Clinical Trial Protocol

	c19245536-03
EudraCT No.:	2017-003452-23
BI Trial No.:	1305-0015
BI Investigational Product:	BI 1015550
Title:	Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects
Lay Title:	This study in healthy men tests how itraconazole influences the amount of BI 1015550 in the blood
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Principal Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 1))
Version and Date:	Version: 2.0 Date: 15 January 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 1015550			
Protocol date: 14 November 2017	**Trial number:** 1305-0015		**Revision date:** 15 January 2018

Title of trial:	Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects
Principal Investigator:	
Trial site:	
Clinical phase:	I
Objective:	To investigate whether and to what extent co-administration of multiple doses of itraconazole affect single dose pharmacokinetics of BI 1015550 in healthy male subjects
Methodology:	Open-label, fixed-sequence trial with two treatments (R and T)
No. of subjects: **total entered:** **each treatment:**	 16 16 (at least 12 completed)
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 55 years, body mass index (BMI) of 18.5 to 29.9 kg/m^2
Trial product 1: **dose:** **mode of admin.:**	BI 1015550 tablet 6 mg Oral with 240 mL of water after an overnight fast of at least 10 h
Trial product 2: **dose:** **mode of admin.:**	Itraconazole solution (Sempera® Liquid 10 mg/mL Lösung zum Einnehmen) 200 mg for 12 days in treatment T Oral with 240 mL of water after an overnight fast of at least 9 h
Duration of treatment:	Treatment R (BI 1015550 alone): Single dose of 6 mg BI 1015550 on Day 1 Treatment T (itraconazole + BI 1015550): 12 days of itraconazole treatment (200 mg itraconazole once daily) combined with a single dose of 6 mg BI 1015550 on the fourth day (Day 1) of the itraconazole treatment (1 h after the itraconazole administration). The BI 1015550 single doses of treatments R and T will be separated by a wash-out period of at least 10 days

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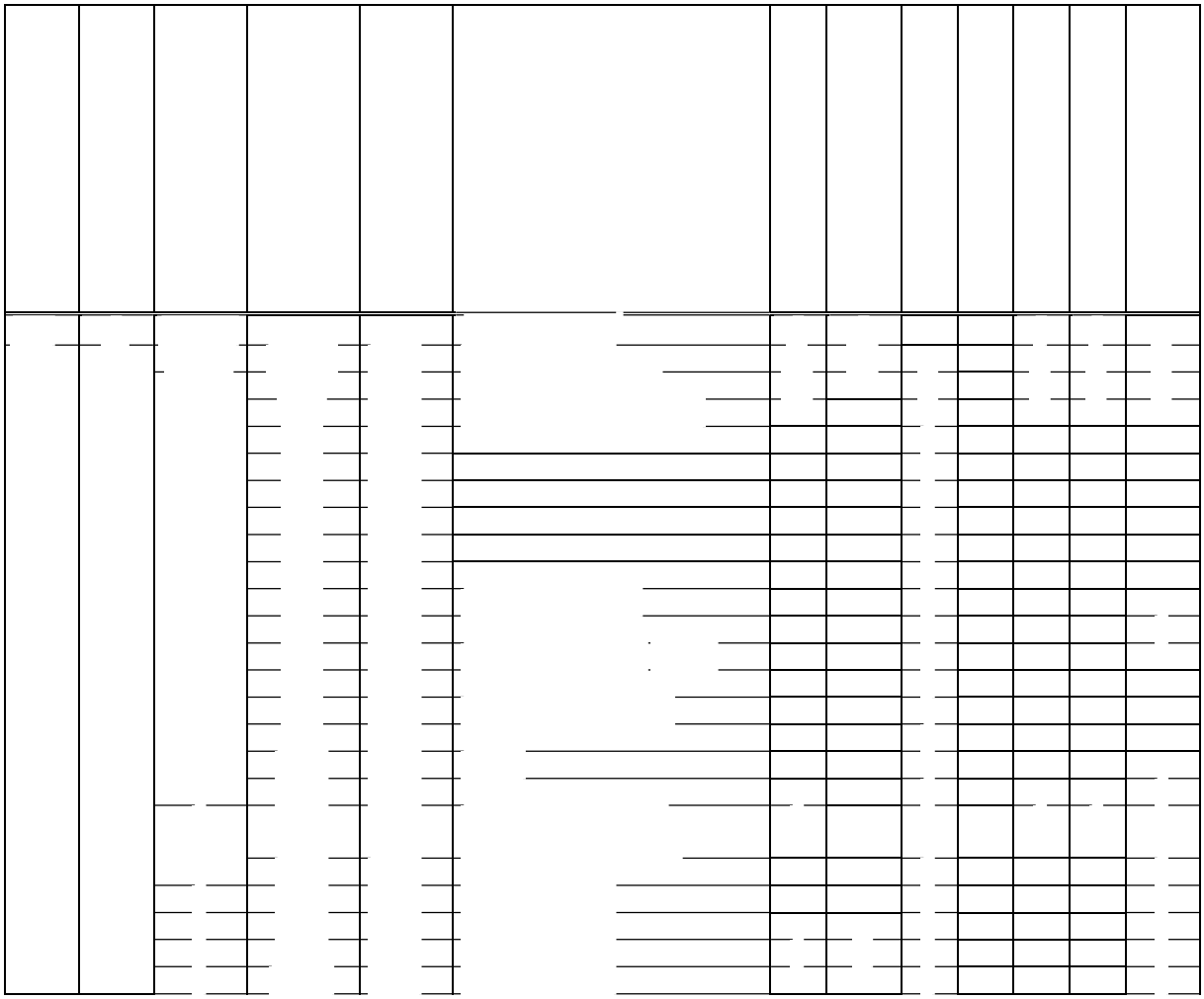
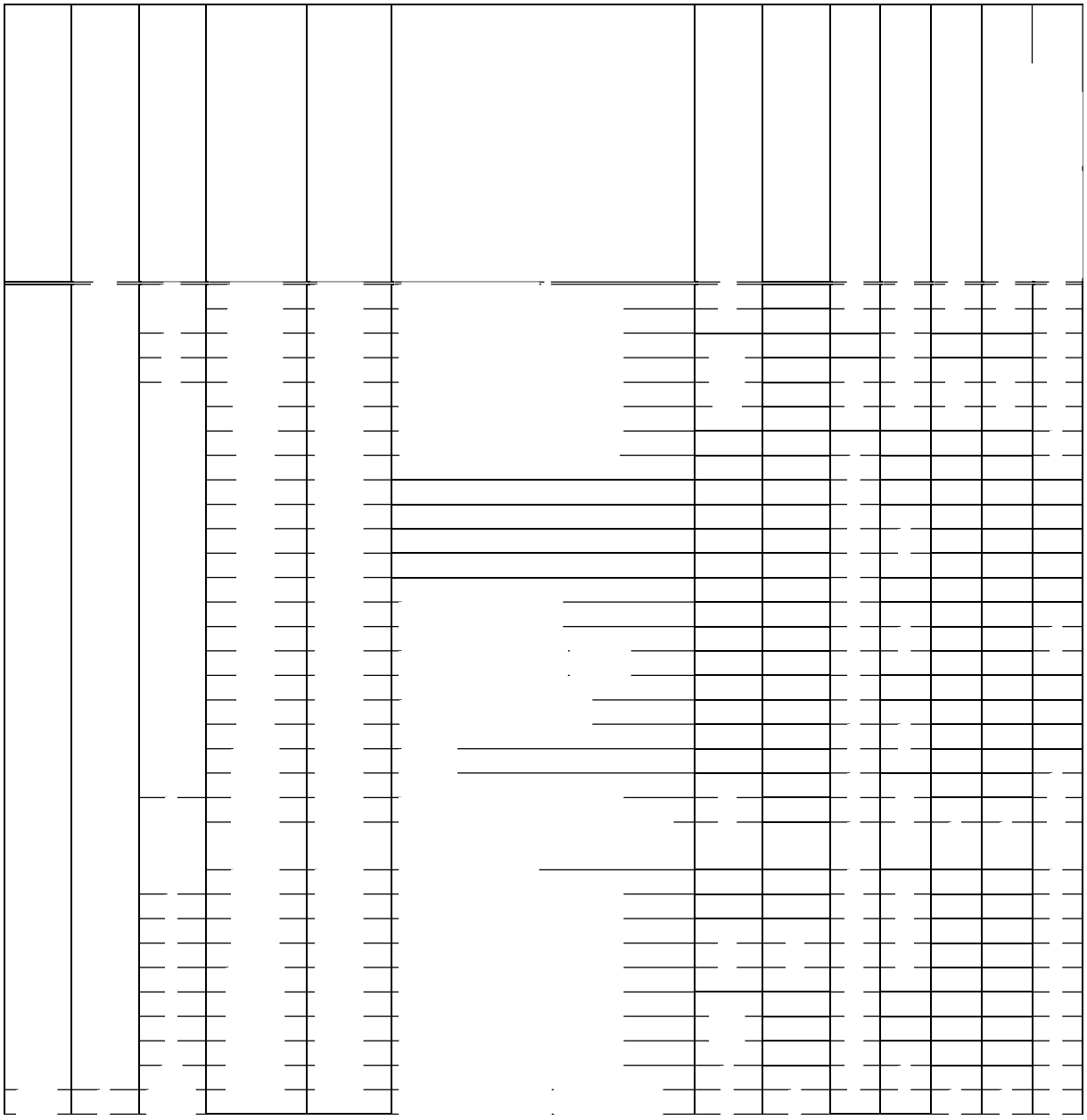
Name of finished product: Not applicable			
Name of active ingredient: BI 1015550			
Protocol date: 14 November 2017	**Trial number:** 1305-0015		**Revision date:** 15 January 2018
Criteria for pharmacokinetics:	Primary endpoints: AUC_{0-119} and C_{max} of BI 1015550 in plasma Secondary endpoints: $AUC_{0-\infty}$ of BI 1015550 in plasma		
Criteria for safety:	Adverse events (AEs) including clinically relevant findings from the physical examination, safety laboratory tests including fecal occult blood and fecal calprotectin testing, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR])		
Statistical methods:	Relative bioavailability will be estimated for BI 1015550 based on the point estimators of the intra-subject ratio (test to reference treatments) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally their corresponding two-sided 90% confidence intervals will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range will not be specified. The statistical model will be a (mixed effects) ANOVA on log transformed parameters, including effects for 'subjects' and 'treatment'. Confidence intervals will be based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.		





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ABBREVIATIONS

AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{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
b.i.d.	*Bis in die*, twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CK	Creatine kinase
CRF	Case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
CYP3A	Cytochrome P450, family 3, subfamily A
DDI	drug-drug-interaction
DILI	Drug induced liver injury
δ	Bioequivalence margin
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
gCV	Geometric coefficient of variation

GI	Gastro-intestinal
gMean	Geometric mean
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IEC	Independent Ethics Committee
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant of the analyte in plasma
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple-rising dose
NIMP	Non-investigational medicinal product
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PfOS	Powder for reconstitution of an oral solution
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
q.d.	*Quaque die*, once daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SmPC	Summary of Product Characteristics
SRD	Single-rising dose
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Test product or treatment
TEAEs	treatment emergent adverse events
TMF	Trial master file

TDMAP	Trial Data Management and Analysis Plan
TSAP	Trial statistical analysis plan
UGT	Uridine 5'-diphospho-glucuronosyltransferase

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

For a more detailed description of the BI 1015550 profile please refer to the current Investigator's Brochure [c02094779-02].

1.2 DRUG PROFILE

1.2.1 BI 1015550

1.2.1.1

For details on nonclinical pharmacology refer to the nonclinical pharmacology section in the Investigator's Brochure [c02094779-02].

For further details on safety pharmacology refer to the Investigator's Brochure [c02094779-02].

For further information please refer to the Investigator's Brochure [c02094779-02].

1.2.1.5.1

Further details can be found in the Investigator's Brochure [c02094779-02].

Clinical experience with other PDE4 inhibitors

Selective PDE4 inhibitors have been approved for COPD with chronic bronchitis and a history of exacerbations (roflumilast), and for moderate to severe plaque psoriasis and active psoriatic arthritis (apremilast). No PDE4 inhibitor has been tested in IPF, yet.

The most common AEs reported for these marketed PDE4 inhibitors were gastrointestinal events (diarrhea, weight loss, nausea, and vomiting, abdominal pain) and headache. For roflumilast, there was an increased incidence of neuropsychiatric adverse reactions such as insomnia, anxiety, nervousness, and depression; in rare instances suicidal ideation or behavior (including completed suicide). The product information of Otezla® (apremilast) also recommends cautious use in patients with a history of depression and/or suicidal thoughts or behavior [R14-1795].
Among the AEs leading to death, cardiac arrest was reported in a higher number of patients who received roflumilast [R10-1555]. Clinical manifestation of mesenteric vasculitis, an adverse effect that has been a concern with PDE4 inhibition in general, was not reported in these clinical studies with roflumilast.

1.2.2 Itraconazole

Itraconazole is an oral broad-spectrum imidazole antifungal agent, indicated for the treatment of systemic fungal infections at doses up to 200 mg twice daily. In-vitro studies suggest that itraconazole impairs the synthesis of ergosterol, a vital component of fungal cell membranes, by inhibiting the fungal CYP450 (CYP51). It is also a competitive inhibitor for CYP3A4, the major drug metabolizing enzyme in the liver, both in-vitro and in-vivo [R12-5255] as well as an inhibitor of P-gp [P12-05791] [R17-3744].

1.2.2.1 Clinical safety

The most common (listed occurrence ≥1%, but <10%) side effects of itraconazole are rash, pyrexia and symptoms of the CNS (headache, dizziness, dysgeusia), the respiratory (dyspnea, cough) or the gastrointestinal (abdominal pain, diarrhea, nausea, vomiting, dyspepsia, uncommonly also obstipation) system. As uncommon (listed occurrence ≥0.1%, but <1%) changes in clinical laboratory and hematology (leukopenia, thrombocytopenia and hypokalemia, also single cases of hypertriglyceridaemia and increased blood creatine phosphokinase), visual (including diplopia and blurred vision) and CNS disturbances (peripheral neuropathy, paresthesia, hypoesthesia), tinnitus, hypersensitivity, urticaria and pruritus, are listed. Further uncommon adverse reactions are hyperbilirubinemia and liver failure, congestive heart failure, as well as myalgia and arthralgia, menstrual disorders and edema. The most serious adverse drug reactions were serious allergic reactions (serum sickness, angioneurotic edema, anaphylactic reactions), serious skin reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson-Syndrome), cardiac failure/congestive heart failure/pulmonary edema, pancreatitis, and serious hepatotoxicity, including some cases of fatal acute liver failure. In most of these cases of serious hepatotoxicity patients suffered from concomitant liver diseases, had other significant diseases, or took concomitant hepatotoxic drugs. Some of these cases have been observed within the first month of treatment, including some within the first week. Single cases of hearing loss (in most cases reversible after cessation of itraconazole treatment) and tinnitus are known. Furthermore, itraconazole may

cause negative inotropic effects, if administered intravenously or at doses exceeding 400 mg per day [R17-3740].

For further information regarding itraconazol solution including additional adverse drug reactions associated with itraconazole in clinical trials please refer to the SmPC [R17-3741] and [R17-3740].

In trials with healthy volunteers, multiple doses of 200 mg itraconazole q.d. over a period of 10-15 days were well tolerated ([R17-3742], R12-5316, c02336088, c03355329, c08928447).

1.2.2.2 Pharmacokinetics and drug metabolism

Absorption of itraconazole solution is fast with maximum plasma concentration being reached within 2.5 h after oral administration in a fasted condition. In contrast to itraconazole administered as capsules where food increases the oral bioavailability of itraconazole, bioavailability of itraconazole liquid is increased by 30% when given in a fasted condition compared to administration together with food (bioavailability in fed condition: 55%) [R17-3740]. Mean peak plasma levels were 547.7 ng/mL after a single dose of 200 mg itraconazole solution (fasted) and 1965 ng/mL after 15 days of daily treatment with 200 mg itraconazole (solution, fasted). Itraconazole has a non-linear kinetics. The half-life of itraconazole after multiple doses of 200 mg once daily with solution formulation was about 40 h [R17-3742]. A large number of itraconazole metabolites with minimal antifungal activities exist and are primarily excreted in the bile since only 0.03% of itraconazole are eliminated unchanged in the urine [R12-5317, [R17-3740]. In the liver, itraconazole is metabolised extensively to more than 30 metabolites [R17-3743]. Its main metabolite, hydroxyitraconazole, accounts for about twice the amount of plasma itraconazole. It has been shown in-vitro that CYP3A4 is mainly responsible for the formation of this metabolite [R17-3740]. Itraconazole is a known and classified potent in-vivo inhibitor of CYP3A4 and P-gp [P15-06991], FDA-webside: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm). However, not only itraconazole contributes to the in vivo inhibition of CYP3A4 observed after itraconazole administration but also three of its metabolites (hydroxyitraconazole, ketoitraconazole and N-desalkyl-itraconazole) [R10-1102].

Due to the inhibitory effect of itraconazol on CYP3A4, co-administration of itraconazole with drugs primarily metabolized by the CYP3A4 should result in increased plasma concentrations over a longer period of time for the affected drugs due to inhibited metabolism and thereby elimination. Co-administration of 200 mg itraconazole once daily with 7.5 mg midazolam, a CYP3A4 substrate, resulted in a decreased plasma clearance of midazolam by 69%, a 6.6-fold increase in $AUC_{0-\infty}$, and a 2.5-fold in C_{max}. Accordingly, the half-life of midazolam was almost doubled [R06-2665].

For a more detailed description of the itraconazole profile please refer to the SmPC [R17-3741] and [R17-3740].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Therefore this trial should investigate whether and to what extent the inhibition of CYP3A mediated by itraconazole affects kinetics of BI 1015550. Itraconazole is a strong CYP3A4 inhibitor and a recommended probe drug to test in-vivo inhibition of CYP3A4 [P15-06991], [P12-05791].

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate whether and to what extent co-administration of multiple doses of itraconazole affect single dose pharmacokinetics of BI 1015550, i.e. to compare the relative bioavailability of 6 mg BI 1015550 when given alone (reference, treatment R) to the relative bioavailability of 6 mg of BI 1015550 given on the 4th day of a 12-day-treatment with itraconazole (test, treatment T) following oral administration in healthy male subjects.

The assessment of safety and tolerability will be an additional objective of this trial.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the development of BI 1015550 as a treatment for IPF. The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

2.3.1 Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

ECG electrodes may cause local and typically transient skin reactions.

2.3.3 Itraconazole-related risks and safety measures

In this trial itraconazole will be used in a standard dose of 200 mg once daily for 12 days. Multiple dosing of 200 mg itraconazole up to 15 days has been well tolerated by healthy subjects [c02336088, c03355329, c08928447, R17-3742].
Considering the risk of hepatotoxicity, only subjects with normal liver enzyme values will be included into the study. Safety laboratory parameters will be monitored closely. An individual subject will be removed from the trial if the subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample, see Section 3.3.4.1). Further, most of the reported cases of serious hepatotoxicity during Itraconazole treatment occurred in patients suffering from concomitant liver diseases, had other significant diseases, or took concomitant hepatotoxic drugs. Therefore only healthy subjects with no history of relevant liver diseases as specified in exclusion criterion 27 (ref exclusion criteria) will be eligible for trial participation.
Considering these safety measures and taking into account the reported good tolerability of itraconazole in healthy subjects, the planned administration of itraconazole does not represent an undue risk to healthy volunteers.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, fixed-sequence trial with two treatments (R and T) in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R).

Each subject will receive the reference treatment at Visit 2 and the test treatment in Visit 3. The two treatments are described below. The administrations of the single dose of BI 1015550 in treatment R (Visit 2) and in the following treatment T (Visit 3) will be separated by a wash-out period of at least 10 days.

Visit 4 will be the end of trial examination.

Treatment R (BI 1015550 alone):

6 mg (1x 6 mg tablet) of BI 1015550 will be given as a single dose on Day 1.

Treatment T (itraconazole + BI 1015550):

200 mg itraconazol (20 mL of Sempera Liquid 10 mg/mL) will be given once daily from Day -3 to Day 9 (12 days of itraconazole treatment in total). In addition, 6 mg (1x 6 mg tablet) of BI 1015550 will be given as a single dose 1 h after the itraconazole administration on Day 1 (corresponding to the fourth day of the 12-day itraconazole treatment).

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.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required 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 monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication BI 1015550 will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany. Itraconazole (Sempera® Liquid 10 mg/mL) will be provided by a public pharmacy.

The trial will be conducted at the Human Pharmacology Centre (HPC) of BI Pharma GmbH & Co. KG, Biberach, Germany, under the supervision of the Principal Investigator.

Safety laboratory tests will be performed by the local laboratory of the trial site

The analyses of BI 1015550 and its metabolites concentrations in plasma will be performed at a suitable contract research organization (CRO) under the responsibility of the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

The analyses of itraconazole and its metabolites concentrations in plasma will be performed at a suitable contract research organization (CRO) under the responsibility of the Department of Drug Metabolism and Pharmacokinetics, BI Pharma GmbH & Co. KG, Biberach, Germany.

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

Statistical evaluation will be done by BI or by a suitable contract research organization (CRO) under the responsibility of BI and according to BI SOPs.

Data management will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organize, 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.

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

This is an open-label trial to investigate the potential effect of multiple dose itraconazole on the single dose pharmacokinetics of BI 1015550. Two treatments will be compared in a descriptive way: a single dose of BI 1015550 given alone (treatment R) and in combination with multiple dose itraconazole (treatment T).

Due to the long half-life of itraconazole (about 40 hours) and its metabolites (ND-itraconazole)
a fixed sequence design was selected, with administration of itraconazole in the second study period only. The fixed-sequence design is not expected to lead to systematic errors in the estimation of the treatment effects, because the trial duration is short enough so that nonspecific time-effects are not expected. This design is also the design for itraconazole DDI studies that is recommended by the Innovation and Quality in Pharmaceutical Development's Clinical Pharmacology Leadership Group (CPLG) [R17-3744].

Blinding is not possible because the treatments are distinguishable.

The open-label treatment is not expected to bias results, since the study endpoints are derived from measurement of plasma concentrations of BI 1015550 provided by a bioanalytical laboratory which is blinded to treatment allocation.

During the test treatment, subjects will receive itraconazole once daily from Day -3 onwards to achieve a sufficient exposure of the perpetrator drug (itraconazole) on Day 1. Predosing of itraconazole is a standard dosing regimen that has been described by several authors [R13-4571, R13-4572, R13-4573].

Itraconazole will be administered 1 h before BI 1015550 on Day 1 of the test treatment to allow for a local inhibition of intestinal CYP 3A4 and P-gp prior to BI 1015550 drug intake.

The single dose administrations of BI 1015550 in the 2 treatments will be separated by a wash-out period of at least 10 days, which should be sufficient for a complete washout of BI 1015550 between treatments.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 16 healthy male subjects (at least 12 completed) will enter the study. They will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

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

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) is deviating from normal and judged 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 judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and 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, including but not limited to mood disorders and any history of suicidality.
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients or other Azoles)
11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 20 g per day)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
18. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
23. Male subjects who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until two months after the study completion. Acceptable methods of contraception comprises barrier contraception and a medically

accepted contraceptive method for the female partner (intra-uterine device, hormonal contraceptive since at least two months)

In addition, the following trial-specific exclusion criteria apply:

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. The subject shows an elevation of AST and/or ALT ≥3-fold ULN combined with 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 physician may discontinue subjects at any time based on his or her clinical judgment.

A subject can also be removed from the trial if eligibility criteria are being violated or if the subject fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if 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.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Trial product 2:

Name:	Sempera® Liquid 10 mg/mL Lösung zum Einnehmen
Substance:	Itraconazole
Pharmaceutical formulation:	Oral solution
Source:	Janssen-Cilag, Neuss, Germany
Unit strength:	10 mg/mL
Posology:	20 mL - 0 mL - 0 mL
Route of administration:	p.o.
Duration of use:	12 days (in treatment T only)

4.1.2 Method of assigning subjects to treatment groups

There is only one treatment sequence in this trial, and each subject will be allocated to the same treatment sequence (R-T). The subjects will be allocated to a study subject number by drawing lots prior to first administration of trial medication in the morning of Day 1 of Visit 2. The randomization list of study subject numbers and assigned treatment sequence will be provided to the trial site in advance. Note that the randomization list is just needed for logistical reasons in this non-randomized, fixed-sequence and open-label trial. Hence, no bias is introduced when providing the randomization list in advance to the site. Test and reference treatments will be administered in the sequence specified in the Flow Chart.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.3 Selection of doses in the trial

The dose of itraconazole selected for this trial reflects standard clinical doses, is considered sufficient to yield significant CYP3A4 inhibition and has been successfully and safely used in previous drug-interaction trials that investigate the effect of CYP3A4 inhibition (c02336088, c03355329, c08928447).

(see section 2.3.4).

4.1.4 Drug assignment and administration of doses for each subject

All subjects will receive two treatments in a fixed-sequence order (R-T). The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
T (Test)	BI 1015550	Tablet	6 mg	1 tablet on Day 1, Visit 3	6 mg
	Itraconazole	Oral solution	10 mg/mL	20 mL (200 mg) on Day -3 to Day 9, Visit 3	2.4 g
R (Reference)	BI 1015550	Tablet	6 mg	1 tablet on Day 1, Visit 2	6 mg

Trial medication (BI 1015550 and itraconazole) will be administered together with about 240 mL of water to a subject in the standing position under supervision of the investigating physician or an authorized designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. Trial medication will be administered at the time points listed in the Flow Chart, following an overnight fast starting no later than 9 h before itraconazole administration or 10 h before scheduled BI 1015550 administration.

Subjects will be kept under close medical surveillance until 24 h following drug administration of BI 1015550. During the first 2 h after drug administration of BI 1015550, they are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture). For restrictions with regard to diet see Section 4.2.2.2.

BI 1015550 administrations in Visit 2 and 3 will be separated by a wash-out phase of at least 10 days.

4.1.5 Blinding and procedures for unblinding

No blinding was performed because the treatments are distinguishable from each another. This Phase I trial will be handled in an open fashion throughout (that is, during the conduct,

including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, since all subjects receive the same dose of different formulations in an open label design.

4.1.6 Packaging, labelling, and re-supply

Itraconazole will be obtained from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

BI 1015550 will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the German Drug Law as well as Annex 13/EU GMP Guideline will be provided on the containers. Containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Batch number

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms. Examples of the labels will be available in the ISF.

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 according to the recommended (labelled) storage conditions. Where 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 local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The investigator will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the 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

Only authorized personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorization by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator 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 products and trial subjects. The investigator will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal, the investigator must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorize 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 medical evaluation results have returned to an acceptable level.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardized meals will be served at the time points described in the Flow Chart. No food is allowed for at least 4 h after drug intake in case of BI 1015550 and for at least 1 h in case of itraconazole administration.

On PK profile days (Day 1, Visit 2 and 3), fluid intake is restricted from 2 h before drug intake of BI 1015550 until lunch to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose of BI 1015550, total fluid intake is restricted to 3000 mL.

Alcoholic beverages are not permitted starting 5 days before the first administration of trial medication until the last PK sample is collected; grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not allowed from 7 days before the first administration until collection of the last PK sample.

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

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 h before until 24 h after administration of BI 1015550.

Excessive physical activity (such as competitive sport) should be avoided starting 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 study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study center under supervision of the investigating physician or a designee. The measured plasma concentrations 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Safety and tolerability of the investigational drugs 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)

These parameters will be evaluated in a descriptive way only, and are therefore considered to be 'further parameters of interest'. A confirmatory analysis is not planned (see Section 7.3).

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

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 hospitalization or
- requires prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect,

  or
- is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize 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 hospitalization or development of dependency or abuse.

AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.2.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 RDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term 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 above.

The following are considered as AESIs:

- Hepatic injury
  A Hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or
  - o aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients 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 these parameters are analyzed, 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.

With the exception of hepatic injury, no AESIs have been defined for this trial.

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

Causal relationship of AEs

Medical judgment should be used to determine the relationship, 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 etiologies 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 diminished)

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

- Additional arguments amongst those stated before, like 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

5.2.2.2 Adverse event collection and reporting

AE collection

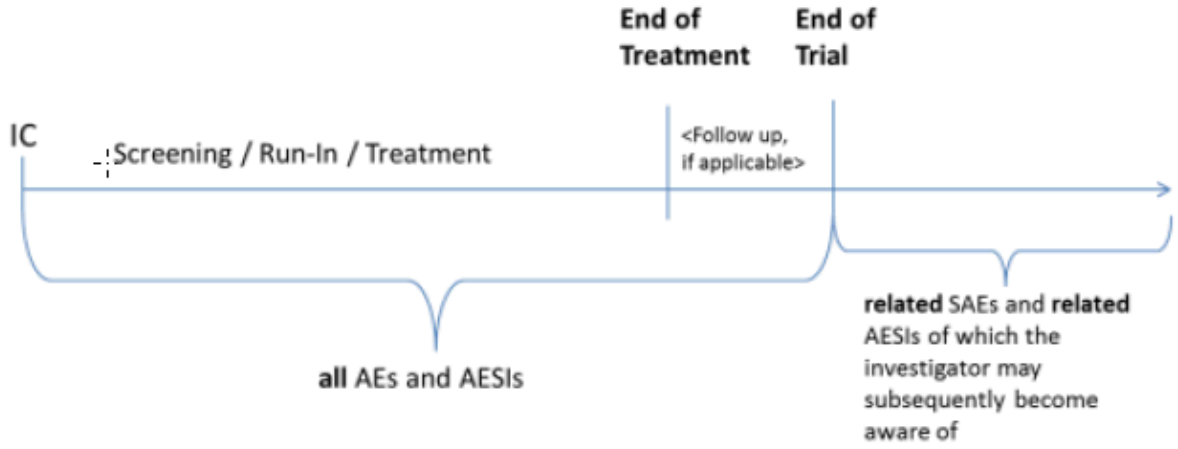
Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end, and intensity of these events. 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 careful 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, and intensity of the event as well as 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:
    - 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 or trial database 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 AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.



In Treatment T, the REP of itraconazole is about 9 days after last administration of itraconazole on day 9, i.e. up to day 18 (Treatment T). Therefore, all AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see Section 7.3.3. Events which occurred after the REP will be considered as follow-up events.

AE reporting to 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 via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)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 CRF only.

All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', or no further information can be obtained.

Pregnancy

Once the male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.3 Assessment of safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designee for retests.

The parameters that will be determined 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 will only be performed if there is an abnormality in the automatic blood cell count, i.e. if automatic count is not feasible or differential WBC is abnormal (i.e. pathological or atypical cells) and clinically relevant in the opinion of the investigator. In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein, microscopic examination of the urine sediment will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Fecal occult blood testing, using an immunochemical test kit for hemoglobin, and fecal calprotectin testing will be performed by the laboratory at the time points indicated in the Flow Chart.
As subjects may not be able to defecate at the trial site in the morning of Visit 1 (Screening) and during the ambulatory phase of Visits 2 and 3, they may collect the specimen at home and bring the test specimen to the trial site.

In case of gastrointestinal AEs (e.g. diarrhea, constipation), additional testing for fecal occult blood and fecal calprotectin may be carried out at the discretion of the investigator.
If a subject tests positive for occult blood in feces, further tests will be performed and the subject will be monitored closely.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	A[1]	B[2]	C[2]	D[3]
Hematology	Hematocrit	x	x	--	x
	Hemoglobin	x	x	--	x
	Red blood cell count (RBC)	x	x	--	x
	Reticulocyte count	x	--	--	x
	White blood cell count (WBC)	x	x	--	x
	Platelet count	x	x	--	x
	Erythrocyte sedimentation rate (ESR)	x	x	--	x
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	--	x
Manual differential WBC (if automatic count is not feasible or differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes				
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	--	x
	Prothrombin time (Quick's test and INR)	x	x	--	x
	Fibrinogen	x	x	--	x
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x	x
	Alkaline phosphatase (AP)	x	x	x	x
	Gamma-glutamyl transferase (GGT)	x	x	x	x
	Glutamate dehydrogenase (GLDH)	x	x	x	x
	Creatine kinase (CK); CK-MB only if CK is elevated	x	x	--	x
	Lactate dehydrogenase (LDH)	x	x	--	x
	Lipase	x	--	--	x
	Amylase	x	--	--	x
Hormones	Thyroid stimulating hormone (TSH)	x	--	--	--
Substrates	Plasma glucose	x	--	--	x
	Creatinine	x	x	--	x
	Total bilirubin	x	x	--	x
	Direct bilirubin	x	x	--	x
	Total protein	x	x	--	x
	High sensitivity C-Reactive Protein (hsCRP)	x	x	--	x
	Uric acid	x	--	--	x
	Total cholesterol	x	--	--	x
	Triglycerides	x	--	--	x
	Albumin	x	x	--	x
Electrolytes	Sodium	x	--	--	x
	Potassium	x	--	--	x
	Calcium	x	--	--	x
	Chloride	x	--	--	x
	Inorganic phosphate	x	--	--	x

[1] Parameters of Set A will be determined at the screening examination.
[2] Parameters of Set B and C will be determined at selected time points during Visit 2 and Visit 3 (ref. Flow Chart)
[3] Parameters of Set D will be determined during the end of trial examination

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	Test name	A[1]	B[2]	C[2]	D[3]
Urinalysis (Stix)	Urine nitrite	x	x	--	x
	Urine protein	x	x	--	x
	Urine glucose	x	x	--	x
	Urine ketone	x	x	--	x
	Urobilinogen	x	x	--	x
	Urine bilirubin	x	x	--	x
	Urine erythrocytes	x	x	--	x
	Urine leukocytes	x	x	--	x
	Urine pH	x	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)				

[1] Parameters of Set A will be determined at the screening examination.
[2] Parameters of Set B and C will be determined at selected time points during Visit 2 and Visit 3 (ref. Flow Chart)
3 Parameters of Set D will be determined during the end of trial examination

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to drug administration on Day 1 of 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/XTC 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 (Alcotest® 7410, Dräger AG, Lübeck, Germany) will be performed prior to drug administration on Day 1 of each treatment period, and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed with the exception of the drug screening tests. These tests will be performed at the trial site using AccuSign® DOA 10 or a comparable test.

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

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph (CardioSoft EKG System, GE Medical Systems, Freiburg, Germany) at the time points given in the Flow Chart.

All ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System (GE Medical Systems, Freiburg, Germany). 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. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.5 Assessment of other safety parameters

5.2.5.1 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, Freiburg, Germany) 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.

5.2.5.2 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, 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.

5.3 OTHER

5.3.1 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 taken 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 final report. However, the data may be part of the report if necessary.

5.4 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded.

Exact time points of plasma sampling will be derived from the study management system ClinBase™ and documented in the CRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

5.5.1.1 Primary endpoints

The following primary endpoints will be determined for BI 1015550:

- AUC_{0-119} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 119 h)

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

5.5.1.2 Secondary endpoints

The following secondary endpoints will be evaluated for BI 1015550:

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

Plasma concentrations of itraconazole and OH-itraconazole will be assessed at the time points given in the Flow Chart to confirm sufficient itraconazole/OH-itraconazole exposure and might be used for modeling to assess the effect of other CYP3A inhibitors (e.g. moderate inhibitors) on BI 1015550 pharmacokinetics.

5.5.2 Methods of sample collection

5.5.2.2 Plasma sampling for pharmacokinetic analysis of itraconazole and OH-itraconazole

For quantification of itraconazole and its metabolite plasma concentrations, 2.6 mL of blood will be taken from an antecubital or forearm vein into a Sodium-Heparin 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 Sodium-Heparin-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at about 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 plasma. Plasma aliquots will be frozen within 2 hours after blood withdrawal (interim storage of blood/plasma at room temperature). For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about - 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 about -20°C or below until analysis.
The sample tube labels should list at least the following information: study number, subject number, visit, and planned time. Further information such as matrix and analyte may also be given.

After completion of the trial the plasma samples may be used for further methodological investigations for e.g. stability testing, assessment of metabolites. However, only data related to the analyte and its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of analyte plasma concentration

The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization (CRO).

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 end of trial examination are given in the Flow Chart.

Study measurements and assessments scheduled to occur 'before' trial medication administration are to be performed and completed within a 3 h-period prior to the trial drug administration as indicated in the Flow Chart.

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 30 min.

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

For planned individual plasma concentration 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 determination of pharmacokinetic parameter.

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 give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening, fecal occult blood testing and fecal calprotectin testing), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

Pharmacogenomic genotyping will be performed in those volunteers whose genotypes are not known (for details see Section 5.3).

6.2.2 Treatment periods

Each subject is expected to participate in two treatment periods (Treatment R, Day -5 to Day 6 followed by Treatment T, Day -3 to Day 10). The washout period between the single dose BI 1015550 administrations in treatments R and T will be at least 10 days.

On Day 1 of each treatment period study participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following administration of BI

1015550. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other study days, the study will be performed in an ambulatory fashion. Likewise, itraconazole administrations on Days -3, -2, -1, 3 to 9 of treatment T will be done 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 5.5.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

6.2.3 End of trial period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

All abnormal values (including laboratory parameters) that are judged 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the effect of multiple doses of itraconazole on the pharmacokinetics of BI 1015550 given as single dose. The reference treatment (R) is administration of BI 1015550 alone, test treatment (T) is the co-administration of BI 1015550 on the fourth day of a 12-day treatment with itraconazole in healthy male volunteers. The trial is designed to allow intrasubject comparisons and will be evaluated statistically by use of an appropriate linear model.

The secondary objective is the evaluation and comparison of several pharmacokinetic parameters between the treatments. The secondary objective(s) will be assessed by descriptive statistics.

The assessment of safety and tolerability will be an additional objective of this trial, and will be evaluated by descriptive statistics.

7.1.2 Endpoints

Relative bioavailability is to be determined on the basis of the primary and secondary pharmacokinetic endpoints (see Section 5.5.1).

Safety and tolerability will be determined on the basis of the parameters specified in Section 5.2.1.

7.1.3 Model

The statistical model used for the analysis of primary and secondary endpoints will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘Subject’ and ‘treatment’. The effect ‘subject’ will be considered as random, whereas the other effect will be considered as fixed. The model is described by the following equation:

$y_{ij} = \mu + s_i + \tau_j + e_{ij}$, where

y_{ij} = logarithm of response (endpoint, see Section 5.5.1) measured on subject i receiving treatment j,

μ = the overall mean,

s_i = the effect associated with the i^{th} subject, i = 1, 2, ..., n

τ_j = the j^{th} treatment effect, j = 1, 2,

e_{ij} = the random error associated with the i^{th} subject who received treatment j.

In addition, the same analysis will be applied using subject as fixed effect.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of BI 1015550 administered alone or in combination with multiple oral doses of itraconazole will be estimated by the ratios of the geometric means (test/reference) for the primary and secondary PK endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-tests procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, an acceptance range was not specified, that is, no hypothesis will be tested.

7.3 PLANNED ANALYSES

7.3.1 Primary analyses

The pharmacokinetic endpoints listed in Section 5.5.1 will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be taken either from the median t_{max} for the reference product or from median t_{max} for the test product, depending on whether the subject had experienced emesis after taken the test or the reference product. Median t_{max} is to be determined excluding the subjects experiencing emesis
- Time deviations
- Use of restricted medications

Violations may lead to exclusion of single measurements/parameters for a subject (e.g. only data of one study period) or even to exclusion of all data of the subject.

The subject set for the evaluation of PK endpoints (PKS) will include all treated subjects that provide at least one observation for at least one primary or secondary endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will also be decided in the Report Planning Meeting which subjects are to be included in the PKS.

Point estimates of bioavailability, the ratios of the geometric means (test/reference) for the primary and secondary endpoints (see 5.5.1.1, 5.5.1.2), and their two-sided 90% confidence intervals (CIs) will be provided.

To this end, the PK endpoints will be log transformed (natural logarithm) prior to fitting the ANOVA model (cf. Section 7.1.3). For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (LeastSquares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/ Pharmacodynamics' (001-MCS-36-472) and will statistically be assessed using the same methods as described for the primary endpoints.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety analysis. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

The analyses will be done by 'treatment at onset'.

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyze 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 planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the end of its residual effect period (REP) will be assigned to the preceding treatment, and those after the REP but prior to the next intake or end of trial examination will be assigned to 'follow-up'. Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until end of the residual effect period (see 5.2.2.2) will be assigned to the treatment period. Events after the residual effect period but prior to next intake or end of trial examination will be summarized as 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database
Additionally, further treatment intervals (analyzing treatments) may be defined 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 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Relevant ECG findings will be reported as AEs.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for BI 1015550 and its relevant metabolites will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472) using validated software programs (preferably Phoenix WinNonlin®).

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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).

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidance. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

As this is a single sequence trial, no randomization is necessary (see also Section 4.1.2).

The sponsor will arrange for the packaging and labelling of BI 1015550 trial medication.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 16 subjects to have at least 12 completed in the trial. The planned sample size is not based on a power calculation but is judged to be adequate to attain reliable results and to fulfil the objectives and requirements of this exploratory trial.
The observed coefficient of variations (gCV) for AUC and C_{max} in previous trials 1305.1 and 1305-0011 [c01843325, c15772185-03] were from 12.7% to 32.0% for $AUC_{0-\infty}$ and 12.6% - 38.9% for C_{max} (Table 1.2.1.5.2: 1). The reported variability originates from parallel group designs where the gCV is an estimate of total variability. For this study an estimate of intra-individual variability is needed. Given the correlation between two responses of the same subject (ρ), the intra-individual variability can be estimated from the total variability. The recommended ranges for ρ in PK trials are (0.5- 0.6) for C_{max} and (0.75- 0.8) for AUC. Assuming conservative values ρ=0.5 for C_{max} and ρ =0.75 for AUC, the intra-individual gCV will be between 8.9% and 27% for C_{max} and between 6.3% and 15.7% for AUC. Hence, four different scenarios are considered for gCV in this trial.

Assuming different gCVs of 15%, 20%, 25% and 30% for AUC and C_{max} and given the chosen sample size of 16 subjects, the precision of the two-sided 90% confidence interval of the bioavailability ratio (upper confidence limit / relative BA estimate) will be from 1.13 to 1.26, and for the least acceptable sample size (i.e. 12 subjects), the precision would be approximately between 1.16 and 1.33. Table 7.6: 1 and Table 7.6: 2 provide an overview of the 90% confidence intervals that are expected with 95% probability, for possible scenarios of the gCV and intra-subject ratios (test/reference) (T/R).

Table 7.6: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs (N=16).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
15	1.13	50	44.38	56.34
15	1.13	100	88.75	112.68
15	1.13	150	133.13	169.01
15	1.13	250	221.88	281.69
20	1.17	50	42.67	58.58
20	1.17	100	85.35	117.17
20	1.17	150	128.02	175.75
20	1.17	250	213.37	292.92
25	1.22	50	41.06	60.89
25	1.22	100	82.12	121.77
25	1.22	150	123.18	182.66
25	1.22	250	205.30	304.44
30	1.26	50	39.53	63.24
30	1.26	100	79.07	126.47
30	1.26	150	118.60	189.71
30	1.26	250	197.67	

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

Table 7.6: 2 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs (N=12).

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
15	1.16	50	43.20	57.88
15	1.16	100	86.39	115.75
15	1.16	150	129.59	173.63
15	1.16	250	215.98	289.38
20	1.21	50	41.18	60.72
20	1.21	100	82.35	121.43
20	1.21	150	123.53	182.15
20	1.21	250	205.88	303.58
25	1.27	50	39.28	63.65
25	1.27	100	78.55	127.31
25	1.27	150	117.83	190.96
25	1.27	250	196.38	318.27
30	1.33	50	37.49	66.68
30	1.33	100	74.99	133.36
30	1.33	150	112.48	200.03
30	1.33	250	187.47	333.39

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

It is planned to enter 16 subjects to have at least 12 completed subjects. This means, in total up to 4 dropouts would be acceptable providing that the number of subjects with evaluable PK data should not be less than 12.
The calculation was performed as described by Julious [R11-5230] using R Version 3.3.2.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

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

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorized monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

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

ClinBase™
In the Human Pharmacology Centre (HPC) – Boehringer Ingelheim's Phase I unit – the validated ClinBase™ system is operated for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

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

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

Trial site:
The trial site must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) 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

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Treatment data may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated 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, i.e. the CA.

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 from clinical trial participants and the corresponding data, in particular:

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		15 January 2018
EudraCT number		2017-003452-23
BI Trial number		1305-0015
BI Investigational Product(s)		BI 1015550
Title of protocol		Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		1. Flow Chart, p 5 2. Section 5.5.2.1, p 52 3. Section 5.5.2.2, p 52
Description of change		Storage temperature of 20° (typo) was corrected to – 20° and a minor inconsistency in the Flow Chart was removed.
Rationale for change		By mistake 20° instead of – 20° was written in the plasma sample handling instruction. This amendment was issued to correct the mistake and ensure correct sample handling. At the same time a minor inconsistency in the Flow Chart was removed.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		15 Jan 2018 15:51 CET
Approval-Trial Clinical Monitor		15 Jan 2018 16:41 CET
Author-Trial Clinical Pharmacokineticist		16 Jan 2018 02:28 CET
Approval-Therapeutic Area		16 Jan 2018 08:25 CET
Verification-Paper Signature Completion		16 Jan 2018 13:29 CET
Approval-Team Member Medicine		24 Jan 2018 09:47 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed