# Clinical Trial Protocol

| | | |
|---|---|---|
| | **Document Number:** | **c34982691-03** |
| **BI Trial No.** | 1425-0008 | |
| **BI Investigational Medicinal Product** | BI 706321 | |
| **Title** | Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design) | |
| **Lay Title** | A study in healthy Japanese and Chinese men to test how well different doses of BI 706321 are tolerated | |
| **Clinical Trial Leader** | [redacted]<br>Telephone: [redacted], Fax: [redacted] | |
| [redacted]<br>**Investigator** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] | |
| **Status** | Final Protocol / Revised Protocol (based on global amendment 2) | |
| **Version and Date** | Version: 3.0 | Date: 10 December 2021 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

| | |
|---|---|
| **Company name** | Boehringer Ingelheim |
| **Protocol date** | 03 Aug 2021 |
| **Revision date** | 10 Dec 2021 |
| **BI trial number** | 1425-0008 |
| **Title of trial** | Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design) |
| [redacted] **Investigator** | [redacted]<br>Phone: [redacted]<br>Fax: [redacted] |
| **Trial site** | SOUSEIKAI Sumida Hospital |
| **Clinical phase** | I |
| **Trial rationale** | Part I:<br>The trial is required to assess the safety, tolerability, and pharmacokinetics of BI 706321 administered in multiple rising oral doses to healthy Japanese male subjects in order to provide the basis for the clinical development of BI 706321 for the treatment of Crohn's disease in Japan.<br>Part II:<br>The trial is required to assess the safety, tolerability, and pharmacokinetics of BI 706321 administered in single oral dose to healthy Chinese male subjects in order to provide the basis for the clinical development of BI 706321 for the treatment of Crohn's disease in China. |
| **Trial objectives** | To investigate safety, tolerability and pharmacokinetics following single and multiple rising doses of BI 706321 |
| **Trial endpoints** | Primary endpoint: Percentage of subjects with drug-related adverse events<br>Secondary endpoints:<br>Part I and II<br>Single dose part (After the first dose) ,<br>$AUC_{0-\infty}$, $C_{max}$ and $t_{max}$ of BI 706321<br>Part I only<br>After the last dose,<br>$AUC_{\tau,ss}$ and $C_{max,ss}$, $C_{min,ss}$, $R_{A,AUC}$, and $R_{A,Cmax}$ of BI 706321 |

# FLOW CHART

Part I:

| Visit | Day | Planned time (relative to first drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | PK $_{blood}$ for BI 706321 and BI 706062 [8] | PK $_{urine}$ for BI 706321 [9] | 12-lead ECG | Vital signs (BP, PR, BT) | Questioning for AEs and concomitant therapy [5] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -28 to -1 | | | Screening (SCR)[1] | x | | | x | x | |
| 2 | -3 to -1 | -72:00[11] | | Admission to trial site[12,13] | x[14] | | | | x | x |
| | 1 | -1:00 | 08:00 | Allocation to treatment[2] | | x[2] | x[2] | x[2,10] | x[2] | x[2] |
| | | **0:00** | **09:00** | First drug administration | | | ▲ | | | |
| | | 0:30 | 09:30 | | | x | \| | | | |
| | | 1:00 | 10:00 | | | x | \| | x[7] | x | |
| | | 2:00 | 11:00 | 240 mL fluid intake | | x | \| | x[7] | x | x |
| | | 3:00 | 12:00 | | | x | \| | | | |
| | | 4:00 | 13:00 | 240 mL fluid intake, thereafter lunch[3] | | x | + | x[7] | x | x |
| | | 5:00 | 14:00 | | | x | \| | | | |
| | | 6:00 | 15:00 | | | x | \| | | | |
| | | 8:00 | 17:00 | | | x | + | x[7] | x | x |
| | | 10:00 | 19:00 | Dinner[3] | | x | \| | | | |
| | | 12:00 | 21:00 | | | x | + | x[7] | x | x |
| | 2 | 24:00 | 09:00 | Breakfast[3] | x | x | + | x[7] | x | x |
| | | 36:00 | 20:00 | | | x | \| | x[7] | | x |
| | 3 | 48:00 | 09:00 | | | x | + | x[7] | | x |
| | 4 | 72:00 | 09:00 | | | x | + | | | |
| | 5 | 96:00 | 09:00 | | | x | + | x | | x |
| | 6 | 120:00 | 09:00 | Drug administration[6] | x[2] | x[2] | ▼ | x | x | x |
| | 7 | 144:00 | 09:00 | Drug administration[6] | | | | x | x | x |
| | 8 | 168:00 | 09:00 | Drug administration[6] | x[2] | x[2] | | | | x |
| | 9 | 192:00 | 09:00 | Drug administration[6] | | x[2] | | x | x | x |
| | 10 | 216:00 | 09:00 | Drug administration[6] | x[2] | x[2] | | | | |
| | 11 | 240:00 | 09:00 | Drug administration[6] | | x[2] | | x | x | x |
| | 12 | 264:00 | 09:00 | Drug administration | x[2] | x[2] | ▲ | | | x |
| | | 264:30 | 09:30 | | | x | \| | | | |
| | | 265:00 | 10:00 | | | x | \| | | | |
| | | 266:00 | 11:00 | 240 mL fluid intake | | x | \| | | | |
| | | 267:00 | 12:00 | | | x | \| | | | |
| | | 268:00 | 13:00 | 240 mL fluid intake, thereafter lunch[3] | | x | + | | | |
| | | 269:00 | 14:00 | | | x | \| | | | |
| | | 270:00 | 15:00 | | | x | \| | | | |
| | | 272:00 | 17:00 | | | x | + | | | |
| | | 274:00 | 19:00 | Dinner[3] | | x | \| | | | |
| | | 276:00 | 21:00 | | | x | + | | | |
| | 13 | 288:00 | 09:00 | Drug administration[6] | | x[2] | ▼ | x | x | x |
| | 14 | 312:00 | 09:00 | Drug administration[6] | x[2] | x[2] | | | | x |

| Visit | Day | Planned time (relative to first drug administration [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | $PK_{blood}$ for BI 706321 and BI 706062 [8] | $PK_{urine}$ for BI 706321 [9] | 12-lead ECG | Vital signs (BP, PR, BT) | Questioning for AEs and concomitant therapy [5] |
|---|---|---|---|---|---|---|---|---|---|---|
| | 15 | 336:00 | 09:00 | Drug administration[6] | | x[2] | | x | x | x |
| | 16 | 360:00 | 09:00 | Drug administration[6] | x[2] | x[2] | | | | x |
| | 17 | 384:00 | 09:00 | Drug administration[6] | | x[2] | | x | x | x |
| | 18 | 408:00 | 09:00 | Drug administration[6] | x[2] | x[2] | | | | x |
| | 19 | 431:45 | 08:45 | | | x[2] | | x[10] | x | x |
| | | 432:00 | 09:00 | Last drug administration | | | ▲ | | | |
| | | 432:30 | 09:30 | | | x | \| | | | |
| | | 433:00 | 10:00 | | | x | \| | x[7] | x | |
| | | 434:00 | 11:00 | 240 mL fluid intake | | x | \| | x[7] | x | |
| | | 435:00 | 12:00 | | | x | \| | | | |
| | | 436:00 | 13:00 | 240 mL fluid intake, thereafter lunch[3] | | x | ┼ | x[7] | x | |
| | | 437:00 | 14:00 | | | x | \| | | | |
| | | 438:00 | 15:00 | | | x | \| | | | |
| | | 440:00 | 17:00 | | | x | ┼ | x[7] | x | |
| | | 442:00 | 19:00 | Dinner[3] | | x | \| | | | |
| | | 444:00 | 21:00 | | | x | ┼ | x[7] | x | |
| | | 446:00 | 22:00 | | | x | \| | | | |
| | 20 | 456:00 | 09:00 | Light breakfast | x | x | ┼ | x[7] | x | x |
| | 21 | 480:00 | 09:00 | | | x | ┼ | x[7] | x | x |
| | 22 | 504:00 | 09:00 | | x | x | ┼ | x | x | x |
| | 23 | 528:00 | 09:00 | | | x | ┼ | | | x |
| | 24 | 552:00 | 09:00 | | | x | ▼ | x | x | x |
| | 25 | 576:00 | 09:00 | | | x | | | | x |
| | 26 | 600:00 | 09:00 | | | x | | | | x |
| 3 | 27 | 624:00 | 09:00 | End of trial (EoTrial) examination[4,13] / Discharge from trial site[12] | x | x | | x | x | x |

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, assessment of body temperature, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedures are to be performed and completed within the 3 hours prior to drug administration on Day 1. On all other days the 3-hour window only applies to safety assessments and PK blood collection. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of fluid and meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, assessment of body temperature, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. 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.
6. On all non-intensive PK days, standard light breakfast will be served approx. 1 hour after the dose. On all study days standard meals (lunch and dinner) will be given approx. 4 and 10 hours post dose.
7. The ECG recording has to be performed in triplicate at this time.
8. Sampling times and periods may be adapted based on information obtained during the trial including addition of samples and visits as long as the total blood volume drawn does not exceed 400 mL per subject.

9. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 h on days 1and 19 for all doses. For 2 mg dose group, samples over the post-dose interval 96-120 h are not to be collected (samples over the post-dose interval 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 are to be collected). On day 12, the samples are to be collected over the stated post-dose intervals (◄—|—|—►) 0-4, 4-8, 8-12, 12-24 h) for all dose groups.
10. At baseline (i.e. Day 1, prior to drug administration) and Day 19, 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
11. This is nominal time. Actual visit procedures may be performed anytime between day -3 and day -1.
12. The hospitalization may be extended for operational reasons.
13. SARS-COV-2/ COVID-19 test (nucleic acid amplification methods) as well as body temperature assessment will be performed once prior to admission to trial site during the period from Day -3 to Day -1, at the end of trial visit unless subject is hospitalized throughout the trial, and when the infection is suspected during the trial.
14. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this repeat safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.

Part II:

| Visit | Day | Planned time (relative to drug administration) [h:min] | Approximate clock time of actual day [h:min] | Event and comment | Safety laboratory | $PK_{blood}$ for BI 706321 and BI 706062 [7] | $PK_{urine}$ for BI 706321 [8] | 12-lead ECG | Vital signs (BP, PR, BT) | Questioning for AEs and concomitant therapy [5] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -28 to -1 | | | Screening (SCR)[1] | x | | | x | x | |
| 2 | -3 to -1 | -72:00[10] | | Admission to trial site[11,12] | x[13] | | | | x | x |
| | 1 | -1:00 | 08:00 | Allocation to treatment[2] | | x[2] | x[2] | x[2,9] | x[2] | x[2] |
| | | **0:00** | **09:00** | First drug administration | | | ▲ | | | |
| | | 0:30 | 09:30 | | | x | \| | | | |
| | | 1:00 | 10:00 | | | x | \| | x[6] | x | |
| | | 2:00 | 11:00 | 240 mL fluid intake | | x | \| | x[6] | x | x |
| | | 2:30 | 11:30 | | | x | \| | | | |
| | | 3:00 | 12:00 | | | x | \| | | | |
| | | 4:00 | 13:00 | 240 mL fluid intake, thereafter lunch[3] | | x | ┼ | x[6] | x | x |
| | | 5:00 | 14:00 | | | x | \| | | | |
| | | 6:00 | 15:00 | | | x | \| | | | |
| | | 8:00 | 17:00 | | | x | ┼ | x[6] | x | x |
| | | 10:00 | 19:00 | Dinner[3] | | x | \| | | | |
| | | 12:00 | 21:00 | | | x | ┼ | x[6] | x | x |
| | 2 | 24:00 | 09:00 | Breakfast[3] | x | x | ┼ | x[6] | x | x |
| | | 36:00 | 20:00 | | | x | \| | x[6] | | x |
| | 3 | 48:00 | 09:00 | | | x | ┼ | x[6] | | x |
| | 4 | 72:00 | 09:00 | | | x | ┼ | | | |
| | 5 | 96:00 | 09:00 | | | x | ┼ | x | | x |
| | 6 | 120:00 | 09:00 | | x | x | ▼ | x | x | x |
| | 7 | 144:00 | 09:00 | | | | | x | x | x |
| | 8 | 168:00 | 09:00 | Discharge from trial site[11] | x | x | | | | x |
| 3 | 15 to 22 | | | End of trial (EoTrial) examination[4,12] | x | x | | x | x | x |

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, assessment of body temperature, ECG, safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedures are to be performed and completed within the 3 hours prior to drug administration on Day 1. On all other days the 3-hour window only applies to safety assessments. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
3. If several actions are indicated at the same time, the intake of fluid and meals will be the last action.
4. At the end of trial visit the EoTrial examination includes physical examination, body weight, vital signs, assessment of body temperature, ECG, safety laboratory, recording of AEs, and concomitant therapies.
5. 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.
6. The ECG recording has to be performed in triplicate at this time.
7. Sampling times and periods may be adapted based on information obtained during the trial including addition of samples and visits as long as the total blood volume drawn does not exceed 400 mL per subject.

8. A blank urine sample (x) is to be obtained prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄—│—│—►) 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96 and 96-120 h on day 1.
9. At baseline (i.e. Day 1, prior to drug administration), 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes.
10. This is nominal time. Actual visit procedures may be performed anytime between day -3 and day -1.
11. The hospitalization may be extended for operational reasons.
12. SARS-COV-2/ COVID-19 test (nucleic acid amplification methods) as well as body temperature assessment will be performed once prior to admission to trial site during the period from Day -3 to Day -1, at the end of trial visit unless subject is hospitalized throughout the trial, and when the infection is suspected during the trial.
13. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this repeat safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1.

# TABLE OF CONTENTS

# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse events of special interest |
| $Ae_{t1\text{-}t2}$ | Amount of analyte eliminated in urine over the time interval $t_1$ to $t_2$ |
| $AUC_{0\text{-}\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| $\%AUC_{tz\text{-}\infty}$ | Percentage of $AUC_{tz\text{-}\infty}$ obtained by extrapolation |
| $AUC_{0\text{-}tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| β | Slope parameter associated with the power model used to evaluate dose proportionality |
| BI | Boehringer Ingelheim |
| BMI | Body mass index (weight divided by height squared) |
| BP | Blood pressure |
| CA | Competent authority |
| CI | Confidence interval |
| CL/F | Apparent clearance of the analyte in plasma after extravascular administration |
| $CL_{R,\ t1\text{-}t2}$ | Renal clearance of the analyte in plasma from the time point $t_1$ to $t_2$ |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| $C_{min}$ | Minimum measured concentration of the analyte in plasma |
| CRA | Clinical Research Associate |
| CRF | Case Report Form, paper or electronic (sometimes referred to as 'eCRF') |
| CTL | Clinical Trial Leader |
| CTM | Clinical Trial Manager |
| CTP | Clinical trial protocol |
| CTR | Clinical trial report |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eDC | Electronic data capture |
| EDTA | Ethylenediaminetetraacetic acid |
| EoTrial | End of trial |
| EudraCT | European Clinical Trials Database |
| F | Absolute bioavailability factor |
| $fe_{t1\text{-}t2}$ | Fraction of administered drug excreted unchanged in urine over the time interval from $t_1$ to $t_2$ |

| | |
|---|---|
| GCP | Good Clinical Practice |
| gMean | Geometric mean |
| HR | Heart rate |
| IB | Investigator's brochure |
| IEC | Independent Ethics Committee |
| iPD | Important protocol deviation |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| $\lambda_z$ | Terminal rate constant of the analyte in plasma |
| LC-MS/MS | Liquid chromatography with tandem mass spectrometry |
| MDA | Methylenedioxyamphetamine |
| MDMA | Methylenedioxymethamphetamine |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRD | Multiple-rising dose |
| $MRT_{,ex}$ | Mean residence time of the analyte in the body, extravascular |
| NOD | Nucleotide Oligomerization Domain |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PKS | Pharmacokinetic set |
| PP | Polypropylene |
| PR | Pulse rate |
| QD | Quaque die |
| 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) |
| $R_{A,AUC}$ | Accumulation ratio based on $AUC_{0-\tau}$ |
| $R_{A,Cmax}$ | Accumulation ratio based on $C_{max,ss}$ |
| REP | Residual effect period |
| RIPK2 | Receptor-Interacting Protein Kinase-2 |
| SAE | Serious adverse event |
| SCR | Screening |
| SOP | Standard operating procedure |
| SRD | Single-rising dose |
| ss | (at) steady state |
| TB | Tuberculosis |
| 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 |
| $t_z$ | Time of last measurable concentration of the analyte in plasma |
| TSAP | Trial statistical analysis plan |
| ULN | Upper limit of normal |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extravascular administration |
| XTC | Ecstasy |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

Crohn's disease is characterized by transmural inflammation with ulcerative lesions affecting any site within the gastrointestinal tract, with most frequent involvement of terminal ileum, often combined with inflammation in colon.

In Crohn's disease, mucosal inflammation is driven by a disruption of the intestinal barrier in the context of dysbiosis of the microbial flora, which leads to aberrant stimulation of immune and non-immune cells in the gut. Microbial stimulation of somatic cells is partially mediated by Nucleotide Oligomerization Domain(NOD) pattern recognition receptors through RIPK2 at the earliest stage in the development of the immuno-inflammatory cascade. RIPK2 inhibition is postulated to blunt the dominant NOD1/2-driven inflammatory response to the microbiome in the gut, while sparing other microbial sensing pathways to prevent broad immunosuppression. This will result in reduced levels of inflammatory cells and inflammatory mediators in intestinal tissue, and improved epithelial barrier function, which is expected to lead to mucosal healing and clinical response in Crohn's disease.

For more details on medical background refer to the Investigator's Brochure (IB) [c26475781].

## 1.2 DRUG PROFILE

### 1.2.1 BI 706321

Mode of action

BI 706321 is a potent and specific inhibitor of the human RIPK2 kinase.

The toxicity profile of BI 706321 has been assessed in a comprehensive set of *in vitro* and *in vivo* safety pharmacology studies, genetic toxicology studies, and repeat dose studies (up to 13-weeks duration) in the rat and cynomolgus monkey. The nonclinical safety package supports administration of BI 706321 to humans for up to 13-weeks duration.

For additional details on the nonclinical pharmacology, pharmacokinetics in animals and toxicology results refer to the IB [c26475781].

Key pharmacokinetic characteristics

After oral administration in humans, BI 706321 concentrations increased slowly and reached peak concentrations in approximately 3.5 to 6 hours. After reaching peak concentration, BI 706321 concentrations decreased in a multiphasic manner. Based on the preliminary data, there was a slight trend of more than dose proportional increase of BI 706321 exposure over the entire dose range tested. Following multiple dosing to a pharmacokinetic steady state, the geometric mean (gMean) terminal elimination half-life ranged from 46.8 to 76.5 hours. BI 706321 accumulated in plasma with accumulation ratios ranged from 2 to 3.34 for $C_{max}$ and from 2.3 to 3.69 for AUC. Exposure to BI 706321 was similar between capsule and tablet

formulation in fasted subjects. When the tablet formulation taken together with a standard high-fat and high caloric meal, exposure was slightly decreased.

Clinical experience

At the time of preparing this protocol, preliminary results are available from two Phase I trials which are clinically completed. The single-rising dose (SRD) trial 1425-0001, was a partially-randomised, single-blind, placebo-controlled parallel-group trial to investigate safety, tolerability, and pharmacokinetics (PK) of BI 706321 after single administration as an oral solution, reconstituted from 20 mg capsules (0.3, 0.6 and 1.2 mg dose groups) and capsules (2, 4, 8, 15 and 25 mg dose groups) to 46 healthy male adult subjects as compared to placebo (n=15). In the SRD part II (BA and FE),12 healthy male subjects were administered 4 mg capsules and tablets under both fed and fasted conditions in an open, randomised, 3-way cross-over design.

In the multiple-rising dose (MRD) trial 1425-0002, healthy male and female subjects of non-child bearing potential were given a single dose of BI 706321; then, following a five-day washout, these subjects were administered BI 706321 daily for 14 days. There were four dose levels of BI 706321 capsules: 2 mg QD, 5 mg QD, 8 mg QD, and 10 mg QD. There were 10 subjects (8 active, 2 placebo) in each dose group.

In addition, Trial 1425-0010, a Phase I DDI trial to assess the effect of itraconazole on the pharmacokinetics of BI 706321 has been clinically completed.

Pharmacokinetics

Following single oral administration as capsule under fasted state, BI 706321 plasma concentrations increased slowly. The median $t_{max}$ for different dose levels was in the range of 3.5 to 6 hours. After reaching peak concentration, BI 706321 concentrations decreased in a multiphasic manner. A summary of PK parameters of BI 706321 in part 1 of trial 1425-0001 is given in Table 1.2.1: 1. The exposure to BI 706321 increased with increasing dose. Exposure to BI 706321 was similar between capsule and tablet formulation in fasted subjects (2% difference in $C_{max}$ and no difference in $AUC_{0-tz}$). Administration of BI 706321 as a tablet together with a standard high-fat and high caloric meal resulted in a slight decrease in $C_{max}$ (22.5%) and $AUC_{0-tz}$ (8%) compared to fasted condition, not considered to be clinically relevant.

Table 1.2.1: 1 PK parameters of BI 706321 after single oral administration of BI 706321 in trial 1425-0001

| | 0.3 mg solution (N=6) | 0.6 mg solution (N=6) | 1.2 mg solution (N=5) | 2 mg capsule (N=6) | 4 mg capsule (N=6) | 8 mg capsule (N=6) | 15 mg capsule (N=5) | 25 mg capsule (N=6) |
|---|---|---|---|---|---|---|---|---|
| $t_{max}$[1] (h) | 6.00 (4.00-6.00) | 6.01 (2.00-8.00) | 6.00 (3.00-6.00) | 6.00 (2.00-8.00) | 5.02 (4.00-6.00) | 4.50 (2.50-6.00) | 4.00 (1.50-6.00) | 3.51 (2.00-8.03) |
| $C_{max}$[2] (nmol/L) | 0.388 (32.8) | 0.781 (21.4) | 1.02 (40.0) | 2.27 (30.1) | 5.19 (38.6) | 11.8 (41.6) | 24.6 (43.0) | 41.1 (32.1) |
| Dose normalized $C_{max}$[2] (nmol/L/mg) | 1.29 (32.8) | 1.30 (21.4) | 0.853 (40.0) | 1.14 (30.1) | 1.30 (38.6) | 1.47 (41.6) | 1.64 (43.0) | 1.64 (32.1) |
| $AUC_{0-\infty}$[2] (nmol•h/L) | 3.83 (37.8)[3,4] | 13.2 (30.5)[4] | 21.9 (33.3)[4] | 51.6 (25.8)[4] | 151 (33.1)[3] | 314 (25.7) | 618 (36.1) | 1130 (24.2) |
| Dose normalized $AUC_{0-\infty}$[2] (nmol•h/L/mg) | 12.8 (37.8)[3,4] | 22.0 (30.5)[4] | 18.3 (33.3)[4] | 25.8 (25.8)[4] | 37.9 (33.1)[3] | 39.3 (25.7) | 41.2 (36.1) | 45.3 (24.2) |
| Terminal $t_{1/2}$[2] (h) | --- | --- | --- | --- | 31.4 (38.7)[3] | 34.7 (26.7) | 37.6 (16.4) | 37.9 (18.2) |

1. Median (range)
2. Geometric mean (gCV%)
3. N=5
4. $AUC_{0-tz}$ value is given since $AUC_{0-\infty}$ is not evaluable

--- not available

The PK of BI 706321 was also evaluated after once daily administration over a period of 14 days. Preliminary PK parameters of BI 706321 derived based on planned time in trial 1425-0002 are summarized in Table 1.2.1: 2. The geometric mean concentration-time profiles are shown in Figure 1.2.1: 1 below. The steady state geometric mean plasma exposure (AUC of 574 nmol·h/L and $C_{max}$ of 39.9 nmol/L) with 10 mg BI 706321 QD was below the maximum allowable BI 706321 exposure predefined in trial 1425-0002 based on NOAEL in the 4-week cynomolgus monkey study ($AUC_{0-24}$ of 693 nmol·h/L and $C_{max}$ of 86.1 nmol/L), although the exposures of 3 subjects were slightly higher than the predefined exposure limit

Table 1.2.1: 2 Preliminary PK parametersP1P of BI 706321 after single and multiple oral administration of BI 706321 over 14 days in the study 1425-0002[1]

| | **2 mg (N=8)** | **5 mg (N=8)** | **8 mg (N=8)** | **10 mg (N=8)** |
|---|---|---|---|---|
| $t_{max}$[2] (h) | 5.00 (2.00-6.00) | 5.00 (2.00-6.00) | 5.50 (3.00-6.00) | 5.00 (4.00-5.00) |
| $t_{max,ss}$[2] (h) | 5.00 (3.00-5.00) | 5.00 (4.00-5.00) | 4.00 (1.00-5.00) | 5.00 (1.00-6.00)[4] |
| $AUC_{0-24}$[3] (nmol*h/L) | 38.3 (48.1) | 85.1 (31.0) | 140 (42.6) | 155 (30.0) |
| $AUC_{\tau,ss}$[3] (nmol*h/L) | 88.1 (34.5) | 234 (34.8) | 517 (29.9) | 574 (35.6)[4] |
| $C_{max}$[3] (nmol/L) | 2.85 (53.8) | 6.47 (29.1) | 10.6 (38.6) | 11.5 (33.6) |
| $C_{max,ss}$[3] (nmol/L) | 5.69 (41.8) | 14.7 (43.1) | 34.7 (38.5) | 39.9 (35.7)[4] |
| $C_{24}$[3] (nmol/L) | 1.27 (38.8) | 2.43 (34.4) | 3.78 (43.6) | 4.68 (26.3) |
| $C_{24,ss}$[3] (nmol/L) | 3.12 (39.9) | 7.93 (32.3) | 16.4 (22.4) | 18.6 (38.0)[4] |
| $t_{1/2}$[3] (h) | 40.8 (37.7) | 41.7 (19.4) | 36.3 (21.4) | 43.2 (20.4) |
| $t_{1/2,ss}$[3] (h) | 74.4 (49.5) | 70.4 (34.8) | 46.8 (21.7) | 76.5 (32.2)[4] |
| $RA_{Cmax}$[3] | 2.00 (27.7) | 2.28 (23.1) | 3.29 (24.5) | 3.34 (15.2)[4] |
| $RA_{AUC\tau}$[3] | 2.30 (33.2) | 2.75 (20.8) | 3.69 (23.9) | 3.58 (19.8)[4] |

1. Derived based on planned time
2. Median (range)
3. Geometric mean (gCV%)
4. N=7

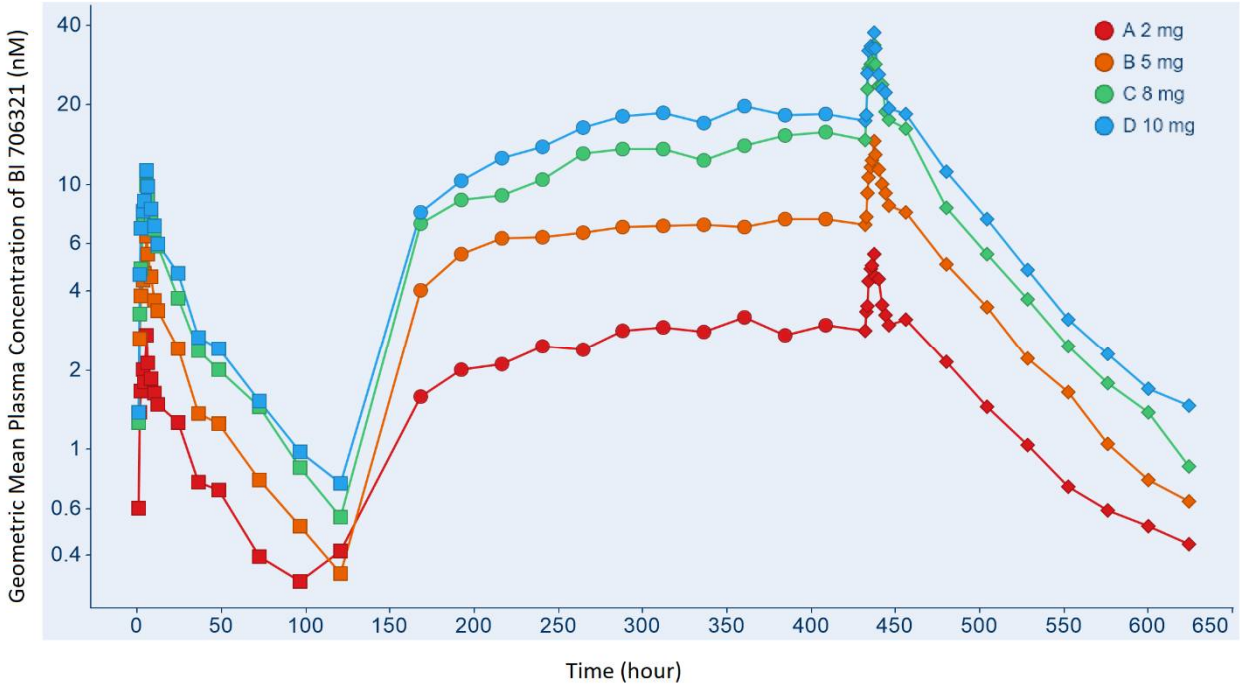



Figure 1.2.1: 1 Geometric mean plasma concentration-time profiles of BI 706321 after single- and multiple-oral administration of BI 706321 over 14 days (log scale).

Clinical safety

In the 1425-0001 trial part I, single doses of 0.3 – 25 mg BI 706321 were well tolerated by healthy male subjects. Based on preliminary analysis, the frequency of subjects with at least one treatment-emergent AE ranged from 0/6 (0%) to 3/5 (60%) on BI 706321 dose groups as compared to 6/15 (40%) on placebo (Table 1.2.1: 3). AEs reported in >1 subject on active treatment were coded as diarrhea (n=2, loose stool (8 mg) and watery stool (25 mg)) and nasopharyngitis (n=2, 0.6 and 15 mg). A total of 5 drug-related AEs have been observed: dry lips (0.3 mg), dizziness (15 mg), generalized sensation of cold (25 mg), loose stool (8 mg) and watery stool (25 mg) (last two coded as diarrhea). All these AEs were of mild intensity. Two subjects had drug-related AEs on placebo.

Table 1.2.1: 3 Number of subjects with on-treatment adverse events in Trial 1425-0001, part I

| Dose groups | Placebo | | 0.3 mg | | 0.6 mg | | 1.2 mg | | 2 mg | | 4 mg | | 8 mg | | 15 mg | | 25 mg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Number of subjects | 15 | 100.0 | 6 | 100.0 | 6 | 100.0 | 5 | 100.0 | 6 | 100.0 | 6 | 100.0 | 6 | 100.0 | 5 | 100.0 | 6 | 100.0 |
| Total with adverse events | 6 | 40.0 | 3 | 50.0 | 2 | 33.3 | 1 | 20 | 0 | 0.0 | 3 | 50.0 | 1 | 16.7 | 3 | 60 | 2 | 33.3 |
| Subjects with investigator defined drug–related AEs | 2 | 13.3 | 1 | 16.7 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 1 | 16.7 | 1 | 20 | 2 | 33.3 |

In the SRD part II (BA and FE), 4 mg tablets and capsules were administered to an additional 12 healthy male subjects under both fed and fasted conditions and were well-tolerated. Based

on preliminary analysis, the total number of subjects with at least one treatment-emergent AE was 4/12 (33.3%) of subjects while on active treatment. Three subjects experienced drug related AEs: headache (4 mg tablet/fed and capsule/fasted), loose stools (4 mg capsule/fasted), and decreased snoring (4 mg tablet/fed).

In the multiple-rising dose (MRD) trial 1425-0002, multiple doses of 2-10 mg BI 706321 (n = 32) were generally well tolerated by healthy subjects for up to 14 days of dosing. Based on preliminary analysis, the frequency of subjects with at least one treatment-emergent AE ranged from 3/8 (37.5%) to 6/8 (75%) subjects on BI 706321 dose groups as compared to 1/7 subjects (14.3%) on placebo (Table 1.2.1: 4). AEs reported in >1 subject on active treatment were coded as influenza like illness (reported as ”flu like symptoms” n=5; 5 mg [1], 8 mg [2], 10 mg [2]), abdominal discomfort (n= 4; 5 mg [3] and 10 mg [1]), diarrhea (n=4; 5 mg [1], 8 mg [1], 10 mg [2]), headache (n=4; 5 mg [2], 8 mg [1], 10 mg [1]), constipation (n=2, 2 mg and 5 mg), and contusion (n=2; 5 mg and 10 mg). No such events were reported for subjects on placebo. One subject (2.6%) had on-treatment AEs which were considered drug related by the investigator (dry mouth and somnolence, 2 mg)

Events coded as diarrhea were all mild in intensity and of short duration (< 1-3 days). Events coded as constipation and abdominal discomfort were all mild in intensity.

”Flu like symptoms” were considered mild-moderate in severity and were characterized by intermittent low-grade temperature elevations (maximum temperature 38.1°C), over a duration of 1-3 days. Concomitant headache and dysuria were experienced by one subject each. Minor, transient, elevations of CRP were noted with these symptoms. All symptoms resolved spontaneously while on continuous BI 706321 treatment. Based on the brief and self-limited nature of the symptoms, they were considered to be of minor clinical significance.

Table 1.2.1: 4 Number of subjects with on-treatment adverse events in Trial 1425-0002

| Dose groups | Placebo | | 2 mg | | 5 mg | | 8 mg | | 10 mg | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % | N | % |
| Number of subjects | 7 | 100.0 | 8 | 100.0 | 8 | 100.0 | 8 | 100.0 | 8 | 100.0 |
| Total with adverse events | 1 | 14.3 | 3 | 37.5 | 5 | 62.5 | 6 | 75.0 | 5 | 62.5 |
| Subjects with investigator defined drug-related AEs | 0 | 0.0 | 1 | 12.5 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |

In the SRD trial 1425-0001, one subject in the 25 mg dose group reported a brief generalized sensation of cold approximately 10 hours after dosing with associated mild transient increase in temperature (37.4°C) and CRP (35.4 mg/L [ULN: 5.0 mg/L]). In the MRD trial 1425-0002, minor transient elevations in CRP, up to a maximum value of 19.7 mg/L (ULN: 5.0 mg/L) were observed in a subset of subjects beginning after approximately 3 to 6 days of multiple dosing. CRP levels subsequently normalized within 48 to 96 hours while dosing was ongoing. Some of these subjects experienced symptoms reported as “flu like symptoms”

described above, while other subjects had no such symptoms associated with these changes in CRP values. No clinically significant changes from baseline in ferritin, haptoglobin, or fibrinogen were observed. Given the minor and transient nature of these observed changes in CRP, in the absence of clinical symptoms, they were not considered clinically relevant.

In both the SRD and MRD trials there were no AEs that led to discontinuation of the study drug; neither SAE nor severe AE were observed. Vital sign evaluation and safety laboratory testing did not reveal clinically relevant findings.

No clinically relevant changes in any cardiac intervals as measured by the ECG core lab were observed in any subject exposed to BI 706321; no relevant blood pressure and heart rate changes were noted.

Trial 1425-0010, is a Phase I DDI trial to assess the effect of itraconazole on the pharmacokinetics of BI 706321 in 14 healthy male subjects using an open-label, two-period fixed sequence design. At the time of drafting of this protocol, preliminary safety data showed that 18 AEs in 10 subjects from the treated set occurred during this trial. 15 AEs in 8 subjects were assessed as drug-related; these AEs did not indicate any potential safety concern. All AEs were of mostly mild or occasionally moderate intensity; neither SAE nor severe AE were reported.

Overall, single dose administration of BI 706321 at doses of up to 25 mg and multiple-dose administration of BI 706321 at doses of up to 10 mg for up to 14 days, was generally well tolerated by the 104 healthy volunteers who have been exposed to active treatment in these studies.

### 1.2.2 Residual Effect Period

The Residual Effect Period (REP) of BI 706321 is 16 days and is projected based on 5*terminal $t_{1/2}$ from preliminary PK data of Trial 1425-0002. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

## 1.3 RATIONALE FOR PERFORMING THE TRIAL

Crohn's Disease patients not responding to conventional therapy of orally administered aminosalicylates (e.g. 5-ASA), glucocorticoids and immunomodulatory agents (azathioprine or 6-MP), are usually treated with biologic TNFα inhibitors (TNFi). Induction therapy with a TNFi results in clinical remission in fewer than 50% of patients, and only about 25% of patients achieve mucosal healing. Other biologics (vedolizumab, ustekinumab) offer alternative additional treatments options for patients who fail TNFi, but response rates to these agents do not exceed those associated with TNFi treatment. Medical treatment options for fistulizing and fibrotic disease remain limited. Thus, a substantial unmet need remains for oral agents with greater efficacy than current therapies, either as a standalone therapy or in combination with existing therapies.

As described in Section 1.1, RIPK2 inhibition is postulated to blunt the dominant NOD1/2-driven inflammatory response to the microbiome in the gut, while sparing other microbial

sensing pathways to prevent broad immunosuppression. This is expected to result in reduced levels of inflammatory cells and inflammatory mediators in intestinal tissue, and improved epithelial barrier function, which is expected to lead to mucosal healing and clinical response in Crohn's disease.

This trial will be the start of the clinical development of BI 706321 in Japan and China. The objective of this trial is to investigate the safety, tolerability and PK of BI 706321 in healthy Japanese and Chinese male subjects. The chosen population is adequate to provide the basis for the clinical development program of BI 706321 in the indication of Crohn's disease in Japan/Asian countries.

## 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 a drug which might improve the therapy of patients with Crohn's disease.

Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

### 1.4.1 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for 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, as well as in feeling of light-headedness or in syncope.

The total volume of blood withdrawn per subject during the entire study will not exceed the volume of a normal blood donation (400 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

ECG electrodes may cause local and typically transient skin reactions.

### 1.4.2 Drug-related risks and safety measures

1.4.2.1 BI 706321

Specific RIPK2 inhibition is a novel mechanism of action for which there is no precedent clinical data for multiple dose administration in patients. No other RIPK2 inhibitors are currently approved that could provide information on identified risks in molecules of this class.

1.4.2.1.1 Drug-related events observed in clinical trials with BI 706321

Single and multiple doses of 0.3 – 25 mg BI 706321 were generally well tolerated by healthy subjects in the first-in-human trial 1425-0001, and the multiple rising dose trial 1425-0002. Below are the theoretical risk considerations based on literature, pre-clinical studies, and

preliminary clinical studies, as well as general safety considerations of immunomodulatory drugs.

As with all drugs, the potential for hypersensitivity and allergic reactions have to be taken into consideration when BI 706321 is administered.

1.4.2.1.2 Risk assessment in the context of SARS-CoV-2 infection

BI 706321 is an immune-modulating drug. Although no clear signal regarding increased risk of infections with BI 706321 has been observed within the non-clinical toxicology or clinical studies, impaired host defense is a theoretical target-related pharmacologic effect of selective RIPK2 inhibition. To date, there is no reliable evidence suggesting a specific link between SARS-CoV-2 infections and the pathway targeted by RIPK2 inhibition. Therefore, based on currently available evidence, there is only minimal theoretical risk that BI 706321 treatment may add undue risk of acquiring SARS-CoV-2 infections or developing more severe COVID-19 in healthy volunteers participating in BI 706321 clinical trials. The short duration of planned exposure to BI 706321 ≤21 days, supports that the risk of immune suppression caused by the administration of BI 706321 in healthy subjects would be very low.

Participation in this clinical trial will increase the risk of COVID-19 exposure due to traveling to the study site and completing the protocol-defined procedures at the study site. A risk management plan has been set up at the clinical site that details specific precautionary measures, (e.g. hygiene rules, wearing of face masks, physical distancing), screening for SARS-CoV-2, and trial drug discontinuation in subjects with COVID-19 infection.

1.4.2.1.3 Events predicted based on pharmacological properties / preclinical information

The toxicity profile of BI 706321 has been assessed in a comprehensive set of *in vitro* and *in vivo* safety pharmacology, genetic toxicology, phototoxicity, general toxicology repeat dose studies (up to 13 weeks duration in the rat and cynomolgus monkey), and embryo-fetal development studies (in rat and rabbit); for details refer to the IB [c26475781]. Exposure multiples were calculated based on the preliminary human steady state exposure of $C_{max}$ = 39.9 nM and AUC = 574 nM•h for the dose of 10 mg once daily, which is the maximum dose planned in this trial. The estimated human therapeutic dose is 3 mg once daily.

**Impaired host defense**

Based on the role of RIPK2 in the innate arm of the immune system, impaired host defense is a theoretical target-related pharmacologic effect of selective RIPK2 inhibition. (ref current IB Version section 7.6.1[c26475781]. However, the translatability between preclinical models of infection or genetic loss of function mutations and usually incomplete pharmacologic inhibition of RIPK2 kinase activity in humans is unknown. It is important to note that RIPK2 inhibition will selectively block the NOD-RIPK2 pathway, but leave the remaining innate pattern recognition receptor signalling pathways (for example (i.e.) Toll-like receptor signalling) intact.

There is no clear signal of infectious risk identified in the nonclinical general toxicity studies with BI 706321. The AE of “nasopharyngitis” was experienced by two subjects in the 1425-0001 trial on active treatment as compared with none on placebo. Five subjects in the 1425-

0002 MRD trial on active treatment with BI 706321 experienced "flu like symptoms" as compared with none on placebo. "Flu like symptoms" were considered mild-moderate in severity and were characterized by intermittent low-grade temperature elevations (maximum temperature 38.1°C), over a duration of 1-3 days. Concomitant headache and dysuria were experienced by in one subject each. Minor, transient, elevations of CRP were noted with these symptoms. All symptoms spontaneously resolved without change in BI 706321 treatment. Based on the brief and self-limited nature of the symptoms, they were considered to be of minor clinical significance.

In the SRD trial 1425-0001, one subject in the 25 mg dose group reported a brief generalized sensation of cold approximately 10 hours after dosing with associated mild transient increase in temperature (37.4°C) and CRP (35.4 mg/L [ULN: 5.0 mg/L]). In the MRD trial 1425-0002, minor transient elevations in CRP, up to a maximum value of 19.7 mg/L [ULN: 5.0 mg/L], were observed in a subset of subjects beginning after approximately 3-6 days of multiple dosing. CRP levels subsequently normalized within 48-96 hours while dosing was ongoing. Some of these subjects experienced symptoms reported as "flu like symptoms" described above, while other subjects had no such symptoms associated with these changes in CRP values. No clinically significant changes from baseline in ferritin, haptoglobin, or fibrinogen were observed. Given the minor and transient nature of these observed changes in CRP, in the absence of clinical symptoms, they were not considered clinically relevant.

*Risk mitigation:* All subjects will be closely monitored by the investigators for the emergence of clinical Adverse Events (AE) related to infection and systemic inflammation. Body temperature and CRP levels in subjects in this trial will be measured. Serum amyloid A, haptoglobin, ferritin and fibrinogen as markers of the acute phase response will also be measured.

**Cardiovascular system**

In rats, repeat dosing up to 13 weeks duration resulted in increased incidence/severity of mononuclear infiltrates. Infiltrates were associated with an increased incidence of myocardial degeneration at higher exposure levels (84X/60X Cmax and AUC respectively). The finding in rats may be a species-specific exacerbation of a common spontaneous background finding in rats. No histopathologic changes to the heart were seen in long term toxicology studies in monkeys. There is low risk for relevant cardiovascular effects to subjects at the clinically relevant short-term exposures planned in this trial. For safety margins between maximum exposure in this trial and findings in the Good Laboratory Practice (GLP) cardiovascular findings in rats refer to the current version of the IB. Studies in monkeys showed potential for prolongation of QT/QTc intervals. In the MRD trial, an exploratory analysis of central ECG data was conducted to characterise the effects of BI 706321 on QT/QTc. Based on preliminary analysis using random coefficient modelling, the predicted mean differences between BI 706321 and placebo in QTcF change from baseline at gMean of $C_{max,ss}$ were below 10 msec at all dose levels; however, they slightly exceeded 5 msec in the 8 and 10 mg dose groups. No clinically relevant individual QTcF

changes have been observed in any subject exposed to BI 706321; no relevant blood pressure or heart rate changes were noted.

*Risk mitigation:*

Subjects with relevant findings in BP, PR or ECG at Screening, cardiovascular disorders, history of relevant orthostatic hypotension, fainting spells or blackouts, use of drugs that might prolong the QT/QTc interval, marked (Section 3.3.3), or subjects with additional risk factors for Torsade de Pointes arrhythmia (Section 3.3.3) are excluded from trial participation.

- A dose escalation stopping criterion based on QT/QTc increase has been defined (Section 3.3.4.3).
- Frequent ECG and vital signs measurements during the time of expected relevant exposure (see Flow Chart).
- Subjects will be in-house at the trial site under close medical observation for the whole duration of the treatment until 48 hours after drug administration (see Flow Chart) They will only be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. If required, inhouse observation period may be prolonged.

**Gastrointestinal system**

A single dose resulted in an increased rate of gastric emptying and intestinal transit, and liquid accumulation to intestinal contents in rats. Repeat dosing resulted in soft, loose, wet, or liquid stool in rats and monkeys. Clinical events coded as diarrhea in the Phase I program were all mild in intensity and of short duration (<1-3 days).

In rats, there were increases in serum AST and ALT that did not consistently correlate with the liver infiltrates. Liver infiltrates did not progress when evaluated in a 13 week exploratory study in rats. In monkeys, there were non-adverse effects to the liver (hypertrophy of sinusoidal (Kupffer) cells) that also were not associated with increases to AST or ALT. Because of the nature of the findings these tissue changes are not considered a relevant risk in humans. No clinically significant changes in liver transaminases have been observed in completed or ongoing clinical studies with BI 706321.

*Risk mitigation:*

- AEs consistent with alterations in stool consistency will be clinically monitored.
- Subjects with liver enzymes (ALT, AST) exceeding upper limit of normal will be excluded from trial participation (Section 3.3.3).
- Liver enzymes (ALT, AST) will be measured before, during and after dosing.
- Standard drug-induced liver injury (DILI) criteria (Section 5.2.5.1.4, adverse events of special interests) are defined, and this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

**Genotoxicity, reproductive and developmental toxicity**

In vitro and in vivo genetic toxicology studies indicated that BI 706321 is free of any genotoxic potential.

Reproductive findings were only seen in the rat studies. In female rats, reversible adverse effects to the ovaries (corpora lutea degeneration) were observed in females at 6X human exposure. These are not of relevance to the exclusively male population included in this study. In male rats, there were reversible decreases in testes weights/size and seminiferous tubular degeneration/atrophy with epididymal oligospermia at very high exposures (60X human exposure). !"# $#%#&#'()*+&,()'+-"/#'# +&0.1##&(2)#' 34 /##51 +2$+1*&(&$&+) () 1"+')#' )'#()6#&) $7'()*+&18

Potential effects on embryo-fetal development were evaluated in pregnant rats and rabbits. In rats, there was embryolethality (increased post-implantation loss) and evidence of fetotoxicity (adverse effects on fetal growth) at 10 mg/kg/day, and no effects to embryo fetal development at ≤ 5 mg/kg/day. In rabbits, there were no effects to embryo-fetal development at ≤ 7 mg/kg/day. BI 706321 is not suspected of human teratogenicity or fetotoxicity at subtherapeutic systemic exposure levels, therefore, the potential risk to embryo-fetal development by male participants in clinical trials with BI 706321 as a result of vaginal or placental transfer is considered negligible.

There is low risk for reproductive effects to male subjects at the clinically relevant short-term exposures planned in this trial. For safety margins between maximum exposures in this trial and findings in the GLP reproductive findings in rats refer to the current version of the IB.

**Integumentary system**

Emerging preliminary interim in-life findings from an ongoing chronic toxicity study in cynomolgus monkeys show depigmentation of skin and hair at 18 and 19 weeks of dosing at 20 and 8 mg/kg/day, respectively. Based on exposure in the completed 13-week study in monkeys, the 8 mg/kg/day dose level in the ongoing chronic toxicity study is estimated to have achieved approximately 11X human exposure for a 10 mg daily dose.

To date, no such effects were observed in monkeys at 1 mg/kg/day (1X human exposure for a 10 mg daily dose) in the ongoing chronic toxicity study. This is a finding not previously observed in the completed 13-week toxicity study in cynomolgus monkeys at doses up to 8 mg/kg/day. As the dose administration phase of the chronic study is still ongoing, it has not yet been established if these effects are reversible. No findings of skin or hair depigmentation have been observed in the clinical studies with BI 706321, where doses of up to 10 mg daily were administered for up to 14 days. There is low risk for skin/hair depigmentation effects at the clinically relevant short-term exposures planned in this trial.

# 2. TRIAL OBJECTIVES AND ENDPOINTS

## 2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

### 2.1.1 Main objectives

Part I: The main objectives of this trial are to investigate safety, tolerability, and pharmacokinetics (PK) of BI 706321 in healthy Japanese male subjects following oral administration of multiple rising doses for 14 days.

Part II: The main objectives of this trial are to investigate safety, tolerability, and pharmacokinetics (PK) of BI 706321 in healthy Chinese male subjects following oral administration of single dose of 10 mg.

### 2.1.2 Primary endpoint

The primary endpoint for assessment of safety and tolerability of BI 706321 is the percentage of subjects with drug-related adverse events.

### 2.1.3 Secondary endpoint

The following pharmacokinetic parameters will be determined if feasible:

Part I and II

Single dose part (after the first dose):

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

Part I only

After the last dose:

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval $\tau$)
- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval $\tau$)
- $C_{min,ss}$ (minimum concentration of the analyte in plasma at steady state over a uniform dosing interval $\tau$)
- $R_{A,Cmax}$ (accumulation ratio based on $C_{max,ss}$)

- $R_{A,AUC}$ (accumulation ratio based on $AUC_{0-\tau}$)

[redacted]

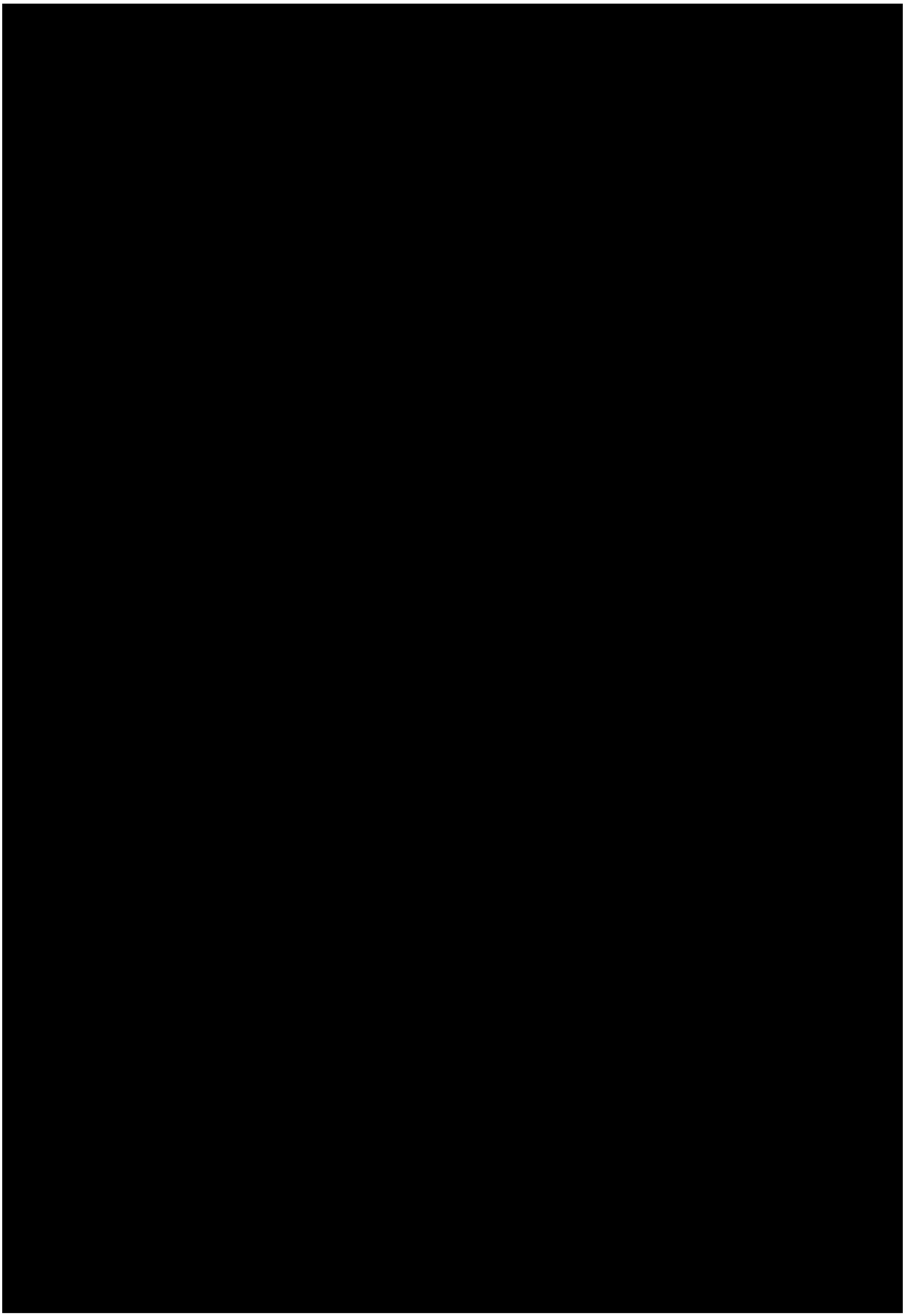
2.2.2.1 Safety and tolerability (Part I and II)

Safety and tolerability of BI 706321 will be assessed based on:

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

[redacted]

[redacted]



[redacted]

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

Part I:

This multiple-rising dose trial is designed as double-blind, randomised, and placebo-controlled within parallel dose groups.

It is planned to include a total of 48 healthy Japanese male subjects in the trial. The subjects will be assigned to 4 groups consisting of 12 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1). Within each dose group, 9 subjects will receive BI 706321 and 3 will receive placebo. Only one dose is tested within each dose group.

The trial schedule and design are depicted in Figure 3.1: 1 below.

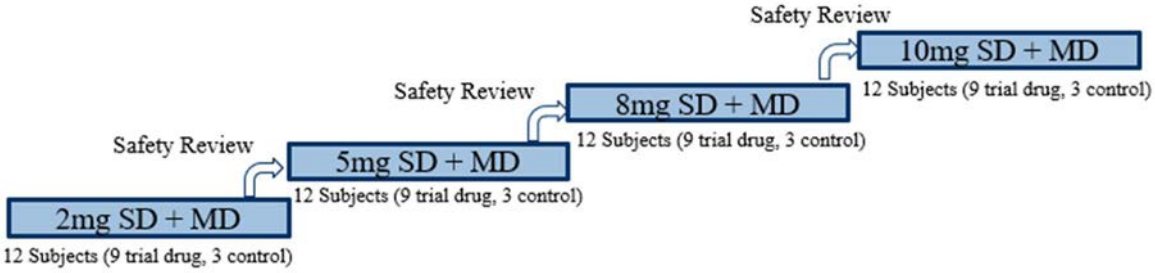



Figure 3.1: 1 Trial design "Part I"

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups

| Dose Group | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Daily dose (mg) | 2 | 5 | 8 | 10 |
| Number of subjects | 12 | 12 | 12 | 12 |
| Subjects receiving placebo | 3 | 3 | 3 | 3 |
| Subjects receiving BI 706321 | 9 | 9 | 9 | 9 |

The groups will be dosed consecutively in ascending order, and a time interval of at least 7 days will be maintained between the last drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose group will be based upon safety and tolerability data of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the investigator, no safety concerns have arisen in the preceding dose groups (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.3).

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime by the Principal Investigator (or an authorised deputy) or the sponsor of the study (for instance, due to the occurrence of any unforeseen adverse events).

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.3).

At minimum, data from 7 subjects on active drug need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 48 h post dosing, including clinically relevant findings from ancillary safety testing listed below (Note: AEs may be ongoing at the time of Safety Reviews and AE information may be subject to change prior to Database Lock)
- Results from 12-lead ECG in the current and preceding dose groups up to at least 48-hour post dosing
- Vital signs in the current and preceding dose groups up to at least 48-hour post dosing
- Clinical laboratory tests in the current and preceding dose groups up to at least 48-ho ur post dosing
- Check of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator (or an authorised deputy) and the Clinical Trial Leader (CTL) (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs, and out-of-range laboratory results (if considered clinically significant). In addition and depending on the results and findings, suitable experts from the sponsor or external institutions may be consulted on an as needed basis. In these cases, expert recommendations will be documented in the minutes of the Safety Review and considered for the decision making. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy) nor the Clinical Trial Leader (or an authorised deputy).

Safety Reviews can be conducted face-to-face or by video/telephone conference. The Clinical Trial Leader is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and Clinical Trial Leader (or an authorised deputy), and will be filed in the ISF and TMF.

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

Part II:

This single dose trial is designed as double-blind, randomised, and placebo-controlled

It is planned to include a total of 12 healthy Chinese male subjects in the trial. 9 subjects will receive BI 706321 and 3 will receive placebo. Only 10 mg dose is tested.

The trial schedule and design are depicted in Figure 3.1: 2 below.

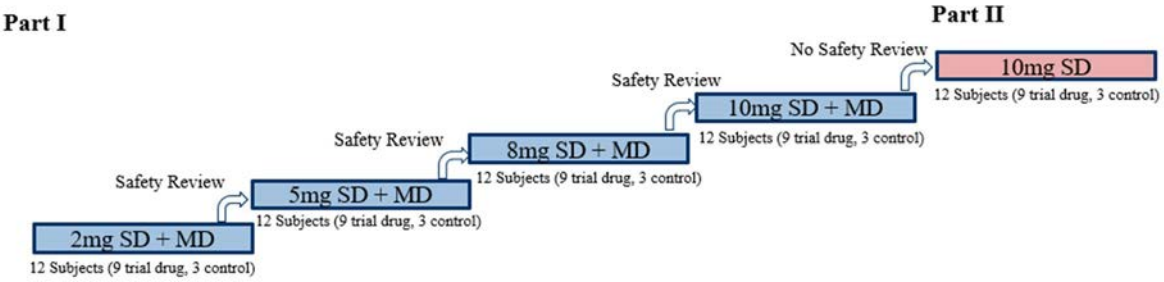



Figure 3.1: 2 Trial design "Part I and II"

The group will be dosed only after all dose groups in Part I have been completed and if, in the opinion of the investigator, no safety concerns have arisen in the preceding dose groups in Part I (i.e. no dose-limiting events occurred), and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.3).

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

Part I:

For multiple-rising dose trials, the sequential rising dose design described in section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks.

Double-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of drug administered. The disadvantage of the trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in multiple rising dose trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication. Each dose group consists of 12 subjects, with 9 on active treatment, and 3 on placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of safety, tolerability and pharmacokinetics.

After the first dose (single dose part), a sufficient wash-out period will be included before the second dose (first dose of the multiple dose part) is administered. This will allow for appropriate calculation of pharmacokinetic parameters after a single dose administration and for comparison with pharmacokinetic parameters at steady state.

Part II:

For single dose trial, the dose designed described in section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks.

Double-blind conditions regarding the subject's treatment (active or placebo) are maintained within the dose group. However, subjects and investigators will be aware of the dose of drug administered.

It is standard in single dose trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication. The dose group consists of 12 subjects, with 9 on active treatment, and 3 on placebo. For data analysis purposes, the placebo control group will include all subjects of all dose groups treated with placebo. Nine subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of safety, tolerability, and pharmacokinetics.

## 3.3 SELECTION OF TRIAL POPULATION

Part I:

It is planned that *48 healthy* Japanese male subjects will enter the study. *Subjects will be recruited from the volunteers' pool of the trial site.*

Part II:

It is planned that *12 healthy* Chinese male subjects will enter the study. *Subjects will be recruited from the volunteers' pool of the trial site.*

Only male subjects will be included in the trial*.

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

* Only male subjects will be enrolled in the study as standard for phase I trials in Japan. Although the pre-clinical data for BI 706321 does not mandate contraception requirements for males, these will be maintained for this study as part of standard precautions for phase I trials in Japan.

### 3.3.1 Main diagnosis for trial entry

The study will be performed in healthy subjects.

### 3.3.2 Inclusion 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 (blood pressure [BP], PR including body temperature, 12-lead ECG, and clinical laboratory tests at screening visit
2. Part I:
   Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years,

- have parents and grandparents who are Japanese

Part II:

Chinese ethnicity including Taiwanese, according to the following criteria:

- have parents and grandparents who are Chinese

3. Age of 20 to 45 years (inclusive) at screening visit
4. Body mass index (BMI) of 18.5 to 25.0kg/$m^2$ (inclusive) at screening visit
5. Signed and dated written informed consent prior to admission to the study, in accordance with Good Clinical Practice (GCP) and local legislation
6. Willingness to comply with contraception requirements. Subjects who are sexually active must use adequate contraception methods throughout the trial and until three months after the last administration of trial medication. Adequate methods are:
   - A vasectomy performed at least 1 year prior to screening and with medical assessment of the surgical success or
   - Surgical sterilisation, including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy, of the subject's female partner or
   - The use of condoms, if the female partner uses an adequate contraception method in addition, e.g., intrauterine device (IUD), or hormonal contraception, such as implants and injectables*, combined with oral or vaginal contraceptives, that started at least 2 months prior to first drug administration, or barrier method, e.g., diaphragm with spermicide*

   * hormonal contraception via implants and injectables, and diaphragm with spermicide are not approved in Japan

   Unprotected sexual intercourse with a pregnant partner is not allowed throughout the trial and until three months after the last administration of trial medication.

### 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, body temperature or ECG) deviating from normal and assessed as clinically relevant by the investigator at screening visit
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 40 to 90 mmHg, or pulse rate outside the range of 40 to 99 bpm at screening visit
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance at screening visit
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, per investigator judgement
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)
12. Intake of an investigational drug in another clinical trial within 30 days (or 5 half-lives (whichever longer)) 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. Alcohol abuse (consumption of more than 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 400 mL within 12 weeks or 200mL within 30 days or plasma donation within 2 weeks prior to administration or intended blood donation during the trial.
18. Intention to perform excessive physical activities within one week 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 prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening visit
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
23. ALT (alanine transaminase) or AST exceed upper limit of normal range at screening visit, confirmed by a repeat test
24. Hb <13.0 mg/dL and platelets and neutrophils below lower limit of normal range at screening, confirmed by a repeat test
25. Positive result for HIV, HBV, HCV, and Syphilis infection at screening.
26. History of Tuberculosis (TB) or positive finding in IGRA.
27. A positive test result for SARS-CoV-2/COVID-19 (nucleic acid amplification methods) or clinical symptoms suggestive for this disease at the test prior to admission to trial site (i.e. Day -3 to Day -1).

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') ; please see sections 3.3.4.1 and 3.3.4.2 below.

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

withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, 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 1.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

Since the risks of drug exposure of a pregnant partner of a study participant via the seminal fluid are yet unknown, adequate contraception as outlined in Section 3.3.2, is a prerequisite for participation in the study and is still necessary even if the subject withdraws consent or is removed from the trial.

#### 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 participate this trial for medical reasons (such as surgery, adverse events [AEs], or diseases)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of:
    - sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg),
    - clinically relevant changes in ECG requiring intervention,
    - moderate to severe acute infection,
    - fever lasting longer than 24 hours, or
    - unexplained clinically relevant hepatic enzyme or CRP elevation, or decrease in red blood cell count, reticulocytes, or thrombocytes at any time during the trial. These respective laboratory tests need to be closely monitored and drug administration continued only if in the opinion of the investigator it is safe to do so.
6. The subject has an elevation of AST and/or ALT ≥3-fold upper limit of normal (ULN) and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

Even if the treatment is discontinued, the subject remains in the trial and, given his 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
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment.
3. Violation of GCP, or the clinical trial protocol (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
5. Dose escalation will be stopped if at least 2 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording

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

If 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. 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

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

### 4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

**BI 706321 Film-coated tablet 1 mg**

| | |
|---|---|
| Substance: | BI 706321 |
| Pharmaceutical formulation: | Film-coated tablets |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 1mg |
| Posology: | 1(1mg) +1(2mg) +1(5mg)-0-0 (DG3) |
| Route of administration: | oral |
| Duration of use: | Part I only<br>1 day single dose and 14 days q.d. dosing |

**BI 706321 Film-coated tablet 2 mg**

| | |
|---|---|
| Substance: | BI 706321 |
| Pharmaceutical formulation: | Film-coated tablets |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 2mg |
| Posology: | 1-0-0 (DG1), 1(1mg) +1(2mg) +1(5mg)-0-0 (DG3) |
| Route of administration: | oral |
| Duration of use: | Part I only<br>1 day single dose and 14 days q.d. dosing |

**BI 706321 Film-coated tablet 5 mg**

| | |
|---|---|
| Substance: | BI 706321 |
| Pharmaceutical formulation: | Film-coated tablets |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 5mg |
| Posology: | 1-0-0 (DG2), 1(1mg) +1(2mg) +1(5mg)-0-0 (DG3),<br>2-0-0 (DG4 and DG5) |

| | |
|---|---|
| Route of administration: | oral |
| Duration of use: | Part I<br>1 day single dose and 14 days q.d. dosing<br>Part II<br>1 day single dose |

The characteristics of the reference product (placebo) are given below:

| | |
|---|---|
| Substance: | Matching placebo in size and weight to 1mg, 2mg, and 5 mg tablet |
| Pharmaceutical formulation: | Film-coated tablet |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | -- |
| Posology: | Matching to the test product |
| Route of administration: | oral |
| Duration of use: | Part I<br>1 day single dose and 14 days q.d. dosing<br>Part II<br>1 day single dose |

### 4.1.2 Selection of doses in the trial

Oral doses in range of 2 mg to 10 mg have been selected in order to assess the safety and tolerability of BI 706321 in healthy male volunteers and investigate the PK of this RIPK2 inhibitor. The doses selected for this trial cover the estimated therapeutic range and expect not to exceed the safety margin (see Sections 1.2, 1.4).

### 4.1.3 Method of assigning subjects to treatment groups

Part I:

Prior to the screening visit, subjects will be informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to 1 of the 4 dose cohorts, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects'

temporal availability. Because the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomisation list will be allocated to subjects. Subjects are then assigned to treatment according to the randomisation list.

Part II:

Prior to the screening visit, subjects will be informed about the planned visit dates. The subjects willing to participate will be recruited to the dose groups according to their temporal availability. Depending on the availability of the site, the Part II will be split into 2 groups. In case 2 groups are required, as soon as enough subjects are allocated to 1 of the 2 groups, the following subjects will be allocated to the other group.

Subjects will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Numbers of the randomisation list will be allocated to subjects. Subjects are then assigned to treatment according to the randomisation list.

The randomisation procedure is described in Section 7.6.

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

Part I:

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the corresponding dose level.

Table 4.1.4: 1 BI 706321 and placebo treatments, oral administration

| Dose group | Substance | Pharmaceutical form | Unit strength | Number of units per administration | Total dose |
|---|---|---|---|---|---|
| 1 | BI 706321 | Film-coated tablet | 2 mg | 1 tablet | 2 mg |
| 2 | BI 706321 | Film-coated tablet | 5 mg | 1 tablet | 5 mg |
| 3 | BI 706321 | Film-coated tablet | 1 mg<br>2 mg<br>5 mg | 1 tablet each | 8 mg |
| 4 | BI 706321 | Film-coated tablet | 5 mg | 2 tablets | 10 mg |
| 1-4 | Placebo* | Film-coated tablet | -- | identical to active treatment | -- |

* Subjects receiving placebo are equally distributed across dose groups

The trial will be divided into two parts (single dose and multiple dose). During the single dose part (Days 1 to 6), subjects will receive one single dose of BI 706321 (or placebo) on Day 1. The multiple dose part starts on Day 6 and subjects will receive a dose of 2 to 10 mg of BI 706321 (or placebo) once daily for 14 days (Days 6 to 19).

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 standing/sitting position. During the first 4 h after drug administration for the single dose part, 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 to sleep. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, 1 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. To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

Subjects will be kept under close medical surveillance from the morning of Day -1 to the morning of Day 3 and again from the evening of Day 5 to the morning of Day 21 for all dose groups. During the first 2 h after drug administration for the multiple dose part, 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 to sleep.

Part II:

The treatments to be evaluated are outlined in Table 4.1.4: 2 below. The number of units for placebo corresponds to the number of units of the corresponding dose level.

Table 4.1.4: 2 BI 706321 and placebo treatments, oral administration

| Dose group | Substance | Pharmaceutical form | Unit strength | Number of units per administration | Total dose |
|---|---|---|---|---|---|
| 5 | BI 706321 | Film-coated tablet | 5 mg | 2 tablets | 10 mg |
| 5 | Placebo* | Film-coated tablet | -- | identical to active treatment | -- |

* Subjects receiving placebo are equally distributed across dose groups

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 standing/sitting position. During the first 4 h after drug administration for the single dose part, 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 to sleep. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, 1 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. To ensure a dosing interval of 24 h, the administration of trial medication should take place at the same time every day.

Subjects will be kept under close medical surveillance from the morning of Day -1 to the morning of Day 3.

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

The trial is designed double-blind. The treatments administered (active or placebo) will be blinded to the subjects and the investigators (outcome assessors) in order to limit the occurrence of any bias which the knowledge of treatment may have.

Regarding the sponsor, all trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including Clinical Trial Leader, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated contract research organization (CRO) personnel). The objective of the trial is not expected to be affected.

The randomization schedule will be access controlled until the randomization has completed.

The trial site will only be unblinded after locking of the database.

Within the central ECG lab, the staff involved with interval measurements and assessments will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the trial.

If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unblinded. This part of the staff will be strictly separated from the blinded staff members who are involved with ECG interval measurements and assessments of ECGs.

#### 4.1.5.2 Unblinding and breaking the code

The investigator or designee will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for breaking the code must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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

The investigational medicinal products will be provided by BI. They 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. Examples of the labels will be available in the ISF.

No re-supply is planned.

### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area 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

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory 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 trial 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.

4.2.2.2 Restrictions on diet and life style

Part I:

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 the drug intake at Days 1, 12, 19. On all other dosing days, food is not allowed 10 hour before and approx. 1 hour after drug intake. On all non intensive PK study days standard meals (light breakfast, lunch, dinner) will be served approx. 1, 4 and 10 hours after drug administration, and 200 mL of fluid will be served to the light breakfast on all non-intensive PK days.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Day 1, 12, 19 at 2 h and 4 h post-dose (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Alcoholic beverages, 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) are not allowed from day -1 for the whole duration of the trial.

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 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

Part II:

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 the drug intake at Day 1.

From 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, and an additional 240 mL of water served on Day1 and 2 h and 4 h post-dose (mandatory for all subjects).

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

Alcoholic beverages, 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) are not allowed from day -1 for the whole duration of the trial.

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 7 days before the first administration of trial medication until the end of trial examination.

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

## 4.3 TREATMENT COMPLIANCE

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

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

# 5. ASSESSMENTS

## 5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

## 5.2 ASSESSMENT OF SAFETY

### 5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history (results not mandatory to be entered into CRF), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body temperature), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of 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 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. Body temperature will be measured at the time points indicated in the Flow Chart using electronic thermometers.

### 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 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required. 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 will be performed if automatic differential WBC is abnormal as per investigator’s judgement

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 as per investigator's judgement) | Neut. Poly (segs)/ Leukocytes; Neutrophils Bands/ Leukocytes; Eosinophils/ Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/Leukocytes | X | X | X |
| Coagulation | Activated Partial Thromboplastin Time | X | X | |
| | Prothrombin time – INR (International Normalization Ratio) | X | X | |
| | Fibrinogen | 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 |
| | Creatine Kinase [CK] | X | X | X |
| | Creatine Kinase Isoenzyme MB [only if CK is elevated] | | | |
| | Lactic Dehydrogenase | X | X | X |
| | Lipase | X | | |
| | Amylase | X | | |
| Hormones | Thyroid Stimulating Hormone | X | | |

Part I

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day -1, 6, 12, 20 and 27 (for time points refer to Flow Chart)
C: parameters to be determined on Days 2, 8, 10, 14, 16, 18 and 22 (for time points refer to Flow Chart)

Part II

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day -1, 6 and 15 to 22 (for time points refer to Flow Chart)
C: parameters to be determined on Days 2 and 8 (for time points refer to Flow Chart)

Table 5.2.3: 1 Routine laboratory tests (cont.)

| Functional lab group | BI test name [comment/abbreviation] | A | B | C |
|---|---|---|---|---|
| Substrates | Glucose (Plasma) | X | X | X |
| | Creatinine | X | X | X |
| | Bilirubin, Total | X | X | X |
| | Bilirubin, Direct | X | X | X |
| | Protein, Total | X | X | X |
| | Albumin (protein electrophoresis) | X | X | |
| | Alpha-1-globulin (protein electrophoresis) | X | X | |
| | Alpha-2-globulin (protein electrophoresis) | X | X | |
| | Beta-globulin (protein electrophoresis) | X | X | |
| | Gamma-globulin (protein electrophoresis) | X | X | |
| | C-Reactive Protein (Quant) | X | X | X |
| | Uric Acid | X | X | X |
| | Cholesterol, total | X | X | X |
| | Triglyceride | X | X | X |
| | Haptoglobin | X | X | |
| | Ferritin | X | X | |
| | Serum Amyloid A Protein | X | X | X |
| Electrolytes | Sodium | X | X | X |
| | Potassium | X | X | X |
| | Calcium | X | X | X |
| | Phosphate (as Phosphorus, Inorganic) | X | X | X |
| | Blood Urea Nitrogen | X | X | X |
| | Chloride | X | X | X |
| | Magnesium | X | X | X |
| Urinalysis[1] (Stix) | Urine Nitrite (qual) | X | X | |
| | Urine Protein (qual) | X | X | |
| | Urine Glucose (qual) | X | X | |
| | Urine Ketone (qual) | X | X | |
| | Urobilinogen (qual) | X | X | |
| | Urine Bilirubin (qual) | X | X | |
| | Urine RBC/Erythrocytes (qual) | X | X | |
| | Urine WBC/Leucocytes (qual) | X | X | |
| | Urine pH | X | X | |
| Urine sediment[1] (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) | X | X | |

Part I

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day -1, 6, 12, 20 and 27 (for time points refer to Flow Chart)
C: parameters to be determined on Days 2, 8, 10, 14, 16, 18 and 22 (for time points refer to Flow Chart)

Part II

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined on Day -1 and 6 and 15 to 22 (for time points refer to Flow Chart)
C: parameters to be determined on Days 2 and 8 (for time points refer to Flow Chart)

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

Table 5.2.3: 2 Exclusionary laboratory tests

| Functional lab group | Test name |
|---|---|
| Drug screening (urine) | Amphetamine/MDA<br>Barbiturates<br>Benzodiazepine<br>Cannabis<br>Cocaine<br>Methadone<br>Methamphetamines/MDMA/Ecstasy (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 antigen-antibodies (qualitative)<br>TB test (IGRA: QuantiFERON® Gold assay/T-SPOT®.TB)<br>Syphilis test (RPR, TP antibody method) |
| COVID 19 infection[1] | SARS-COV-2/ COVID-19 test (nucleic acid amplification methods) |

[1] will be performed shortly (within 72 hours) before admission to the site as per Flow Chart

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to treatment period and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site or/and at a clinical research organization (CRO) designated by the trial site. Laboratory data will be transmitted electronically from the site to BI.

### 5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor's database.

Storing

All ECGs will be stored electronically in the System provided by a designated central ECG lab.

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation

a) Central ECG lab

Central ECG lab evaluation will be performed for all time points with triplicate ECGs. For some time points, as indicated in the Flow Chart, three triplicate ECGs are recorded (i.e. on days 1 and 19 in Part I and on day 1 in Part II). Always, only the first single ECG per triplicate will be evaluated. This will include the determination of cardiac QRS-axis, as assessed by the ECG machine's algorithm, as well as the intervals RR, PR, QRS and QT measured semi-automatically.

The remaining second and third ECGs of the triplicate ECGs will be stored for additional analysis if required, e.g., by authorities at a later time point.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see trial statistical analysis plan (TSAP) for details).

All semi-automatic interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

For automatic interval measurements no lead will be provided. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

For blinding arrangements see Section 4.1.5. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular subject should be evaluated by a single reader. For quality assurance and control of the measurements, all ECG of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false subject assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologists assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site

All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF values generated by the computerised ECG system or their manual corrections by the investigators will be used.
In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

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

### 5.2.5 Assessment of adverse events

#### 5.2.5.1 Definitions of adverse events

##### 5.2.5.1.1 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.

##### 5.2.5.1.2 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

An AE that possibly leads to disability will be 'deemed serious for any other reason' and reported as an SAE.

5.2.5.1.3 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 5.2.5.2, 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 electronic data capture (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.

5.2.5.1.4 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 5.2.5.2.2.

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - o An elevation of AST (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
  - o Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.5.1.5 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 |

5.2.5.1.6 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

5.2.5.2 Adverse event collection and reporting

5.2.5.2.1 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(s) by the investigator:

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

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information.

5.2.5.2.3 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 assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.5.2.4 Pregnancy

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

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

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

### 5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis of BI 706321 and BI 706062

For quantification of BI 706321 and BI 706062 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into an $K_2$-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at approximately 4 to 8 °C. Two plasma aliquots for each analyte will be obtained and stored in polypropylene tubes. The first aliquot for each analyte should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed in less than 60 min, with interim storage of blood samples in ice water or on ice. The time each aliquot was placed in the freezer will be documented.

Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -70°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -70°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided.

After analysis, the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations.

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

5.3.2.2 Urine sampling for pharmacokinetic analysis of BI 706321

A blank urine sample will be collected before administration of trial medication (within 3 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in polyethylene (PE) or polypropylene (PP) containers and stored at room temperature or in a refrigerator. Subjects are told to empty their bladders at the end of each sampling interval.

To avoid adsorption of the drug (its metabolites) to the container wall, suitable amount of 10% Tween 20 solution will be added to each collection container prior to the start of urine sampling. Details will be specified in the lab manual. The weight of the empty container will be determined, 10% Tween 20 will be added, and the weight of the container at the end of each sampling interval will be determined.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done; i.e., 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurements. If more than one collection container is used in a sampling interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device made of PE, PP, Teflon, or glass). Generally, the collection container should be shaken upon addition of every urine fraction to ensure proper distribution of Tween and Urine.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, and planned collection time. Further information, such as matrix and analyte may also be provided.

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

After analysis, the samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations.

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

### 5.6 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 and pharmacodynamic 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 5.4 are generally used assessments of drug exposure.

## 6. INVESTIGATION PLAN

### 6.1 VISIT SCHEDULE

Part I:

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

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

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on Day 1, ± 60 min on Day 2 (except for urinalysis which can performed between wake-up time to the scheduled time), and ± 120 min from 48 h post administration onwards.

The tolerance for drug administration will be ± 1 min on Days 1, 12, 19 and ± 10 min on all other treatment days.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times and urine 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.

Part II:

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

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

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on Day 1, ± 60 min on Day 2 (except for urinalysis which can performed between wake-up time to the scheduled time), and ± 120 min from 48 h post administration onwards.

The tolerance for drug administration will be ± 1 min on Days 1.

If several activities are scheduled at the same time point in the Flow Chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times and urine 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

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 5.2.3 to 5.2.4.

### 6.2.2 Treatment period

Part I:

Each subject will receive a single dose of BI 706321 or placebo on Day 1 and then daily multiple daily doses of BI 706321 or placebo for 14 days from Day 6 onwards.

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

All subjects will be admitted to the trial site on Day -1 and kept under close medical surveillance until Day 27.

For details on time points and procedures for collection of plasma and urine 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.

Part II:

Each subject will receive a single dose of BI 706321 or placebo on Day 1.

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

All subjects will be admitted to the trial site on Day -1 and kept under close medical surveillance for at least 168 h following the last drug administration.

For details on time points and procedures for collection of plasma and urine 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 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

If a subject discontinues from the trial, the subject will be followed until the investigator or sub-investigator is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subject stops attending trial assessments, the investigator should assess the subject's status as comprehensively as possible and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he cannot be compelled.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial will be assessed by calculating descriptive statistics for safety and tolerability, as well as for PK parameters, which will be compared between the treatment groups (active treatment to placebo). [redacted]

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

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

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the study; i.e., confidence intervals are considered as interval estimates for effects.

## 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 randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. 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 not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the DV domain, 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 2.1.3 and 2.2 for drug BI 706321 and BI 706062 will be calculated according to BI Standards.

Plasma and urine 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 violation 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 violations 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

- The subject experienced emesis that occurred at or before two times median $t_{max}$ of the respective treatment (Median $t_{max}$ is to be determined excluding the subjects experiencing emesis),
- 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.

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 as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

### 7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature.

### 7.3.2 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively. Analyses will be performed for BI 706321.

[redacted]

[redacted]

[redacted]

### 7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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. The placebo group in the safety evaluation will consist of all subjects treated with placebo, regardless of the dose group in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between the first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to 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 database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study 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 5.2.5.1) 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 possibly clinically significant values 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.

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

For QTcF and HR changes from baseline, the relationship to the corresponding plasma concentrations (if applicable both for BI 706321 and BI 7060602) will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug plasma concentrations will be included.

[redacted]

## 7.4 INTERIM ANALYSES

A preliminary analysis of PK parameters ($AUC_{0-24}$ and $C_{max}$ of BI 706321) provided as individual values and geometric means of the first 3 cohorts in Part I may be performed.

In contrast to the final PK/[redacted] calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration/effect-time profiles and summary statistics of individual values without subject identification information. The preliminary results will be distributed to the investigator and the trial team.

Depending on the results of available preliminary PK/[redacted] analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses),) and additional PK/[redacted] preliminary analysis may be performed if requested by the Clinical Trial Leader, the investigator, or Trial Clinical Pharmacokineticist. Preliminary PK/[redacted] results will not be reported in the CTR.

No inferential statistical 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.

Subjects who are not included in the PKS will be reported with their individual plasma/ urine concentrations and individual PK parameters. However, they will not be included in descriptive statistics for plasma/ urine concentrations, PK parameters or other statistical assessment.

## 7.6 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo).

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

## 7.7 DETERMINATION OF SAMPLE SIZE

Part I:
It is planned to include a total of 48 subjects in this trial. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group (9 on active treatment, and 3 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 48, but will not exceed 72 subjects entered.

Part II:
It is planned to include a total of 12 subjects in this trial. The planned sample size is not based on a power calculation. The size of 12 subjects (9 on active treatment, and 3 on placebo) is commonly used in single dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

Additional subjects may be entered to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of subjects entered may exceed 12, but will not exceed 36 subjects entered.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) 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. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

The certificate 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 responsible 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 investigator or delegate must give a full explanation to trial subjects based on the subject information form. A language understandable to the subject should be chosen and technical terms and expressions avoided, if possible.

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 (IQRMP) documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

## 8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. 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 (CRA), auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

### 8.3.3 Storage period of records

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

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

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

## 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.

## 8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first subject in the whole trial signs informed consent.

The **end of the trial** is defined as the 'date of the last visit of the last subject in 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.

When the trial is completed, the investigator should inform the head of the trial site in writing of the completion of the trial, and the head of the trial site should promptly inform the IRB and sponsor in writing of the completion.

## 8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial

- Ensure appropriate training and information of Clinical Trial Manager (CTM), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

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

Analyses of BI 706321 concentrations in plasma and urine will be performed at BI or CRO appointed by BI according to BI SOPs.

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation for evaluation.

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

Data management and statistical evaluation will be done by BI or CRO appointed by BI according to BI SOPs.

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

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005)

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R16-0366 E14 Implementation Working Group
ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2016) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015)

## 9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c26475781 Investigator's Brochure BI 706321 Crohn's Disease. Current version.

# 10. APPENDICES

## 10.1 SARS-COV-2/ COVID-19 RELATED MEASURES AT THE STUDY SITE

### Introduction

Due to the SARS-CoV-2/ COVID-19 pandemic outbreak early 2020 additional measures were implemented to protect study participants and personnel involved in clinical trials. This document summarizes these measures.

### Screening

The following measures will be performed:

(1) A test for SARS-CoV-2/ COVID-19 (nucleic acid amplification methods), as offered by the trial site, will be performed at once prior to admission to trial site during the period from Day -3 to Day -1

(2) Evaluation of subjects before admission to the centre:
- Temperature assessment
- Subjects are interviewed about the recent behaviours in relation to the prevention of COVID-19 infections (e.g., to avoid crowded places, to wear masks)

### Trial Conduct

Site-specific Measures

The following site specific measures will be adhered to during the conduct of the trial:

(1) Requirement that everyone (staff/subjects/visitors) wear masks

(2) Daily evaluation for centre staff (at beginning of shift):
- Temperature assessment
- Self-assessment and disclosure of any symptoms

(3) Ongoing evaluation of subjects during their stay in the unit

(4) Separation of subjects in the centre:
- Food is taken in a room where each table is separated by a partition
- Until further note: visitors for subjects are not allowed

(5) Mandatory: SARS-CoV-2/ COVID-19 test in case of suspicion of infection and at the end of trial visit

(6) General measures in place include: entry checks for monitors, CRO visitors; minimization of Face-to-Face meetings; hygiene and social distancing measures

Documentation of Adverse Events

SARS-CoV-2/ COVID-19 related adverse events will be documented as follows:

(1) Continue regular AE and SAE documentation, there is no change in the requirements of what to document and how.

(2) If a patient experiences a SARS-CoV-2/ COVID-19 Virus infection, this will be entered as (S)AE (even if the subject did not experience symptoms).

(3) AE Start Date: The day when the subject experienced SARS-CoV-2/ COVID-19 symptoms or the day of the positive test should be entered as AE start date, whichever occurred first.

(4) AE End Date: The date of the last available negative test should be entered as AE end date. If the negative test date is not available, the date by when the subject has been received notice to be virus free should be used.

For any AE related to SARS-CoV-2/ COVID-19, standard processes should be followed, meaning:

(1) If a SARS-CoV-2/ COVID-19 virus Infection is associated with clinical symptoms (AE´s):

- Report as a non-serious AE, if the serious criteria are not met
- Report as a SAE, if serious criteria are met – e.g., hospitalization, serious for medical reasons, or AE term describing the clinical symptoms is on the “always serious list”
- The mere fact that someone is infected with the SARS-CoV-2/ COVID-19 should not lead to a judgement of seriousness
- Thus, no adaptation to standard procedures, CTPs or CRFs is required

(2) If a SARS-CoV-2/ COVID-19 virus or any other infection is not associated with clinical symptoms, meaning there is just a positive SARS-CoV-2/COVID-19 test:

- The recommendation would be to consistently capture as a (non-serious) AE, as a positive Corona test means a patient has an infection
- This also would not require any adaptation to standard processes, CTP or CRF

Here are some examples from other events to illustrate the standard process:

(1) Event of Pneumonia

- Pneumonia is not on the always serious list, from that perspective it is not serious AE
- However, if the patient is hospitalized with acute hypoxaemic respiratory failure due to SARS-CoV-2/ COVID-19 virus, then it certainly qualifies for a serious AE

(2) Event of Viral Infection

- Viral infection treated as an out-patient or day-care is an AE (irrespective of SARS-CoV-2/ COVID-19 positive, negative or unknown)
- Viral infection treated with hospitalization is a SAE (irrespective of SARS-CoV-2/ COVID-19 positive, negative or unknown)

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

## 11.1 GLOBAL AMENDMENT 1

| | | |
|---|---|---|
| **Date of amendment** | | 12 Oct 2021 |
| **BI Trial number** | | 1425-0008 |
| **BI Investigational Medicinal Product(s)** | | BI 706321 |
| **Title of protocol** | | Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design) |
| | | |
| **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** | | CLINICAL TRIAL PROTOCOL SYNOPSIS |
| **Description of change** | | Main criteria for inclusion<br>From:<br>(…)<br>Part II: Healthy Chinese male subjects, age of <u>18</u> to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m (inclusive)<br>(…)<br><br>To:<br>Part II: Healthy Chinese male subjects, age of <u>20</u> to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m (inclusive)<br>(…) |
| **Rationale for change** | | To be consistent with the Japanese regulations |
| | | |
| **Section to be changed** | | FLOW CHART |
| **Description of change** | | Ambulatory visit from Day 22 and Day 26 for Part I were deleted as all subjects in Part I will be hospitalized until End of trial (EoTrial) |
| **Rationale for change** | | To clarify the visit requirements |

| | | |
|---|---|---|
| **Section to be changed** | | Section 1.4.2.1.3 |
| **Description of change** | | The following descriptions were added at the end of the section:<br><br>**<u>Integumentary system</u>**<br><br><u>Emerging preliminary interim in-life findings from an ongoing chronic toxicity study in cynomolgus monkeys show depigmentation of skin and hair at 18 and 19 weeks of dosing at 20 and 8 mg/kg/day, respectively. Based on exposure in the completed 13-week study in monkeys, the 8 mg/kg/day dose level in the ongoing chronic toxicity study is estimated to have achieved approximately 11X human exposure for a 10 mg daily dose.</u><br><br><u>To date, no such effects were observed in monkeys at 1 mg/kg/day (1X human exposure for a 10 mg daily dose) in the ongoing chronic toxicity study. This is a finding not previously observed in the completed 13-week toxicity study in cynomolgus monkeys at doses up to 8 mg/kg/day. As the dose administration phase of the chronic study is still ongoing, it has not yet been established if these effects are reversible. No findings of skin or hair depigmentation have been observed in the clinical studies with BI 706321, where doses of up to 10 mg daily were administered for up to 14 days. There is low risk for skin/hair depigmentation effects at the clinically relevant short-term exposures planned in this trial.</u> |
| **Rationale for change** | | To add emerging preliminary toxicology findings |
| | | |
| **Section to be changed** | | Section 3.3.2 |
| **Description of change** | | From:<br>(…)<br>3. <u>Part I:</u><br><u>Age of 20 to 45 years (inclusive) at screening visit</u><br><u>Part II:</u><br><u>Age of 18 to 45 years (inclusive) at screening visit</u><br>(…)<br><br>To:<br>(…) |

| | | |
|---|---|---|
| | | 3. Age of 20 to 45 years (inclusive) at screening visit<br>(…) |
| **Rationale for change** | | To be consistent with the Japanese regulations |
| | | |
| **Section to be changed** | | Section 6.2.2 |
| **Description of change** | | From:<br>(…)<br>All subjects will be admitted to the trial site on Day -1 and kept under close medical surveillance for at least 48 h following the last drug administration. On all other study days, subjects will be treated in an ambulatory fashion.<br>(…)<br><br>To:<br>(…)<br>All subjects will be admitted to the trial site on Day -1 and kept under close medical surveillance until Day 27.<br>(…) |
| **Rationale for change** | | To clarify the visit requirements |
| | | |
| **Section to be changed** | | All Sections |
| **Description of change** | | Some typos corrected and descriptions updated to provide more clarification |
| **Rationale for change** | | Description adjustment |

## 11.2 GLOBAL AMENDMENT 2

| | | |
|---|---|---|
| **Date of amendment** | | 10 Dec 2021 |
| **BI Trial number** | | 1425-0008 |
| **BI Investigational Medicinal Product(s)** | | BI 706321 |
| **Title of protocol** | | Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design) |
| | | |
| **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** | | FLOW CHART |
| **Description of change** | | The duration of Visit 1 (Screening) was changed from "-28 to -3" to "-28 to -1" for both Part I and Part II |
| **Rationale for change** | | To clarify the requirements for safety laboratory test during screening period |
| | | |
| **Section to be changed** | | FLOW CHART |
| **Description of change** | | The following description was added at the end of footnote in Part I:<br><br>14. Safety laboratory to be taken and to be medically evaluated within 3 days prior to administration of study drug; this repeat safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1. |
| **Rationale for change** | | To clarify the requirements for safety laboratory test during screening period |
| | | |
| **Section to be changed** | | FLOW CHART |
| **Description of change** | | The following description was added at the end of footnote in Part II:<br><br>13. Safety laboratory to be taken and to be |

| | | |
|---|---|---|
| | | medically evaluated within 3 days prior to administration of study drug; this repeat safety laboratory can be omitted, if the screening examination is performed on Days -3, -2 or -1. |
| **Rationale for change** | | To clarify the requirements for safety laboratory test during screening period |
| | | |
| **Section to be changed** | | Section 3.3.3 |
| **Description of change** | | From:<br>(…)<br>24. Hb >13.0 mg/dL and platelets and neutrophils below lower limit of normal range at screening, confirmed by a repeat test<br>(…)<br><br>To:<br>(…)<br>24. Hb <13.0 mg/dL and platelets and neutrophils below lower limit of normal range at screening, confirmed by a repeat test<br>(…) |
| **Rationale for change** | | Description adjustment |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c34982691** **Technical Version Number:3.0**

**Document Name:** clinical-trial-protocol-version-03

**Title:** Safety, tolerability, and pharmacokinetics of single rising oral dose and multiple rising oral doses of BI 706321 in healthy Japanese male subjects and single oral dose of BI 706321 in healthy Chinese male subjects (double-blind, randomised, placebo-controlled, parallel group design)

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Clinical Trial Leader | [redacted] | 12 Dec 2021 23:42 CET |
| Author-Trial Statistician | | 13 Dec 2021 12:36 CET |
| Approval-Team Member Medicine | | 13 Dec 2021 20:20 CET |
| Verification-Paper Signature Completion | | 15 Dec 2021 02:35 CET |

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

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