# Clinical Trial Protocol

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| | **Document Number:** | **c24519579-01** |
| **EudraCT No.** | 2020-005934-13 | |
| **BI Trial No.** | 1305-0016 | |
| **BI Investigational Medicinal Product** | BI 1015550 | |
| **Title** | A phase I, open-label, non-randomized, single-dose, single-arm, single-period study to investigate the metabolism and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects | |
| **Lay Title** | A study in healthy men to find out how BI 1015550 is taken up and handled by the body | |
| **Clinical Phase** | I | |
| **Clinical Trial Leader** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] | |
| **Principal Investigator** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] | |
| **Status** | Final Protocol | |
| **Version and Date** | Version: 1.0 | Date: 28 January 2021 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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|---|---|
| **Company name** | Boehringer Ingelheim |
| **Protocol date** | 28 January 2021 |
| **Revision date** | Not applicable |
| **BI trial number** | 1305-0016 |
| **Title of trial** | A phase I, open-label, non-randomized, single-dose, single-arm, single-period study to investigate the metabolism and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects |
| **Principal Investigator:** | [redacted] |
| **Trial site** | [redacted] |
| **Clinical phase** | I |
| **Trial rationale** | To characterize mass balance, metabolic profile and routes of elimination of BI 1015550 |
| **Trial objectives** | The main objective of this trial is to investigate the basic pharmacokinetics of BI 1015550 and its metabolite BI 764333 (M480), [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose BI 1015550 (C-14) administered to healthy male subjects.<br><br>The primary objective is:<br>• To assess the mass balance recovery of [$^{14}$C]-radioactivity from urine and faeces as well as vomit in case of occurrence after a single oral dose of BI 1015550 (C-14) administered to healthy male subjects<br><br>The secondary objectives are:<br>• To assess the pharmacokinetics of [C-14]-BI 1015550 and BI 1015550 as well as its metabolite BI 764333 in plasma following a single oral dose of BI 1015550 (C-14)<br>• To assess the safety and tolerability of BI 1015550 |
| **Trial design** | Open-label, non-randomized, single-dose, single-arm, single-period design |

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| **Trial endpoints:** | **Primary endpoints:**<br>Mass balance recovery of total [C-14] BI 1015550 radioactivity:<br>• Amount of [$^{14}$C]-radioactivity excreted as a percentage of the administered single oral dose of BI 1015550 (C-14) in urine ($fe_{urine, 0-t2}$) and faeces ($fe_{faeces, 0-t2}$) as well as vomit ($fe_{vomit, 0-t2}$), if applicable<br>**Secondary endpoints:**<br>Pharmacokinetics:<br>• Assessment of $C_{max}$ and $AUC_{0-tz}$ for [C-14]-BI 1015550 and BI 1015550 as well as its metabolite BI 764333 in plasma<br>Safety:<br>• Percentage of subjects with treatment emergent adverse events (TEAEs)<br>[redacted] |
| **Number of subjects**<br>**total entered**<br>**each treatment** | <br>6*<br>6*<br>* In case a subject is discontinued from the trial an additional subject may be entered and dosed in order to assure a minimum of 4 evaluable subjects, i.e. the actual number of subjects entered may increase up to but will not exceed 8 |
| **Diagnosis** | Not applicable |
| **Main criteria for inclusion** | Healthy male subjects, age of 18 to 65 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m$^2$ (inclusive) |
| **Test product**<br>**Dose**<br>**mode of admin.** | $^{14}$Carbon-labelled BI 1015550 (BI 1015550 (C-14)) as oral solution (0.5 mg/mL)<br>18 mg of BI 1015550 (C-14) consisting of 17.16 mg unlabelled BI 1015550 mixed with 0.84 mg [C-14]-BI 1015550 as 36 mL of oral solution (0.5 mg/mL) containing a radioactive dose of 3.7 MBq (100µ Ci, corresponding to 0.2864 mSV)<br>Oral with 240 mL of water after an overnight fast of at least 10 h |
| **Reference product** | Not applicable |
| **Duration of treatment** | Single dose on Day 1 |
| **Statistical methods** | Descriptive statistics will be calculated for all endpoints. |

# FLOW CHART

| Visit | Day | Planned time (relative to drug administration) [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | PK blood / plasma [7] | PK urine [8] | PK faeces [9] | Blood sampling for metabolic profiling [15] | 12-lead ECG | Vital signs (BP, PR) | Questioning for AEs and concomitant therapy [6] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -21 to -1 | | | Screening (SCR)[1] | A | | | | | x | x | x |
| 2 | -1 | -18:00 | 14:00 | Admission to trial site | B[5, 16,17] | | | x[14] | | | | x |
| | | -14:00 | 18:00 | Dinner | | | | | | | | |
| | | -10:30 | 21:30 | Snack (voluntary) | | | | | | | | |
| | 1 | -2:00 | 06:00 | | x[2,10] | x[2] | x[2] | x[14] | x[2] | x[2] | x[2] | |
| | | 0:00 | 08:00 | Drug administration | | | ▲ | ▲ | | | | |
| | | 0:30 | 08:30 | | | x | ┼ | ┼ | | | | |
| | | 0:45 | 08:45 | | | x | ┼ | ┼ | | | | |
| | | 1:00 | 09:00 | | | x | ┼ | ┼ | x | | | |
| | | 1:30 | 09:30 | | | x | ┼ | ┼ | | | | |
| | | 2:00 | 10:00 | 240 mL fluid intake | | x | ┼ | ┼ | x | | | |
| | | 4:00 | 12:00 | 240 mL fluid intake, thereafter lunch[3] | x[10] | x | ┼ | ┼ | x | x | x | |
| | | 8:00 | 16:00 | Snack (voluntary)[3] | | x | ┼ | ┼ | x | | | |
| | | 11:00 | 19:00 | Dinner | | | ┼ | ┼ | | | | |
| | | 12:00 | 20:00 | | | x | ┼ | ┼ | x | | | |
| | 2 | 24:00 | 08:00 | | x[10,16] | x | ┼ | ┼ | x | x | x | |
| | | 36:00 | 20:00 | | | x | ┼ | ┼ | x | | | |
| | 3 | 48:00 | 08:00 | | x[10] | x | ┼ | ┼ | | | | |
| | 4 | 72:00 | 08:00 | | | | ┼ | ┼ | | | | |
| | 5 | 96:00 | 08:00 | | | x | ┼ | ┼ | | | | |
| | 6 | 120:00 | 08:00 | | | | ┼ | ┼ | | | | |
| | 7 | 144:00 | 08:00 | | | x | ┼ | ┼ | | | | |
| | 8 | 168:00 | 08:00 | | x[10] | x | ┼ | ┼ | | | | |
| | 9 | 192:00 | 08:00 | | | x | ┼ | ┼ | | | | |
| | 10 | 216:00 | 08:00 | Discharge from trial site[18] | B[17] | x | ▼ | ▼ | | x | x | |
| | 15 | 336:00 | 08:00 | Start home collection | | | | ▲ | | | | |
| | 16 | 360:00 | 08:00 | Admission to trial site[11,12,16] | | | ▲ | ┼ | | | | |
| | 17 | 384:00 | 08:00 | Discharge from trial site | | | ▼ | ▼ | | | | |
| | 22 | 504:00 | 08:00 | Start home collection | | | | ▲ | | | | |
| | 23 | 528:00 | 08:00 | Admission to trial site[11,12,16] | | | ▲ | ┼ | | | | |
| | 24 | 552:00 | 08:00 | Discharge from trial site | | | ▼ | ▼ | | | | |
| | 29 | 672:00 | 08:00 | Start home collection | | | | ▲ | | | | |
| | 30 | 696:00 | 08:00 | Admission to trial site[11,12,16] | | | ▲ | ┼ | | | | |
| | 31 | 720:00 | 08:00 | Discharge from trial site | | | ▼ | ▼ | | | | |
| 3 | 11 to 31 | | | End of trial (EoTrial) examination[4,13] | C[16] | | | | | x | x | x |

A, B & C: safety laboratory sets (see Table 5.2.3: 1)

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening), demographics (including determination of body height and body weight, smoking status and alcohol history), suicidality assessment (C-SSRS), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 2 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.

4. End-of-trial (EoT) examination to be performed within 1 to 7 days after last discharge from the trial site, or, if all once-weekly 24 h sampling periods are needed, prior to discharge on Day 31. EoT examination includes physical examination, vital signs, ECG, safety laboratory, body weight, suicidality assessment (C-SSRS), recording of AEs and concomitant therapies.
5. Safety laboratory including urine drug screening and alcohol urine test will be performed at this time (see Section 5.2.3).
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Pharmacokinetics (PK): BI 1015550 and its metabolite in plasma (see Section 5.3.2); [C-14] BI 1015550-radioactivity in whole blood and plasma (see Section 5.3.2). Blood sampling for an individual subject can be stopped, if [$^{14}$C]-BI 1015550-radioactivity in plasma is below limit of detection (< LLOQ 30 dpm/mL) at two consecutive sampling time points for this subject (earliest stopping after Day 10).
8. Urine collection intervals (for PK of [C-14] BI 1015550-radioactivity assessment and metabolic profiling; planned time): on Day -1 or Day 1 pre-dose (blank) sample, on Day 1 prior to start of urine collection voiding of the bladder, 0-4 , 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192 and 192-216 hours after administration of [C-14] BI 1015550. Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on Day 16. When the release criteria for radioactivity recovery have been met then urine sampling for PK will be stopped (earliest stop on Day 10).
9. All stools (for PK and metabolic profiling) will be collected quantitatively in portions up to 216 hours (sampling intervals of 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192 and 192-216 hours) after drug administration. Thereafter, if warranted, 24 h collections are to be performed every 7 days starting on Day 16. A blank sample will be collected on Day -1 or Day 1 prior to drug administration. Collection of the predose faeces sample will start from approximately -48 h before admission (see Section 5.3.2). When the release criteria for radioactivity recovery have been met then faeces sampling for PK will be stopped (earliest stop on Day 10).
10. At this time point, only a sample for haematocrit measurement is collected.
11. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 hours to the planned time. If not feasible due to logistic reasons the time window may be extended up to 8 hrs after the planned time.
12. Subjects are to collect faeces at home within 24 h intervals before admission to once-weekly in-house collection intervals. Home collection intervals: Day 15-16, 22-23 and 29-30. If faeces are collected in the subsequent in-house collection interval, faeces collected at home will be discarded. If no faeces is collected in the subsequent in-house collection interval (no defecation), faeces collected at home will be used instead for analysis.
13. For definition of the individual subject's end of trial, see Section 6.2.3.
14. Subjects will collect a pre-dose faeces sample at home or at the site on Day -1 or Day 1 in specific containers provided by PRA.
15. Metabolite sampling times may be adapted based on information obtained during trial conduct (e.g. levels of radioactivity in each urine and/or plasma sample) as long as the overall blood volume stays the same.
16. PCR testing for SARS-CoV-2 will be performed on Day -1 prior to admission, on Day 2, at each admission to the trial site for 24-hours visits and at EOT (see Appendix 10.3).
17. Subjects are to be fasted for at least 10 h before sample is taken.
18. Prior to discharge from trial site on Day 10 confirmation of fitness will be performed including physical examination, vital signs, ECG, recording of AEs and concomitant medication, safety laboratory and C-SSRS. An additional body weight will be measured at this time point.

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[redacted]

# ABBREVIATIONS

| | |
|---|---|
| ADME | Absorption, distribution, metabolism, and excretion |
| AE | Adverse event |
| $Ae_{faeces, 0-t2}$ | Amount of analyte that is eliminated in faeces over the time interval from time 0 to the last quantifiable time point |
| $Ae_{faeces, t1-t2}$ | amount of analyte that is eliminated in faeces from the time interval $t_1$ to $t_2$ |
| $Ae_{urine, 0-t2}$ | amount of analyte that is eliminated in urine over the time interval from time 0 to the last quantifiable time point |
| AESI | Adverse events of special interest |
| ALAT | Latin American Thoracic Association |
| ALT | Alanine Transaminase |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $\%AUC_{tz-\infty}$ | Percentage of $AUC_{0-\infty}$ obtained by extrapolation |
| $AUC_{t1-t2}$ | Area under the concentration-time curve of the analyte in plasma over the time interval $t_1$ to $t_2$ |
| $AUC_{\tau,ss}$ | Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval $\tau$ |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| BI | Boehringer Ingelheim |
| BLQ | Below limit of quantification |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| CA | Competent authority |
| cAMP | Cyclic adenosine monophosphate |
| [C-14] BI 1015550 | $^{14}$Carbon-labelled BI 1015550 |
| CL/F | Apparent clearance of the analyte in plasma after extravascular administration |
| $CL_{R, t1-t2}$ | Renal clearance of the analyte in plasma from the time point $t_1$ to $t_2$ |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CNS | Central Nervous System |
| COVID-19 | Coronavirus disease 2019 |
| CRF | Case Report Form, paper or electronic |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTM | Clinical Trial Monitor |
| CTP | Clinical trial protocol |

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|---|---|
| CTR | Clinical trial report |
| DDI | Drug Drug Interaction |
| DILI | Drug induced liver injury |
| ECG | Electrocardiogram |
| ECM | Extracellular Matrix |
| eCRF | Electronic case report form |
| eDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EoTrial | End of trial |
| ERS | European Respiratory Society |
| EudraCT | European Clinical Trials Database |
| F | Absolute bioavailability factor |
| $fe_{faeces,\ t1\text{-}t2}$ | Fraction of administered drug excreted unchanged in faeces from time point $t_1$ to $t_2$ |
| $fe_{urine,\ t1\text{-}t2}$ | fraction of administered drug excreted unchanged in urine from time point $t_1$ to $t_2$ |
| GCP | Good Clinical Practice |
| gCV | Geometric coefficient of variation |
| GI | Gastro-intestinal |
| gMean | Geometric mean |
| HIV | Human Immunodeficiency Virus |
| HVs | Healthy volunteers |
| IB | Investigator's brochure |
| ICH | International Council for Harmonisation |
| IC50 | Inhibitory concentration 50% |
| IEC | Independent Ethics Committee |
| ILD | interstitial lung disease |
| IMP | Investigational Medicinal Product |
| iPD | Important protocol deviation |
| IPF | Idiopathic pulmonary fibrosis |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| $\lambda_z$ | Terminal rate constant in plasma |
| LC-MS/MS | Liquid chromatography with tandem mass spectrometry |
| LLOQ | Lower limit of quantification |
| LOAEL | low observed adverse effect level |
| MBq | Megabecquerel |
| MDA | Methylenedioxyamphetamine |

| | |
|---|---|
| MDMA | Methylenedioxymethamphetamine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | Multiple-rising dose |
| $MRT_{,ex}$ | Mean residence time of the analyte in the body, extravascular |
| mSV | Millisievert |
| PDE | Phosphodiesterase |
| PDE4 | Phosphodiesterase 4 |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic set |
| PR | Pulse rate |
| PRA | Pharmaceutical Research Associates |
| QT | Time between start of the Q-wave and the end of the T-wave in an electrocardiogram |
| QTc | QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB) |
| REP | Residual effect period |
| SAE | Serious adverse event |
| SARS-CoV | Severe acute respiratory syndrome coronavirus |
| SCR | Screening |
| SOP | Standard operating procedure |
| SRD | Single-rising dose |
| Ss | (at) steady state |
| T | Test product or treatment |
| TEAEs | Percentage of subjects with treatment emergent adverse events |
| TK | Toxicokinetics |
| TMF | Trial master file |
| $t_{1/2}$ | Terminal half-life of the analyte in plasma |
| $t_{max}$ | Time from (last) dosing to the maximum measured concentration of the analyte in plasma |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| $t_z$ | Time of last measurable concentration of the analyte in plasma |
| ULN | Upper limit of normal |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extravascular administration |
| WHO | World Health Organization |
| XTC | Ecstasy |

# 1. INTRODUCTION

BI 1015550 is a selective inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP) and shows broad anti-inflammatory and anti-fibrotic activities. It is under development for the treatment of idiopathic pulmonary fibrosis (IPF). This trial is a mass balance study to investigate the basic pharmacokinetics, excretion pathways as well as metabolism of BI 1015550 and its major metabolite BI 764333 (M480).

## 1.1 MEDICAL BACKGROUND

IPF is a progressive, fibrosing interstitial lung disease (ILD) characterized by decline in lung function and worsening dyspnea [R18-2794]. IPF carries a poor prognosis, with a median post-diagnosis survival in untreated patients of approximately 3 years [R18-1413]. IPF occurs worldwide. The prevalence of the disease appears to be increasing, although it is unclear whether this reflects increased recognition or a true increase in incidence. The incidence of IPF appears to be higher in North America and Europe (3 to 9 cases per 100,000 person-years) than in South America and East Asia (fewer than 4 cases per 100,000 person-years) [R17-4284]. In the United States, the prevalence of IPF has been reported to range from 10 to 60 cases per 100,000 [R16-1737], [R18-0408], [R14-2284]. Increasing rates of hospital admissions and deaths due to IPF also suggest an increasing burden of disease [R17-4284], [R14-4266], [P13-05880].

Nintedanib and pirfenidone are the only drugs registered for the treatment of IPF and recommended in the recent ATS/ERS/JRS/ALAT Clinical Practice Guideline for the Treatment of Idiopathic Pulmonary Fibrosis [R18-2794]. Despite the availability of these drugs, the medical need remains high in this devastating disease.

Preclinical experiments have shown that BI 1015550 affects the fibrotic pathway and the effects may be complementary and/or synergistic to those of nintedanib. PDE4 inhibition is expected to inhibit pro-fibrotic growth factors, to decrease fibroblast proliferation, transformation of fibroblast to myofibroblast, and fibroblast motility, as well as to promote cell death of fibroblasts, and to decrease synthesis, release, and function of ECM components [R12-5544, R12-5545, R12-5546]. Interference with pro-fibrotic factors/ inflammatory cascades may translate in clinical improvement of lung function, symptoms and quality of life in patients with IPF.
Based on this, it is postulated that BI 1015550 may provide therapeutic benefit to patients with IPF or other progressive fibrosing ILDs [c02094779].

## 1.2 DRUG PROFILE

BI 1015550 is a potent inhibitor of human PDE4 B, showing mean half-maximal inhibition ($IC_{50}$) at 10 nM with a nine-fold selectivity over phosphodiesterase 4D (PDE4 D) (mean $IC_{50}$ 91 nM) without relevant known interaction with other targets, (78 receptors and 42 enzymes tested at the very high concentration of 10 000 nM). In-vitro anti-inflammatory activity has been confirmed for TNF-α ($IC_{50}$: 12 nM) and IL-2 release ($IC_{50}$: 5 nM) from purified human peripheral blood mononuclear cells respectively.

For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

### 1.2.1 Non-clinical pharmacokinetics

Potential drug-drug interactions (DDIs) may occur for concomitantly administered medications that are substantially metabolized by CYP3A4 due to induction of CYP3A4 by BI 1015550 at total steady state plasma concentrations greater than 634 nM, or at oral doses exceeding 16 mg. In addition, as CYP3A is predicted to contribute to ~70% of the hepatic metabolism of BI 1015550, concomitant therapies that are inhibitors or inducers of CYP3A may cause clinically significant changes in BI 1015550 exposure.

For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

### 1.2.2 Pre-clinical safety pharmacology and toxicology

Safety pharmacology:
Safety pharmacology studies have been conducted to address cardiovascular, CNS, respiratory, renal and liver function in rats or minipigs. BI 1015550 administration did not result in any adverse effects on CNS, respiratory, liver, renal, and gastrointestinal functions. Cardiovascular telemetry studies in the minipig and electrocardiographs recorded during the 2 week minipig toxicity study at doses of 3, 10, and 30 mg/kg indicated non-biologically significant changes in PR interval and heart rate, respectively. Because these changes were not of a significant magnitude they were not considered adverse, but may indicate a threshold effect for cardiovascular changes above 30 mg/kg.

Toxicology:
The toxicity profile for BI 1015550 has been assessed in safety pharmacology studies, genetic toxicology studies, and repeat dose studies in the rat and minipig of up to 26 and 39 weeks, respectively. The results of the repeat-dose toxicity studies support the 12-week Phase II clinical trial (1305-0013) in IPF patients with and without background antifibrotic treatment. No single-dose toxicity studies have been conducted with BI 1015550.

*Repeat Dose Toxicology Studies:*
Repeat dose administration of BI 1015550 was well tolerated in the rat when administered at up to 6 mg/kg/day for 13 weeks and 2 mg/kg/day for 26 weeks. Dose escalation of the 6 mg/kg/day dose group in the 4-week study to 12 mg/kg/day resulted in morbidity and mortality secondary to vasculopathy. Morbidity secondary to vasculopathy was observed in the 13-week study at 9 mg/kg/day and in the 26-week study at 4 and 7.5 mg/kg/day.
The early decedents observed in the 4, 13, and 26-week studies in rats, either died or were euthanized due to morbidity. These early deaths were predominantly a result of vasculopathy in the mesentery and gastrointestinal tract, although periosteal inflammation contributed to morbidity in the 26-week trial.

BI 1015550 adverse findings in rats included vasculopathy in the stomach, duodenum, jejunum, ileum, colon, Peyer's patches, mesentery, pancreas, and vagina and hypertrophic osteopathy.
In minipigs, mortality attributed to BI 1015550-related vasculopathy occurred in one 30 mg/kg/day female in the 2-week study immediately following a toxicokinetics (TK) bleed on Day 14. No mortality was observed in the 13-week study where dose levels up to 20 mg/kg/day were administered. In the 39-week study, repeat-dose of 25 mg/kg/day was associated with overt adverse clinical signs in minipigs, including decreased activity and reduced food consumption, with a consequent reduction to 20 mg/kg/day in the third week of the 39-week study. Two animals given 25/20 mg/kg/day (dose level reduced within 3 weeks of dose initiation due to overt toxicity) were euthanized moribund due to clinical signs judged related to polyarteritis.
In minipigs, perivascular/vascular degeneration/necrosis was observed at high dose levels in multiples tissues such as the mesenteric connective tissue or parenchyma of liver, gallbladder, kidney, urinary bladder, ovary, vagina, cervix, stomach, lungs, spleen, heart, coronary artery, periaortic, sciatic nerve, and connective tissues around the tarsus.
Vasculopathy, characterized by inflammation, haemorrhage, and necrosis of blood vessels, is a known class effect of PDE4 inhibitors [R10-1559].

*Clinical pathology changes:*
No adverse clinical pathology changes related to BI 1015550 administration were observed in rats administered 6 mg/kg/day for 2 or 13 weeks or 2 mg/kg/day for 26 weeks. Hematology changes were observed in rats following administration of 6/12, 9, or ≥4 mg/kg/day for 4, 13, or 26 weeks, respectively, as evidenced by increases in white blood cell, neutrophil, lymphocyte, and/or monocyte counts in both sexes. In the 4-week rat study at 6/12 mg/kg/day, there was also a minimal increase in percent and absolute reticulocytes, which were also noted in the 26-week study at ≥4 mg/kg/day. These changes correlated with and were secondary to adverse vasculopathy and neutrophil infiltration seen microscopically in tissues. There were no adverse BI 1015550-related changes in serum chemistry observed in the rat in studies up to 13 weeks. In the 26-week study decreases in albumin with resultant decreases in albumin to globulin (A/G) ratios at 7.5 mg/kg/day and dose-dependent increases in fibrinogen at ≥2 mg/kg/day were observed.
BI 1015550-related changes in clinical pathology were observed in minipigs in the 39-week study and included elevated white blood cell counts, neutrophils, fibrinogen, globulin, and decreased A/G ratio, predominantly in early death animals.

*Histopathological changes*:
No adverse histopathologic changes were observed following administration of 6, 3, 6, and 2 mg/kg/day BI 1015550 to rats over 2, 4, 13 and 26 weeks, respectively. Administration to rats of 6/12 mg/kg/day (4 weeks), 9 mg/kg/day (13 weeks), and 4 or 7.5 mg/kg/day (26-weeks) resulted in adverse changes including mesenteric perivascular/vascular inflammation and inflammation in the following tissues: gastrointestinal tract, Peyer's patches, pancreas, and/or vagina. These findings were reversible. With longer (26-week) treatment in rats, periosteal inflammation and new bone formation were observed, which were reversible or partially reversible, respectively.

In the minipig, 30 mg/kg/day administered for 2 weeks was associated with alterations in the gallbladder (cholecystitis) and the arteries of the gallbladder (vasculopathy), as well as inflammation of the cecum, which were reversible or partially reversible. No test article related pathology was observed in the 13-week minipig study at dose levels up to 20 mg/kg/day. In the 39-week minipig study, administration of 3 or 10 mg/kg/day resulted in effects in the lungs and/or heart of one animal per group. Changes in the lung consisted of vascular/perivascular degeneration/necrosis in arteries and alveolar capillaries. In the heart, findings noted included degeneration/necrosis in a coronary artery, its surrounding arteries, and arteries around the aorta, myocardial degeneration/necrosis of the left ventricular papillary muscle, and inflammation in adipose tissue of the coronary groove.
At 25/20 mg/kg/day in minipigs administered for 39 weeks, vascular/perivascular degeneration/necrosis around the aorta, hypertrophy/hyperplasia of arteries throughout the heart, a thrombus in a left ventricular artery, myocardial fibrosis in the left ventricle and atrium, and/or myofiber degeneration designate heart as a target organ of PDE4i-related effects in minipigs. In early death 25/20 mg/kg/day minipigs, polyarteritis that affected tissues surrounding the tarsus on all limbs, around the aorta, and around the iliac artery, and the ovary, vagina, spleen, mesentery, and sciatic nerve were observed. The low-dose of 3 mg/kg/day was considered a low observed adverse effect level (LOAEL) in the 39- week minipig study.

Genetic toxicity:
The genetic toxicology results for BI 1015550 indicate that this compound is not genotoxic.

Phototoxicity:
The phototoxicity assessments suggest a low potential of phototoxicity for BI 1015550.

For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

### 1.2.3 Residual Effect Period

The Residual Effect Period (REP) of BI 1015550 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

### 1.2.4 Clinical experience in humans

BI 1015550 was well tolerated following single dose administration up to 48 mg in healthy volunteers and following multiple administrations up to 18 mg bid over a treatment period of up to 12 weeks in patients.
Six Phase I clinical studies have been completed with BI 1015550 in healthy volunteers (1305-0001, 1305-0002, 1305-0011, 1305-0015, 1305-0020, 1305-0017). The most commonly reported events in healthy volunteer studies were headache and gastrointestinal (GI) events, particularly abdominal pain and diarrhea, all of mild to moderate intensity. There was a trend for increased treatment emergent reporting of headache in those treated with verum. No apparent dose dependency has been observed for the GI treatment emergent adverse events (TEAEs). A trend toward weight loss in subjects treated with BI 1015550 has

been observed in study 1305-0011 in healthy volunteers. No severe, serious, fatal events or SUSARs have been reported in healthy volunteers.
One Phase Ic study has been completed in 15 patients (10 on active, 5 on placebo) with IPF on no background antifibrotic treatment (1305-0012) testing safety, tolerability and PK of BI 1015550 at a dose of 18 mg b.i.d for 4 to 12 weeks. Dose escalation to 24 mg bid was stopped because the protocol-defined stopping criterion on exposure was met. There were no safety concerns. In this study, the most frequently reported TEAEs were gastrointestinal disorders. One patient was hospitalized for two SAEs which were not deemed as related to the study drug but were rather related to long-term pre-existing conditions requiring elective surgery (anal fistula and anal incontinence).
No adverse vascular changes in humans have been reported.
Overall, based on available data a single dose of 18 mg BI 1015550 is expected to be safe and well tolerated.
For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

### 1.2.5 Clinical pharmacokinetics

Pharmacokinetics of BI 1015550 were investigated in healthy male volunteers given multiple oral doses of 6 and 12 mg bid under fed conditions over 14 days [1305-0011, c22991937] and in patients with IPF given multiple oral doses of 18 mg bid over 14 days.
The geometric Mean of selected single and multiple dose PK parameters in HV and IPF patients are shown in Table 1.2.5: 1 and 1.2.5: 2. BI 1015550 was rapidly absorbed after oral dosing reaching peak level usually within 1.5 h - 3h. Plasma concentration/ time profiles showed a biphasic decline. The increase in BI 1015550 exposure (AUC and $C_{max}$) was approximately dose proportional after single and multiple doses over the entire dose range tested (SRD 0.6 to 48 mg, MRD 6 to 12 mg). AUC and $C_{max}$ values were up to 1.85-fold higher at steady state with twice daily administered doses compared with single dose administration. Steady state was attained by Day 7 (Trial 1305-0002 and Trial 1305-0011). Exposure to BI 1015550 did not change relevantly when taken together with a high caloric, high fat breakfast.
The $C_{max}$ was slightly decreased (~20%), $t_{max}$ slightly delayed, while AUC remained unchanged (Trial 1305-0020). The PK of BI 1015550 was comparable between healthy volunteers and IPF patients. However, the variability of the PK parameters was higher in IPF patients as compared to HV.

Table 1.2.5: 1 Selected Geometric Mean PK parameters of BI 1015550 after single dose in HVs 1305-0001 [U13-1792]

| | **1305-0001 in HV, single oral dose** | | | | | |
|---|---|---|---|---|---|---|
| | **8 mg (n=6)** | | **16 mg (n=6)** | | **24 mg (n=6)** | |
| | **gMean** | **(gCV)** | **gMean** | **(gCV)** | **gMean** | **(gCV)** |
| $AUC_{0-\infty}$ [nmol·h/L] | 1210 | (18.3) | 2180 | (19.9) | 3650 | (22.6) |
| $C_{max}$ [nmol/L] | 176 | (12.6) | 292 | (22.2) | 542 | (12.1) |
| $t_{max}$[a] [h] | 1.01 | (0.500-1.50) | 1.25 | (1.00-2.48) | 1.00 | (1.00-1.50) |

a: Median (min-max)

Table 1.2.5: 2 Selected Geometric Mean PK parameters of BI 1015550 after single and multiple doses in HVs 1305-0011 and IPF patients 1305-0012 [c02094779]

| | 1305-0011 in HV | | | | 1305-0012 in IPF patients | |
|---|---|---|---|---|---|---|
| | 6 mg b.i.d (n=8) | | 12 mg b.i.d (n=8) | | 18 mg b.i.d (n=10) | |
| | gMean | (gCV) | gMean | (gCV) | gMean | (gCV) |
| $AUC_{\tau,ss}$ [nmol·h/L] | 1050 | (25.7) | 2300 | (15.8) | 3720 | (49.5) |
| $C_{max,ss}$ [nmol/L] | 164 | (21.3) | 348 | (14.1) | 460 | (41.7) |
| $t_{max,ss}$[a] [h] | 1.38 | (0.500-3.00) | 1.50 | (0.500-1.50) | 3.92 | (1.47-8.00) |

a: Median (min-max)

For a more detailed description of the BI 1015550 profile, please refer to the current Investigator's Brochure (IB) [c02094779].

### 1.2.6 Drug interactions

CYP450 3A4 is regarded as the major enzyme responsible for BI 1015550 metabolism in human hepatocytes. CYP3A is predicted to contribute to ~70% of the hepatic metabolism of BI 1015550. Furthermore, non-clinical *in vitro* assays showed that BI 1015550 is a P-gp substrate, but not a P-pg inhibitor. The effect of 200 mg qd itraconazole (a strong CYP3A4/ Pgp inhibitor) at steady state (Day -3 to Day 9) on a single dose of 6 mg BI 1015550 (administered at Day 1) was investigated in 16 HVs within DDI trial 1305-0015 [c24902949]. Itraconazole increased the exposure to BI 1015550 by 1.3-fold ($C_{max}$) and 2.2-fold AUC. The metabolite BI 764333 created via the CYP3A4 pathway was not detectable when BI 1015550 was administered together with itraconazole. Strong CYP 3A4 inhibitors are therefore prohibited as concomitant medication in this trial.
Based on non-clinical *in vitro* data BI 1015550 might be a mild to moderate CYP3A4 inducer and might affect co-medications that are CYP3A4 substrates at total plasma concentrations of BI 1015550 > 637 nM. The gMean $C_{max,ss}$ of the highest planned dose in this trial was below that threshold (460 nM). A clinical trial (1305-0021) to investigate the CYP 3A4 induction potential of BI 1015550 is planned.

## 1.3 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to examine the metabolism in humans, the mass-balance of excretion, plasma and urinary concentrations of BI 1015550 and its metabolite BI 764333 as well as the resulting PK parameters and [$^{14}$C]-radioactivity in blood, plasma, urine and faeces as well as vomit, if applicable, following a single oral dose of 18 mg of [$^{14}$C]-BI 1015550 containing a radioactive dose of 3.7 MBq (100 µCI, corresponding to 0.2864mSV) in healthy male volunteers.
The investigation of these processes, including the quantitative assessment of elimination pathways and drug metabolites, is necessary for an in-depth understanding of the pharmacokinetics of BI 1015550. In addition the data are required for future submission to regulatory authorities.

## 1.4 BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 1015550. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication as well as to [$^{14}$C]-radioactivity.

Procedure-related risks
The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

Drug-related risks and safety measures
Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety; see also Section 5.2.6.1.4, adverse events of special interest.

*Potential Risks related to BI 1015550 administration*

- Pharmacokinetic interaction with strong CYP3A4 inhibitors:
  CYP3A4 is regarded as the major enzyme responsible for the metabolism of BI 1015550 in human hepatocytes and contributes to ~70% of its hepatic metabolism (see Section 1.2.6) In this trial, concomitant medication is prohibited in general and potent CYP3A4 inhibitors specifically are a restricted medication.

- Vasculitis:
  Vasculopathy is an established toxicity of PDE4 inhibitors in rats. Vasculitis has been shown in both the rats and minipigs following oral administration of BI 1015550 and it has been the basis of the NOAEL (No Observable Adverse Effect Level) definition. Vasculitis is listed as an important potential risk in the RMP (Risk Management Plan) for the marketed PDE4 inhibitors apremilast. In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans. However, baseline condition or medical history of vasculitis is an exclusion criterion in this trial and increased awareness will be given to any occurrences of vasculitis including expedite reporting (AESI).

- Gastrointestinal disorders (e.g. diarrhoea, nausea, vomiting, abdominal pain):
  Vomiting and diarrhea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. Gastrointestinal events of mostly mild intensity have been reported for BI 1015550, therefore increased awareness will be accounted to gastrointestinal symptoms in this trial. Hydration in patients with diarrhea will be carefully monitored clinically.

- Weight decrease in underweight patients:
  For the marketed PDE4-inhibitors apremilast and roflumilast weight loss in underweighted patients is identified as an important risk. A trend toward weight loss in subjects treated with BI 1015550 has been observed in study 1305-0011 in healthy volunteers but due to the limited strength and amount of available data has not been established as adverse drug reaction for the BI 1015550. However, body weight will be monitored in this trial and underweight subjects with a BMI <18.5 kg/m$^2$ at screening visit will be excluded from trial participation.

- Suicidality:
  Two of the currently marketed PDE4 inhibitors are associated with increased risk of depression with some patients reporting suicidal ideation and attempts as well as with reported cases of completed suicide. Subjects with any history suicidal behavior in their life-time and/or any suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity Ranking Score (C-SSRS) within the past 12 months prior to screening visit will be excluded from trial participation.

*Risks related to BI 764333 (M480)*
Pharmacological activity of the major human metabolite M480 was evaluated in a non-clinical study testing 13 different phosphodiesterases. At a concentration of 10 µM BI 764333 inhibited PDE4A1A, PDE4B1 and PDE4D2 for 51.9%, 77.2%, and 60.4% respectively, with inhibition values ≤ 15.5% for the other tested enzymes [n00261809]. In clinical studies the gMean $C_{max,ss}$ exposure values of BI 764333/4 at 12 mg bid / 18 mg bid BI 1015550 are 38.7 nM / 68.7 nM respectively, which is much lower than 10 µM. Therefore, pharmacological contribution of this metabolite is considered to be low.

*Potential Risks related to administration of [C-14]-BI 1015550*
[C-14]-BI 1015550 is labelled with the isotope [$^{14}$C] which is necessary for the purposes of this mass balance trial. Therefore, subjects will be exposed to ionizing radiation. The effective dose that each subject receives from one administration of 3.7 MBq is approximately 0.29 mSv. The radioactive dose of 0.29 mSv proposed for administration in this human ADME study, is lower than the limit specified by WHO Category 1, (<0.5mSv – within variations of natural background radioactivity) and lower than the limit proposed b ICRP Category 2a, (<1 mSv – risk defined as minor).
For clinical investigations to study the disposition, metabolism and excretion of new pharmaceutical compounds in human an effective dose of 0.1 – 1.0 mSv is considered acceptable [R15-3219]. For details on the radiation burden calculation please refer to Appendix 10.1.
To minimize any risks resulting from exposure to ionizing radiation in this trial female subjects will be excluded from study participation. Furthermore, contraception requirements in this study will apply for the participating male subjects as well as their female partners.

Summary of benefit-risk assessment
The available results of completed Phase I and Phase Ic trials in HVs and IPF patients respectively, show a favorable safety profile at single doses administered up to 48 mg in HVs and at up to 18 mg b.i.d administered in multiple doses over a treatment period of up to 12

weeks in IPF patients, in which administration of BI 1015550 was safe and well tolerated (Section 1.2.4). No clinically relevant findings in vital signs and ECG were observed. There are no adverse events reported with regard to bodyweight. Gastrointestinal AEs and headache of mostly mild intensity have been reported. No severe, serious, fatal adverse events nor SUSARS have been reported in the healthy volunteers studies.
Therefore a single oral dose of 18 mg BI 1015550 administered to healthy male volunteers is considered to be acceptable from both a preclinical (i.e supported by the 13 weeks toxicology data) and clinical point of view.

In the current trial, healthy male volunteers will receive a single oral dose of 18 mg of BI 1015550. Therefore each participating subject will receive only one single radioactive dose. The risk associated with the expected maximal radiation burden of 0.29 mSv falls in ICRP category 2a with minor level risk and in WHO Category 1, i.e. within variations of natural background radioactivity and is therefore considered to be acceptable.

There is always the potential for subjects receiving medication to experience adverse events (AEs), and rarely also serious adverse events (SAEs). However, the risks to subjects are minimized and addressed by eligibility criteria, safety laboratory examinations, ECG and vital sign measurements, in-house observation periods and verbal communication concerning AEs. If the investigator should have any clinical concern, the safety of the subjects will be of paramount importance. The investigator has the discretion to remove subjects from the study should there be any safety concerns or if the subject's wellbeing is at jeopardy.
The trial design is optimized to collect as much relevant information as possible on the pharmacokinetics of BI 1015550 without exposing participating volunteers to undue risk.

The results of this trial are necessary for the further development of BI 1015550. Successful development of BI 1015550 is expected to provide a new valuable treatment to patients with pulmonary fibrosis. The risks of the participating volunteers are minimized and justified when compared to the potential benefits of this trial.

For assessment of risks associated with Covid-19 pandemic refer to Appendix 10.3.

# 2. TRIAL OBJECTIVES AND ENDPOINTS

## 2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

### 2.1.1 Main objectives

The main objective of this trial is to investigate the basic pharmacokinetics of BI 1015550 and its metabolite BI 764333, [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 18 mg [$^{14}$C]-BI 1015550 administered to healthy male subjects.

The primary objective is:

- To assess the mass balance recovery of [$^{14}$C]-radioactivity from urine and faeces as well as vomit in case of occurrence after a single oral dose of 18 mg BI 1015550 (C-14) administered to healthy male subjects

The secondary objectives are:

- To assess the pharmacokinetics of [C-14] BI 1015550 and BI 1015550 as well as its metabolite BI 764333 in plasma following a single oral dose of BI 1015550 (C-14)
- To assess the safety and tolerability of BI 1015550

### 2.1.2 Primary endpoint

The following pharmacokinetic parameters will be determined for [C-14] BI 1015550:

Mass balance recovery of [$^{14}$C]-radioactivity:

- Amount of [$^{14}$C]-radioactivity excreted as a percentage of the administered single oral dose of BI 1015550 (C-14) in urine ($fe_{urine,\ 0\text{-}t2}$) and faeces ($fe_{faeces,\ 0\text{-}t2}$) as well as vomit ($fe_{vomit,\ 0\text{-}t2}$), if applicable

### 2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined for [C-14] BI 1015550 and BI 1015550 as well as its metabolite BI 764333 in plasma:

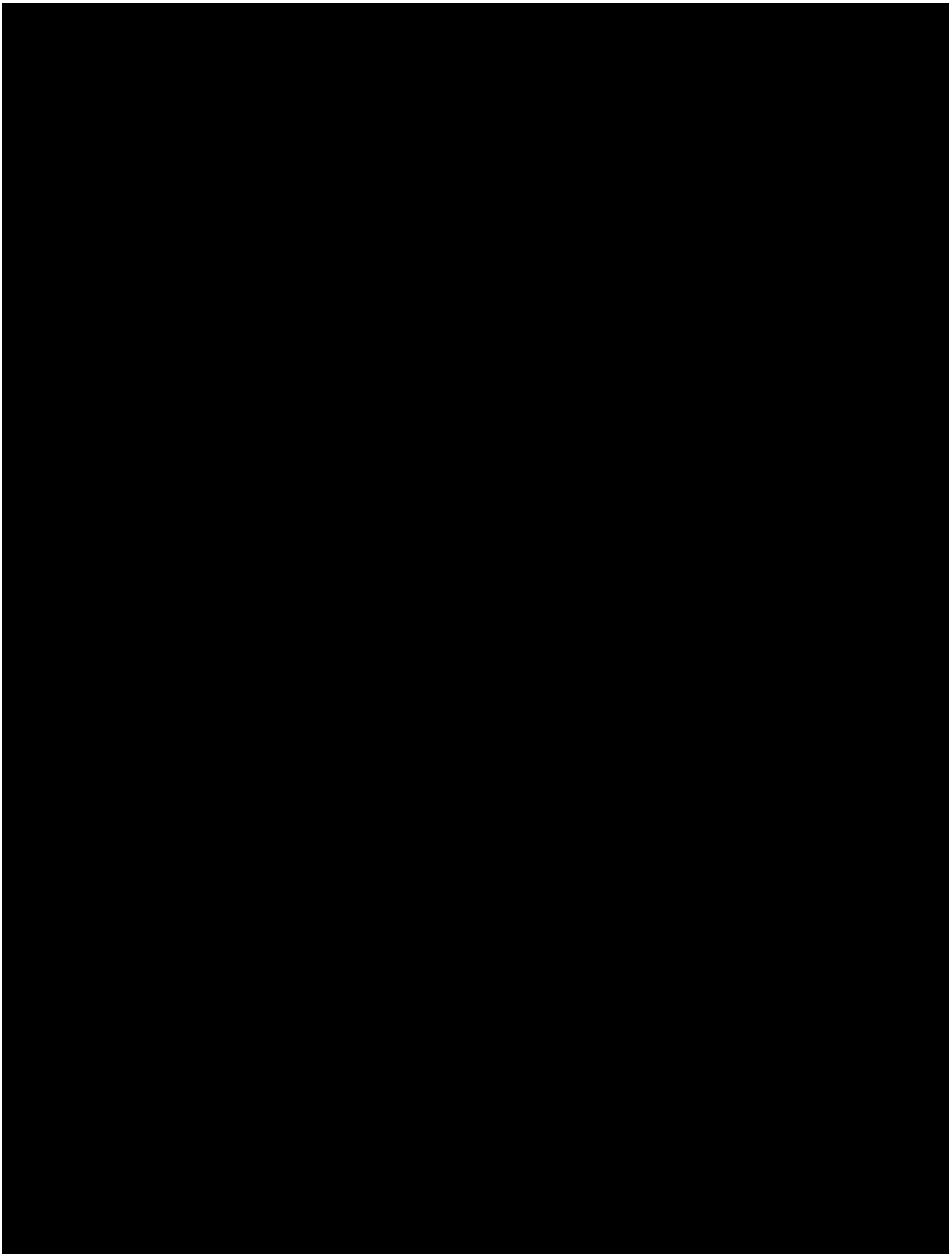
Pharmacokinetics:

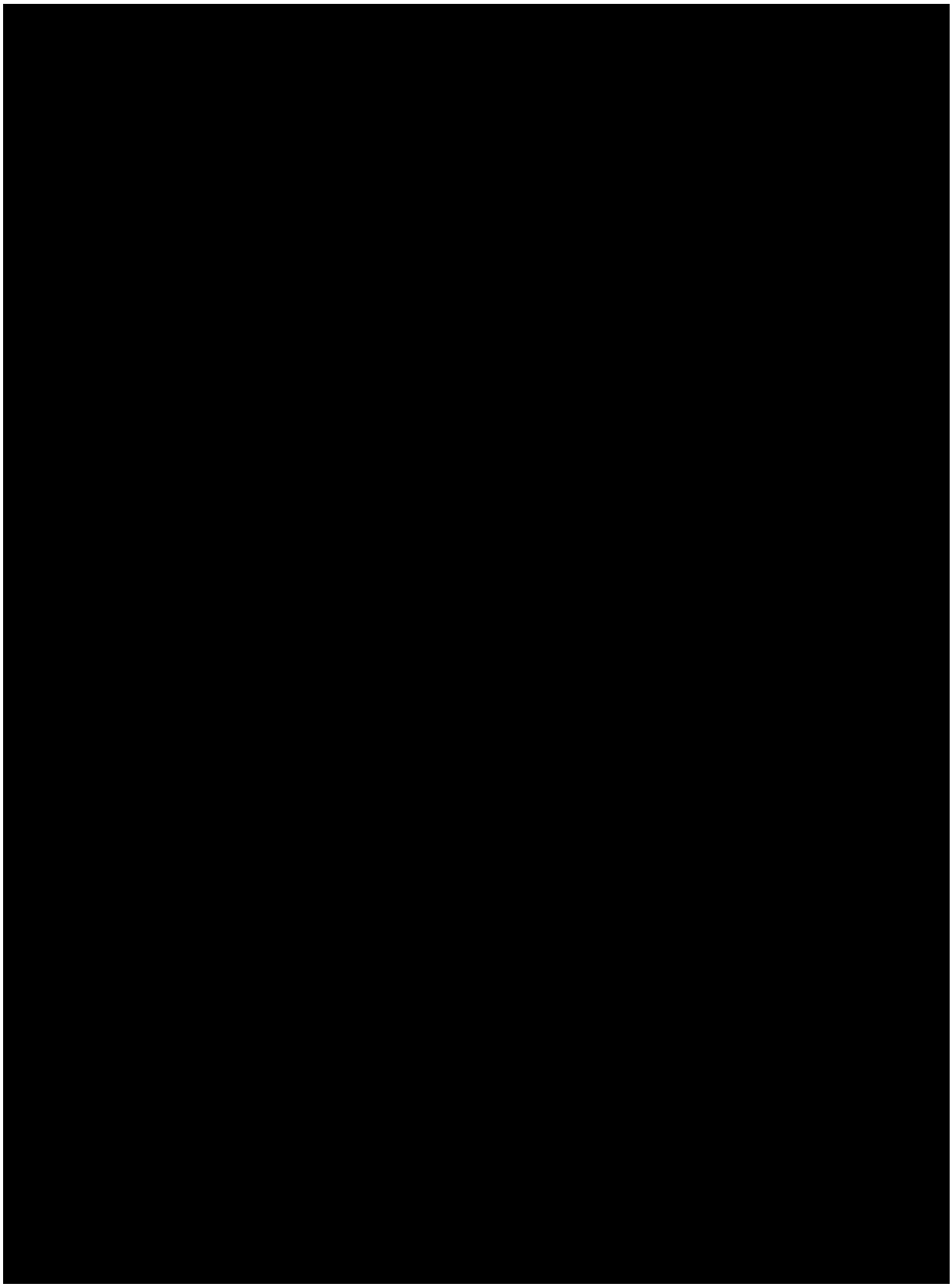
- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)

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

Safety:

- Percentage of subjects with treatment emergent adverse events (TEAEs)





[redacted]

2.2.2.4 Safety and tolerability

Safety and tolerability of BI 1015550 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, body weight)
- Suicidality assessment (C-SSRS)

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as an open-label, non-randomized, single-dose, single-arm, single-period trial in healthy male subjects in order to investigate the basic pharmacokinetics of BI 1015550, its metabolite BI 764333 and [$^{14}$C]-radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 18 mg BI 1015550 (C-14).

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

The planned radioactive dose per subject is 3.7 MBq (100 µCi, corresponding to 0.2864 mSv), which is equivalent to 0.0774 mSv/MBq (please refer to Appendix 10.1).

On Day 1 subjects will be administered with 18 mg BI 1015550 (C-14). Subjects will remain at the study site from admission on Day -1 until discharge on Day 10. Subjects will be readmitted to the study centre for 24 h collection intervals of urine and faeces on Days 16, 23 and 30 respectively, if release criteria have not been met in the preceding collection interval. Within 24 h prior to each of these once weekly in-house collection intervals, subjects are to collect faeces at home. This 24-h interval home collection faeces will be used for analysis in case no defecation occurs in the subsequent 24 h in-house collection interval or otherwise discarded.

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

If one of the following release criteria is true (i.e., release criteria have been met), 24 h collection intervals after Day 10 will not be performed any longer/will be stopped:

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

*or*

- If <1% of the dose administered has been collected in urine and faeces within 2 separate, consecutive 24 h intervals

*and*

- Concentration of total radioactivity in plasma and in blood is <5% of $C_{max}$ of total radioactivity in plasma

If the mass balance recovery on Day 10 is less than 90%, subjects will be discharged from the research site but have to return to the clinic for 24 h collection of urine and faeces on Days 16, 23 and 30 until the recovery is deemed to be sufficient for mass balance purposes. No PK plasma sampling will be performed at these 24 h collection intervals. If a subject is unable to attend one of these visits, subject may be allowed to reschedule the visit, if needed. Irrespective of whether release criteria have been met or not after collection interval Day 30-31, no further collections are planned.

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

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

This is a standard design for a [$^{14}$C]-human study for investigation of absorption, distribution, metabolism, and excretion including determination of mass balance. Inclusion of a control groups is not required for this investigation.
The elimination of BI 1015550 is biphasic, therefore it cannot be excluded that prolonged sampling is necessary in humans. Therefore, following in-house excreta collection after radioactive dosing on Day 1, subjects will return on a weekly basis for 24 h in-house collection intervals for up to 4.5 weeks after last dosing as long as release criteria are not met (Section 3.1).
Blinding does not apply for this trial as all subjects receive the same treatment.

## 3.3 SELECTION OF TRIAL POPULATION

It is planned that 6 healthy male subjects will enter the study. They will be recruited from the volunteers' pool of the trial site or, if necessary, via external databases and advertisements. In case a subject is discontinued from the trial an additional subject may be entered and dosed to assure that a minimum of 4 evaluable subjects will complete the study as per protocol. The actual number of subjects entered may increase up to but will not exceed 8.

Only healthy male subjects will be included in this trial because they are an ideal population for the objectives of this trial, since they provide relatively stable physiological, biochemical and hormonal conditions, i.e. the absence of disease-related variations and relevant concomitant medications.

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

### 3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

### 3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 65 years (inclusive)
3. BMI of 18.5 to 29.9 kg/m$^2$ (inclusive)

4. Signed and dated written informed consent prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects who meet any of the following criteria from screening until 90 days after trial completion:
    - Use of adequate contraception of the female partner, e.g. any of the following methods *plus* condom: implants, injectables, combined oral or vaginal contraceptives, intrauterine device, which started at least two months prior to first study drug administration or barrier method (e.g. diaphragm with spermicide) or,
    - Sexually abstinent or,
    - A vasectomy performed at least 1 year prior to screening (with medical assessment of the surgical success) or,
    - Surgically sterilised female partner (including hysterectomy, bilateral tubal occlusion, or bilateral oophorectomy) or,
    - Postmenopausal female partner, defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

### 3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 45 to 90 mmHg, or pulse rate outside the range of 40 to 100 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
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)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation, potent CYP3A4 inhibitors, selective and non-selective PDE inhibitors as well as vaccination of any kind with or without re-vaccination required during the course of the trial).

12. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
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. Average intake of more than 21 units of alcohol per week (1 unit of alcohol equals approximately 250 mL of beer, 100 mL of wine or 35 ml of spirits)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within 4 days prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the 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 *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

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

23. A medical history of vasculitis
24. Any lifetime history of suicidal behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour)
25. Any suicidal ideation of type 4 or 5 in the C-SSRS in the past 12 months (i.e. active suicidal thought, active suicidal thought with method, active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent)
26. Participation in another ADME study with a radiation burden of >0.1 mSv in the period of 1 year prior to screening or 1.1-2.0 mSv in the past 2 years or 2.1-3.0 mSv in the past 3 years etc.
27. Exposure to radiation for diagnostic reasons (except dental X-rays and plain X-rays of thorax and bony skeleton (excluding spinal column)) in the period of 1 year prior to screening
28. Irregular defecation pattern (less than a mean of one bowel movement every 1 or 2 days)

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

29. A positive test indicating an ongoing infection with SARS-CoV-2 and/or clinical symptoms suggestive of the disease.

For study restrictions, refer to Section 4.2.2.

### 3.3.4 Withdrawal of subjects from treatment or assessments

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

If a subject is removed from or withdraws from the trial prior to administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF 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 CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

#### 3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF
6. 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<90/45 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.
7. The subject experiences a serious adverse reaction which is considered at least possibly related to the IMP administration

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Section 6.2.3.

#### 3.3.4.2 Withdrawal of consent to trial participation

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

#### 3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least 1 drug-related serious adverse event is reported
3. Violation of GCP or the CTP or the contract with BI impairing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

### 3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. Replacement of subjects and dosing of additional subjects should always be done in mutual agreement with the principal investigator. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

# 4. TREATMENTS

## 4.1 INVESTIGATIONAL TREATMENTS

BI 1015550 (C-14) is administered as oral solution. The oral solution contains a mixture of [C-14] BI 1015550 and non-radiolabelled BI 1015550 and is manufactured by [redacted].

### 4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

| | |
|---|---|
| Name: | BI 1015550 (C-14) oral solution |
| Substance: | BI 1015550 mixed with [C-14]-BI 1015550 |
| Pharmaceutical formulation: | Oral solution |
| Source: | [redacted] |
| Unit strength: | 18 mg |
| Posology: | 1-0-0 |
| Route of administration: | oral |
| Duration of use: | single dose |

### 4.1.2 Selection of doses in the trial

The dose selected for this trial is one single oral dose of 18 mg BI 1015550, which is below the highest dose of BI 1015550 already tested in previous trials (1305-0011: single dosing of 48 mg BI 1015550 in healthy volunteers and 1305-0012: multiple dosing of 18 mg BI 1015550 over 12 weeks bid in patients see Section 1.2). In addition, this dose of 18 mg BI 1015550 is being tested over 12 weeks bid in patients in the ongoing phase II study 1305-0013. In healthy volunteers, a single dose of 18 mg was safe and well-tolerated (see Section 1.2) and is considered adequate for the objectives of this trial.

The 18 mg dose of BI 1015550 administered as oral solution will contain 3.7 MBq of [C-14] BI 1015550. The radio-labelled dose of 3.7 MBq is required to provide sufficient analytical sensitivity for the quantification of radioactivity in plasma, urine, faeces and vomit, if applicable, at a sufficiently low level of detection. The total effective dose (radiation burden) amounts to 0.2864 mSv and lies below the limit of ICRP Category 2a (1.0 mSv), which is considered acceptable for this biomedical investigation. Radiation burden calculations are presented in Appendix 10.1. For risk-benefit assessment, see Section 1.4.

### 4.1.3 Method of assigning subjects to treatment groups

This is an open-label, phase I, single-dose study. All subjects receive the same dose. Each subject will be assigned a subject number prior to dosing on Day 1 of Visit 2.
Once a subject number has been assigned, it cannot be reassigned to any other subject.

### 4.1.4 Drug assignment and administration of doses for each subject

This trial is an open-label, single-period and single-arm study. All subjects will receive the same treatment. The treatment to be evaluated is 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 product) | BI 1015550 | Oral solution | 0.5 mg/mL | 36 mL (18 mg) once | 18 mg |

[redacted] will determine both the weight of drug product and the total dose of [$^{14}$C]-radioactivity administered for each subject.

In the morning of Day 1, all subjects will receive one single oral dose of BI 1015550 (C-14) as an oral solution of 0.5 mg/mL (36 mL, 3.7 MBq).

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a sitting position.

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

Subjects will be kept under close medical surveillance until Day 10 after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture) except for medical examination or if necessary for any medical reasons (e.g. AEs).

### 4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout the entire 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, because the dose of trial medication is known to investigators and subjects.

### 4.1.6 Packaging, labelling, and re-supply

Non-radiolabelled and radiolabelled drug substance will be manufactured and mixed by BI and provided to PRA. Manufacturing of the investigational medicinal product (oral solution)

will be provided by PRA. The investigational medicinal product will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

### 4.1.7 Storage conditions

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

### 4.1.8 Drug accountability

PRA pharmacy will deliver the investigational drugs to the investigator upon availability of a valid prescription from the investigator. The investigator will not order the drugs from the PRA pharmacy before the following requirements are fulfilled:

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

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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

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

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

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

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF. CYP3A4 is regarded as the major enzyme responsible for the metabolism of BI 1015550, therefore potent CYP3A4 inhibitors are specifically restricted in this trial.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake on Day 1.

On Day 1 fluid intake is restricted from 1 h before drug intake until lunch, to 240 mL of the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake should be within about 1000 to 3000 mL.

During the days of urine collection, subjects will be advised that total fluid intake should be at least 1.5 liters and should not exceed 3.5 liters.

Alcoholic beverages are not allowed within 48 h before screening and before first admission to and during in-house confinement at the trial site. During ambulatory phases alcohol consumption is restricted to 2 units per day.
Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample of each study period is collected.

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

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

Smoking is not allowed during in-house confinement while admitted to the trial site.

Excessive physical activity (such as competitive sport) should be avoided from 4 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 centre under supervision of the investigating physician or a designee. The measured plasma concentrations as well as urinary and faecal excretion of trial medication will provide additional confirmation of compliance.

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

# 5. ASSESSMENTS

## 5.1 ASSESSMENT OF EFFICACY

Not applicable.

## 5.2 ASSESSMENT OF SAFETY

### 5.2.1 Physical examination

At screening, the medical examination will include demographics, body height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, C-SSRS and a physical examination. At the end of trial examination, medical examination will include review of vital signs, 12-lead ECG, laboratory tests, C-SSRS and a physical examination including determination of body weight. Furthermore on Day 10, prior to discharge from trial site, confirmation of fitness will be performed including vital signs, 12-lead ECG, laboratory tests, C-SSRS and a physical examination, including body weight.

### 5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor (e.g. Dinamap CareScape VC 150, [redacted]) at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

### 5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 4 h at screening and EOT visits and at least 10 h for all other time points. At the discretion of the investigator or designee, overnight fasting is not required for drug screening, for infectious serology and 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, Section 10.

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

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

Table 5.2.3: 1 Routine laboratory tests

| Functional lab group | BI test name [comment/abbreviation] | A | B | C |
|---|---|---|---|---|
| Haematology | Haematocrit | X | X | X |
| | Haemoglobin | X | X | X |
| | Red Blood Cell Count/Erythrocytes | X | X | X |
| | Reticulocytes, absol. | X | X | X |
| | Reticulocytes/Erythrocyte | X | X | X |
| | White Blood Cells/Leucocytes | X | X | X |
| | Platelet Count/Thrombocytes (quant) | X | X | X |
| Automatic WBC differential, relative | Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes | X | X | X |
| Automatic WBC differential, absolute | Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol. | X | X | X |
| Manual differential WBC (if automatic differential WBC is abnormal), % | Neut. Poly (segs); Neutrophils Bands; Eosinophils; Basophils; Monocytes; Lymphocytes | | | |
| Coagulation | Activated Partial Thromboplastin Time | X | X | X |
| | Prothrombin time – INR (International Normalization Ratio) | X | X | X |
| | Fibrinogen | X | X | X |
| Enzymes | AST [Aspartate transaminase] /GOT, SGOT | X | X | X |
| | ALT [Alanine transaminase] /GPT, SGPT | X | X | X |
| | Alkaline Phosphatase | X | X | X |
| | Gamma-Glutamyl Transferase | X | X | X |
| | Glutamate Dehydrogenase (GLDH) | X | X | X |
| | Creatine Kinase [CK] | X | X | X |
| | Creatine Kinase Isoenzyme MB [only if CK is elevated] | X | X | X |
| | Lactic Dehydrogenase | X | X | X |
| | Lipase | X | X | X |
| | Amylase | X | X | X |
| Hormones | Thyroid Stimulating Hormone | X | -- | -- |
| Substrates | Glucose (Serum) | X | X | X |
| | Creatinine | X | X | X |
| | Bilirubin, Total | X | X | X |
| | Bilirubin, Direct | X | X | X |
| | Protein, Total | X | X | X |
| | Albumin | X | X | X |
| | C-Reactive Protein (Quant) | X | -- | -- |
| | Uric Acid | X | -- | -- |

Table 5.2.3: 1 Routine laboratory tests (cont.)

| Functional lab group | BI test name [comment/abbreviation] | A | B | C |
|---|---|---|---|---|
| Electrolytes | Sodium | X | X | X |
| | Potassium | X | X | X |
| | Chloride | X | X | X |
| | Calcium | X | X | X |
| | Phosphate (as Phosphorus, Inorganic) | X | X | X |
| Urinalysis[1] | Urine Nitrite (qual) | X | X | X |
| | Urine Protein (qual) | X | X | X |
| | Urine Glucose (qual) | X | X | X |
| | Urine Ketone (qual) | X | X | X |
| | Urobilinogen (qual) | X | X | X |
| | Urine Bilirubin (qual) | X | X | X |
| | Urine RBC/Haemoglobin (qual) | X | X | X |
| | Urine WBC/Leucocyte esterase (qual) | X | X | X |
| | Urine pH | X | X | X |
| 1: Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine) | Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes) | | | |

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

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and at admission to trial site on Day -1.

Table 5.2.3: 2 Exclusionary laboratory tests

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

To encourage compliance with alcoholic and drug restrictions, a urine alcohol and drug test (eg. ADVIA Chemistry XPT system) will be performed at admission on Day -1, 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 Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted]. 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 computerised electrocardiograph (e.g.Mortara Eli 250 C) at the times provided in the Flow Chart.

To achieve a stable heart rate at rest and to assure high quality recordings, subjects will be resting for at least 5 min in a supine position prior to start of measurement. The site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

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

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

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be

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

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

### 5.2.5 Other safety parameters

#### 5.2.5.1 Suicidality assessment

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.
The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report.
The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the 'screening / baseline' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the screening or baseline visit. In this trial the entire life time history of suicidal ideation and behavior will be recorded.
After the baseline visit the assessment 'since last visit' will be performed at the time points indicated in the Flow Chart. The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist.
If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.
All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator. For "Self-injurious behaviour, no suicidal intent" (Type 11) standard AE/SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2, or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.
The original English version can be found in Appendix 10.2.

### 5.2.6 Assessment of adverse events

#### 5.2.6.1 Definitions of adverse events

##### 5.2.6.1.1 Adverse event

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

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

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

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

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

##### 5.2.6.1.2 Serious adverse event

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

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

##### 5.2.6.1.3 AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported

as described in Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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 eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

#### 5.2.6.1.4 Adverse events of special interest

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

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

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

- Vasculitis
  In this trial protocol vasculitis is defined as any adverse event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels.

#### 5.2.6.1.5 Intensity (severity) of AEs

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

| | |
|---|---|
| Mild: | Awareness of sign(s) or symptom(s) that is/are easily tolerated |
| Moderate: | Sufficient discomfort to cause interference with usual activity |
| Severe: | Incapacitating or causing inability to work or to perform usual activities |

#### 5.2.6.1.6 Causal relationship of AEs

Medical judgment should be used to determine 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 aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced)

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- 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

#### 5.2.6.2 Adverse event collection and reporting

##### 5.2.6.2.1 AE collection

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

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

The following must be collected and documented on the appropriate CRF 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 any occurrence of cancer and 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.

##### 5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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.

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial.

Once a 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. This requires 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 well as non-trial specific information and consent for the pregnant partner.
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.

## 5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

### 5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood and urine samples will be collected at the time points / time intervals indicated in the Flow Chart. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

### 5.3.2 Methods of sample collection

5.3.2.1 Sampling of whole blood and plasma

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

- To determine [$^{14}$C]-radioactivity concentrations in whole blood and plasma
- To determine concentrations of BI 1015550 and its metabolite BI 764333 in plasma
- To identify additional metabolites of BI 1015550 in plasma
- To determine the blood cell/plasma and blood/plasma ratios of [$^{14}$C]-radioactivity

#### 5.3.2.2 Sampling of whole blood and plasma for [$^{14}$C]-radioactivity analysis and quantification of BI 1015550 and its metabolite in plasma

Blood for quantification of BI 1015550 and its metabolite BI 764333 in plasma will be drawn from an antecubital or forearm vein into an $K_2$-EDTA (dipotassium ethylenediaminetetra-acetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

At each time point listed in the Flow Chart, approximately 9 mL of whole blood will be taken. These 9 mL divide into 3 aliquots of 3 mL each.

An aliquot of 3 mL of whole blood is required for the quantification of BI 1015550 and its metabolite in plasma.

Two aliquots of 3 mL of whole blood each are required for determination of [$^{14}$C]-radioactivity in whole blood and plasma.

Bioanalysis of BI 1015550 and its metabolite BI 764333 in plasma is planned to be prepared as long as PK blood samples are collected for determination of total radioactivity.

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

Premature stopping of blood sampling

In case [$^{14}$C]-radioactivity in plasma samples is not detectable (<LLOQ 30 dpm/mL) at two consecutive time points for a subject, blood sampling can be stopped for this subject. However, all samples until and including the 216 hrs sample have to be collected.

#### 5.3.2.3 Sampling of plasma for metabolic profiling and structural elucidation

Additional $K_2$-EDTA (dipotassium ethylenediaminetetraacetic acid) plasma samples for the identification of drug metabolites will be taken.
The blood samples will be drawn at certain time points in parallel to pharmacokinetic time points (see Flow Chart). Sample volume will differ between the timepoints. For timepoints at predose, 1 h and 2 h after drug administration, 10 mL is required for each sample. For timepoints at 4 h and 8 h after drug administration, the required sampling volume will be 30 mL each. For timepoints at 12 h, 24 h and 36 h after drug administration, the sampling volume required will be 50 mL, 80 mL and 40 mL, respectively. Overall, 260 mL will be needed for metabolic analyses.
The maximum possible volume of blood will be drawn according to what is allowed considering all other blood samples taken for all other samples except metabolic profiling.
For exact sample volume as well detailed description of blood sampling, sample handling, sample preparation, sample storage, tube labelling and sample shipment refer to the laboratory manual.

#### 5.3.2.4 Sampling of blood for hematocrit for blood cell/plasma ratio

At each time point listed in the Flow Chart, a blood sample approximately 3 mL will be drawn for measurement of hematocrit, which is needed for determination of blood cell/plasma ratio (see Section 2.2.2.3).
For a detailed description of blood sampling, sample volume, sample handling, sample preparation, sample storage, tube labelling and sample shipment, refer to the laboratory manual.

#### 5.3.2.5 Urine sampling for pharmacokinetic analysis

During the trial urine will be collected in defined containers at time points or in intervals as indicated in the Flow Chart:

- To determine [$^{14}$C]-radioactivity concentrations in urine
- To determine concentrations of BI 1015550 in urine
- To investigate the metabolite profiling of BI 1015550 in urine

A blank urine sample will be collected prior to administration of trial medication.

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

All samples after intake of BI 101550 (C-14) are planned to be used for determination of [$^{14}$C]-radioactivity.

Samples until 216 hrs on Day 10 are planned to be used for analysis of BI 1015550 and its metabolite BI 764333.

Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each urine sample interval.

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

#### 5.3.2.6 Sampling of faeces

Faeces will be collected for the analysis of [$^{14}$C]-radioactivity and for metabolic profiling in intervals as indicated in the Flow Chart. A blank sample will be taken prior to drug administration.
All faeces samples after intake of BI 1015550 (C-14) are planned to be used for determination of [$^{14}$C]-radioactivity.
Samples to be used for metabolic profiling will be selected according to the levels of radioactivity in each faeces sample interval.

All stools will be collected quantitatively in portions up to Day 10 after drug administration. The weight of the faeces and the exact times of faeces collection will be recorded in the eCRF.
For a detailed description of faeces sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.3.2.7 Collection of vomit

If after trial drug administration vomiting occurs in a volunteer within 8 h after radioactive drug administration, the vomit will be collected for determination of weight and [$^{14}$C]-radioactivity.
For a detailed description of vomit sampling, sample preparation, sample storage, labelling, and sample shipment refer to the laboratory manual.

5.3.2.8 Further investigations

After completion of the trial, blood, plasma, urine, vomit and faeces samples may be used for further methodological investigations, e.g. for stability testing of the drug and/or drug metabolites, assessment of drug metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations.

All 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.

### 5.3.4 Pharmacokinetic - pharmacodynamic relationship

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

## 5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

## 5.5 BIOBANKING

Not applicable.

## 5.6 OTHER ASSESSMENTS

Not applicable.

## 5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure in human mass-balance trials.

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

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

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day 1 and ± 90 min on all subsequent days of Visit 2. The planned times for admission, discharge, start and end of the urine and faeces collection intervals are approximate. The procedures are to be performed within a time window of ± 4 hrs to the planned time. If not feasible due to logistic reasons the time window may be extended up to 8 hrs after the planned time.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Vital signs will be measured after ECG and prior to urine/faeces collection. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters. If required for logistical reasons, start of urine and faeces collection can be initiated after venipuncture.

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

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.4.

### 6.2.2 Treatment period

On Day -1, all study participants will be admitted to the trial site and kept under close medical surveillance until discharge on Day 10 as indicated in the Flow Chart. Subjects will receive a single dose of BI 1015550 (C-14) in the morning of Day 1.

Subjects will be readmitted to the trial site for 24-hours collection intervals of urine and faeces on Days 16, 23 and 30, if release criteria have not been met. Within 24 h prior to each of these once-weekly in-house collection intervals, subjects are to collect faeces at home. This 24-hours interval home collections will be used for analysis in case no defecation occurs in the subsequent 24-h in-house collection interval. Otherwise it will be discarded.
Once release criteria are met, home collections will be stopped. If a subject is unable to attend one of these visits, they may be allowed to reschedule the visit, if needed. Irrespective of whether release criteria have been met or not after the last collection interval on Day 31, no further collections are planned.
For details on time points and procedures for collection of plasma, urine and faeces samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.3 of this protocol and in the Flow Chart.

For details on times of 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 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Sections 5.2.1 to 5.2.6.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN – MODEL

The main objective of this trial is to investigate the basic pharmacokinetics of BI 1015550 and its metabolites, total radioactivity, including mass balance, excretion pathways and metabolism following a single oral dose of 18 mg of BI 1015550 (C-14) administered to healthy male subjects.

The primary objective is to assess the mass balance recovery of [$^{14}$C]-radioactivity from urine and faeces as well as vomit in case of occurrence. Secondary objectives are the evaluation of pharmacokinetic parameters specified in Section 2.1.3 and safety and tolerability. Further objectives are to evaluate further pharmacokinetic, mass balance and tolerability parameters as specified in Section 2.2.2.

No statistical comparison will be conducted for this study. Data will be reported with descriptive statistics.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

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

## 7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

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

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

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 1015550 (C-14) as well as for its metabolite will be calculated according to the relevant SOP of the Sponsor [001-MCS-36-476].

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

Relevant protocol deviations may be

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

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

- Missing samples/concentration data at important phases of PK disposition curve

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

### 7.3.1 Primary endpoint analyses

All parameters will be calculated and analysed descriptively.

### 7.3.2 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be calculated according to the BI SOP 001-MCS-36-476 (TMCP Data Analysis) and its reference documents and will be assessed statistically using the same methods as described for the primary endpoints.

### 7.3.4 Safety analyses

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

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

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

Measurements (such as 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 intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

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

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

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

Relevant ECG findings will be reported as AEs.

## 7.4 INTERIM ANALYSES

No interim analysis is planned.

## 7.5 HANDLING OF MISSING DATA

### 7.5.1 Safety

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

### 7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant Corporate Procedure [001-MCS-36-476].

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

## 7.6 RANDOMISATION

Randomisation is not applicable in this open-label, single arm clinical study. All subjects will receive the same treatment. Consecutive subject numbers will be assigned via the eDC system.

## 7.7 DETERMINATION OF SAMPLE SIZE

For this exploratory study, no prospective calculations of statistical power have been made. The sample size of at least 4 evaluable subjects has been selected to provide sufficient information on safety, tolerability and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs) and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to archiving of the CTR.

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

## 8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

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

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

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

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

## 8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

## 8.3 RECORDS

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

### 8.3.1 Source documents

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

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

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

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

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

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history

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

### 8.3.2 Direct access to source data and documents

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

### 8.3.3 Storage period of records

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

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

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

## 8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

### 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, biobanking and future use of biological samples and clinical data, in particular

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

Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

## 8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first subject in the trial.

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

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

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

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

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

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

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

## 8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required trial activities, in order to

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

The radiolabelled drug substance will be provided by BI Pharma GmbH & Co. KG, Biberach, Germany.
The oral solution of trial medication will be manufactured by [redacted]
Safety laboratory tests including haematocrit analysis will be performed by the local laboratory of the trial site ([redacted]).
Analyses of non-radiolabelled BI 1015550 and metabolite concentrations in plasma will be performed at [redacted]

Analyses of [$^{14}$C]-radioactivity concentrations in whole blood, plasma, urine and faeces will be performed at the Bioanalytical Lab of [redacted]
Metabolic identification will be performed at the [redacted]

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.
Data management and statistical evaluation will be done by BI according to BI SOPs or a contract research organisation appointed by BI.

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

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

P13-05880 Hassan Z, Muzaimi M, Navaratnam V, Yusoff NHM, Suhaimi FW, Vadivelu R, Vicknasingam BK, Amato D, Hoersten S von, Ismail NIW, Jayabalan N, Hazim AI, Mansor SM, Muller CP. From Kratom to mitragynine and its derivatives: physiological and behavioural effects related to use, abuse, and addiction. Neurosci Biobehav Rev;37(2):138-151. 2013.

R10-1559 Giembycz MA. Life after PDE4: overcoming adverse events with dual specificity phosphodiesterase inhibitors. Curr Opin Pharmacol;5:238- 244. 2005.

R12-5544 Insel PA, Murray F, Yokoyama U, Romano S, Yun H, Brown L, Snead A, Lu D, Aroonsakool N. cAMPand Epac in the regulation of tissue fibrosis. Br J Pharmacol 166, 447 - 456 (2012).

R12-5545 Udalov S, Dumitrascu R, Pullamsetti SS, Al-Tamari HM, Weissmann N, Ghofrani HA, Guenther A, Voswinckel R, Seeger W, Grimminger F, Schermuly RT. Effects of phosphodiesterase 4 inhibition on bleomycininduced pulmonary fibrosis in mice BMC Pulmonary Medicine. 2010.

R12-5546 Cortijo J, Iranzo A, Milara X, Mata M, Cerda-Nicolas M, Ruiz-Sauri A, Tenor H, Hatzelmann A, Morcillo E. Roflumilast, a phosphodiesterase 4 inhibitor, alleviates bleomycin-induced lung injury. British Journal of Pharmacology 156, 534–544. (2009).

R14-2284 Raghu G, Chen SY, Yeh WS, Maroni B, Li Q, Lee YC, Collard HR. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001 - 11. Lancet Respiratory Medicine. Early Online Publication, 27 May 2014

R14-4266 Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Increasing global mortality from idiopathic pulmonary fibrosis in the 21st century. Annals of the American Thoracic Society, Articles in Press, published on 28-August-2014, doi: 10.1513/AnnalsATS.201404-145OC; p. 1176-1185. 2014.

R15-3219 International Commission on Radiological Protection (ICRP). 2007 Recommendations of the International Commission on Radiological Protection (users edition): abstract. webpage.icrp.org/publication .asp?id=ICRP%20Publication%20103%20(Users%20Editi on (ICRP Publication; 103 (Users Edition)) International Commission on Radiological Protection (ICRP). 2007.

R16-1737 Esposito DB, Lanes S, Donneyong M, Holick CN, Lasky JA, Lederer D, Nathan SD, O'Quinn S, Parker J, Tran TN. Idiopathic pulmonary fibrosis in United States automated claims: incidence, prevalence, and algorithm validation. Am J Respir Crit Care Med 192(10):1200-1207. 2015

R17-4284 Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. Eur Respir J 46(3):795-806. 2015

R18-0408 Raghu G, Morrow E, Collins BF, Ho LAT, Hinojosa MW, Hayes JM, et al. Laparoscopic anti-reflux surgery for idiopathic pulmonary fibrosis at. a single centre. Eur Respir J;48:826-832. 2016

R18-1413 Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. Advances in Therapy, Published online p. 724-736. 11 April 2018

R18-2794 Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al, American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, Latin American Thoracic Society. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med 198(5):e44-e68. 2018;

## 9.2 UNPUBLISHED REFERENCES

001-MCS-36-476 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version.

c02094779 [redacted] Investigator's Brochure BI 1015550 for Idiopathic Pulmonary Fibrosis. Current version.

c22991937 Safety, tolerability and pharmacokinetics of single and multiple rising oral doses of BI 1015550 in healthy subjects 1305-0011. 15 November 2018

c24902949 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. 1305-0015. 15 March 2019

n00261809 Eurofins, In Vitro Pharmacology: Study of 16726375, Study Nr. 100044125.11 May 2018.

s00092835 [redacted] B-R assessment_COVID-19_BI1015550. Current version.

U13-1792 Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy male volunteers (a partially randomised, single blinded, placebo-controlled Phase I study). Clinical Trial Report 1305.1. 21 June 2013

# 10. APPENDICES

## 10.1 RADIO BURDEN CALCULATION

[redacted]



### Radiation Burden Calculation Report EDS-NL

| | |
|---|---|
| **Title (provisional):** | A phase I, single center, open-label, non-randomized, non-placebo-controlled study to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics of orally administered BI 10155550 in HV |
| **Sponsor:** | Boehringer Ingelheim GmbH |
| **Protocol No:** | TBD |
| **PRA Project Id:** | TBD |
| **Version Date:** | 30 August 2018 |

### Calculation of Radiation Burden (Dosimetry)

BI 10155550 is a selective inhibitor of the phosphodiesterase 4B (PDE4) isoenzyme which hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP). This compound is being developed by Boehringer Ingelheim for the treatment of idiopathic pulmonary fibrosis.
Excretion and pharmacokinetic studies using BI 10155550 were conducted on rats[1], and quantitative tissue distribution studies on pigmented and non-pigmented rats[2,3]. A radiation dose assessment was made based on these studies. In addition, data from studies in humans[4] were taken into consideration.
The following assumptions, based on the data from these experiments, and taking the worst-case scenario, were made to be able to estimate the effective radiation dose:

- After oral dosing, BI 10155550 and possible metabolites are considered to be distributed more or less homogeneously throughout the body. Higher concentrations or longer half-lives are seen for the liver and the uveal tract, but not sufficiently high to warrant a separate calculation.
- The major part of the administered amount of $^{14}$C-radiolabeled BI 10155550 and possible metabolites show reasonably fast elimination from the body, mostly via fecal and for a smaller part via urinary excretion.
- Using the data of the BI 10155550 study in rats a half-life of total $^{14}$C-activity of 15 hours is estimated[1], with a half-life of BI 10155550 2.6 hours. In humans a terminal phase half-life of BI 10155550 of approximately 23 hours is assumed[4]. In the current estimation a half-life of
- 23 / 2.6 x 15 = 133 hours is used.
- The absorbed fraction is 1, based on rat data[1]. This and the preceding assumption are clearly overestimations, but taken as worst-case scenario.
- Based on the excretion study in rats[1] $^{14}$C-radiolabeled BI 10155550 is found to be excreted both in feces and in urine. For the calculation is assumed: 88% of the administered radioactivity is excreted via the gastrointestinal tract in feces and 12% is excreted via the kidneys in urine.

Based on these assumptions the maximal estimated effective radiation burden after a single oral radioactivity dose of 3.7 MBq $^{14}$C-radiolabeled BI 10155550 is approximately 0.29 mSv. For biomedical investigations in small groups of human volunteers an effective dose of 0.1 – 1.0 mSv is considered acceptable [5].

[redacted]



## References:

1: Excretion and pharmacokinetics of radioactivity after oral and intravenous administration of [14C]BI 1015550 to rats, dated 03 December 2012.
2.: Quantitative whole-body autoradiography in male albino rats after single intravenous or oral administration of [14C]BI 1015550, dated 14 February 2014.
3.: Quantitative whole-body autoradiography after single peroral administration of [14C]BI 1015550 to male pigmented rats, dated 04 November 2013
4.: Investigator's brochure Version 4 Dated 22 February 2018
5.: Recommendations of the International Commission on Radiological Protection. User's ICRP publication 60, Pergamon Press 1992 and update from ICRP 103.

[redacted]



## Appendix A1: Radiation burden of the gastrointestinal tract after oral administration of 3.7 MBq $^{14}$C BI 10155550

Using SEE-values, an organ-specific radiation burden can be estimated. The SEE-value is dependent, among other factors, on the mass of the target organ and the type of radiation.
With these SEE-values and the number of disintegrations U in the target organ, the organ dose equivalent $H_t$ is calculated:
$H_t$= constant x U x SEE (mSv); using a target organ-related weight factor, the contribution of the organ burden to the body burden is translated as: $H_{wb,t}$ = $H_t$ x weight factor (mSv)

In order to be able to calculate the radiation burden of the GI tract, this has been divided in five sections, i.e., the stomach (st), the small intestines (si), the right part of the large intestines, the left part of the large intestines (lc) and the rectum / sigmoid (rs).
The SEE-values for these organs are:

| | | |
|---|---|---|
| ST: | 1.0 x 10 -5, | (weight factor = 0.12) |
| SI: | 3.2 x 10 -7, | (weight factor = 0.01) |
| RC: | 2.3 x 10 -10, | (weight factor = 0.048) |
| LC: | 2.9 x 10 -10. | (weight factor = 0.045) |
| RS: | 9.2 x 10 -10. | (weight factor = 0.027) |

The number of disintegrations U in each target organ depends on the amount of radioactivity excreted, or any metabolites that are eliminated via the gall bladder that is standardised for the various compartments of the GI tract (constant). $I_0$ = 3.7 MBq; Excretion via GI tract: 88% of the dose, excretion via urine: 12% of the dose. These assumptions give:

| | |
|---|---|
| $H_{st}$= | 0.0030 mSv |
| $H_{si}$= | 0.0000 mSv |
| $H_{RC}$= | 0.0000 mSv |
| $H_{LC}$= | 0.0000 mSv |
| $H_{RS}$= | 0.0000 mSv |
| total GI: | 0.0030 mSv |

The total contribution of the GI tract to the effective dose (body radiation burden) amounts to 0.0030 mSv.

## Appendix A2: Radiation burden of the central compartment after oral administration of 3.7 MBq $^{14}$C BI 10155550

Average body weight = 70 kg; SEE = 7.1905 x 10-7; 100% of the dose excreted with a half-life of 133 hours. Total number of disintegrations in the central compartment after oral administration of 3.7 MBq [$^{14}$C] BI 10155550 is 2531 x $10^9$ with a tissue weighting factor of 1 giving a $H_{bw}$ of 0.2834 mSv.

The total effective dose (radiation burden), based on the above-mentioned worst-case scenario amounts to 0.0030 + 0.2834 = 0.2864 mSv.

| **Name and Date:** | **Signature:** |
|---|---|
| [redacted] | [redacted] Signed by: [redacted] PI Reason: I am the author of this document Date & Time: 30 Aug 2018 10:43 AM -07:00 DocuSign |

## 10.2 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

### 10.2.1 Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form,*** *developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*



C-SSRS Baseline Screening - United States/English - Mapi.
C-SSRS-BaselineScreening_AU5.1_eng-USori.doc

## SUICIDAL IDEATION

*Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*

| | Lifetime: Time He/She Felt Most Suicidal | Past Months |
|---|---|---|
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it... and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |

## INTENSITY OF IDEATION

*The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.*

| | Most Severe | Most Severe |
|---|---|---|
| Lifetime - ***Most Severe Ideation:*** ___ (*Type # (1-5)*) ___ (*Description of Ideation*) | | |
| Past X Months - ***Most Severe Ideation:*** ___ (*Type # (1-5)*) ___ (*Description of Ideation*) | | |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ___ | ___ |
| **Duration**<br>***When you have the thoughts how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ___ | ___ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ___ | ___ |
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ___ | ___ |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ___ | ___ |

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| ***SUICIDAL BEHAVIOR*** *(Check all that apply, so long as these are separate events; must ask about all types)* | **Lifetime** | **Past __ Years** |
|---|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you_____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes ☐ No ☐<br>Total # of Attempts<br>_____ | Yes ☐ No ☐<br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br>Total # of interrupted<br>_____ | Yes ☐ No ☐<br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br>Total # of aborted<br>_____ | Yes ☐ No ☐<br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ | Yes ☐ No ☐ |

| *Answer for Actual Attempts Only* | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |

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### 10.2.2 Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit

# COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

*Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.*

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*



C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AUS.1_eng-USori.doc

## *SUICIDAL IDEATION*

*Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*

Since Last Visit

**1. Wish to be Dead**
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
***Have you wished you were dead or wished you could go to sleep and not wake up?***
If yes, describe:
Yes ☐ No ☐

**2. Non-Specific Active Suicidal Thoughts**
General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
***Have you actually had any thoughts of killing yourself?***
If yes, describe:
Yes ☐ No ☐

**3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".*
***Have you been thinking about how you might do this?***
If yes, describe:
Yes ☐ No ☐

**4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".*
***Have you had these thoughts and had some intention of acting on them?***
If yes, describe:
Yes ☐ No ☐

**5. Active Suicidal Ideation with Specific Plan and Intent**
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***
If yes, describe:
Yes ☐ No ☐

## *INTENSITY OF IDEATION*

*The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe).*

***Most Severe Ideation:*** _____ _____
***Type # (1-5)*** ***Description of Ideation***

Most Severe

**Frequency**
***How many times have you had these thoughts?***
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
—

**Duration**
***When you have the thoughts how long do they last?***
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
—

**Controllability**
***Could/can you stop thinking about killing yourself or wanting to die if you want to?***
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
—

**Deterrents**
***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
—

**Reasons for Ideation**
***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
—

 C-SSRS—Since Last Visit (Version 1/14/09) Page 1 of 2

| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Since Last Visit** |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you_____?***<br>***Or Did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____<br><br>Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ |
| **Suicide:** | Yes ☐ No ☐ |
| ***Answer for Actual Attempts Only*** | Most Lethal Attempt Date: |
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding, sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ |

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## 10.3 COVID-19 RISK ASSESSMENT AND SPECIFIC MEASURES

This section contains a risk assessment for study 1305-0016 with BI 1015550 due to the circumstances created by the coronavirus disease-19 (COVID-19) pandemic. In addition, this section summarizes the mitigation approaches to be followed to minimize the risk of spreading severe acute respiratory syndrome coronavirus 2 (SARS CoV-2).

Assessment of risks associated with Covid-19 pandemic
For BI 1015550 an assessment specific to the COVID-19 pandemic has been performed based on the current knowledge to evaluate, if the treatment with BI 1015550 may pose a higher risk associated with SARSCoV-2 infection and COVID-19 disease.
Based on the pharmacological mechanism and existing nonclinical and clinical data there is no indication that treatment with BI 1015550 may increase the risk of severe clinical courses of SARS-COV-2 infection.
Even though an increased risk of SARS-CoV-2 infection, or of a more severe COVID-19 disease in case of such an infection appears unlikely, subjects with active or recent SARS CoV-2 infection will not be included in the trial.
For further details refer to benefit risk assessment BI 1015550 COVID19 [s00092835]

Every subject will be assessed thoroughly and individual benefit-risk assessments will be performed by the investigator prior to study participation of a subject. In respect of potential COVID-19, the risk for subjects participating in this trial will not differ from the current general risk of COVID-19 with all its consequences.
The investigator will take the totality of information related to each single subject and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each subject's (continued) participation in this trial. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, well- being and/or is in the best interest of the subject.

Risk mitigating measures in study design
The study population for this study consists of healthy subjects with minimized risk of SARS-CoV-2 infection (free of COVID-19 symptoms, negative PCR tests prior to investigational medicinal product administration) and with minimized impact of COVID-19, if contracted during the study (e.g., upper age ≤65 years, upper BMI ≤29.9 kg/m$^2$). Physical examination will be limited to screening, discharge on Day 10 and EoT as indicated in the Flow Chart. Subjects will be admitted for in-house confinement from Day -1 until Day 10 following a single dose administration on Day 1. Subjects will be readmitted to the research site for 24-h in-house stay at several time points as specified in the Flow Chart, if they do not meet the release criteria. At the time of EoT examination (Day 11 - Day 31) BI 1015550 is expected to be eliminated.

SARS-CoV-2 containment measures at research site
The following SARS-CoV-2 containment measures will be taken during the study:

- The study will be conducted in accordance with guidance from the Central Committee on Research Involving Human Subjects (CCMO [Centrale Commissie Mensgebonden

Onderzoek]) on conducting Phase 1 trials in Clinical Research Units in The Netherlands during the COVID 19 pandemic.

- During the entire study, the clinical research unit will implement all recommendations issued by the Dutch Government, including specific guidelines related to clinical research executed in clinical research units with respect to minimizing the risk of disease spreading, e.g., social distancing, disinfection, hygiene, and wearing of personal protection equipment by study staff. Details on specific procedures are described in the Site Specific Manual.
- In cases where subjects are not able to attend study visits due to the presence of a SARS-CoV-2 infection, the Investigator will discuss with the Sponsor potential mitigation approaches (including, but not limited to, extending the visit window, conducting evaluations via video link or phone call, allowing for safety procedures to be conducted at a local facility). The rationale (e.g., the specific limitation imposed by the SARS-CoV-2 infection that led to the inability to perform the protocol-specified assessment) and outcome of the discussion will be documented in the electronic case report form (eCRF).
- Polymerase chain reaction (PCR) testing for SARS CoV-2 will be performed at the time points indicated in the Flow Chart:
- A subject should not be admitted to the research site, if there was any contact with a person tested positive for SARS CoV-2 or a COVID-19 patient within the last 2 weeks prior to admission to the clinical research center.
- If a subject is tested to be positive for SARS-CoV-2 on Day -1, the subject will be excluded from participation in trial with reference to exclusion criterion #29, and referred for treatment.
- If a subject becomes ill and/or is tested to be positive for SARS-CoV-2 after administration of study treatment, the subject will be isolated from other study participants and referred for treatment. The subject will be followed up in quarantine in the clinical research unit until complete elimination of the study compound or will be asked to quarantine at home according to guidelines of the Dutch government.

*Conclusion of COVID-19 risk containment*
Given the profile of the compound and given the study design, the COVID-19 risk minimization strategy as described above is considered adequate.

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

## 11.1 GLOBAL AMENDMENT 1

| | | |
|---|---|---|
| **Date of amendment** | | |
| **EudraCT number**<br>**EU number** | | |
| **BI Trial number** | | |
| **BI Investigational Medicinal Product** | | |
| **Title of protocol** | | |
| | | |
| **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** | | |
| **Description of change** | | |
| **Rationale for change** | | |

**APPROVAL / SIGNATURE PAGE**

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**Document Name:** clinical-trial-protocol-version-01

**Title:** A phase I, open-label, non-randomized, single-dose, single-arm, single-period study to investigate the metabolism and pharmacokinetics of [C-14]-labelled BI 1015550 after oral administration in healthy male subjects

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Trial Statistician | [redacted] | 28 Jan 2021 13:22 CET |
| Author-Clinical Trial Leader | | 28 Jan 2021 13:25 CET |
| Approval-Team Member Medicine | | 28 Jan 2021 13:25 CET |
| Verification-Paper Signature Completion | | 28 Jan 2021 14:25 CET |
| Author-Trial Clinical Pharmacokineticist | | 28 Jan 2021 16:55 CET |
| Approval-Therapeutic Area [redacted] | | 29 Jan 2021 12:49 CET |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|