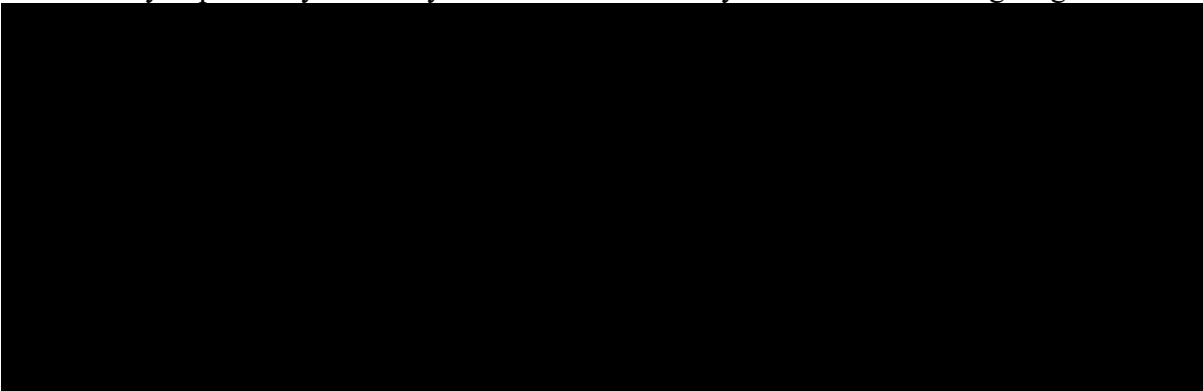
Table 1.2.1: 3 Investigator-defined drug-related adverse events by treatment, primary system organ class, and preferred term in the SRD part of trial 1484-0001

Table 1.2.1: 4 Investigator-defined drug-related adverse events by treatment, primary system organ class, and preferred term in trial 1484-0001

The clinical laboratory evaluation included the analysis of haematology, coagulation, enzymes, substrates, electrolytes, urinalysis, and inflammatory parameters

Pharmacokinetic results from trial 1484-0001

Preliminary exploratory PK analysis included 48 healthy volunteers receiving single doses in



A summary of the preliminary PK parameters of BI 1584862 derived based on planned time in the SRD part of this trial is provided in Table 1.2.1: 5 below.

Table 1.2.1: 5 Preliminary gMean (gCV %) PK parameters of BI 1584862 in plasma from SRD part in trial 1484-0001

A large black rectangular redaction box covering the entire content of Table 1.2.1: 5.

* median (min - max) ** terminal half-life

1.2.2 Itraconazole

Absorption of itraconazole solution is rapid with maximum plasma concentration being reached within 2.5 h after oral administration in fasting condition. Bioavailability of itraconazole liquid increases by 30% when given under fasting condition compared to administration together with food [[R23-0681](#)].

Mean peak plasma concentrations were 545.7 ng/mL after a single dose of 200 mg itraconazole solution (fasting) and 1965 ng/mL after 15 days of daily treatment with 200 mg itraconazole solution (fasting). Pharmacokinetics of itraconazole is non-linear. The half-life of itraconazole after multiple doses of 200 mg once daily with solution formulation was about 40 h [R17-3742].

In the liver, itraconazole is metabolised extensively to more than 30 metabolites [R17-3743]. Its main metabolite, hydroxy-itraconazole, accounts for about twice the concentration of plasma itraconazole at trough. It has been shown in vitro that CYP3A4 is mainly responsible for the formation of this metabolite [R23-0681]. FDA classifies itraconazole as strong index inhibitor of CYP3A and as inhibitor of P-glycoprotein (P-gp) [R18-0241]. However, not only itraconazole contributes to the in vivo inhibition of CYP3A observed after itraconazole administration but also three of its metabolites (hydroxy-itraconazole, keto-itraconazole, and N desalkyl-itraconazole) [R10-1102].

For a more detailed description of itraconazole, please refer to the German Summary of Product Characteristics (SmPC) for Sempera® Liquid 10 mg/ml [R23-0681].

1.2.3 Residual Effect Period

The Residual Effect Period (REP, the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 1584862 is conservatively assumed to be [REDACTED] i.e. a minimum observation period of at least 10-fold estimated $t_{1/2}$ has been selected for treatment period 1 (BI 1584862 alone, treatment reference).

When given together with itraconazole (Treatment T), it is expected [REDACTED]

For the use of itraconazole in Treatment T, the REP is defined as 8 days after last administration of itraconazole in Period 2.

1.3 RATIONALE FOR PERFORMING THE TRIAL

[REDACTED] the focus is on the drug-drug interaction (DDI) victim potential of BI 1584862 with regard to CYP3A4 and P-gp as this may lead to clinically relevant increases in exposures with potential impact on patient safety.

Itraconazole is chosen for this trial as perpetrator drug, as this drug is recommended as strong inhibitor of CYP3A by EMA and PMDA [P15-06991, P15-06298], and as strong index inhibitor of CYP3A and inhibitor of P-gp by FDA [R18-0241].

Moreover, safety and tolerability of itraconazole were acceptable in several previous DDI trials.

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 1584862

1.4.2 Risks

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

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

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
<u>Investigational Medicinal Product:</u> BI 1584862		
		Close monitoring for adverse events

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

Clinical data from first-in man trial 1484-0001	An overview on AEs is provided in Section 1.2.1.	Stringent in- and exclusion criteria define a relatively homogenous population and exclude subjects that might be at increased risk for adverse events (see Section 3.3). Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.
Investigational Medicinal Product: Itraconazole (Sempera® Liquid 10 mg/mL)		
Side effects described in the SmPC of the product [R23-0681]	Gastrointestinal side effects including hepatotoxicity are amongst the side effects that were most frequently reported. Other potential side effects are described in the SmPC of Sempera® Liquid 10 mg/mL. Overall, the risks associated with treatment with 200 mg/day itraconazole are considered acceptable.	Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously. Stringent in- and exclusion criteria define a relatively homogenous population and exclude subjects that might be at increased risk for adverse events (see Section 3.3). Criteria for withdrawal of individual subjects from trial treatment are defined in Section 3.3.4.1.

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

<u>Potential interaction between BI 1584862 and itraconazole</u>		
		<ul style="list-style-type: none">• Subjects are in-house under close observation for at least [REDACTED]• Subjects will be asked at pre-defined time points for AEs (see Flow Chart) and will be instructed to report AEs spontaneously.• ECG, VS, and safety laboratory will be performed as scheduled in the Flow Chart.
<u>Trial procedures</u>		
Blood sampling: Bruising and, in rare cases, phlebitis, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain; blood loss	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Medical expertise of the trial site. Total volume of blood withdrawn during the entire trial will not exceed the volume of a normal blood donation (500 mL).
ECG recording: Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes.

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 1584862 is well understood. Based upon the available preclinical information, first clinical data from SRD trial with BI 1584862, [REDACTED] healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of BI 1584862. Considering the medical need for the development of [REDACTED] the expected benefit outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the effect on the exposure of BI 1584862 in plasma when [REDACTED] together with multiple oral doses of itraconazole (Test, T) as compared to BI 1584862 [REDACTED] (Reference, R).

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for BI 1584862:

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

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for BI 1584862:

- 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)

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.

2.2.2 Further endpoints

2.2.2.1 Further pharmacokinetic endpoints

2.2.2.2 Further PK endpoints will be calculated as appropriate, and may include, but are not limited to:

For BI 1584862

- $\%AUC_{tz-\infty}$ (the percentage of $AUC_{0-\infty}$ obtained by extrapolation)
- t_{max} (time from dosing to maximum measured concentration of the analyte in plasma)
- λ_z (terminal rate constant in plasma)
- $t_{1/2}$ (terminal half-life of the analyte in plasma)

- $AUC_{t_1-t_2}$ (area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2)
- MRT_{po} (mean residence time of the analyte in the body [REDACTED])
- CL/F (apparent clearance of the analyte in the plasma [REDACTED])
- V_z/F (apparent volume of distribution during the terminal phase [REDACTED])

For itraconazole

Plasma concentrations of itraconazole will be assessed at the time points indicated in the [Flow Chart](#).

2.2.2.3 Safety and tolerability

Safety and tolerability of treatment with BI 1584862 and itraconazole will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as an open-label, two-treatment, two-period, fixed sequence design trial in healthy male subjects to compare the test treatment (T) to the reference treatment (R). The treatments will be [REDACTED] BI 1584862 administered as [REDACTED] together with multi [REDACTED] aconazole as oral solution (20 mL) (treatment T) and [REDACTED] BI 1584862 [REDACTED] alone (R).

In both treatments, BI 1584862 is administered to subjects in the fasting state. In the first treatment period (Period 1, Visit 2), all subjects are planned to undergo treatment R, and in the second treatment period (Period 2, Visit 3), all subjects are planned to undergo treatment T. For details, refer to Section 4.1. [REDACTED]

[REDACTED]

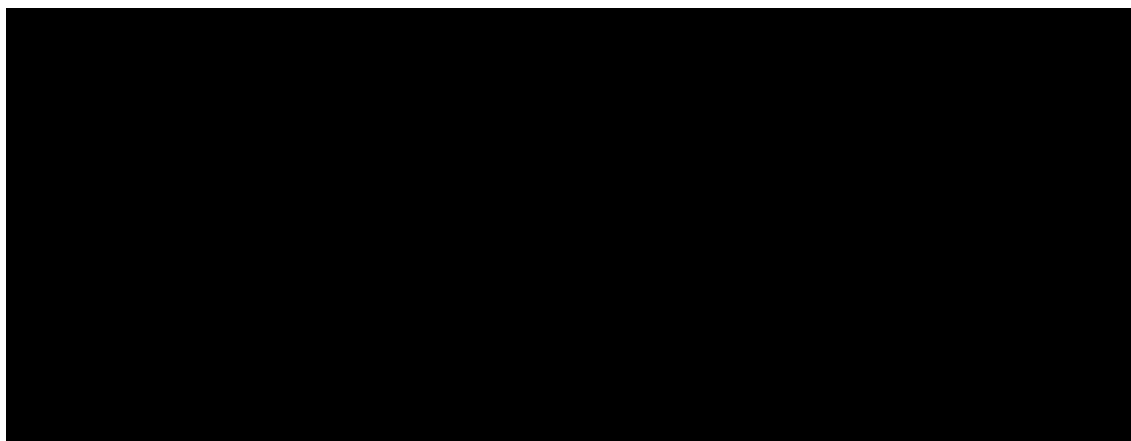


Figure 3.1: 1 Trial design

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

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

For drug interaction trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [[R94-1529](#)].

Because of the long half-life (about 40 h) of itraconazole and its metabolites, a two-period fixed sequence design was selected, with administration of itraconazole in the second study period only. This design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration.

For itraconazole studies, this design is recommended by the Innovation and Quality in Pharmaceutical Development's Clinical Pharmacology Leadership Group (CPLG) [[R17-3744](#)].

For this PK drug-drug interaction trial, open-label treatment is acceptable, because the primary and secondary endpoints of this trial are PK endpoints derived from measurement of plasma concentrations of BI 1584862. These endpoints are not expected to be affected by 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.

Due to the reproduction toxicity itraconazole has shown in nonclinical studies, only male subjects will be included in this trial.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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

3.3.2 Inclusion criteria

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

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 50 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m² (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 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 24 g per day)
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. Subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of administration of trial medication until 30 days thereafter
25. Liver enzymes (ALT, AST, GGT) above upper limit of normal or creatinine in serum exceeding 1.2 mg/dl at the screening examination, confirmed by a repeat test
26. History of drug induced liver injury, heart failure, or any evidence of ventricular dysfunction
27. Thyroid dysfunction based medical history, physical examination and TSH outside the normal range confirmed by repeat test
28. Subject is committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
29. Subject is dependent on the investigator or investigational site

For restrictions of the trial, refer to Section [4.2.2](#).

3.3.4 Withdrawal of subjects from treatment or assessments

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

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

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

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section [1.2.3](#), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the

subject cannot be guaranteed as he / 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). This may include:
 - The subject has an elevation of AST and/or ALT ≥ 3 -fold ULN
 - The subject has a serious adverse reaction
5. The subject has an elevation of AST and/or ALT ≥ 3 -fold ULN and an elevation of total bilirubin ≥ 2 -fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

If new efficacy or safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section [3.3.4.1](#) above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. The sponsor decides to discontinue the further development of the investigational products
3. Deviation from GCP or the CTP impairing the appropriate conduct of the trial
4. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
5. More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported

3.3.5 Replacement of subjects

In case more than 2 subjects do not complete the trial (including subjects non-evaluable for PK), subjects may be replaced, i.e. will be recruited in addition, 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. The total number of replacements may not exceed 1/3 of the total number of evaluable subjects anticipated to complete the trial, i.e. up to 4 subjects may be replaced. A replacement subject will be assigned a unique trial subject number and is planned to receive all treatments of both periods.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Trial Product 1

Substance: BI 1584862
Pharmaceutical formulation: [REDACTED]
Source: BI Pharma GmbH & Co. KG, Germany
Unit strength: [REDACTED]
Posology: [REDACTED]
Mode of administration: [REDACTED]
Duration of use: single dose in treatments R and T

Trial Product 2

Name: Sempera[®] Liquid 10 mg/ml
Substance: Itraconazole
Pharmaceutical formulation: Oral solution
Source: Public pharmacy or wholesale
Holder of marketing authorisation: Janssen-Cilag GmbH, Neuss, Germany
Unit strength: 10 mg/mL
Posology: 20 mL -0-0
Mode of administration: Oral
Duration of use: Once daily for [REDACTED] in treatment T

4.1.2 Selection of doses in the trial

The dose of itraconazole selected for this trial reflects standard clinical doses, is considered sufficient to yield significant CYP3A and P-gp inhibition and has been used successfully and safely in previous drug-drug interaction trials. Multiple DDI studies using 100 - 200 mg/day of itraconazole with a 3-day lead-in have demonstrated that adequately strong CYP3A inhibition is observed with this strategy [[R17-3744](#)].

[REDACTED]

For the current trial, a dose of [REDACTED] BI 1584862 is selected, in order to ensure that BI 1584862 plasma concentrations, even in case of a substantial increase when given with itraconazole, are within the range of concentrations that were explored in the SRD part of trial 1484-0001 and that were associated with good safety and tolerability (ref. Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

There is only one treatment sequence investigated in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a trial subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2. Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are summarised in Table 4.1.4: 1 below. All subjects will receive the 2 treatments in a fixed order. The administrations of BI 1584862 in the 2 treatments will be separated by a wash-out phase of at least [REDACTED]

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
R (Reference)	BI 1584862	[REDACTED]			
T (Test)	BI 1584862				
	Itraconazole	Oral solution	10 mg/mL	20 mL once daily for [REDACTED]	[REDACTED]

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled administration of BI 1584862 or 9 hours before itraconazole administration. The investigator (or authorised designee) will administer the trial medication [REDACTED]

[REDACTED] For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until [REDACTED] in each period. During the first 4 h after BI 1584862 administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

4.1.5 Blinding and procedures for unblinding

This non-randomised open-label Phase I trial will be handled in an open fashion throughout. The treatment assignment will be available to all involved parties.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal product BI 1584862 will be provided by BI. It will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

The label will be prepared according to Regulation (EU) No 536/2014, Annex 6 omitting certain particulars with the following justifications:

- The investigator name is omitted from the label because it is included on the Trial Identification Card, which will be issued to each trial participant.
- The "keep out of reach of children" statement is omitted from the label because the product will remain at the clinical site.

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form.

Itraconazole will be obtained from a public pharmacy or from wholesale. The wording "Zur klinischen Prüfung bestimmt" may be added to the packaging if required. The drug will be dispensed out of the otherwise original, unmodified packages.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered from the sponsor when the following requirements are fulfilled:

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

Sempera® Liquid 10 mg/ml (itraconazole) can be sent to the trial site at any time.

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

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

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

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. This includes (re-)vaccination of any kind and medication that might reasonably influence the results of the trial or interfere with the subject's safety. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

Known inhibitors/inducers of CYP3A4 or P-gp activity, drugs with a known hepatotoxicity profile, drugs which are contraindicated to be co-administered with itraconazole [[R23-0681](#)] should be avoided during the entire study; if necessary, short term use of ibuprofen is acceptable.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the [Flow Chart](#). No food is allowed for at least 10 h before [REDACTED] BI 1584862. Subjects will be advised to not consume any food within 9 h before and 1 h after itraconazole administrations.

PK profiling days (Day 1 in each period): from 1 h before [REDACTED] until lunch, fluid intake is restricted to [REDACTED]

From lunch until 23 h post-dose

BI 1584862, total fluid intake is restricted to 3000 mL.

Grapefruits, green tea, 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 of the trial is collected.

Alcoholic beverages are forbidden from 5 days before the first administration of trial medication until after the last PK sample of the trial.

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug-screen.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) and smoking are not allowed during inhouse 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.

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](#)).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

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

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, GE Medical Systems, [REDACTED]) at the times indicated in the [Flow Chart](#), after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 9 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

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

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B	C
Haematology	Haematocrit	X	--	X
	Haemoglobin	X	--	X
	Red Blood Cell Count/Erythrocytes	X	--	X
	White Blood Cells/Leucocytes	X	--	X
	Platelet Count/Thrombocytes (quant)	X	--	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	--	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	--	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.			
Coagulation	Activated Partial Thromboplastin Time	X	--	X
	Prothrombin time (Quick)	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
Hormones	Thyroid Stimulating Hormone	X	--	--
	NTBNP (NT-proBNP)	X	--	X
Substrates	Glucose (Plasma)	X	--	X
	Creatinine	X	X	X
	GFR/CKD-EPI	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	--	X
	C-Reactive Protein (Quant)	X	--	X
Electrolytes	Sodium	X	--	X
	Potassium	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 HGB (qual)	X	--	X
	Urine leukocyte esterase (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 and 3 at various time points as indicated in the [Flow Chart](#)

C: parameters to be determined at Visit 4 (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 upon admission to trial site in each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, Bluepoint Medical GmbH & Co. KG) will be performed at admission to the trial site in each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [REDACTED] with the exception of drug screening tests. These tests will be performed at the trial site using M-10/14-PDT Surestep Multiline Urine Drug Test or comparable test systems. Confirmatory drug screen may be performed at [REDACTED]

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

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

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, GE Medical Systems, [REDACTED]) at the times provided in the [Flow Chart](#).

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

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

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, [REDACTED]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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

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

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered ‘Always Serious’

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

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

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Potential severe DILI

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

- o 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
- o Aminotransferase (ALT, and/or AST) elevations ≥ 10 -fold ULN

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

5.2.6.1.5 Causal relationship of AEs

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

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

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

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- There is an alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned)
- Disappearance of the event even though the trial drug treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual subject's end of trial (the End of Study (EoS) visit):
 - All AEs (serious and non-serious) and all AESIs
 - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF and will not be reported in the CTR.

- After the individual subject's end of trial:
 - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point without undue delay but not later than within 24 hours of becoming aware of the event. The country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the [Flow Chart](#). The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

BI 1584862 in plasma

For quantification of BI 1584862 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K₂-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be

completed within 120 min, with interim storage of blood samples in ice water or on ice. The time each aliquot was placed in the freezer will be documented.

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

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time, and analyte 'BI 1584862'.

Itraconazole in plasma

For quantification of itraconazole concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K₂-EDTA blood drawing 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.

Blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 min, with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time, and analyte 'Itra'.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of BI 1584862 plasma concentration

BI 1584862 concentrations in plasma will be determined by [REDACTED]
[REDACTED] All details of the analytical method will be available prior to the start of sample analysis.

5.3.3.2 Analytical determination of itraconazole plasma concentration

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

5.3.3.3 Further use of plasma samples

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

However, only data related to the analytes and/or their metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. More specifically, the back-up samples (2nd aliquot) of BI 1584862 might be used to get a PK-profile of itraconazole if deemed necessary.

The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

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 [REDACTED] and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section [5.3](#) are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

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

In treatment period T, a time window of ± 120 min around planned time applies to itraconazole dosings [REDACTED]. The same time windows will be applied for assessments scheduled before administration of itraconazole on these days.

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests [REDACTED] will be ± 60 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.

Snack and dinner [REDACTED] may be served within a time window of ± 30 min.

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](#).

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section [5.6](#)).

6.2.2 Treatment periods

Each subject is expected to participate in 2 treatment periods [REDACTED] will separate drug [REDACTED] in the first and second treatment period.

[REDACTED] each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for [REDACTED]. 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 continuously from obtaining subject's written informed consent until the end of trial examination.

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

6.2.3 Follow-up period and trial completion

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

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

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this trial.

The relative bioavailability of BI 1584862 administered together with itraconazole (Test) compared with BI 1584862 (Reference) alone will be estimated by the ratios of the geometric means (test/reference), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

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

7.2.1.2 Pharmacokinetics

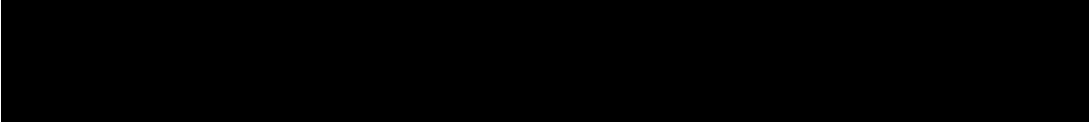
The pharmacokinetic parameters listed in Section [2.1](#) and [2.2.2](#) for BI 1584862 will be calculated according to the relevant BI internal procedures.

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

Important protocol deviations may be

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

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

- 
- The subject experiences emesis at any time during the period of itraconazole administration; the potential impact on the concentration levels/evaluation will be assessed at the report planning meeting
- A predose concentration is $>5\%$ C_{\max} of BI 1584862 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 endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subjects and treatment. The effect 'subjects' will be considered as random, whereas 'treatment' will be considered as fixed. The model is described by the following equation:

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

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

μ = the overall mean

s_m = the effect associated with the m^{th} subject, $m = 1, 2, \dots, n$

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 and n is the total number of subjects included in the trial.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section [2.1](#)) and their two-sided 90% confidence intervals (CIs) will be provided.

For each primary endpoint, the difference between the expected mean for log response of the test treatment – log response of the reference treatment 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 the primary endpoints will be analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (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 for BI 1584862 and itraconazole 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 assigned treatment will be discussed in the minutes of the Report Planning Meeting).

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

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section [4.1](#)) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to [REDACTED] will be assigned to the screening period, those between [REDACTED] and end of REP (see Section [1.2.3](#)) will be assigned to the treatment period.

Events occurring after the REP but prior to [REDACTED] or end of trial termination date will be assigned to 'follow-up'. These assignments [REDACTED] the corresponding time intervals will be defined in detail in the TSAP.

Note that AEs occurring after the last per protocol contact but entered before data base lock the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

Vital signs 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

In this trial subjects receive all treatments in the same order, thus no randomisation for the treatment assignment is performed.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 14 subjects in the trial with the aim of ≥ 12 evaluable subjects (see also Section 3.3.5), because this sample size is considered sufficient to achieve sufficient precision in estimating the ratio of geometric means (test/reference). Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed total geometric coefficient of variation (gCV) after single administration of BI 1584862 in the previous trial 1484-0001 was roughly

Assuming the correlation between two responses of the same subjects $\rho=0.5$ for C_{\max} and $\rho=0.75$ for $AUC_{0-\infty}$, the intra-individual geometric coefficient of variation can be estimated as

Table 7.5: 1 provides an overview of the precision that is expected with 95% probability and two-sided 90% confidence interval of various gCVs and gMean ratios (T/R) based on a sample size of $N=12$, respectively 14 evaluable subjects.

Table 7.5: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a 2-period fixed sequence trial ($N=12, 14$)

N	gCV [%]	Precision upper CI limit / relative BA estimate	90% CI [%] of respective ratio*		
			100	200	300

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.2.

Thus, based on a sample size of $N=12$ evaluable subjects and assuming

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

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. As a general rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a subject's participation in the trial, written informed consent must be obtained from each subject according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent, and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section [4.1.8](#).

ClinBase™

██ – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as database. Instead of being entered into CRFs, selected data are directly entered into the ClinBase™ system.

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 atttributable, 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)
- 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.

Data directly entered into ClinBase™ (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ are available for inspection at any time.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA).

They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section [8.3.1](#). The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:

The trial site must retain the source and essential documents (including ISF) according to the local requirements valid at the time of the end of the trial.

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

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

- Sample and data usage have to be in accordance with the informed consent

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

8.6 TRIAL MILESTONES

The first act of recruitment represents the start of the trial and is defined as the date when the first trial participant (subject) in the whole trial signs informed consent.

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [REDACTED] under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required trial activities, in order to

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

The trial medication BI 1584862 will be provided by the Clinical Trial Supplies Unit, BI Pharma GmbH & Co. KG, Biberach, Germany. The trial medication itraconazole will be obtained from public pharmacy or wholesale.

Safety laboratory tests will be performed by the local laboratory of the trial site ([REDACTED])

Analyses of BI 1584862 concentrations in plasma will be performed at [REDACTED]

Analyses of itraconazole concentrations in plasma will be performed at [REDACTED], [REDACTED]

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

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

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

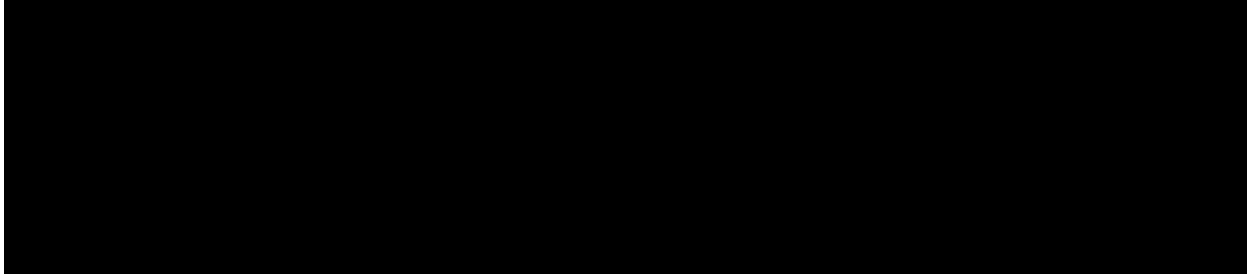
9. REFERENCES

9.1 PUBLISHED REFERENCES

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- R18-0241 Guidance for industry: clinical drug interaction studies - study design, data analysis, and clinical implications (draft guidance, this guidance document is being distributed for comment purposes only) (October 2017, clinical pharmacology). <https://www.fda.gov/downloads/drugs/guidances/ucm292362.pdf> (access date: 19 January 2018); Silver Spring: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2017.
- R23-0681 Sempera Liquid 10 mg/ml, Lösung zum Einnehmen (Janssen-Cilag) (Fachinformation, Stand der Information: December 2022). 2022.
- R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992.

9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 August 2023
EU number		2023-503542-31-00
BI Trial number		1484-0003
BI Investigational Medicinal Product(s)		BI 1584862
Title of protocol		Effect of itraconazole on the pharmacokinetics of a single [REDACTED] dose of BI 1584862 in healthy male subjects (an open-label, two-period, fixed-sequence design study)
Substantial Global Amendment due to urgent safety reasons To be implemented immediately in order to eliminate hazard – IEC / Competent Authority to be notified of change with request for approval.		
		<input type="checkbox"/>
Substantial Global Amendment e.g. changes in safety or physical or mental integrity of trial subjects, or in interpretation of scientific documents/value of the trial, or in conduct/management of the trial, or change/addition of principal investigators, co-ordinating investigators, or trial sites – implementation only after IEC / Competent Authority approval.		
		<input checked="" type="checkbox"/>
Non-substantial Global Amendment e.g. changes that involve logistical or administrative aspects, or exploratory endpoints only – can be implemented without IEC / Competent Authority approval		
		<input type="checkbox"/>
Section to be changed	1	Flow Chart
	2	Section 3.3.3 Exclusion criteria
	3	Table 5.2.3: 1 Routine laboratory tests
	4	Section 5.2.6.2.2 AE reporting to the sponsor and timelines
Description of change	1	ECG introduced on Day 2 in Visit 2 and 3
	2	Exclusion criteria no. 27, 28 and 29 introduced
	3	Parameter NT-proBNP added
	4	Reporting timelines rephrased
Rationale for change	1	Requested by health authority / ethics committee
	2	Requested by health authority / ethics committee
	3	Requested by health authority / ethics committee
	4	Requested by health authority / ethics committee

APPROVAL / SIGNATURE PAGE**Document Number:** c40933306**Technical Version Number:**2.0**Document Name:** clinical-trial-protocol-version-02

Title: Effect of itraconazole on the pharmacokinetics of a single [REDACTED] dose of BI 1584862 in healthy male subjects (an open-label, two-period, fixed-sequence design study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[REDACTED]	17 Aug 2023 09:19 CEST
Approval-Clinical Program [REDACTED]		17 Aug 2023 09:55 CEST
Author-Trial Statistician		17 Aug 2023 10:12 CEST
Verification-Paper Signature Completion		17 Aug 2023 13:15 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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