# CLINICAL TRIAL PROTOCOL

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| | **Document Number:** | **c09013915-08** |
| **EudraCT No.:** | 2016-001504-31 | |
| **BI Trial No.:** | 1363.2 | |
| **BI Investigational Product(s):** | BI 443651 | |
| **Title:** | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects. | |
| **Lay Title:** | BI 443651 multiple rising dose in Healthy Volunteers followed by a cross-over in CF subjects | |
| **Clinical Phase:** | Phase Ib | |
| **Trial Clinical Monitor:** | Tel: Fax:<br>Email: | |
| **Coordinating Investigators:** | Tel: Fax:<br>Email: | |
| **Status:** | Final Protocol (Revised Protocol (based on Amendment 7)) | |
| **Version and Date:** | Final Version: 8.0 | Date: 09 November 2017 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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| **Name of company:** | | **Boehringer Ingelheim** | |
| **Name of finished product:** | | NA | |
| **Name of active ingredient:** | | BI 443651 | |
| **Protocol date:**<br>01 August 2016 | **Trial number:**<br>1363.2 | | **Revision date:**<br>09 November 2017 |

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|---|---|
| **Title of trial:** | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects. |
| **Coordinating Investigators:** | Tel: Fax:<br>Email: |
| **Clinical phase:** | Ib |
| **Objective(s):** | The primary objectives of this trial are to:<br>(Part 1 MRD part) Investigate the safety and tolerability of inhaled BI 443651 in comparison to placebo in healthy volunteers.<br>(Part 2 Cross-over part) Investigate the safety and tolerability of inhaled BI 443651 in a cross-over design, in comparison to placebo in Cystic Fibrosis (CF) subjects.<br>The secondary objective is to investigate pharmacokinetics of BI 443651.<br>All doses of BI 443651 and placebo will be given via the Respimat®. |
| **Methodology:** | Part 1: Multiple rising dose in healthy volunteers, double blind within dose groups, randomised;<br>Part 2: Two period cross-over part in CF subjects, double blind, randomized with at least 30 day washout. |
| **No. of subjects:** | |
| **total entered:** | 64 (Additional subjects may be entered to allow testing of additional (e.g. intermediate) doses within the planned dose range on the basis of experience gained during trial conduct, i.e. the actual number of subjects entered may differ from 64) |
| **each treatment:** | Part 1: Healthy volunteers in all four dose groups: 10 per dose group (8 on active drug and 2 on placebo) = 40 total<br>Part 2: CF subjects in a two period, two treatment design: 24 subjects (12 per |

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| **Protocol date:**<br>01 August 2016 | **Trial number:**<br>1363.2 | | **Revision date:**<br>09 November 2017 |

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| | sequence) |
| **Diagnosis :** | Part 1: Healthy male or female volunteers<br>Part 2: Stable male or female Cystic Fibrosis subjects |
| **Main criteria for inclusion:** | Healthy volunteers: age ≥18 and ≤55 years; BMI range: ≥18.5 and ≤32 kg/m$^2$; male or female (complying with highly effective methods of contraception)<br>CF: Subjects with confirmed diagnosis of CF; $FEV_1$ ≥ 70% predicted; age ≥ 18 and ≤55; male or female (complying with highly effective methods of contraception) |
| **Test product(s):** | BI 443651 via the Respimat® |
| **dose:** | All doses are ex-mouthpiece b.i.d for six and a half day for Healthy Volunteers and thirteen and a half days for CF subjects.<br>Healthy volunteers: 100 µg, 400 µg, 1200 µg and 1800 µg BI 443651 b.i.d. CF: 600 µg BI 443651 b.i.d<br>Doses may change based on data obtained during the study (will not exceed 1800 µg BI 443651 b.i.d, ex mouthpiece) |
| **mode of administration:** | Inhalation via the Respimat® |
| **Comparator products:** | Placebo via the Respimat® |
| **dose:** | N/A |
| **mode of administration:** | Inhalation via the Respimat® |
| **Duration of treatment:** | Part 1: 6.5 days treatment for healthy volunteers<br>Part 2: two 13.5 days treatment periods separated by a wash-out of at least 30 days for CF subjects. |
| **Endpoints** | **Primary endpoint:**<br>Safety and tolerability of BI 443651, as assessed by frequency (in percent) of Healthy volunteers and CF subjects respectively with treatment-emergent adverse events (TEAE) over the treatment period (results for each of the subject populations will be reported separately)<br>**Secondary endpoints:**<br>For Part 1, after the first dose: $AUC_{0-12}$ and $C_{max}$<br>After the last dose at steady state: $AUC_{\tau, ss}$ and $C_{max, ss}$ |

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| | |
| **Criteria for safety:** | Safety and tolerability of BI 443651, as assessed by frequency (in percent) of Healthy volunteers and CF subjects with treatment-emergent adverse events (TEAE) over the treatment period (results will be reported separately for each group). |
| **Statistical methods:** | The two trial parts will be evaluated separately.<br>Descriptive statistics will be calculated for all endpoints.<br>If feasible, in Part 1 only, dose proportionality of BI 443651 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed. |

# FLOW CHART I – HEALTHY VOLUNTEERS

| Visit | Day | Planned Time relative to first drug administration [h:min] | Approximate clock time (actual day) [h:min] | Event and comment | Safety Laboratory[3] | PK blood | | 12-lead ECG[6] | Pulmonary function testing[17] | Body plethysmography | Vital signs (BP, PR)[12] | Adverse events / Concomitant Meds[11] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | -21 to -3 | | | screening[1] | X[3,15,19] | | | x | x | x | x | x |
| 2 | -7 to -3 | | | **in-clinic visit** | X[3,4] | | | | | | | x |
| | 1 | -02.00 | 06:00 | **admission,** device train[14] | x[8,15,19] | | | | | | | x |
| | | -01:30 | 06:30 | **allocation to treatment**[14] | | | | | x | x | x | x |
| | | -01:00 | 07:00 | | | | | x[16] | | | | x |
| | | -00:15 | 07:45 | | | x[2] | | | | | | x |
| | | 00:00 | 08:00 | drug administration[7], 250 mL water intake | | | | | | | | x |
| | | 00:05 | 08:05 | | | | | | x | | | x |
| | | 00:15 | 08:15 | | | x | | | | | | x |
| | | 00:30 | 08:30 | | | x | | | x | x | x | x |
| | | 00:45 | 08:45 | | | x | | x[16] | | | | x |
| | | 01:00 | 09:00 | | | x | | | x | | x | x |
| | | 02:00 | 10:00 | 250 mL water intake, thereafter breakfast[13] | | x | | x[16] | x | x | x | x |
| | | 04:00 | 12:00 | 250 mL water intake, thereafter lunch[13] | | x | | x[16] | x | | x | x |
| | | 06:00 | 14:00 | | | x | | | | | | x |
| | | 08:00 | 16:00 | snack (voluntary)[13] | | x | | | | | x | x |
| | | 10:00 | 18:00 | dinner | | | | | | | | x |
| | | 11:00 | 19:00 | | | | | x[16] | x | | x | x |
| | | 11:45 | 19:45 | | | x[2] | | | | | | x |
| | | 12:00 | 20:00 | drug administration[7] | | | | | | | | x |
| | | 12:05 | 20:05 | | | | | | x | | | x |
| | | 12:30 | 20:30 | | | | | | x | x | | x |
| | | 13:00 | 21:00 | | | | | | x | | x | x |
| | 2 | 23:00 | 07:00 | | | | | x[16] | x | | x | x |
| | | 23:45 | 07:45 | | x[8] | x[2] | | | | | | x |
| | | 24:00 | 08:00 | drug administration[7] | | | | | | | | x |
| | | 24:05 | 08:05 | | | | | | x | | | x |
| | | 24:30 | 08:30 | | | | | | x | | x | x |
| | | 25:00 | 09:00 | | | | | | x | | | x |
| | | 26:00 | 10:00 | breakfast[13] | | | | | x | | x | x |
| | | 28:00 | 12:00 | lunch | | | | | | | | x |
| | | 32:00 | 16:00 | snack (voluntary) | | | | | | | | x |
| | | 34:00 | 18:00 | dinner | | | | | | | | x |
| | | 35:00 | 19:00 | | | | | | x | | x | x |
| | | 36:00 | 20:00 | drug administration[7] | | | | | | | | x |
| | 3 | 47:00 | 07:00 | | | | | | x | | x | x |
| | | 47:45 | 07:45 | | x[8] | x[2] | | | | | | x |
| | | 48:00 | 08:00 | drug administration[7] | | | | | | | | x |
| | | 48:30 | 08:30 | | | | | | x | | x | x |
| | | 49:00 | 09:00 | | | x | | | | | | x |
| | | 50:00 | 10:00 | breakfast[13] | | | | | | | x | x |
| | | 52:00 | 12:00 | lunch | | | | | | | | x |
| | | 56:00 | 16:00 | snack (voluntary) | | | | | | | | x |
| | | 58:00 | 18:00 | dinner | | | | | | | | x |
| | | 59:00 | 19:00 | | | | | | x | | x | x |
| | | 60:00 | 20:00 | drug administration[7] | | | | | | | | x |

# FLOW CHART I – HEALTHY VOLUNTEERS (cont.)

| Visit | Day | Planned Time relative to first drug administration [h:min] | Approximate clock time (actual day) [h:min] | Event and comment | Safety Laboratory[3] | PK $_{blood}$ | | 12-lead ECG[6] | Pulmonary function testing[17] | Body plethysmography | Vital signs (BP, PR)[12] | Adverse events / Concomitant Meds[11] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 4 | 71:00 | 07:00 | | | | | x | x | | x | x |
| | | 71:45 | 07:45 | | x[8] | x[2] | | | | | | x |
| | | 72:00 | 08:00 | drug administration[7] | | | | | | | | x |
| | | 73:00 | 09:00 | | | x | | | | | | x |
| | | 74:00 | 10:00 | breakfast[13], **discharge** | | | | | | | x | x |
| | | 83:00 | 19:00 | | | | | | | | x | x |
| | | 84:00 | 20:00 | in-clinic drug admin[7] | | | | | | | | x |
| | 5 | 96:00 | 08:00 | in-clinic drug admin[7] | x[8] | | | | | | | x |
| | | 108:00 | 20:00 | in-clinic drug admin[7] | | | | | | | | x |
| | 6 | 119:45 | 07:45 | **in-clinic** | x[8] | x[2] | | | | | | x |
| | | 120:00 | 08:00 | in-clinic drug admin[7] | | | | | | | | x |
| | | 121:00 | 09:00 | **allow home** | | x | | | | | | x |
| | | 132:00 | 20:00 | in-clinic drug admin[7] | | | | | | | | x |
| | 7 | 143:00 | 07:00 | **admission** | | | | x[16] | x | x | x | x |
| | | 143:45 | 07:45 | | x[3,8,15] | x[2] | | | | | | x |
| | | 144:00 | 08:00 | drug administration[7], 250 mL water intake | | | | | | | | x |
| | | 144:05 | 08:05 | | | | | | x | | | x |
| | | 144:15 | 08:15 | | | x[18] | | | | | | x |
| | | 144:30 | 08:30 | | | x[18] | | | x | x | x | x |
| | | 144:45 | 08:45 | | | x[18] | | x[16] | | | | x |
| | | 145:00 | 09:00 | | | x[18] | | | x | | x | x |
| | | 146:00 | 10:00 | 250 mL water intake, thereafter breakfast[13] | | x[18] | | x[16] | x | x | x | x |
| | | 148:00 | 12:00 | 250 mL water intake, thereafter lunch[13] | | x[18] | | x[16] | x | | x | x |
| | | 150:00 | 14:00 | | | x[18] | | | | | | x |
| | | 152:00 | 16:00 | snack (voluntary)[13] | | x[18] | | | | | x | x |
| | | 154:00 | 18:00 | dinner | | | | | | | | x |
| | | 155:00 | 19:00 | | | | | x[16] | x | x | x | x |
| | | 155:45 | 19:45 | | | x[18, 2] | | | | | | x |
| | | 156:00 | 20:00 | | | | | | | | | x |
| | 8 | 167:00 | 07:00 | | | | | x[16] | x | | x | x |
| | | 168:00 | 08:00 | breakfast (voluntary), **discharge** | x[8] | x | | | | | | x |
| | 12 | 264:00 | 08:00 | **follow-up in-clinic visit** | | x | | | | | | x |
| | 16 | 360:00 | 08:00 | **follow-up in-clinic visit** | x[8] | x | | x | x | | x | x |
| | 23 | 528:00 | 08:00 | **follow-up in-clinic visit** | x[8] | x | | x | x | | x | x |
| | 30 | 696:00 | 08:00 | **follow-up in-clinic visit** | x[8] | x | | x | x | | x | x |
| 4 | 37-44 | 9999:00 | 08:00 | e.o.s.[9] | X[3,15] | x | | x | x | x | x | x |

**Note:** - The cumulative times specified in the planned time column are for orientation only. Depending on the actual a.m. dosing time at the given day, the procedures and observations related to that a.m. dosing (such as pre a.m. dose and post a.m. dose measurements of the same day) have to be adapted respectively:

- Pre-dose procedures will be performed in the following order, ensuring that PK bloods take priority with regards to timing:
  1. ECGs

2. Vital signs
3. PFTs
4. Body Plethysmography
5. PK blood (on the time-point)
6. Meals

- Post-dose procedures will be performed in the following order, ensuring that PK bloods take priority with regards to timing:
  1. ECGs
  2. Vital signs
  3. PK blood (on the time-point)
  4. PFTs
  5. Body Plethysmography
  6. Meals

1) Screening including subject information, informed consent, physical examination and review of vital signs/ECG/ safety laboratory tests, drug screening (urine at site), alcohol breath test; additionally, demographics including determination of the body weight/height, smoking and alcohol history, relevant medical history, concomitant medication, pregnancy test for female subjects of childbearing potential and review of inclusion/exclusion criteria.
2) Pre-dose blood samples for PK will be taken from approximately 15 minutes prior to dosing. All remaining PK samples will be taken as close as possible to the planned times, as mentioned in section 6.1.
3) Full Clinical Safety Labs as per section 5.3.7, unless otherwise specified. Safety labs for electrolytes should be centrifuged and stored as per requirements in section 5.3.7.
4) Safety laboratory to be taken and to be medically evaluated within 7 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days -7,-6, -5, -4 or -3.. Female subjects of childbearing potential will have progesterone levels measured (between Day 7 and Day 10 of their pill packet) during the screening period and Day-5 to -3.

6) ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position. Screening ECG can be performed with site ECG equipment but transferred to
7) All pre-dose measurements to be completed prior to dosing. Drug inhalation will take place at the same clock time, for morning and evening dosing, throughout the investigational period. Dosing will be under supervision at the trial site for all days.
8) Serum electrolyte samples only to be collected on Day 1, 2, 3, 4, 5, 6, 7, 8, 16, 23, 30 using local laboratory values in addition to central laboratory values.
9) End-of-study visit ; Including physical examination, weight, pregnancy test, review of vital signs/ECG/laboratory, serum pregnancy test (WOCBP only) at the end-of-study examination.

11) AEs and concomitant therapies will be recorded throughout the trial but will be specifically asked for at the time points indicated in the Flow Chart above
12) 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
13) If several actions are indicated at the same time point, the intake of fluid/meals will be the last action.
14) The time is approximate; the respective procedure is to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to first drug administration.
15) Urine pregnancy test for females (WOCBP only) on Day 1 and Day 7. Serum pregnancy test at screening, Day-5 to -3, and e.o.s. visit.
16) All ECGs on Day 1, Day 2, Day 7 & Day 8 will be in triplicate. All other ECGs to be single.
17) Body Plethysmography / Pulmonary function to be performed using Investigative site spirometry equipment.
18) On Day 7 for dose group 400µg and 1200µg only, for each PK timepoint, both a PK sample and a metabolite identification (MIST) sample will be taken (refer to Section 5.4.2.2).
19) Urine drug screen and alcohol breath test to be performed at screening and Pre-dose Day 1.

# FLOW CHART II – CF SUBJECTS

| Period | Visit | Day | Planned Time relative to first drug administration [h:min] | Planned Time relative to a.m. drug administration at corresponding day ) [h:min] | Approximate clock time (actual day) [h:min] | Event and comment | Safety Laboratory[3] | PK blood | 12-lead ECG[6] | CASA-Q & CFQ-R | | Pulmonary function testing[5] | Vital signs (BP, PR)[18] | Adverse events / Concomitant Meds[16] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SCR | 1 | -21 to -3 | | | | screening[1,] | X[19,22] | | x | | | x | x | x |
| **Period 1 / 2 – Two identical periods with a wash-out of at least 30 days** | 2 / 3 | -7 to -3[25] | | | 08:00 | **in-clinic visit,** device training[17], **allow home** | x[4,19] | | | x | | x[13] | x | x |
| | | 1 | -01:00 | -01:00 | 07:00 | **in-clinic visit** | x[,19,22,24] | | x[21] | | | | | x |
| | | | -00:30 | -00:30 | 07:30 | | | | | | | x | x | x |
| | | | -00:15 | -00:15 | 07:45 | **randomisation[15]** | | x[2] | | | | | | x |
| | | | 00:00 | 00:00 | 08:00 | drug administration[7,] 250 mL water intake | | | | | | | | x |
| | | | 00:05 | 00:05 | 08:05 | | | | | | | x | | x |
| | | | 00:15 | 00:15 | 08:15 | | | | | | | | | |
| | | | 00:30 | 00:30 | 08:30 | | | x | x | | | x | x | x |
| | | | 00:45 | 00:45 | 08:45 | device instruction[17] | | x | | | | | | x |
| | | | 01:00 | 01:00 | 09:00 | | | | | | | x | x | x |
| | | | 02:00 | 02:00 | 10:00 | 250 mL water intake, thereafter, breakfast[12] **allow home** | | | | | | x | x | x |
| | | | 12:00 | 12:00 | 20:00 | drug administration | | | | | | x[20] | | x |
| | | 2 to 6 | | 00:00 | 08:00 | drug administration | | | | | | x[20] | | x[14] |
| | | | | 12:00 | 20:00 | drug administration | | | | | | x[20] | | x[14] |

# FLOW CHART II – CF SUBJECTS (cont.)

| Period | Visit | Day | Planned Time relative to first drug administration [h:min] | Planned Time relative to first drug administration [h:min] | Approximate clock time (actual day) [h:min] | Event and comment | Safety Laboratory[3] | PK blood | 12-lead ECG[6] | CASA-Q & CFQ-R | | Pulmonary function testing[5] | Vital signs (BP, PR)[18] | Adverse events / Concomitant Meds[16] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Period 1 / 2 – Two identical periods with a wash-out of at least 30 days between drug administration** | 2 / 3 | 7 (+/- 2 days) | 143:00 | -01:00 | 07:00 | **in-clinic visit** | | | x | | | | | x |
| | | | 143:30 | -00:30 | 07:30 | | | | | | | x | x | x |
| | | | 143:45 | -00:15 | 07:45 | | X[19, 24] | x[2] | | | | | | x |
| | | | 144:00 | 00:00 | 08:00 | device instruction[17], drug administration[7], | | | | | | | | x |
| | | | 144:30 | 00:30 | 08:30 | **allow home** | | x | | | | x | x | x |
| | | | 156:00 | 12:00 | 20:00 | drug administration | | | | | | x[20] | | x[14] |
| | | 8 to 13 | | 00:00 | 08:00 | drug administration | | | | | | x[20] | | x[14] |
| | | | | 12:00 | 20:00 | drug administration | | | | | | x[20] | | x[14] |
| | | 14 (-1/+3 days) | 311:00 | -01:00 | 07:00 | **in-clinic visit** | | | x | x | | x | | x |
| | | | 311:30 | -00:30 | 07:30 | | | | | | | x | x | x |
| | | | 311:45 | -00:15 | 07:45 | | x[19,24] | x | | | | | | x |
| | | | 312:00 | 00:00 | 08:00 | drug administration[7], 250 mL water intake | | | | | | | | x |
| | | | 312:05 | 00:05 | 08:05 | | | | | | | x | | x |
| | | | 312.15 | 00:15 | 08.15 | | | | | | | | | x |
| | | | 312:30 | 00:30 | 08:30 | | | x | | | | x | x | x |
| | | | 312:45 | 00:45 | 08:45 | | | x | | | | | | x |
| | | | 313:00 | 01:00 | 09:00 | | | | | | | x | x | x |
| | | | 314:00 | 02:00 | 10:00 | 250 mL water intake, thereafter, breakfast[12] **allow home** | | | | | | x | x | x |
| | | 23 (+/-2 days) | 528:00 | 00:00 | 08:00 | **telephone call** | | | | | | | | x |
| | | 30 (+/- 5 days) | 696:00 | 00:00 | 08:00 | **in-clinic visit** | x[19] | | x | | | x | x | x |

| | After Day 14 of Visit 2 (Period 1), subjects will washout for at least 30 days prior to crossing-over and commencing Day 1 of Visit 3 (Period 2). A second baseline (Day-7 to -3) will be conducted within the washout period. At the end of Visit 3 (Period 2), subjects will continue to the end of study visit (Visit 4). |
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| Period | Visit | Day | Planned Time relative to first drug administration [h:min] | Planned Time relative to first drug administration [h:min] | Approximate clock time (actual day) [h:min] | Event and comment | Safety Laboratory[3] | PK blood | 12-lead ECG[6] | CASA-Q & CFQ-R | | Pulmonary function testing[5] | Vital signs (BP, PR)[18] | Adverse events / Concomitant Meds[16] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| EOS | 4 | –44-51 | 9999:00 | 00:00 | 08:00 | e.o.s.[9], **in-clinic visit** | X[19] | x | x | | | x | x | x |

**Note:** The cumulative times specified in the planned time column are for orientation only. Depending on the actual a.m. dosing time at the given day, the procedures and observations related to that a.m. dosing (such as pre a.m. dose and post a.m. dose measurements of the same day) have to be adapted respectively:

- Pre-dose procedures will be performed in the following order, ensuring that PK bloods take priority with regards to timing:
  1. ECGs
  2. Vital signs

  4. PFTs
  5. Safety labs/ PK blood (on the time-point)
  6. Meals

- Post-dose procedures will be performed in the following order, ensuring that PK bloods take priority with regards to timing:
  1. ECGs
  2. Vital signs

  4. Safety labs/ PK blood (on the time-point)
  5. PFTs
  6. Meals

- If mentioned at the same time point meals will be served after completion of the planned procedure (i.e. PK, pulmonary function).
- Urinalysis and urine samples can be performed any time pre-dose.

1) Screening including subject information, informed consent, physical examination and review of vital signs/ECG/safety laboratory tests, drug screening; additionally, demographics including determination of the body weight/height, smoking and alcohol history, relevant medical history, concomitant medication, pregnancy test for female subjects and review of inclusion/exclusion criteria.
2) Pre-dose blood samples for PK will be taken from approximately 15 minutes prior to dosing. All remaining PK samples will be taken as close as possible to the planned times, as mentioned in section 6.1.
3) Full Clinical Safety Labs as per section 5.3.7, unless otherwise specified. Safety labs for electrolytes should be centrifuged and stored as per requirements in section 5.3.7.
4) Must be completed and medically evaluated within 7 days prior to administration of study drug; this safety laboratory can be omitted, if the screening examination is performed on Days-7, -6, -5, -4 or -3. Female subjects of childbearing potential will have progesterone levels measured (between Day 7 and Day 10 of their pill packet) during the screening period and Day -5 to -3 then prior to the second treatment period.
5) Should be completed at relevant visits. Pulmonary function to be performed using Investigative site spirometry equipment ($FEV_1$, FVC, $FEF_{25-75}$) at in-house visits except Day -7 to -3 of each treatment period. ($FEV_1$,) to be used at home (ex-clinic).
6) ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position
7) All pre-dose measurements should be completed prior dosing. Dosing will be under supervision at the trial site during all in-house test-days (Period 1 & 2 - Days 1, 7, and 14).
9) End-of-study visit; including physical examination, review of vital signs/ECG/laboratory at the end-of-study examination
12) If several actions are indicated at the same time point, the intake of fluids/meals will be the last action.
13) Unsupervised Pulmonary Function ($FEV_1$, PEF) with AM3® device
14) Phone call to be made twice a day, ideally at the time of study drug administration (see section 5.3.6). During the afternoon or evening calls, AEs should be collected in line with a morning call
15) Allocation to treatment may be performed at any time following enrolment but must be completed prior to first drug administration. Randomisation not required for CF subjects undergoing second treatment period
16) AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart II above including during phone calls when patients are ex clinic.
17) Respimat device and AM3® device training initially, then instruction (if required).
18) 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 II, after subjects have rested for at least 5 min in a supine position.
19) Includes, urine pregnancy test for females at Screening, Day 1, Day 7, Day 14 and Day 30. Serum pregnancy test at Day-5 to -3, and e.o.s. visit.
20) To be measured on home based spirometer (AM3®), prior to drug administration.
21) Baseline ECG (Day 1) must be in triplicate. All other ECGs to be single.
22) Urine drug screen and alcohol breath test to be performed at both screening and Pre-dose Day 1,.

24) Serum electrolytes to be collected using local laboratory values in addition to central laboratory values.
25) Planned time is required for technical reasons and the actual dates and times could be between Day -7 to -3.

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# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ASL | Airway Surface Liquid/Airway Surface Layer |
| ATS | American Thoracic Society |
| AUC | Area under the concentration-time curve of the analyte in plasma |
| $AUC_{0-12}$ | Area under the concentration-time curve of the analyte in plasma until 12 h after the first dose |
| $AUC\tau_{,13}$ | Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ on day 7 |
| AUCτ, ss | Area under the concentration-time curve of the analyte in plasma at steady state, over a uniform dosing interval τ |
| b.i.d. | bis in die (twice daily dosing) |
| BLQ | Below the Lower Limit of Quantification |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| CF | Cystic Fibrosis |
| CFTR | Cystic Fibrosis Transmembrane conductance Regulator |
| CI | Confidence Interval |
| CML | Local Clinical Monitor |
| COPD | Chronic Obstructive Pulmonary Disease |
| $C_{1,N}$ | Concentration of the analyte in plasma 1 hour after administration of the Nth dose |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| $C_{max,ss}$ | Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ |
| $C_{max,13}$ | Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ on day 7 |
| $C_{pre,N}$ | Predose concentration of the analyte in plasma immediately before administration of the next dose |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DILI | Drug Induced Liver Injury |
| ECG | Electrocardiogram |
| ENaC | Epithelial Sodium Channel |
| EDC | Electronic Data Capture |
| ePRO | Electronic Patient Reported Outcome |
| EudraCT | European Clinical Trials Database |
| FAS | Full Analysis Set |
| FC | Flow Chart |
| FEF | Forced Expiratory Flow |
| FEV | Forced Expiratory Volume |

| | |
|---|---|
| FIM | First-into-Man |
| FRC | Functional Residual Capacity |
| FVC | Forced Vital Capacity |
| GCP | Good Clinical Practice |
| hERG | Human Ether-A-go-Go Related Gene |
| IB | Investigator's Brochure |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ISF | Investigator Site File |
| i.v. | Intravenous |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| NOA | Not Analysed |
| NOP | No Peak Detectable |
| NOR | No Valid Result |
| NOS | No Sample Available |
| OPU | Operative Unit |
| PD | Pharmacodynamics |
| PEF | Peak expiratory flow |
| PK | Pharmacokinetics |
| PR | Pulse Rate |
| $R_{A,AUC,13}$ | Accumulation ratio of the analyte in plasma at steady state after multiple oral administration over a uniform dosing interval τ, expressed as ratio of AUC on Day 7 at steady state and after single dose |
| $R_{A,Cmax,13}$ | Accumulation ratio of the analyte in plasma at steady state after multiple oral administration over a uniform dosing interval τ, expressed as ratio of $C_{max}$,13 on Day7 at steady state and Day 1 |
| $R_{aw}$ | Airway resistance |
| REP | Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Precedure |
| SPC | Summary of Product Characteristics |
| TCM | Trial Clinical Monitor |
| $t_{1/2}$ | Half life of the analyte in plasma |
| $t_{max}$ | Time from dosing to maximum concentration of the analyte in plasma |
| TEAE | Treatment-Emergent Adverse Events |
| TMF | Trial Master File |
| TSAP | Trial Statistical Analysis Plan |
| WOCBP | Women of Child-Bearing Potential |
| $\lambda_{z, N}$ | Terminal rate constant in plasma |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

BI 443651 is an oral inhaled ENaC inhibitor in phase I of clinical development for the indications of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD).

CF chronic respiratory disorders characterised by airflow obstruction. ENaC is expressed on airway epithelial cells and functions as an ion channel for sodium. It mediates sodium reabsorption and regulates the water content and volume of the luminal fluid thereby maintaining airway surface liquid (ASL) and in turn regulating mucociliary clearance.

Cystic fibrosis is a lethal, inherited, multi-organ disease. Exocrine gland dysfunction predominantly affects the lower respiratory tract and pancreas leading to chronic respiratory failure and pancreatic insufficiency. It is the most common lethal inherited disease in Caucasians [R01-1277]. Pulmonary treatments include supportive care (airway clearance techniques), pharmacotherapy and lung transplantation. Despite recent advances, over 90% of patients surviving the neonatal period will develop pulmonary involvement and at least 90% will die due to pulmonary complications [P96-3855]. The median age of death remains below 40 years old [R15-5546].

In CF, the cystic fibrosis transmembrane conductance regulator (CFTR) gene is dysfunctional resulting in impaired epithelial chloride (Cl-) transport [R15-5486] leading, in turn, to reduced water secretion into the airway surface layer (ASL). This is aggravated by the fact that the functional defect of the CFTR is associated with increase of ENaC activation and increased sodium [R15-5507] and water absorption from the airway epithelial lining fluid. These effects lead to changes in the biophysical properties of the mucus resulting in poor mucus clearance [R15-4955]. The static mucus can trigger an inflammatory response, and lead to bacterial colonisation and infection. Lung destruction is caused by a cycle of infection, inflammation, and injury, with obstruction of the airways.

COPD results from an inflammatory process driven by exogenous stimuli such as cigarette smoke and air pollution. Mucus hyper secretion is an important manifestation of COPD and is associated with adverse outcomes including mortality and forced expiratory volume in 1 second ($FEV_1$) decline [R15-4986, R99-0658]. Recent data suggests that increased mucus concentration is associated with reduced mucus clearance, which in turn is associated with reduced $FEV_1$ in chronic bronchitis patients [R15-5502]. The airways of COPD patients are often colonized by bacteria, and higher airway bacterial loads are associated with increased airway inflammation [R15-4985], more frequent exacerbation [R02-2234] and faster lung function decline [R15-4945] in smokers [P94-2812]. The airway surface layer (ASL) is dehydrated in COPD patients attributable to a tobacco smoke-induced decrease in CFTR-mediated anion secretion, which may be worsened by ENaC channel activation [R15-4947]. Together with a concomitant increase in mucus secretion, these effects may lead to mucus plugging, bacterial infection, and chronic neutrophilia [R15-5506, R15-4975, R15-4987]. Furthermore, preclinical data in smoke models suggests improvements in ASL hydration and mucus clearance following ENaC inhibition [R15-4976], supporting the hypothesis that ENaC is involved in the pathogenesis of COPD.

ENaC is expressed on the apical side of lung epithelial cells and evidence is available to suggest a role in the pathogenesis of both CF and COPD. Despite the differences in the underlying pathology between the two diseases, changes in the biophysical characteristics of the mucus are apparent with impaired transport of mucus (reduced mucus clearance) leading to mucus plugging, airflow obstruction and a milieu conducive to bacterial colonisation which in turn leads to worsening symptoms and lung function, and an increase in exacerbations. In both CF and COPD, inhibition of ENaC is anticipated to reduce epithelial sodium uptake and water absorption in the airways which should translate to improvement of mucociliary clearance, pulmonary function, symptoms and quality of life, while reducing bacterial colonization of the lower airways exacerbations and hospitalizations. Administration of an inhaled formulation of the potassium sparing diuretic amiloride, an ENaC inhibitor, resulted in increased mucus clearance in cystic fibrosis patients [R15-5487, R15-5485, R15-5349] although poor pharmacokinetics , poor pharmacokinetic properties with inhalation are likely responsible for a lack of efficacy observed in some clinical trials. [R15-5349, R15-5599, R15-5505]. The more favourable potency and kinetics demonstrated by BI 443651 are expected to translate into clinical efficacy.

## 1.2 DRUG PROFILE

BI 443651, an epithelial sodium channel (ENaC) inhibitor, is in phase I clinical development in cystic fibrosis (CF).For a detailed review see the investigator brochure [c02337864]

### 1.2.1 Nonclinical pharmacology

In the CEREP screen, BI 443651 revealed an inhibition of acetylcholine esterase with an IC50 value of 1.6 µM. Therefore, BI 443651 was tested in the model of acetylcholine (ACh)-induced bronchoconstriction in anaesthetized guinea pigs. BI 443651 dose-dependently enhanced the magnitude of the ACh-induced bronchoconstriction by 51 and 117% at the doses of 80, and 160 µg/kg (reflecting 3.3 and 5 fold ED50) respectively. The potential reinforcement effect of BI 443651 on the cholinergic pathway tone was also assessed in the model of methacholine (MCh)-induced bronchoconstriction in anaesthetized guinea pigs. As with the ACh, BI 443651 at doses of 80 and 160 µg/kg also enhanced the magnitude of the MCh-induced bronchoconstriction's. Inhalation of ipratropium at 60 µg/kg with Respimat®

led to an instantaneous and full inhibition of MCh-induced bronchoconstriction in those studies in which ipratropium was administered.

### 1.2.2 Safety pharmacology

*Cardiovascular*

### 1.2.3 Toxicology

BI 443651 did not demonstrate systemic adverse effects in repeat-dose toxicity studies in dogs.

In two in vitro and one in vivo tests, BI 443651 was non-genotoxic. BI 443651 was not a locally irritant or and was not phototoxic.

In summary, the non-clinical safety data of BI 443651 support clinical Phase I trials in healthy volunteers or patients with inhaled administration for up to 4 weeks.

### 1.2.5 Drug product

BI 443651 is delivered via the Respimat® as an inhalation solution contained in a drug reservoir / cartridge inserted into the inhaler. Several solutions, including a placebo solution, with different drug substance concentrations have been developed for use in clinical studies (delivered strengths of 10 µg, 100 µg and 300 µg BI 443651 per actuation ex mouthpiece). A spray volume of 11.05 µL per actuation is nebulized by the device.

### 1.2.6 Clinical studies and experience in humans

Systemic ENaC inhibitors such as amiloride have been used for years as potassium sparing diuretics in the treatment of hypertension, congestive heart failure and cirrhotic ascites. The side effect profile is well documented. Amiloride is normally well tolerated and, except for hyperkalaemia, significant side effects are infrequent. Nausea, anorexia, abdominal pain, flatulence and mild skin rashes are considered potentially related to amiloride but other side effects are generally associated with diuresis.

In addition there are clinical data of inhaled ENaC inhibitors administered to healthy volunteers and patients with cystic fibrosis for up to 6 months [R15-5485, R15-5349, R15-5599, R15-5505]. Phase II studies with competitor ENaC inhibitors are ongoing. The compounds appear to have been well tolerated, with effects limited to serum potassium increases after multiple dosing, particularly in a compound with an active metabolite [R15-0689].

# 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

## 2.1 RATIONALE FOR PERFORMING THE TRIAL

This is the first of two multiple dose administration trials for BI 443651 the other being a multiple dose study in asthma subjects. The objective of this study is to investigate the safety, tolerability, and pharmacokinetics of BI 443651 in male and female healthy volunteers. A sparse PK investigation will be undertaken in subjects with cystic fibrosis (CF), along with exploratory efficacy.. The study will use multiple rising orally inhaled doses, to provide the basis for development of BI 443651 in cystic fibrosis. The safety, pharmacokinetic and exploratory efficacy data obtained in this study will help to assess an appropriate dosing range for further studies with this compound.

The study will be conducted in two parts. The first part is a multiple rising dose design in healthy volunteers. In the second part, cystic fibrosis subjects will participate in a cross-over design to placebo or active treatment, after safety has been demonstrated at the twice higher dose level in healthy volunteers.

By including subjects with CF, this allows initial safety to be obtained in the target population as well as completely healthy volunteers. The pharmacokinetic information at steady state exposure from healthy volunteers will act as a bridging safety study for later studies of longer duration. The exploratory efficacy outcome measures include spirometry and body plethysmography (healthy volunteers only), in CF subjects may help guide decision making and dose selection for phase II studies.

## 2.2 TRIAL OBJECTIVES

**The primary objectives of part one of the study is to investigate safety, and tolerability of inhaled administration of:**

**BI 443651 100 µg b.i.d., 400 µg b.i.d., 1200 µg b.i.d. and 1800 b.i.d. µg BI 443651 in healthy male and female volunteers over 6.5 days.**

**The primary objective of part two of the study is to investigate the safety and tolerability of orally inhaled administration of BI 443651 in stable male and female CF subjects following administration of repeated doses of 600 µg b.i.d. BI 443651 over 13.5 days.**

A secondary objective is the exploration of the pharmacokinetics of BI 443651 after multiple dosing in healthy volunteers.

## 2.3 BENEFIT - RISK ASSESSMENT

BI 443651 is being developed as a therapy for obstructive airways diseases such as cystic fibrosis and COPD. Participation in this study is without any (therapeutic) benefit for healthy

volunteers. Their participation in the study is of importance as a safety bridge to investigate effective treatment in COPD and CF. CF subjects may have a short term benefit during the present trial.

The subjects are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication as outlined below.

During the whole course of the trial, sites will provide open-label salbutamol/albuterol or atrovent HFA MDI to be used as rescue medication for all CF subjects from screening, after they have signed their informed Consent. For the CF patients, safety information from the healthy volunteer portion of the study will be available and fully analysed.

### 2.3.1 Procedure-related risks

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

The total volume of blood to be withdrawn during the entire study will be below 300 mL per subject and thereby a little bit more than the half of a normal blood donation (450-500 mL). No safety-related risk to study participants is expected from this blood withdrawal over a minimum 3 week period. Sampling times and visits may be adapted based on emerging information during the trial conduct.

### 2.3.2 Drug-related risks and safety measures

The nature of the target and the mechanism of action of BI 443651, ENaC inhibition, are well documented. The side effect profile of systemic ENaC inhibitors (amiloride) is well understood and the adverse events observed in rats following administration of BI 443651 are consistent with the mechanism. Inhaled amiloride has been administered to patients [R15-5349; R15-5505]. The animal models are believed to be predictive for the effects in humans. ENaC inhibition is not expected to be involved in cascading of any pharmacologic pathways, exaggerated pharmacodynamic effects, pleiotropy of mechanism, or amplification and bypass properties of normal physiological control mechanisms.

Based on clinical safety data exposed in section 1.2.6 above, BI 443651 was well tolerated in male healthy volunteers either after single dose up to 3600 µg or after chronic dosing up to 1800 µg bid over 6.5 days. There were no relevant adverse effects on lung function, serum and urine electrolytes, vital signs or ECG.

Side effects were restricted to dose-dependent administration-related events such as cough, throat irritation and taste complaints. These adverse events, frequently seen with inhaled products, were all mild in intensity and mostly of short duration.

Safety margins (dose multiples) are calculated from the predicted quantity of drug deposited in the preclinical species lung compared to the human lung, assuming 100% of the human dose is deposited in the lung i.e. worst case scenario. The current dose multiples are:

- 5 for the NOAEL dose in the 4-week rat study versus the maximum planned human daily dose ( 1800 µg b.i.d or 3600 µg/day) based on mg BI 443651 deposited per g lung weight
- 3.7 for the NOAEL dose in the 4-week dog study versus the maximum planned human daily dose based (1800 µg b.i.d or 3600 µg/day) on mg BI 443651 deposited per g lung weight

Non-clinical studies support repeat-dose clinical trials of up to 4 weeks duration. The relevant systemic findings in the toxicology studies in the rat were changes in serum and urine electrolytes, at delivered doses of 4200 µg/kg/day (4-times higher than the NOAEL dose of 1080 µg/kg) and were consistent with the mode of action of an ENaC antagonist in the kidney. The most sensitive species for these effects was the rat with no relevant effects observed in the dog, even at high doses, on serum or urinary electrolytes. The effects on electrolytes are consistent with the urinary exposure to drug. No other systemic safety findings were observed in either the toxicology or safety pharmacology studies.

Exposure in the present study, for the highest dose of 1800 µg b.i.d (3600 µg/day) is predicted to be approximately 2-fold lower for Cmax and similar exposures for $AUC_{0\text{-}24\ 0\text{-}}$as to the NOAEL values observed in the 4 week rat study. For the highest single dose of 3600ug, less than 1% of parent drug was measured in urine over the first 48 h post dose period (gmean 0.27%, CV 45%).

Off target inhibition of ACh has been observed pre-clinically with augmented effects in non-clinical ACh/MCh challenge guinea pig models. No adverse respiratory effects were detected in the 4-week toxicology studies or in the safety pharmacology studies at doses of up 7,750 µg/ kg in dog or rat. The off target effect is not considered relevant in unchallenged healthy volunteers, and otherwise CF patients. An additional study is planned to assess possible effects in those exposed to acetylcholine or methacholine. Effects on respiratory function will be monitored and are reversible with standard inhaled anticholinergic therapy.

BI 443651 does not present a genotoxic hazard. BI 443651 is considered to be low risk for phototoxicity, based on its absorbance pattern and lack of toxicity in 4-week repeat dose studies.

Fertility has not been assessed in nonclinical species, but no adverse effects have been observed on reproductive organs in 4-week toxicity studies in rats and dogs, suggesting that there is a low risk to fertility. At the time this current study is planned to start, embryo-fetal development studies of BI 443651 will not have been conducted. Therefore only female subjects of child bearing potential willing to accept highly effective methods of contraception [See exclusion criteria section 3.3.3 for definition of highly effective methods of contraception] through the duration of this study and for 30 days after will be included, otherwise only males, and females of non-child bearing potential and non-lactating women will be included in this study.

The nonclinical safety studies (safety pharmacology and pivotal toxicity studies) to support the clinical study 1363.2 are described and referred to in the Investigator's Brochure for BI 443651 in Cystic Fibrosis and COPD. These studies have been conducted in compliance with Good Laboratory Practice and have been carried out in an OECD country.

The only exception is the study on the effects of BI 443651 on the hERG (human ether-a-go-go related gene)-mediated potassium current [n00248843]. This study was performed in an OECD country but without formal adherence to the principles of GLP (non-GLP). Data quality and integrity of the study however are given as study reconstruction is ensured through adequate documentation of the study conduct and archiving of data. Therefore the validity of the study is considered not compromised by its non-GLP status and as such there is no impact on the evaluation of the respective endpoints of this safety pharmacology study.

Whilst not all safety effects may be predicted, based on mechanism and systemic toxicological finding the only potential systemic toxicity is changes in serum electrolytes and particularly increases in serum potassium. These changes are easily monitored and treatable if observed. The following safety measures will be applied in this study in order to minimize the risk for the healthy volunteers and CF subjects:

- Frequent safety laboratory testing will be performed with a focus on electrolytes (see Flow Chart I & Flow Chart II. Dose escalation will be stopped as soon as at least 2 subjects at one dose level within one population type on active drug showed serum potassium levels ≥ 5.5 mmol/L in non-haemolysed blood
- Selection of a starting dose for healthy volunteers (100 µg b.i.d.) that is at least 107 and 63 fold below the plasma $C_{max}$ and $AUC_{0-24}$ respectively (at the NOAEL in the most sensitive species (see memo for details [c09837286] and section 4.1.2 for justification of dose selection.
- Treatment of patient populations will occur in a staggered fashion to healthy volunteers. For CF subjects, an exposure of 600 µg b.i.d. will only occur after 1200 µg b.i.d. is safely administered to healthy volunteers (see section 3.1).
- Dose escalation for healthy volunteers is based on adequate safety in a preceding lower dose cohort. For each dose level the starting of subsequent dose groups will be separated by at least 9 days, implying 7 days of blinded safety and tolerability data (see section 3.1.2). Specific stopping criteria are specified in section 3.3.4.1 with the potential to either not dose or delay dosing the next cohort is also based on physician judgment.
- Dose escalation factor is limited to less than 2 at the highest dose step in healthy volunteers (1200 to 1800 µg b.i.d.).
- The maximum total daily dose in healthy volunteers (1800 µg b.i.d.) is limited to the same maximum single dose (3600 µg) administered in the FIM study 1363.1. The total daily dose for CF is lower than the maximum dose delivered in the 1363.1 (See section 4.1.2 for dose justification).
- All subjects will be monitored throughout the study via in-clinic visits to site or interim telephone calls at home. Healthy volunteers will remain at the study site for at least four days following first study drug administration at each dose level, with medication administered under supervision of the site staff. Thereafter, dependent on medical assessment, subjects will be allowed to leave the site. Once discharged from site and whilst continuing treatment, volunteers will undertake twice daily in-clinic visits to site for supervision of medication administration. CF subjects are allowed to leave the site at an earlier time point as safety information will already have been collected for healthy volunteers. Nevertheless CF subjects will be required to attend the clinic for in-clinic

visits and medical examination including safety laboratories. An ambulatory spirometer, Asthma Monitoring Device (AM3®), will be used to monitor lung function at home.

- All randomised CF subjects must have stable disease (see section 3.3.2) and will continue their regular medication (e.g. pulmozyme and antibiotics ). Worsening of disease is not expected. No therapy is being withdrawn from patients and the addition of placebo treatment on top of usual care in this study is considered acceptable. Nevertheless, subjects will be closely monitored for worsening of CF by monitoring of symptoms and pulmonary function in the clinic. In the event of deterioration subjects will be immediately invited back to the site. It is not expected that these co-medications interact with BI 443651.
- Although based on pre-clinical data no signal for QT prolongation has been observed, dosing will be stopped as soon as at least 2 subjects, on active drug at one dose level showed relevant and confirmed individual QTc prolongation (see section 3.3.4.1 and 4.1.5).
- Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects´ safety, see also section 5.3.10.1.

In summary, BI 443651 is in early clinical development. Single doses up to 3600 µg have been safely administered in study (1363.1). Multiple doses of up to 1800 µg b.i.d. are supported by preclinical safety data results from study 1363.1. Based on preclinical data for BI 443651 and clinical information from systemically administered ENaC inhibitors and other inhaled compounds previously tested in the clinic, which have been well tolerated, along with the implemented safety measures described above, healthy subjects and subjects with CF will not be exposed to undue risks. Healthy volunteers are not expected to have any direct medical benefit from participation in this clinical trial with BI 443651, as is the usual case in such phase I trials. CF subjects may receive transient benefit from participating in this trial. BI 443651 has the potential to be an inhalative treatment for CF, a disease of high unmet medical need. The expected potential benefits for patients and the important information expected from this trial as a basis for further clinical development of this compound are felt to outweigh the potential risks and justify exposure of healthy human subjects and CF subjects in the clinical development of BI 443651.

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be composed of two parts – a multiple rising-dose (MRD) part and a cross-over part. Both parts will be randomised, placebo-controlled and double-blind.

**Part 1 (MRD):** MRD part will be double-blind within dose groups and includes healthy volunteers.

A total of 40 healthy volunteers are planned to participate in the trial according to 4 sequential dose groups compromising 10 subjects per group. Within each dose group 8 volunteers will receive the active drug and 2 will receive placebo.

For healthy volunteers, one dose will be tested within each dose group. The groups will be treated consecutively in ascending order of dose. The dose groups to be evaluated are as outlined in Table 3.1: 1 below.

Additional subjects may be entered to allow testing of additional (e.g. intermediate) doses within the planned dose range on the basis of experience gained during trial conduct, i.e. the actual number of subjects entered in Part 1 may exceed 40 subjects. Such a change would be implemented as a non-substantial CTP amendment provided that the additional dose levels to be tested were within the approved dose range.

Table 3.1: 1 Dose groups for Part 1 (MRD) and Part 2 (cross-over)

| **Dose group** | **1** | **2** | **3** | **5** | **7** |
|---|---|---|---|---|---|
| **Subjects** | HV | HV | HV | HV | CF |
| **Dose** | 100 µg b.i.d. | 400 µg b.i.d. | 1200 µg b.i.d. | 1800 µg b.i.d. | 600 µg b.i.d. |
| **Daily dose (µg)** | 200 | 800 | 2400 | 3600 | 1200 |
| **No. of subjects** | 10 | 10 | 10 | 10 | 24 |
| **Subjects on placebo** | 2 | 2 | 2 | 2 | 24 |
| **Subjects on active drug** | 8 | 8 | 8 | 8 | 24 |

For healthy volunteers four different dose groups (100, 400, 1200 and 1800 µg b.i.d.) will be investigated consecutively in ascending order of daily doses (see section 3.1.2 for information on dose escalation).

**Part 2 (cross-over):** 24 CF subjects will be included in the second part of the study (cross-over design). Each CF subject will receive both placebo and the active drug at one dose-level in a randomised sequence with 12 subjects on each of the following sequences: Active/Placebo, Placebo/Active (See section 3.1.1 for starting rules).

### 3.1.1 Start of CF dose groups:

The second part of the study including CF subjects will only start once the 1200 µg b.i.d dose been shown to be well tolerated in healthy volunteers (see table 3.1.2: 1).

The decision to administer BI 443651 to CF subjects will be taken in a documented safety review meeting (see section 3.1.2).

### 3.1.2 Dose escalation:

The dose groups will be investigated consecutively in ascending order of doses with a dose escalation review between each dose group.

Healthy volunteers: The healthy volunteer dose groups will be investigated first. Each cohort of healthy volunteers, 10 subjects (8 on active, 2 on placebo) will be dosed up to 7 days in an incremental order with a dose escalation meeting in between each dose step. Only if the previous dose of BI 443651 is safe and well tolerated in the prior dose group, without meeting any stopping criteria (see Section 3.3.4.1), will the subsequent dose be administered (see table 3.1.2: 1).

For each dose level in healthy volunteers, the dosing of the first subject in subsequent dose groups will be separated by at least 9 days, implying at least 7 days of blinded safety and tolerability data from the preceding dose group, which is expected to cover the period to predicted steady state.

Table 3.1.2: 1 Dose escalation schedule (b.i.d.)

| Time | Healthy volunteer | CF |
|---|---|---|
| ↓ | DG1 (100 µg) | - |
| | DG2 (400 µg) | - |
| | DG3 (1200 µg) | - |
| | DG5 (1800 µg) | DG7 (600 µg) |
| | - | - |

A documented dose escalation safety review meeting must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or an authorised deputy) or the sponsor of the study, e.g. because of any unforeseen adverse events, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the safety review committee, with appropriate representation from Sponsor company and the Principal Investigator (or an authorised deputy).

The minimum data set for review consists of the following data on 8 Healthy Volunteers (see section 3.3.5 for subject replacement):

- AEs in the current and preceding dose groups up to at least end of treatment (including clinically relevant findings from ancillary safety testing listed below) (Note: AEs may be ongoing at the time of Safety Reviews)
- Clinical laboratory tests in the current and preceding dose groups
- Results from 12-lead EGG in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Pulmonary function (in clinic) tests in the current and preceding dose groups
- 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 safety review committee, with appropriate representation from Sponsor company and the Coordinating Investigator (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). Safety Reviews can be conducted face-to-face or by video/telephone conference. The Trial Clinical Monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator is allowed to alter the scheduled dose levels (e.g. add an intermediate dose level, decrease the planned dose, give the same dose again) within the planned and approved dose range on the basis of experience gained during the study. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop dose escalation in case the safety evaluation leads to concerns that would not allow higher dosing.

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

### 3.1.3 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim Pharma GmbH (BI).
The Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract. Healthy subjects will only be recruited at one site, thus the dose escalation meeting will comprise of appropriate personnel, with appropriate representation from Sponsor company and the Coordinating Investigator (or an authorised deputy). Minutes of the dose escalation meetings will be documented and filed in the TMF.

The composition of the dose escalation committee will be documented in the Trial Master File (TMF).

Relevant documentation on the participating (Principal) Investigators and other relevant site study team members, including their curricula vitae, will be filed in ISF.

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

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

- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

The two trial parts will be evaluated separately depending on their completion, for details refer to Section 7.4.

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.

A central laboratory service, ECG and an IRT vendor will be used in this trial. Details will be provided in IRT Manual, ECG and Central Laboratory Manual, available in ISF.

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

**Part 1 (MRD part):** For multiple rising dose trials, the design described in Section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability as well as pharmacokinetics of BI 443651.

With the rising dose design, double -blind conditions regarding the subjects' treatment (active or placebo) are maintained within each dose group, however the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose dependent effects as well as time effects but it has the virtue of minimising subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the difference between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected. It is standard in trials in early development involving healthy volunteers and subjects, to use placebo as a control group in order to evaluate safety, tolerability and pharmacokinetics.

Healthy volunteers: Each dose group of healthy volunteers consists of 10 volunteers with 8 on active treatment, and 2 on placebo. The placebo control group includes all subjects on placebo of all dose groups. 8 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics and safety.

**Part 2 (cross-over part of the study):** A total of 24 CF subjects are included which is considered sufficient to assess the safety, tolerability, sparse pharmacokinetics and exploratory efficacy (see section 7.7).The cross over design and the within patient

comparisons is implemented to limit the number of subjects required for the assessment of exploratory efficacy in this early phase I study. A washout of at least 30 days and a maximum of 6 weeks is regarded as a sufficient time period between treatment periods. Depending on emerging data, the washout period if required may be extended to prevent carryover of drug from Active to Placebo.

All CF subjects included in the study will have stable disease and be of mild or moderate severity. The subjects will be on standard of care treatment and thus the use of placebo in this setting is considered acceptable.

## 3.3 SELECTION OF TRIAL POPULATION

This trial will be conducted in at least 6 sites in at least 2 European countries (UK & Germany – 1 site for healthy subjects and at least 6 sites for CF). The selected sites participating in the study will have expertise in conducting studies for respiratory and pharmacokinetic assessments. All sites participating in the assessments of lung clearance index will have expertise in the conduct of this type of study.

**Part 1 (MRD part):** The inclusion and exclusion criteria are designed to include healthy volunteers.

It is planned that 40 healthy volunteers will be randomised in the study. Volunteers will be recruited from the volunteer's pool and EC approved advertisement from the

.

**Part 2 (cross-over part of the study):** The inclusion / exclusion criteria are designed to include mild stable CF subjects. To ensure the safety of the CF subjects in this trial, subjects must be stable without recent exacerbation or acute respiratory tract infection and have a pre-bronchodilator $FEV_1$ ≥70% at Visit 1 (screening) and prior to randomisation. A sufficient number of volunteers will be randomised (at least 24) to ensure a minimum of 20 CF subjects complete treatment.

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

### 3.3.1 Main diagnosis for trial entry

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

### 3.3.2 Inclusion criteria

**Part 1: (MRD part)**

**Healthy volunteers:**

1. Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial.

2. Healthy male or female subjects (see exclusion criteria regarding contraceptive measures) according to the investigators assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests.
3. Women of childbearing potential (WOCBP) should only be dosed after a confirmed menstrual period and/or with a progesterone level at Day -5 to Day -3 that demonstrates a dip from baseline, indicating a menstrual bleed prior to dosing.
4. Age of 18 to 55 years (incl.) on the day of subject´s signature of informed consent.
5. BMI of 18.5 to 32.0 kg/$m^2$ (incl.)
6. $FEV_1$ and FVC of equal or greater than 80% of predicted normal, at screening and prior to randomisation.

**Part 2: (Cross over part)**

**Cystic Fibrosis**

1. Signed informed consent consistent with ICH-GCP guidelines and local legislation prior to participation in the trial. Medication washout and medication restrictions are allowed only after signed informed consent is obtained.

2. Males or females (see exclusion criteria regarding contraceptive measures) with a documented diagnosis of cystic fibrosis (confirmed by a positive sweat chloride of 60 mEq/L or more, measured by pilocarpine iontophoresis) or a genotype with 2 identifiable mutations consistent with cystic fibrosis accompanied by 1 or more clinical features with the cystic fibrosis phenotype.

3. Women of childbearing potential (WOCBP) should only be dosed after a confirmed menstrual period and/or with a progesterone level at Day -5 to Day -3, that demonstrates a dip from baseline, indicating a menstrual bleed prior to dosing. For CF subjects of child bearing potential this must confirmed prior to second treatment period.

4. Age of between 18 and 55 years (each inclusive) of age, on the day of subject´s signature of informed consent.

5. BMI of 18 to 32.0 kg/$m^2$ (incl.).

6. Pre-bronchodilator $FEV_1$ greater than or equal to 70% of predicted normal at screening and prior to randomisation.

7. Clinical stability as defined by:
    a. No evidence of acute upper or lower respiratory tract infection within 4 weeks of screening.
    b. No pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics, or oral corticosteroids within 4 weeks of screening or prior to randomisation.
    c. No change in pulmonary disease therapy within 4 weeks of study day 1. If on cycling antibiotics, these must be initiated 2 weeks prior to randomisation.

d. No acute (serious or non-serious) illness not related to cystic fibrosis within 4 weeks of Day 1.

e. No infection with an organism associated with more rapid decline in pulmonary function (eg, Burkholderia cenocepacia, B dolosa, or Mycobacterium abscessus).

8. Subjects must be able to perform technically acceptable pulmonary function tests (forced spirometry).

### 3.3.3 Exclusion criteria (all Parts)

1. Any evidence of a concomitant disease judged as clinically relevant by the investigator including gastrointestinal, hepatic, renal, respiratory*, cardiovascular, metabolic**, immunological, dermatologic, hematologic, neurological and psychiatric, oncological, coagulation or hormonal disorders as determined by medical history, examination, and clinical investigations at screening that may, in the opinion of the investigator, result in any of the following:

    a. Put the subject at risk because of participation in the study.

    b. Influence the results of the study.

    c. Cast doubt on the subject's ability to participate in the study.

* except cystic fibrosis subjects who may be included with concomitant asthma provided on stable medications for 6 weeks prior to inclusion into the study. Patients with acute bronchopulmonary aspergillosis may not be included.

** CF subjects with diabetes are allowed to participate if their disease is under good control prior to screening as assessed by the principal investigator.

2. Chronic or relevant acute infections.
3. History of relevant orthostatic hypotension, fainting spells, or blackouts.
4. History of myocardial infarction; history of acute coronary syndrome within 6 months of the screening visit (Visit 1) or between the screening visit (Visit 1) and randomization.
5. History of and/or active life-threatening cardiac arrhythmia, as assessed by the investigator.
6. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 12 months after screening, e.g. hip replacement.
7. A history of chronic kidney disease (EGFR $\underline{<59}$ mls/min including corrections as per ethnicity)
8. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients).
9. Unsuitable veins for venipuncture (for instance, veins which are difficult to locate, access or puncture, veins with a tendency to rupture during or after puncture) as assessed by the investigator.
10. Any finding in the medical examination (including BP, PR or ECG) is deviating from normal and judged as clinically relevant by the investigator.

11. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance, specifically volunteers with serum potassium > upper limit of normal should be excluded; Safety laboratory screening and Day -7 to Day -3, evaluation can be repeated twice during screening.
12. For healthy volunteers, repeated measurement (i.e. > 2 measurements) of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg. Volunteers will be excluded with a pulse rate outside the range of 45 to 90 bpm.
13. A marked baseline prolongation of mean QT/QTcF interval (such as QTcF intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening or prior to randomisation (see section 5.3.8).
14. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome).
15. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTcF interval
16. Intake of drugs with a long half-life (more than 24hrs) within 30 days or less than 10 half-lives of the respective drug prior to administration of trial medication unless this is allowed medications as indicated in Table 4.2.2.1:1.
17. CF subjects treated with non-permitted concomitant medication. Specifically medications causing changes in serum potassium are restricted (please refer to Table 4.2.2.1:1)
18. Current or previous participation in another interventional trial, including where an investigational drug has been or will be administered within 60 days or 5 half-lives (whichever is longer) prior to screening.
19. For healthy volunteers and CF subjects: current smokers or ex-smokers of less than 12 months and/or with a pack year history of more than 5 years.
20. Positive test for alcohol or drugs, at screening or pre-dose on Day 1 prior to randomization. (Unless this can be explained by the subject's medication).
21. Drug or alcohol abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial. Consumption of 20 g/day (2 units of alcohol) in females, or 30 g/day (3 units of alcohol) in males.
22. Subjects who have donated more than 100 mL blood in the 4 weeks prior to Visit 1 and between Visit 1 and Visit 3 or subjects who have the intention to donate blood between Visit 3 and four weeks after the end of trial visit.
23. Intention to perform excessive physical activities within 72 hours prior to administration of trial medication or during the trial.
24. Inability to comply with dietary regimen of the trial site.
25. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
26. Women of childbearing potential (WOBCP) not willing to use highly effective methods of birth control per ICH M3 [R09-1400] during the study and for 30 days after. All female subjects (and female partners of male subjects) are regarded as being of childbearing potential unless they are either post-menopausal or permanently sterilised.

Post-menopausal is defined as having had, at least, 12 months spontaneous amenorrhea with an appropriate clinical profile (age, vasomotor symptoms, etc.). Females may have been permanently sterilised by means of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, confirmed tubal occlusion or tubal ligation (see Section 10.7).

27. Male subjects who do not agree to minimize the risk of female partners becoming pregnant (including sperm donation) from the first dosing day until 3 months after the trial medication treatment has finished. Male subjects with pregnant partners are excluded.
28. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because he/ she is considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study.
29. Previous randomisation in this trial.

### 3.3.4 Removal of subjects from therapy or assessments

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep subjects in the trial as scheduled. This includes careful subject selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

An individual subject is to be withdrawn from trial treatment if:

- The subject has a confirmed increase in serum potassium of ≥ 5.5 mmol/L in non-haemolysed blood.
- The subject shows relevant individual QT prolongation, i.e. a QTcF increase of greater 60 ms (mean where triplicate is performed) from baseline (pre-dose Day 1) in connection with absolute QT or QTcF greater than 500 ms, which has been confirmed by a repeat ECG recording.
- CF: A CF exacerbation occurs during treatment (for definition see Appendix 10.6). Patients may continue in the study if an exacerbation occurs during the washout period between treatment period 1 and 2, provided that patients have been off antibiotics (IV or oral, prescribed for the exacerbation) for at least 4 weeks and $FEV_1$ has returned to within 10% of the baseline values. Treatment washout between the two treatment periods can be extended up to a maximum of 6 weeks.
- The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.

  The investigator should ask the subject who withdraws consent whether the withdrawal is related to the further administration of trial medication or to all trial-related observations and procedures. The investigator should explain the importance of the further measures for the assessment of the subject´s safety. The observations and procedures to be followed for subjects who terminate the administration of trial medication prematurely (please see details below) will be performed accordingly.
- The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication (see Section 4.2.2)

- The subject experiences a serious adverse event or any AE, that in the opinion of the investigator, may jeopardise the safety of the trial participant.
- 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 stick to the trial requirements in the future.
- The subject can no longer be treated with trial medication for any medical reason (e.g. surgery, adverse events, other diseases, or pregnancy)
- Decision by Boehringer Ingelheim to discontinue treatment of a specific subject (for instance, in case of the occurrence of an SAE that would be incompatible with trial continuation)

Given the subject's agreement, the subject will undergo the procedures for early treatment discontinuation and follow up as outlined in Flow Chart I & Flow Chart II and section 6.2.3.

For all subjects the reason for withdrawal (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported. In case of patient's discontinuation, the investigator/site staff will inform the sponsor in a timely manner. This communication should always include the reason for withdrawal.

#### 3.3.4.1 Discontinuation of the trial

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

1. At least 2 subjects at one dose level within one population type, on active drug showed serum potassium levels $\geq$ 5.5 mmol/L in non-haemolysed blood
2. At least 2 subjects at one dose level within one population type, on active drug showed relevant individual QT prolongation, i.e. a QTcF increase of greater 60 ms from baseline (mean where applicable) in connection with absolute QT or QTcF greater than 500 ms, which has been confirmed by a repeat ECG recording. For CF subjects, the baseline for Treatment Period 2 will be calculated again at Visit 3 Day 1.
3. Failure to meet expected enrolment goals overall or at a particular trial site.
4. Emergence of any efficacy/safety information invalidating the earlier positive benefit risk- assessment that could significantly affect the continuation of the trial.
5. Violation of GCP, the CTP, or the contract disturbing the appropriate conduct of the trial.
6. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment.
7. For healthy volunteers, in the event of any subject having an, at least, possibly related SAE or in case of the occurrence of two, at least, possibly related severe AEs the study group will be halted. No further dosing, dose escalation or inclusion of any further subjects at the same dose will occur without approval of a substantial amendment
8. For CF subjects, in the event of 2 subjects having an, at least, possibly related SAE or in case of the occurrence of three, at least, possibly related severe AEs the study group

will be halted. No further dosing, dose escalation or inclusion of any further subjects at the same dose will occur without approval of a substantial amendment

The Investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the fifth reason).

### 3.3.5 Subject replacement

If more than 2 healthy volunteers per dose group do not complete up to the end of the dosing periods, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced.

A sufficient number of CF subjects (planned 24) should be recruited to ensure at least 20 completed both dosing periods. If less than 20 subjects complete both dosing periods, the trial clinical monitor together with the trial statistician are to decide if and how many subjects will be replaced.

To be considered as completing the dosing period, volunteers or subjects are required to be 80 - 120% compliant with treatment (section 4.3).

A replacement subject will be assigned a unique study subject number, and will be assigned to the same sequence as the subject he/she replaces.

# 4. TREATMENTS

## 4.1 INVESTIGATIONAL TREATMENTS

**The study medication below will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG**

1 mg BI 443651 (MW 571.12 g/mol) equals 1.26 mg BI 443651 salt form (MW 721 g/mol). The doses given below refer to the respective free base.

BI 443651 inhalation solution is administered via the Respimat® inhaler (Version 5).

### 4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product:

| | |
|---|---|
| Substance: | BI 443651 |
| Pharmaceutical formulation: | inhalation solution |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | 100 µg/actuation, 300 µg/actuation |
| Posology | b.i.d. |
| Route of administration: | Inhalation |
| Device: | RESPIMAT A5 |
| Duration of use: | 6.5 days, 13.5 days |

Table 4.1.1: 2 Placebo:

| | |
|---|---|
| Substance: | Placebo to BI 443651 |
| Pharmaceutical formulation: | inhalation solution |
| Source: | BI Pharma GmbH & Co. KG, Germany |
| Unit strength: | Not applicable |
| Posology | b.i.d. |

Table 4.1.1: 2 Placebo (cont.):

| | |
|---|---|
| Route of administration: | Inhalation |
| Device: | RESPIMAT A5 |
| Duration of use: | 6.5 days, 13.5 days |

A placebo matching the Respimat® platform Inhalation Solution will be used. It uses the same excipients as the verum. All Respimat® treatments will be double-blind.

### 4.1.2 Selection of doses in the trial

The dose levels to be studied in this trial are 100 µg, 400 µg, 1200 µg and 1800 µg b.i.d. in healthy volunteers and 600 µg b.i.d. in CF subjects. The background for this dose selection is described as follows:

*Starting and maximum dose*

Whilst 100 µg may be an efficacious dose, the selection of 100 µg as the starting dose is supported by the benign safety profile of BI 443651 observed in study 1363.1 at single doses of up to 3600 µg, including a lack of effect on serum electrolytes

To adequately address all these aspects 1800 µg b.i.d. has been selected as the maximum dose to be delivered in healthy volunteers. The highest doses for CF subjects will be 600 µg b.i.d, administered once the 1200 µg b.i.d. dose level is confirmed as safe and well tolerated in healthy volunteers.

The investigator can decide at any time to discontinue dosing, to decrease the dose escalation by adding intermediate doses in case of intolerability or decrease the dose based on safety concerns.

### 4.1.3 Method of assigning subjects to treatment groups

**Part 1 (MRD part):**
At Visit 2 (Day 1) eligible subjects will be randomized to treatment groups active or placebo for the current dose level under investigation in a 4:1 ratio. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT). To facilitate the use of the IRT, the investigator will receive all necessary instructions.

**Part 2 (cross-over part):**
At Visit 2 (Day 1) of the first period eligible CF subjects will be randomized to treatment sequences active-placebo/placebo-active in a 1:1 ratio. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT). To facilitate the use of the IRT, the investigator will receive all necessary instructions.

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

The trial will be divided into two parts:

1. multiple rising dose (Healthy volunteers)
2. multiple single dose (CF subjects)

For both parts of the study the treatment phase includes a multiple-dose phase starting on Day 1 in the morning and subjects will receive medication twice daily for:

- 6 days (Day 1-6) in healthy volunteers, with a single dose administration on Day 7
- 13 days (Day 1-13) in CF subjects in a cross-over design, with a single dose administration on Day 14

For CF subjects, a second treatment phase will follow a washout period of at least 30 days. (cf. Table 4.1.4: 1 and Table 4.1.4: 2 for treatments and posology overview)

Generally medication intake will be at the same time every day during the entire study to ensure a dose interval of 12 hours, respectively. The same study medication will be used during in-house confinement and outpatient periods.

Table 4.1.4: 1 Treatment overview healthy volunteers

| Treatment | Formulation, dose regimen | Route of administration | Number of actuations per single administration | Unit strength [µg] | Total dose per administration [µg] | Posology distribution over the treatment period |
|---|---|---|---|---|---|---|
| 1 | Inhalation solution, 13 administrations 12 hours apart | Inhalation | 1 | 100 | 100 | Day 1 to Day 6 a.m./ p.m. and Day 7 a.m. |

Table 4.1.4: 1 Treatment overview healthy volunteers (cont.)

| Treatment | Formulation, dose regimen | Route of adminis tration | Number of actuations per single administra tion | Unit strength [µg] | Total dose per administration [µg] | Posology distribution over the treatment period |
|---|---|---|---|---|---|---|
| 2 | Inhalation solution, 13 administrations 12 hours apart | Inhalation | 4 | 100 | 400 | Day 1 to Day 6 a.m./ p.m. and Day 7 a.m. |
| 3 | Inhalation solution, 13 administrations 12 hours apart | Inhalation | 4 | 300 | 1200 | Day 1 to Day 6 a.m./ p.m. and Day 7 a.m. |
| 4 | Inhalation solution, 13 administrations 12 hours apart | Inhalation | 6 | 300 | 1800 | Day 1 to Day 6 a.m./ p.m. and Day 7 a.m. |
| Placebo* | Inhalation solution, 13 administrations 12 hours apart | Inhalation | Matching active treatment | - | - | Day 1 to Day 6 a.m./ p.m. and Day 7 a.m. |

* Subjects receiving placebo are equally distributed across dose groups

Table 4.1.4: 2 Treatment overview CF

| Treatment | Formulation, dose regimen | Route of adminis tration | Number of actuations per single administra tion | Unit strength [µg] | Total dose per Administration [µg] | Posology distribution over the treatment period |
|---|---|---|---|---|---|---|
| 1 | Inhalation solution, 27 administrations** 12 hours apart | Inhalation | 2 | 300 | 600 | Day 1 to Day 13 a.m./ p.m. and Day 14 a.m. |
| Placebo* | Inhalation solution, 27 administrations 12 hours apart | Inhalation | Matching active treatment | - | - | Day 1 to Day 13 a.m./ p.m. and Day 14 a.m |

* Each subject will receive active and placebo
** Theoretical number of administrations when no time windows applied

Each newly assembled RESPIMAT Inhaler has to be primed by qualified, trained, unblinded study personnel, e.g. pharmacist at the trial site under the responsibility of the investigator, who is not involved in the conduct of the trial. Except those devices used for training, priming should NOT take place in the same room where the subject is inhaling trial medication or PK sample preparation. The inhaler should be primed by actuating it until an aerosol is visible plus three additional actuations. For detailed priming instructions please refer to the RESPIMAT Inhaler handling instructions in Appendix 10.1.

Both the study drug as well as the placebo treatment (depending on randomisation) will be inhaled with the RESPIMAT in a sitting or standing position under supervision of the investigating physician or an authorised designee (see section 4.3). Inhalation of study drug should NOT take place in the same room where the blood samples are taken, to prevent contamination of samples from airborne drug. If more than one actuation is needed, planned time 0:00h will always be the first actuation. If more than one actuation will be needed, the duration from first to last actuation will be recorded. After study drug inhalation, subjects will drink 250 mL of water.

The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. assembling of device), if correct dosage cannot be ensured otherwise.

For restrictions with regard to diet see section 4.2.2.3.

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

Patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock. According to the rising dose design, the current dose level will be known to subjects and investigators. At the trial site, access to the randomisation schedule is restricted to unblinded pharmacists.
The randomization code will be kept secret by Clinical Trial Support up to database lock. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.
The randomization codes will be provided to bioanalytics prior to last patient out to allow them to exclude PK samples taken from placebo subjects from the bioanalytical analyses.

The Trial Bioanalyst will sign a confirmation that the codes will be treated confidentially and that all unblinding information is restricted to the laboratory staff involved in sample analysis.

In addition, the trial pharmacometrician may receive the randomisation codes of part 1 of the trial prior to official unblinding to carry out analyses to guide further internal decision making. He or she will confirm in writing that the codes will be treated confidentially. The unblinded results are not to be presented prior to official unblinding of the trial.

In addition, the trial pharmacokineticist may receive the randomisation codes of part 1 of the trial prior to official unblinding to perform preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially. The unblinded results are not to be presented prior to official unblinding of the trial.

Within the ECG laboratory, 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 time the 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 study.

If an interim safety analysis of ECG data is required, a part of the staff of the ECG laboratory may be unblinded. This part of the staff is strictly separated from those parts of the staff, which is involved with interval measurements and assessments of single ECGs (blinded).

After completion of part 1 with HV an interim database lock will be made. After this the data of HV will be unblinded. The objective of the trial especially part 2 is not expected to be affected by this as part 1 with HV will be completed and the analysis will have no impact on the conduct (in the sense of randomisation, blinding and analyses of primary endpoint) of the second part.
After completion of part 2 the final database lock of the trial will occur and the trial will be fully unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation 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 subjects or in order to make decisions on dose escalation in case of stopping criteria being triggered. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date of when the code was broken.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual subjects during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

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

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

### 4.1.8 Drug accountability

The Investigator, Pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

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

The Investigator, Pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial subjects. The Investigator, Pharmacist and/or investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor, the Investigator, Pharmacist and/or investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator's possession.

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

For healthy subjects, no special emergency procedures are to be followed. However, in case of adverse events in need of treatment (e.g. treatment of hyperkalaemia), the investigator can authorise any required therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level, same holds true for patients.

#### 4.2.1.1 Rescue medication

Administration of PRN (Pro re nata (as occasion requires)) inhaled short acting β-adrenergics, inhaled short acting anticholinergics or combinations of both can occur at any time during the trial as deemed necessary by the subject or the investigator. However, the medication restrictions prior to lung function testing (please refer to section 4.2.2.2) must be observed as long as this is compatible with the safety of the subject. Otherwise there are no special emergency procedures to be followed.

During the whole course of the trial the site will be responsible for providing open-label

salbutamol/albuterol and / or atrovent HFA MDI to be used as rescue medication for all CF subjects at screening after they have signed their informed Consent.

Regarding the use of salbutamol for post-bronchodilator spirometry measurement please refer to Section 5.3.6.

If rescue medication is administered during clinic visits, the 24-hour clock time of rescue medication, total number of inhalations of salbutamol used, visit number, date and the name, route and dosage of any additional rescue medication will be recorded on the Rescue Medication eCRF page.

The use of rescue medication during all visits with laboratory sampling does not necessitate discontinuation of the visit. The subject should remain in the clinic in order to complete the blood sampling.

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medications causing alterations in serum electrolytes should not be administered during the study (a list of common medications effecting serum electrolyte balance is included in Table 4.2.2.1: 1). All concomitant medications must be assessed by the investigator for potential effects on serum electrolytes based on the summary of product characteristics (SPC), if applicable. Specific questions of eligibility based on this criterion should be clarified by the clinical monitor prior to inclusion. Medications not included in Table 4.2.2.1:1 may be administered at the discretion of the investigator e.g. paracetamol.

In case of adverse events in need of treatment, symptomatic therapy will be permitted as considered appropriate by the investigator. All concomitant and/or rescue therapies will be recorded (including time of intake on study days, except for salbutamol or atrovent rescue medication) on the appropriate pages of the CRF.

In addition, please note Section 4.2.2.2 regarding restrictions prior to forced spirometry and Section 4.2.2.3 regarding restrictions on diet and life style.

**Part 1 (MRD part)**

Healthy volunteers
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. Hormonal contraception must be used in WOCBP (section 10.7).

**Part 2 (cross-over part)**

Cystic Fibrosis

Table 4.2.2.1:1 provides an overview of permitted and restricted medications.

Table 4.2.2.1:1 Permitted and restricted medications

| **Class** | **Permission / Restriction and explanation** |
|---|---|
| Hormonal contraceptives | **Permitted** prior screening visit (Visit 1) and during the trial. |
| Pulmozyme® | **Permitted** provided that Pulmozyme has been stabilized at least 6 weeks prior to randomisation (Day 1) and will continue to be used during the trial in a stable manner. |
| Intravenous / oral antibiotics | **Not permitted** within 4 weeks of screening and during each treatment period when prescribed for exacerbation or acute infection. Continued stable therapy is permitted if given at that dose for at least 2 months prior to the screening visit (Visit 1) and will continue to be used during the trial in a stable manner. |
| Inhaled antibiotics | **Permitted** provided that antibiotics are started within 2 weeks prior to randomisation (Day 1) and will continue to be used during both treatment periods (including washout period),<br>**or** are started within 2 weeks prior to randomisation and re-started within 2 weeks prior to treatment period 2 (Visit 3). |
| Ivacaftor | **Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial. |
| Lumacaftor | **Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial. |
| Mucolytics including inhaled hypertonic saline, Inhaled or oral N-acetylcysteine, or inhaled glutathione | **Not permitted** 2 weeks prior randomization (Day 1) and during the trial. |
| Inhaled corticosteroids | **Permitted** provided that inhaled corticosteroids have been stabilized at least 6 weeks prior to randomization (Day 1) and will continue to be used during the trial in a stable manner (including combinations containing β-adrenergics). |
| Systemic corticosteroids | **Not permitted** 6 weeks prior screening visit (Visit 1) and during the trial. |
| Short acting inhaled β-adrenergics | **Not permitted except for supplied rescue medication.** Regarding restrictions for forced spirometry bronchodilators see Section 4.2.2.2. |
| Long acting inhaled β-adrenergics (mono-product or combined) | **Permitted** provided that inhaled long-acting anticholinergics have been stabilized at least 6 weeks prior to randomization (Visit 2) and will continue to be used during the trial in a stable manner. Regarding restrictions for forced spirometry bronchodilators see Section 4.2.2.2. |
| Antihistamines | **Permitted** if prescribed for non-asthma condition |

Table 4.2.2.1:1 Permitted and restricted medications (cont.)

| Class | Permission / Restriction and explanation |
|---|---|
| Investigational drugs | **Not permitted**, see exclusion criterion number 17 |
| Medications that may lead to alterations in serum electrolytes (particularly potassium) including but not limited diuretics* angiotensin convertase/ angiotensin receptor inhibitors**, nonsteroidal anti-inflammatory drugs (NSAIDs)***, cyclosporine or tacrolimus, Pentamidine, Trimethoprim-sulfamethoxazole, Heparin, Ketoconazole and Metyrapone | **Not permitted** 4 weeks prior screening visit (Visit 1) and during the trial |

*includes frusemide, spironolactone, amiloride
** includes Captopril, Zofenopril, enalapril, ramipril, Quinapril, Perindopril, Lisinopril, Benazepril, Imidapril Trandolapril, Fosinopril, Cilazapril;
*** includes ibuprofen, diclofenac, naproxen, celecoxib, mefenamic acid,etoricoxib, indomethacin, aspirin (doses > 600 mg)

### 4.2.2.2 Medication restrictions for all lung function testing

*CF subjects*

Throughout the study and post treatment period including end of study visit usual background medications and trial medication should not be taken before the morning pre-dose pulmonary function testing (forced spirometry) (Flow Chart II). An 8-hour minimum washout period for inhaled short-acting bronchodilators (such as salbutamol and ipratropium) must be maintained.

On visits with several spirometry (Day 1 and Day 14), background therapy may be given after the 30 min spirometry post BI 443651 administration.

For all subjects, even if subjects violated restrictions, as a general rule, scheduled procedures (after randomization) should neither be postponed nor skipped. Regarding diet and lifestyle restrictions for forced spirometry testing please refer to Section 4.2.2.3.

### 4.2.2.3 Restrictions on diet and life style

Diet and lifestyle restrictions before and after administration of trial medication:
While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in Flow Chart I & Flow Chart II.

Day 1, Day 7 and Day 14
While admitted to site on Day 1, Day 7 and Day 14, from 1 hour before drug intake until lunch, water intake and meals are restricted as per Flow Chart I & Flow Chart II. From lunch onwards (on Day 1, Day 7and Day 14), for healthy volunteers only, water intake must be up to an additional 750 mL (maximum 1,500 mL) until 1 hour prior to the evening drug administration.

The total amount of liquid intake will be documented.

For all subjects while in the unit, standardised meals will be served at the time points described in respective flowcharts. A snack is allowed (if completed) 1 hour prior to the morning dose, or started 30 minutes after the evening dose, post-body plethysmography (healthy volunteers only), if required. Use of additional table salt is not allowed during in-house confinement at the trial site.

On all other days (excl. Day 1, Day 7 and Day 14), no time restrictions will occur to meals outside of 07:00 to 20:00.

Grapefruits, Seville oranges and their juices should be avoided 7 days before and until the last PK timepoint. Excess of dried fruits (defined at > 1 standard adult portion per day) and dietary supplements containing high level of sodium and potassium should also be avoided during the trial. All non-prescribed supplements should be avoided.

For HV subject alcoholic beverages are not permitted from 48 hours prior to:

- screening
- study drug administration at Day 1, until after safety laboratory tests at Day 12.
- end of study visit

For CF subjects excess of alcoholic beverages are not permitted 48 hours prior to:

- screening
- each treatment period (Visit 2 & 3) at Day 1, until after safety laboratory tests at Day 14.
- end of study visit

Intake of methylxanthine-containing drinks or foods (coffee*, tea, cola*, energy drinks*, chocolate, etc.) are not allowed during in-house confinement and 8 hours prior to the morning of in-clinic appointments with pulmonary function tests.
*Decaffeinated beverages are allowed.

Subjects will have to adhere to restrictions resulting from ATS/ERS guidelines (P05-12782) for conduct of correct pulmonary function testing.

Excessive strenuous physical activities should be avoided starting from 72 hours prior to study drug administration and until the end-of-study examination.

Diet and lifestyle restrictions for lung function testing
The subject must refrain from strenuous activity for at least 24 hours prior to lung function testing (forced spirometry, body plethysmography ). Subjects should

also avoid cold temperatures, environmental smoke, dust or areas with strong odours (e.g. perfumes). Coffee, tea, chocolate, cola and other caffeine-containing beverages and foods, and ice-cold beverages are not allowed at least 8 hours prior to and during the pulmonary function testing period at site visits. Decaffeinated beverages are acceptable.

4.2.2.4 Restrictions regarding women of childbearing potential

WOCBP must use the highly effective methods of contraception as described in the subject information.

## 4.3 TREATMENT COMPLIANCE

Each subject will be trained in the correct use of the Respimat® inhaler using the training Respimat® inhaler with inserted placebo cartridge. Please refer to section 10.1.

Patients will be asked to return inhalation aerosols and devices (used and unused) to the study site. The trial medication adherence should be reviewed by the investigator and recorded on the appropriate drug accountability forms.

Compliance whilst in clinic will be assured by administration of all study medication under supervision of the investigating physician or a designee.

CF subjects will be reminded to administer drug during a phone call from site (morning and evening). The AM3® device will alarm to remind the patient to take drug. Drug administration (morning and evening) will be captured by site staff directly (whilst in clinic) or via telephone (whilst ex-clinic).
The measured plasma concentrations will provide additional information about compliance.

Estimating Compliance to trial medication

Compliance for Healthy Volunteers will be observed and recorded by site staff at the trial site. Compliance for CF subjects will be estimated using the records by site staff at the trial site (dosing in-clinic) and telephone calls to subjects (dosing at home). The acceptable medication compliance should have an overall value in the range from 80% to 120%. If the compliance is less than 80% or greater than 120%, the patient needs to be retrained. Randomised patients should not be discontinued for a lack of compliance without prior discussion with the clinical monitor.

# 5. VARIABLES AND THEIR ASSESSMENT

## 5.1 TRIAL ENDPOINTS

All endpoints listed below apply for both parts of the trial.

### 5.1.1 Primary Endpoint(s)

The primary endpoint to assess safety and tolerability of BI 443651, is the frequency (in percent) of subjects with treatment-emergent adverse events (TEAE) over the treatment period. The primary endpoint will be reported separately for Healthy volunteers and CF subjects.

### 5.1.2 Secondary Endpoint(s)

The following pharmacokinetic parameters will be determined if feasible forhealthy volunteers in Part 1

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After the first dose on Day 1:

- $C_{max}$ (maximum measured concentration of the analyte in plasma)
- $AUC_{0-12}$ (area under the concentration-time curve of the analyte in plasma until 12 h after the first dose)

After the last dose on Day 7 (:

- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval $\tau$)
- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval $\tau$)

### 5.1.3 Further Endpoint(s)

Further safety criteria of interest:

- Related AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)
- Pulmonary function tests ($FEV_1$, FVC, $FEF_{25-75}$)

## 5.3 ASSESSMENT OF SAFETY

### 5.3.1 Physical examination

A physical examination will be carried out according to the Flows Chart I & Flow Chart II and will be performed as complete physical examination; at screening and end of study (e.o.s.) visits. In addition further physical examination should be performed if clarification of an AE is necessary.
All clinically significant findings at screening will be documented on the source documents and recorded in the eCRF as baseline conditions.

After randomization, new clinically significant findings or worsening of screening conditions that are, in the opinion of the investigator, clinically significant or meet other adverse event criteria defined in Section 5.3.9 will be reported as adverse events.

Body weight and height will be determined at the screening visit (Visit 1) as per Flow Chart I & Flow Chart II. In addition body weight will be determined at end of study (e.o.s.) visit. Body weight and height will be documented on the source documents and recorded. Body height will be recorded in the spirometry measurement device and the body weight of the screening Visit 1 (relevant for body plethysmography assessment in CF subjects) will be recorded in the body plethysmography device and used for subsequent measurements.

### 5.3.2 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 Flow Chart I & Flow Chart II after subjects have rested for at least 5 min in a supine position (if blood sampling for PK/safety purposes will be drawn from a cannula, this procedure will not affect the resting time). Where possible, all recordings should be made using the same blood pressure recording instrument on the same arm.

### 5.3.3 Medical examinations

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

### 5.3.4 Spirometry

Spirometry will be performed according to ATS/ERS guidelines for pulmonary function testing [P05-12782] in order to characterise the study population, to monitor individuals safety in regard to CF and as an exploratory assessment of drug effect. The CF subjects must qualify by demonstrating a pre-bronchodilator clinic measured $FEV_1$ ≥70% of predicted normal (calculated according to GLI [R15-0845]) measured ≥ 8 hours after the last use of short acting bronchodilator at Visit 1 and prior to randomisation.

PFTs will be performed in triplicate using spirometry equipment provided by the site and calibrated by study staff on all test days. Equipment and techniques should conform to American Thoracic Society (ATS) criteria [P05-12782]. An ambulatory spirometer, Asthma Monitoring Device (AM3®), will be used to perform PFTs while the subject is at home (ex-clinic).

Spirometry in-clinic will be conducted with the subject in a seated position. Spirometry using the AM3® device will be conducted in a standing position. It is preferable that the same trained individual performs the PFTs for a given subject. The best of three efforts will be defined as the highest $FEV_1$ and the highest FVC each obtained on any of three blows meeting the ATS criteria (with a maximum of eight attempts). $FEV_1$, FVC, $FEF_{25-75}$ and PEF will be measured as indicated in Flow Chart I & Flow Chart II and recorded in the eCRF. Ex-clinic measured values of PEF will not need to be collected in the database. The best of the

three pre-dose $FEV_1$ measurements will be defined as trough $FEV_1$. The 24-hour clock time of the first manoeuvre for each PFT time point will be recorded.

### 5.3.5 Body Plethysmography

Airway resistance (Raw) will be measured with a constant volume whole-body plethysmograph as supplied and calibrated by the trial site. Measurements will be taken with the subject in the sitting position and carried out by an observer. The mean of at least three values recorded, will be taken as airway resistance. Refer to Flow Chart I for time points. Practice sessions can be performed with volunteers from consent and screening onwards for those volunteers that would like to experience the body plethysmography prior to collecting data. This data will not be captured or collected.

### 5.3.6 CF control during the trial

The safety of the subjects regarding CF during the trial will be assured by monitoring of $FEV_1$ and assessment of rescue and controller medication use and CF signs and symptoms. Subjects should be discontinued from the trial if, in the opinion of the Principle investigator, the subject is developing unstable CF, based on assessment of safety parameters described above.

The subjects will be instructed to make themselves available for the regular telephone monitoring for drug administration and their general well-being. Site staff will assess drug compliance, a subject's general well-being, rescue medication use and $FEV_1$ measurements via in-clinic visits, documented telephone monitoring and the AM3® device.

*At home (ex-clinic) $FEV_1$ measurements:*

At Day 1 for CF subjects, eligible subjects will receive hand-held electronic spirometers, [AM3®, eResearch Technology, Inc] from the site for their regular use during the entire study to monitor their $FEV_1$ whilst at home (Flow Chart II). In addition, CF subjects will perform an unsupervised manoeuvre on their AM3® device at screening (Day -7 to -3). The subject should perform three $FEV_1$ manoeuvres consistently, in a standing position with the AM3®. Instructions for use of the AM3® device will be provided to the subject.

All acceptable $FEV_1$ values are stored in the AM3® device with date and time of recording.

CF subjects:
Whilst the subject is at home (ex-clinic) morning and evening $FEV_1$ measurements will be performed on the AM3® prior to administration of study medication and background respiratory medication. In the morning, whilst the subject is at home (ex-clinic), the manoeuvre will be performed prior to or as part of the telephone visit under the supervision of the study site staff. If a relevant drop in $FEV_1$ compared to baseline (Day -7 to Day -3, morning, unsupervised AM3® manoeuvre) is observed the site staff will evaluate whether the subject needs to return to clinic prior to the morning visit.
During in clinic visits the AM3® data will be downloaded to a computer, the corresponding report printed and the data reviewed by the site in the morning on each visit day. The investigator will review/discuss the data with the subject and assesses the subject in regard to the data observed.
$FEV_1$ should also be measured at any time whenever the subject feels breathless or otherwise uncomfortable. The AM3® is primed to alarm following a 20% relative drop vs. baseline in

$FEV_1$. Subjects must not take their trial medication dose, and must call the site if the device alarms.
$FEV_1$ data will be downloaded to a computer at each visit and printed out for review, signature and date by the investigator. Equipment will be withdrawn at end of study. Print-outs will be filed in the ISF.

**Telephone visits:**
During the treatment period when subjects are at home (ex-clinic), regular appointments for telephone calls between subject and investigator will be made. Calls will be made in the morning and evening for CF subjects. The following issues will be covered at each telephone visits in a sequential way:

1. Subjects will be reminded to take their correct trial medication dose.
2. Subjects will be questioned regarding general wellbeing.
3. Whether the subjects have performed a $FEV_1$ measurement with the AM3® that evening or that morning, if not subjects will need to perform the measurements during the course of the telephone calls. Site staff will ask whether the AM3 device has alarmed.
4. Subjects will be asked whether any AEs have occurred
5. Subjects will be reminded to conduct a $FEV_1$ reading and subsequently administer drug in the following evening or morning.

In any case of emergency during the trial the investigator must be available by phone for immediate assistance, therefore the subjects will be provided with 24-hour contact details.

Note: Documentation of AE if any (also if related due to i.e. a worsening of AE), change of any medication and intake of study medication have to be captured in the medical records and eCRF.

Details of any telephone visits as mentioned above, will be documented as source data in the subjects medical records.

### 5.3.7 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in Flow Chart I & Flow Chart II.

If safety laboratory measurement is performed with other blood collection, e.g. PK sampling, safety laboratory measurement will always be performed first, preferably without any tourniquet.
The parameters that will be determined are listed in Tables 5.3.7: 1 and 5.3.7: 2. Reference ranges will be provided in the ISF

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

Table 5.3.7: 1 Routine laboratory tests

| Category | Test name | A[1] | B[2] | C[3] |
|---|---|---|---|---|
| Haematology | Haematocrit | X | X | X |
| | Haemoglobin | X | X | X |
| | Red blood cells (RBC) | X | X | X |
| | White blood cells (WBC) | X | X | X |
| | Platelets | X | X | X |
| | Reticulocyte count | X | X | X |
| Automatic WBC differential (relative and absolute) | Neutrophiles | X | X | X |
| | Eosinophils | X | X | X |
| | Basophils | X | X | X |
| | Monocytes | X | X | X |
| | Lymphocytes | X | X | X |
| Manual differential WBC (if automatic differential WBC is abnormal) | Polymorphnuclear neutrophils (segs), band (only for HV) neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes | | | |
| Coagulation | Activated partial thromboplastin time (aPTT) | X | X | X |
| | Prothrombin Time (Quick and INR) | X | X | X |
| Enzymes | Aspartate aminotransferase (AST/GOT, SGOT) | X | X | X |
| | Alanine aminotransferase (ALT/GPT, SGPT) | X | X | X |
| | Alkaline phosphatase | X | X | X |
| | Gammaglutamyl transferase (GGT) | X | X | X |
| | Lactate dehydrogenase | X | X | X |
| | Amylase | X | X | X |
| | Lipase | X | X | X |

Table 5.3.7: 1 Routine laboratory tests (cont.)

| Category | Test name | A[1] | B[2] | C[3] |
|---|---|---|---|---|
| Substrates | Glucose (plasma) | X | - | - |
| | Creatinine | X | X | X |
| | eGFR, calculated from serum creatinine using | X | X | X |
| | CKD-EPI formula | - | - | - |
| | Bilirubin, total | X | X | X |
| | Bilirubin, direct | X | X | X |
| | Cholesterol, total | X | X | X |
| | Triglycerides | X | X | X |
| | C-reactive protein | X | X | X |
| | Urea | X | X | X |
| Electrolytes | Calcium | X | X | X |
| | Sodium | X | X | X |
| | Potassium | X | X | X |
| | Chloride | X | X | X |
| Hormones | Thyroid stimulating hormone (TSH) | X | - | - |
| | Progesterone | X | ** | - |
| Urinalysis (Stix) [Urin-Sediment will be performed, if urinalysis abnormal] | Urine nitrite | X | - | X |
| | Urine protein | X | - | X |
| | Urine glucose | X | - | X |
| | Urine ketone | X | - | X |
| | Urobilinogen | X | - | X |
| | Urine bilirubin | X | - | X |
| | Urine RBC | X | - | X |
| | Urine WBC | X | - | X |
| | Urine pH | X | - | X |
| * From urine collection at 0-4, 4-8 and 8-12 hr | Urine potassium | - | X | - |
| | Urine sodium | - | X | - |
| | Urine chloride | - | X | - |
| | Urine creatinine | - | X | - |
| | Potassium-creatinine-quotient | - | X | - |
| | Sodium-creatinine-quotient | - | X | - |
| Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine) | Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes) | | | |

[1]A: parameters to be determined at screening examination
[2]B: parameters to be determined during the study (for time points refer to Flow Chart I & Flow Chart II)
[3]C: parameters to be determined during the Follow-up-examination
* Urine collected and samples taken from 0-12h will be stored at room temperature. Only to be collected on PK profile days for HV.
** Progesterone will need to be taken prior to second treatment period, for WOCBP.

The tests listed in Table 5.3.7: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. It is planned to perform these tests during screening only. Drug screening will be performed at screening and on Day 1.

Table 5.3.7: 2 Exclusionary laboratory tests

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

The laboratory tests listed in Table 5.3.7: 1 and 5.3.7: 2 will be performed by the central laboratory, with the exception of the urine pregnancy tests (administered using a urine dipstick), urine drug abuse and alcohol breath tests.

With regards to serum electrolytes samples, where local laboratory results are also used, central laboratory results will take precedence in the interpretation of the results. Local laboratory results will be stored as source data at the trial site and will take precedence for initial and continued dosing decisions (e.g. K+). Local laboratory values will not be entered into the database.

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

### 5.3.8 Electrocardiogram

Standard 10 second twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (MAC 2000, GE Medical Systems, Freiburg, Germany) at the time points given in Flow Chart I & Flow Chart II. 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.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5 min in a supine position (if blood sampling for PK/safety purposes will be drawn from a cannula, this procedure will not affect the resting time). The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point to avoid impact of sampling on the ECG quality.

Triple ECGs (three ECGs recorded within 180 sec) will be recorded as the baseline on Day 1, before the first drug administration for all volunteer and subject groups. A second baseline

will be performed on Day 1 of Treatment Period 2 for CF subjects. For the healthy volunteers group all ECGs on Day 1, 2, 7 and 8, will be recorded in triplicate. For all other subject groups, single ECGs will be recorded, except for baseline (Day 1).

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation).

All ECGs that are locally printed will be evaluated by the investigator or a designee. For triplicate ECG QTcF values, the mean value will be calculated and interpreted by the investigator or designee. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths and not evaluated centrally.

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 ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralised evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment. For all volunteers and subjects, for determination of safety and continued inclusion in the study the mean ECG of triplicates will be used for the evaluation.

All ECGs will be stored electronically and transmitted to an ECG core lab
). At minimum, electrocardiograms recorded at the following time points will be evaluated centralized at the core lab:

- Healthy volunteers: Days 1 and 2, and Days 7 and 8 (triplicate ECGs, only)
- CF subjects: All ECGs

The analysis will include the determination of the intervals RR, PR, QRS and QT measured semi-automatically. Other parameters (e.g. cardiac axis) are determined by a validated GE 12-SL-algorithm or equivalent but do not undergo semi-automatic evaluation. All 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. HR and QTc (QT interval corrected for HR, e.g. QTcF and QTcB) will be determined in-house (see TSAP for details).

For CF subjects, morphological analyses of the centrally evaluated ECGs (see above) will be performed by a board-certified cardiologist or equivalent. In case of triplicate ECGs recorded at a time point one ECG will be selected randomly for this evaluation. In case additional (unscheduled) ECGs due to safety reasons are recorded at the study site, these ECGs are assigned to the previous scheduled time point, and all ECGs of this time point including the additional ECGs will undergo interpretation. The ECG interpretation will include an overall assessment and a classification of each finding (normal, abnormal clinically relevant, abnormal clinically not relevant, not assessable), in regard to rhythm, conduction and morphological abnormalities, presence of myocardial infarction, ST segment deviations, T-wave morphology (normal, flat, inverted or biphasic) and presence of U-wave (normal and

abnormal). Abnormalities detected during centralised ECG evaluation will not necessarily qualify as AE.

For blinding arrangements see section 4.1.5.

For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs. After the quality control the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311, R13-0801, R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

### 5.3.10 Assessment of adverse events

5.3.10.1 Definitions of Adverse Events (AEs )

**Adverse event**
An adverse event (AE) is defined as any untoward medical occurrence in a subject 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.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

**Serious adverse event**
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the subject or might require intervention to prevent one of the other outcomes listed above. 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. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

**AEs considered "Always Serious"**
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 given above. Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

The latest list of "Always Serious AEs" can be found in the Remote Data Capture (RDC) system. These events should always be reported as SAEs as described above.

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

The following are considered as AESIs in this trial:

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- an elevation of AST and/or ALT $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations $\geq$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 RDC system
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results

(ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

**Intensity of AEs**

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

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

**Causal relationship of AEs**

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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 diminished).

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

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

- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

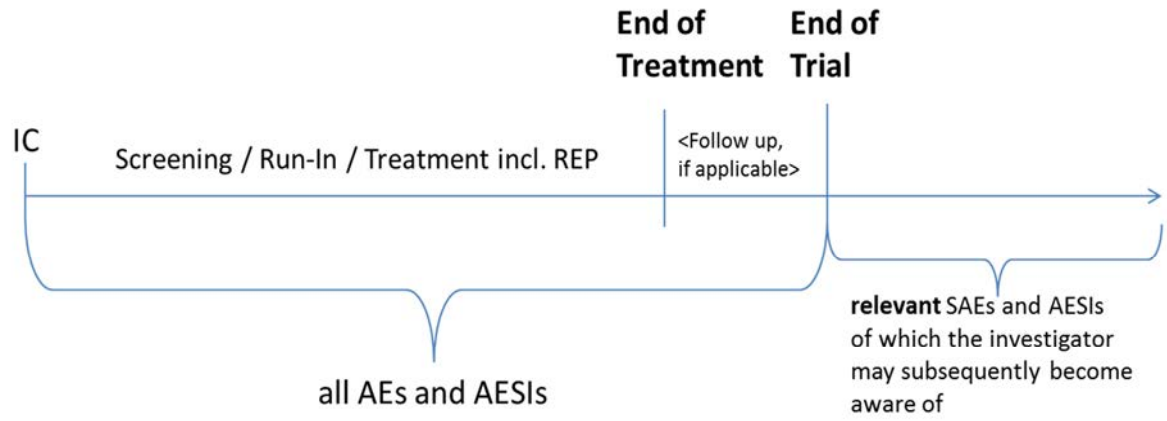
5.3.10.2 Adverse event collection and reporting

**AE Collection**
Upon enrolment into the trial, a subject's baseline conditions will be assessed (by documentation of medical history, concomitant diagnoses etc) at screening, and relevant changes from baseline will be subsequently noted.

Subjects will be required to report any AEs as well as the time of onset, end, and intensity of these events. In addition, each subject will be regularly assessed for AEs 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 Flow Chart I & Flow Chart II. Where no AEs are observed at these time points, the Investigator, or other members of site staff should document, 'No AEs Observed'. 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.
The Investigator shall maintain and keep detailed records of all AEs in their patient files.

A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.
The following must be collected and documented on the appropriate CRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until 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, 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 into the CRF or trial database and will not be reported in the CTR.
  - However, if an individual subject discontinues trial medication prematurely but stays in the trial (i.e. if further visits at home incl. telephone visits are planned) from then on and until the individual subject's end of the trial the Investigator must report related SAEs and related AESIs.
- After the individual subject's end of trial:
  the Investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.




The REP for BI 433651 is defined as 30 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please see Section 7.3.4. Events which occurred after the REP and before trial termination date will be considered as follow-up events.

**AE reporting to sponsor and timelines**
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours ) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

**Information required**
For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug and a Non-Investigational Medicinal Product (NIMP).

The following should also be recorded as an (S)AE in the CRF and 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 trial inclusion they will be considered as baseline conditions.

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

**Pregnancy**
In rare cases pregnancy may occur in a clinical trial. Once a subject has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) any potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used. This includes if the subject is female and becomes pregnant, or the subject is male and his female partner becomes pregnant.

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 B).

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

## 5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

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

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken per subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

### 5.4.1 Assessment of Pharmacokinetics

Pharmacokinetic endpoints are listed in section 5.1. Further details will be given in the TSAP.

### 5.4.2 Methods of sample collection

5.4.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 443651 plasma concentrations, 4.0 mL of blood will be taken from an antecubital or forearm vein into a K-EDTA (potassium ethylenediaminetetraacetic acid) anticoagulant blood drawing tube at the times indicated in Flow Chart I & Flow Chart II. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The K-EDTA-anticoagulated blood samples will be centrifuged for about 10 min at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in

polypropylene (PP) tubes. The first aliquot should contain at least 1.0 mL plasma, the second aliquot will contain the remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min. Immediately after centrifugation the samples should be pipetted and put into the freezer. For each aliquot the time when the sample was placed in the freezer will be documented.

The plasma samples have to be stored at about -20°C or below at the clinical site until shipment on dry ice to the logistic CRO. They will also be stored at about -20°C or below at the logistic CRO and the analytical laboratory until analysis. Further details on sample collection, preparation of plasma aliquots, sample handling, and shipping are provided in the lab manual.

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

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

### 5.4.3 Analytical determinations

BI 443651 concentrations in plasma will be determined by validated LC-MS/MS

(liquid chromatography tandem mass spectrometry) assays. All details of the analytical methods will be available prior to the start of sample analysis. Analyses will be performed at Drug Metabolism & Pharmacokinetics Germany, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis..

### 5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

If applicable, an exploratory PK-PD analysis may be undertaken.

## 5.5 ASSESSMENT OF BIOMARKER(S)

This section is not applicable.

## 5.7 APPROPRIATENESS OF MEASUREMENTS

The primary and secondary endpoints are standard and accepted for evaluation of safety, tolerability, and PK of an inhaled drug, and are widely used in this kind of studies.

The PK parameters and measurements outlined in Section 7.3.5 are generally used as measurements to assess drug exposure.
All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine PK parameters in an appropriate way.

Therefore, overall, all measurements applied in this trial are considered by the sponsor to be appropriate.

# 6. INVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows are given in Flow Chart I & Flow Chart II.

Study measurements and assessments scheduled to occur 'before' trial medication administration on the main PK sampling days - Day 1, Day 7 and Day 14 - are to be performed and completed within 180 mins prior to drug administration.

The acceptable deviation from the scheduled time for vital signs, ECG, lung function testing and laboratory tests will be ±15 min during the 2 hours after the first drug administration on the main PK sampling days (Day 1, Day 7 and Day 14) and ±45 min for vital signs, ECG, lung function testing and laboratory tests at all other time points.

Pre-dose blood samples for PK will be taken from 15 minutes prior to dosing. The acceptable deviation from the scheduled time for PK sampling on the main PK sampling days (Day 1, Day 7 & Day 14) will be ±5 min during the 4 hours after the first drug administration, ±10 min from 4h to 8h and ±15 min from 8h to 12h. On all other days, the acceptable deviation from the scheduled time for PK sampling will be ±15 min.

The tolerance for drug administration will be the following:

- ± 30 min on Days 1 and 7
- ± 30 min on Day 14 for CF subjects
- ± 45 min on all other treatment days.

If scheduled in Flow Chart I & Flow Chart II at the same time as a meal, blood sampling and vital signs, the 12- lead ECG recordings have to be done first. In general, if several measurements including venepuncture are scheduled for the same time, venepuncture should be on the time-point of the measurements, and lung function will be the last procedure due to its inconvenience to the patient and possible influence on physiologic parameters (see section 5.3.4).

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

If a volunteer/subject misses an appointment, it will be rescheduled if possible. Relevant time violations will be identified and their handling discussed no later than at the Report Planning Meeting.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening and run-in period(s)

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.3.1 to 5.3.8.

### 6.2.2 Treatment period(s)

Each subject will receive the respective trial medication (BI 443651 or placebo b.i.d.) at Day 1 until Day 6 for healthy volunteers, and Day 13 for CF subjects, and then one dose of the respective trial medication (BI 443651 or placebo) in the morning of the final day. CF subjects will undergo subsequent washout period of at least 30 days prior to an additional two weeks of respective trial medication i.e. the alternative medication administered during the first treatment period.

Trial medication will be administered by each subject (under direct supervision, whilst in-clinic of the investigator or his designee). Details on treatments and procedures of administration are described in Section 4.1.4.

All healthy volunteers and CF subjects will attend the trial site, as per Flow Chart I & Flow Chart II, after formal assessment and confirmation of their fitness by the investigator or designee. On all other study days, the study will be performed in an ambulatory fashion (at home / ex-clinic).

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

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

### 6.2.3 End of Trial Period

For AE assessment, laboratory tests, recording of ECG and vital signs, physical examination, weight and pregnancy test for female subjects of child bearing potential, during the end of trial period, see Sections 5.3.1 to 5.3.7.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the follow-up and end of trial visit.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

### 7.1.1 Objectives

Part 1 (MRD): The primary objective is to investigate safety, and tolerability of orally inhaled administration of BI 443651 for 6.5 days b.i.d, in healthy male and female volunteers following administration of 100 µg b.i.d., 400 µg b.i.d., 1200 µg b.i.d. and 1800 b.i.d. µg.

Part 2 (cross-over): The primary objective is to investigate the safety and tolerability of orally inhaled administration of BI 443651 in stable male and female CF subjects following administration of repeated doses of 600 µg b.i.d. BI 443651 over 13.5 days.

For both parts, the primary safety endpoint is defined in Section 5.1.1. Inferential statistics are not planned (as explained in Section 7.2).

The secondary objective for part 1 is the exploration of the pharmacokinetics of BI 443651 after multiple dosing.

PK endpoints as specified in Section 5.1 will be analysed by descriptive statistics.

Secondary PK endpoints as defined in Section 5.1.2 will be subjected to analysis of dose proportionality by use of the power model for part 1 of this trial.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 5 groups of 5 different dose levels of BI 443651 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.
For both trial parts, confidence intervals will be computed and will have 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

The statistical analysis will be based on the following analysis sets.

- Enrolled set (ES): This subject set includes subjects that signed informed consent and underwent screening procedures.
- Randomized set (RS): This subject set includes all randomised subjects, whether treated or not.
- 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.

- Pharmacokinetic set (PKS): The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description in Section 7.3.2. Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

All individual data will be listed.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Blinded Report Planning Meeting and pre-defined in the TSAP.

### 7.3.1 Primary endpoint analyses

Analysis of safety and tolerability is described in Section 7.3.4.

### 7.3.2 Secondary endpoint analyses

The secondary PK parameters (refer to Section 5.1.2) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472, current version). Analyses will be performed for parent drug.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol violation relevant to the evaluation of PK (to be decided no later than in the Blinded 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 concentrations and/or parameters of a subject will be considered as non-evaluable, if for example missing samples/concentration data occur at important phases of the PK disposition curve.

Assessment of dose proportionality (Part 1 only)

Dose proportionality will be assessed using the secondary pharmacokinetic endpoints after the first dose $AUC_{0-12}$, $C_{max}$ and after the last dose $AUC_{\tau,ss}$, $C_{max,ss}$ as specified in Section 5.1.2 for HV.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

| | |
|---|---|
| $Y_{ij}$ | logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, …, 4, j = 1, …, 8 for HV |
| $\alpha$ | intercept parameter; |
| $\beta$ | slope parameter; |
| $X_i$ | logarithm of dose i; |
| $\varepsilon_{ij}$ | random error associated with subject j at dose level i (assumed to be independent and identically normally distributed). |

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

For further details refer to the TSAP (such as selection of covariance structure and comparison of time points).

### 7.3.4 Safety analyses

Safety will be assessed for the endpoints and parameters of interest listed in Section 5.1.1 and 5.1.3 based on the treated set. Safety analyses (except of ECG data) will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The control group for HV in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. For CF, each subject will appear in the active treatment group and the placebo group, due to the cross-over structure. The active treatment groups will be compared to the respective 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.
The analyses will be done by 'randomised treatment'.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until next intake or the end of REP will be assigned to the preceding treatment, and all AEs occurring between the end of REP and next treatment intake or trial termination date respectively will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Please note that AEs occurring after the last per protocol contact but entered before database lock will be reported to drug safety only and will not be captured in the trial database.

Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment emergent'.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.3.10.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial, follow-up period and at the end of trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment. Baseline refers to the last measurement before drug administration.

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.

### 7.3.5 Pharmacokinetic and pharmacodynamic analyses

The pharmacokinetic parameters listed in Section 5.1 for BI 443651 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3) will be reported with their individual plasma / urine concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

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

## 7.4 INTERIM ANALYSES

No formal inferential statistical interim analysis is planned. However, after each dose group the investigator (or deputy) is allowed to postpone further dose progression until a preliminary safety review (refer to Section 3.1.2) of the data already obtained has been performed. For details of handling of treatment blinding refer to Section 4.1.5.

As this trial is conducted in two separate parts, these two parts will be evaluated separately after each completion.

### 7.4.1 Analysis of Part 1 (HV)

After completion of part 1 with HV the final unblinded analysis of this data will be performed to enhance further project planning. As this will only occur after all HV have completed the trial the potential for bias seems to be low and does not outweigh practical considerations.

To support this analysis the data obtained from part 1 will be cleaned and an interim database lock will be made before unblinding and finalization of the outputs. For details of handling of treatment blinding refer to Section 4.1.5. Logistical details will be documented in a separate logistics plan stored in TDMAP. The unblinded results will be summarized in a draft CTR. It is not planned to repeat the final analyses of part 1 data after completion of both trial parts. However, the analyses could be repeated in case of changes of the underlying data (e.g. update of MedDRA version) are necessary.

### 7.4.2 Analysis of Part 2 (CF)

After completion of part 2 with CF subjects the final analyses of this study will be performed. The draft CTR containing the results from part 1 will be updated with the final analysis.

## 7.5 HANDLING OF MISSING DATA

### 7.5.1 Safety and efficacy

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

For the assessment of lung function, missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

### 7.5.2 Plasma drug concentration - time profiles

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

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

### 7.5.3 Pharmacokinetic parameters

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

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

## 7.6 RANDOMISATION

For Part 1, healthy volunteers will be randomised within each dose group in a 4:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

For Part 2, otherwise healthy CF subjects will be randomised to one of the two treatment sequences in a 1:1 ratio. The block size will be documented in the CTR.

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, which involves 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).

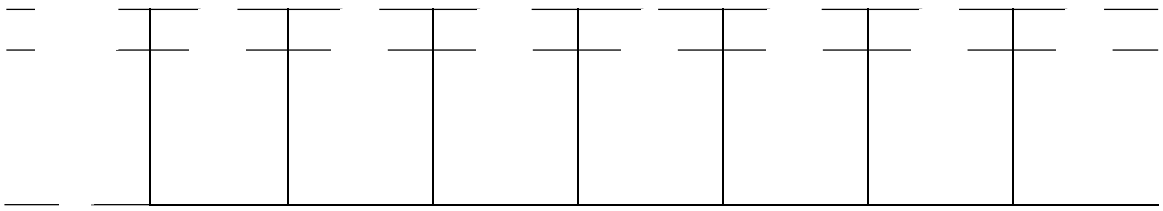
Access to the codes will be controlled and documented.

## 7.7 DETERMINATION OF SAMPLE SIZE

For Part 1, it is planned to include a total of 40 healthy volunteers. The planned sample size is not based on a power calculation. The size of 10 healthy volunteers per dose group (8 on active treatment, and 2 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 [R95-0013].

Additional healthy volunteers may be entered to allow testing of additional intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 40.

For Part 2, it is planned to include a total of 24 (12 per sequence) otherwise healthy CF subjects



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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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 Tripartite 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.

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also 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 rule, no trial results should be published prior to finalization of the Clinical Trial Report. The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF (Investigator Site File).

## 8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to subject 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 patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each subject or the subject's legally accepted representative."

The Investigator must give a full explanation to trial subjects based on the patient information form. A language understandable to the subject should be chosen, technical terms and expressions avoided, if possible. The subject must be given sufficient time to consider participation in the trial. The Investigator 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 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.

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

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

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, 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

Case Report Forms (CRF) 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 that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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

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

If the subject is not compliant with the protocol, any corrective action e.g. re-training must be documented in the subject file.
For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, date or 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
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (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)
- Completion of Subject's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- 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 subject 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 sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The Investigator /institution will allow on-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 CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor 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 ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to subject safety and data quality.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents

(paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor 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 ICH GCP.
An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

The Investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results The CRA and auditor 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 ICH GCP.

### 8.3.3 Storage period of records

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

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local 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 below. Subject privacy will be ensured by using subject identification code numbers.

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

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 as a result of the trial

need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

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

## 8.6 TRIAL MILESTONES

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

**The end of the trial** is defined as the date of the last visit of the last subject in the whole trial ("Last Patient Out") 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. The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last subject at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

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# 10. APPENDICES

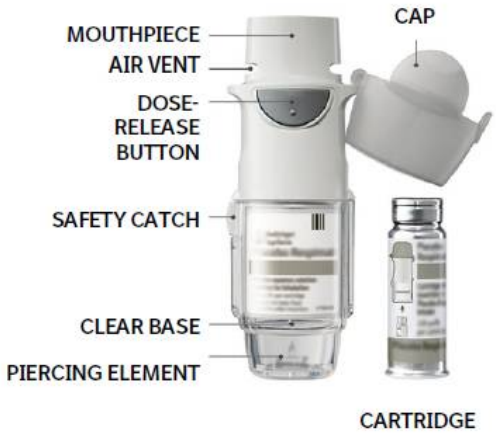
## 10.1 HANDLING INSTRUCTIONS FOR RESPIMAT INHALER FOR USE IN CLINICAL TRIALS

**Instructions For Demonstration**

These instructions explain generally the use of BI 443651 RESPIMAT inhaler. Depending on the clinical study, the product is administered under direct medical supervision or used by patients at home. Depending on the situation, the Instructions can be adapted to the specific situation as need be.

Read these Instructions for Use before you start demonstrating or using RESPIMAT.

**Figure 10.1:1**




**How to store BI 443651 RESPIMAT**

- Keep BI 443651 RESPIMAT out of the sight and reach of children.
- Do not freeze BI 443651 RESPIMAT. For further storage conditions, please refer to product label.
- If BI 443651 RESPIMAT has not been used for more than 1 day, repeat steps 4 to 6 under ‘Prepare for first Use’ until a cloud is visible. Then repeat steps 4 to 6 three more times.
- Do not use BI 443651 RESPIMAT after the expiry date

**How to care for BI 443651 RESPIMAT**

Clean the mouthpiece including the metal part inside the mouthpiece with a damp cloth or tissue only, at least once a week.
Any minor discoloration in the mouthpiece does not affect BI 443651 RESPIMAT inhaler performance.

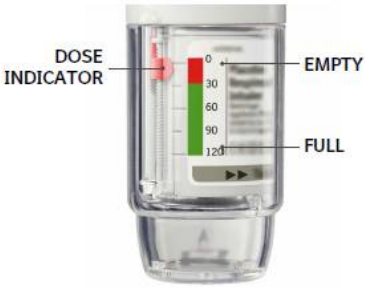
## When to get a new BI 443651 RESPIMAT

**Figure 10.1:2**

| | |
|---|---|
| **1. Remove clear base**<br>• Keep the cap closed.<br>• Press the safety catch while firmly pulling off the clear base with your other hand. |  |
| **2. Insert cartridge**<br>• Insert the narrow end of the cartridge into the inhaler.<br>• Place the inhaler on a firm surface and push down firmly until it snaps into place. |  |
| **3. Replace clear base**<br>• Put the clear base back into place until it clicks. |  |
| **4. Turn**<br>• Keep the cap closed.<br>• Turn the clear base in the direction of the arrows on the label until it clicks (half a turn). |  |
| **5. Open**<br>• Open the cap until it snaps fully open. |  |
| **6. Press**<br>• Point the inhaler toward the ground<br>• Press the dose-release button.<br>• Close the cap.<br>• Repeat steps 4-6 until a cloud is visible.<br>• After a cloud is visible, repeat steps 4-6 three more times. |  |

**Prepare for first use**

**Figure 10.1: 3**

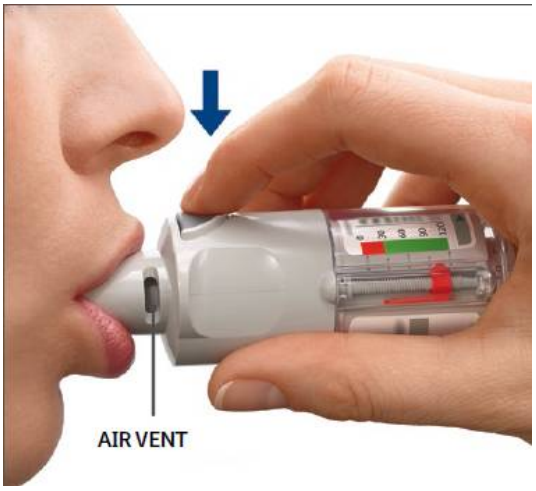



BI 443651 RESPIMAT inhaler contains 120 puffs if used as indicated.

- The dose indicator shows approximately how much medication is left.
- When the dose indicator enters the red area of the scale, get a new BI 443651 RESPIMAT from the investigational site; there are approximately 30 puffs left.
- Once the dose indicator reaches the end of the red scale, BI 443651 RESPIMAT locks automatically – no more doses can be released. At this point, the clear base cannot be turned any further. The inhaler should not be discarded; it should be returned to investigational site.

**Daily use**

**Figure 10.1:4**

| | |
|---|---|
| **TURN**<br>• Keep the cap closed.<br>• TURN the clear base in the direction of the arrows on the label until it clicks (half a turn). |  |
| **OPEN**<br>• OPEN the cap until it snaps fully open. |  |
| **PRESS**<br>• Breathe out slowly and fully.<br>• Close your lips around the mouthpiece without covering the air vents.<br>• While taking a slow, deep breath through your mouth, PRESS the dose-release button and continue to breathe in.<br>• Hold your breath for 10 seconds or for as long as comfortable.<br>• Repeat Turn, Open, Press for a total of puffs required by the clinical trial protocol. |  |

## Answers to Common Questions

**It is difficult to insert the cartridge deep enough.**

**Did you accidentally turn the clear base before inserting the cartridge?** Open the cap, press the dose-release button, then insert the cartridge.
**Did you insert the cartridge with the wide end first?** Insert the cartridge with the narrow end first.

**I cannot press the dose-release button.**

**Did you turn the clear base?** If not, turn the clear base in a continuous movement until it clicks (half a turn).
**Is the dose indicator on BI 443651 RESPIMAT pointing to zero?** BI 443651 RESPIMAT inhaler is locked after 120 puffs. Prepare and use a new BI 443651 RESPIMAT inhaler.

**I cannot turn the clear base.**

**Did you turn the clear base already?** If the clear base has already been turned, follow steps "OPEN" and "PRESS" under "Daily Use" to get your medicine.
**Is the dose indicator on the BI 443651 RESPIMAT pointing to zero?** The BI 443651 RESPIMAT inhaler is locked after 120 puffs. Prepare and use your new RESPIMAT inhaler.

**The dose indicator on the BI 443651 RESPIMAT reaches zero too soon.**

**Did you turn the clear base before you inserted the cartridge?** The dose indicator counts each turn of the clear base regardless whether a cartridge has been inserted or not.
**Did you spray in the air often to check whether the BI 443651 RESPIMAT is working?** Once you have prepared BI 443651 RESPIMAT, no test-spraying is required if used daily.
**Did you insert the cartridge into a used RESPIMAT?** Always insert a new cartridge into a **NEW** RESPIMAT.

**BI 443651 RESPIMAT sprays automatically.**

**Was the cap open when you turned the clear base?** Close the cap, then turn the clear base.
**Did you press the dose-release button when turning the clear base?** Close the cap, so the dose-release button is covered, then turn the clear base.
**Did you stop when turning the clear base before it clicked?** Turn the clear base in a continuous movement until it clicks (half a turn).

**BI 443651 RESPIMAT doesn't spray.**

**Did you insert a cartridge?** If not, insert a cartridge.
**Did you repeat Turn, Open, Press less than three times after inserting the cartridge?** Repeat Turn, Open, Press three times after inserting the cartridge as shown in the.steps 4 to 6 under "Prepare for first Use".
**Is the dose indicator on BI 443651 RESPIMAT pointing to 0?** If the dose indicator points to 0, you have used up all your medication and the inhaler is locked.

Once BI 443651 RESPIMAT is assembled, do not remove the clear base or the cartridge. Always insert a new cartridge into a **NEW** RESPIMAT.

**Further information**

BI 443651 RESPIMAT inhaler must not be disassembled after inserting the cartridge and replacing the clear base.
Do not touch the piercing element inside the base.

Boehringer Ingelheim Pharma GmbH & Co. KG
D - 55216 Ingelheim, Germany

## 10.4 PHARMACOKINETIC ANALYSES

N/A

## 10.5 HANDLING PROCEDURE OF BLOOD SAMPLES FOR PLASMA CONCENTRATION-TIME MEASUREMENTS

N/A

## 10.6 CF EXACERBATION

A CF Pulmonary exacerbation is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (equivalent to approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination (PE) of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

## 10.7 CONTRACEPTION SECTION

All female subjects (and female partners of male subjects) are regarded as being of childbearing potential unless they are either post-menopausal or permanently sterilised. Post-menopausal is defined as having had, at least, 12 months spontaneous amenorrhea with an appropriate clinical profile (age, vasomotor symptoms, etc.). Females may have

been permanently sterilised by means of hysterectomy, bilateral salpingectomy, bilateral oophorectomy, confirmed tubal occlusion or tubal ligation.

All female subjects of child bearing potential must use two acceptable methods of contraception with their partners, from screening until 30 days after the last dose of IMP. Male subjects with female partners of child bearing potential must use condoms plus any one other acceptable method of contraception together with their partners, from first dose until 3 months after the last dose of IMP. Alternatively, true heterosexual abstinence is also acceptable (this must be due to subject's lifestyle choice i.e. the subject should not become abstinent just for the purpose of study participation; withdrawal or calendar methods are not considered acceptable).

Acceptable methods of contraception for female subjects:

• Condoms

• Established hormonal contraception in the form of combined oral monophasic contraception

Acceptable methods of contraception for male subjects with female partners of childbearing potential include:

• Condoms

• Established hormonal contraception

• Intrauterine device (IUD) / intrauterine hormone-releasing system (IUS).

Male subjects with pregnant partners are excluded. Male subjects must not donate sperm until 3 months after the dose of IMP

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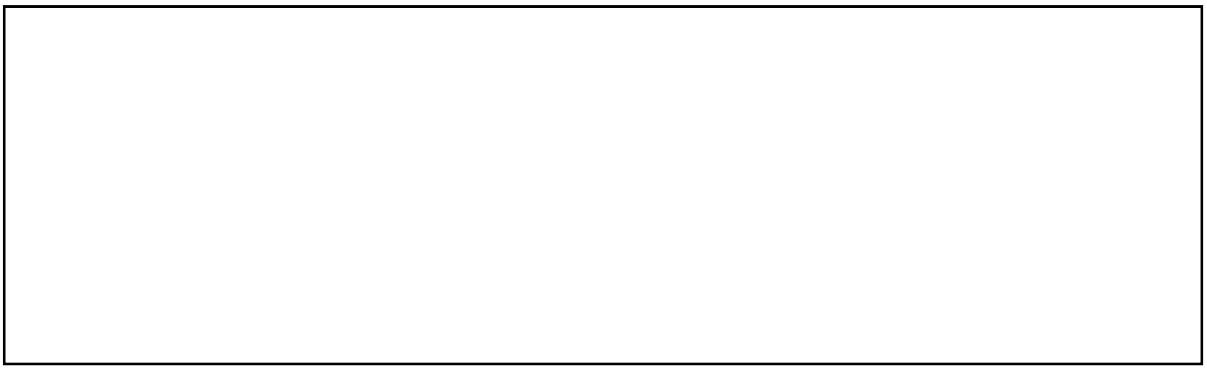

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

| | | |
|---|---|---|
| **Number of global amendment** | | 1 |
| **Date of CTP revision** | | 13 October 2016 |
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers, and COPD and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | X | |
| **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 I, II & III; Sections 3.1.2, 4.1.4, 4.2.2.3, 5.1.2, 5.1.3, 5.3.9, 5.4.2.3, 6.1, 6.2.2, 7.1, 7.3 |
| **Description of change** | | Reduction to 7 days treatment for healthy volunteers, removal of body plethysmography time points, |
| **Rationale for change** | | Review of data from 1363.1. |
| | | |
| **Section to be changed** | | Section 5.3.4, 5.3.7, 5.3.10 |
| **Description of change** | | Clarity over details entered in the database: spirometry ex-clinic, local laboratory values, AEs considered ”always serious”, in appendices |
| **Rationale for change** | | Clarification. |
| | | |
| **Section to be changed** | | Flow Chart I, II & III; Sections 3.1.2, |
| **Description of change** | | Clarification over follow-up period and REP. |
| **Rationale for change** | | Response to MHRA questions / clarification, |

| | | |
|---|---|---|
| **Number of global amendment** | | 2 |
| **Date of CTP revision** | | 01 December 2016 |
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers, and COPD and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | X | |
| **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 Charts I, II & III; Sections 3.1.2, |
| **Description of change** | | Extension of follow-up period and REP from 14 to 30 days. Extension of wash-out period for CF cohort from 14 to 30 days. |
| **Rationale for change** | | Response to MHRA questions /clarification, |
| | | |
| **Section to be changed** | | Section 1.2 |
| **Description of change** | | Clarifications on safety margins and drug profile. |
| **Rationale for change** | | Response to MHRA questions /clarification, |
| | | |
| **Section to be changed** | | Section 3.3.4 |
| **Description of change** | | Addition of one criterion for individual withdrawal: subject experiencing a serious adverse event or any AE that, in the opinion of the investigator, may jeopardise the safety of the trial participant. |
| **Rationale for change** | | Response to MHRA questions /clarification, |

| | | |
|---|---|---|
| **Number of global amendment** | | 3 |
| **Date of CTP revision** | | 08 March 2017 |

| | | |
|---|---|---|
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers, and COPD and CF subjects. |
| **Comment** | | A CTP version 4 (revision 3) exists but this version will not be submitted to IRB/ IEC / CA. It has been issued by error but the archiving system doesn't allow to disregard the corresponding version numbering. |

| | | |
|---|---|---|
| **Number of global amendment** | | 4 |
| **Date of CTP revision** | | 31 March 2017 |
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers, and COPD and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | X | |
| **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** | | TCM name |
| **Description of change** | | replaced as TCM |
| **Rationale for change** | | Administrative change |
| | | |
| **Section to be changed** | | Section 2.3.2 Drug-related risks and safety measures |

| | | |
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| **Description of change** | | 1) Modification of the safety margins (dose multiples) for the NOAEL dose in the 4-week rat study and for the NOAEL dose in the 4-week dog study.<br>2) Change in the values for the multiples for the starting dose for both HV and COPD populations |
| **Rationale for change** | | To align with the values indicated in the IB dated of 16 Dec 2016 |

| | | |
|---|---|---|
| **Number of global amendment** | | 5 |
| **Date of CTP revision** | | 20 April 2017 |
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | X | |
| **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** | | |
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| **Section to be changed** | | Title and all subsequent mentions of COPD patients, pathology except in section 1. |
| **Description of change** | | Deletion of the word COPD and references to COPD subjects. |
| **Rationale for change** | | COPD cohorts will not be performed then the whole references to COPD subjects assessments have been removed |
| | | |
| **Section to be changed** | | Flowcharts I and II and footnotes |
| **Description of change** | | Visit 1 timeframe changed as well as first day of |

| | | |
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| | | Visit 2. The footnotes where this time windows appear have been changed accordingly. |
| **Rationale for change** | | To guarantee safety laboratory results review before first dosing within the protocol requirements |
| | | |
| **Section to be changed** | | Flowchart I |
| **Description of change** | | 1) Footnote 6 : Add the opportunity to perform screening ECG on the site's device and then to transfer the data to the vendor<br>2) ECG Day -7 to -3 : deleted<br>3) Footnote 8 added for day 7, pre-dose measurement. Footnote also corrected |
| **Rationale for change** | | 1) To allow more flexibility<br>2) Not necessary as already taken at screening and then pre-dose<br>3) To correct a mistake |
| | | |
| **Section to be changed** | | Flowchart II |
| **Description of change** | | 1) Deletion of footnote 24 to first laboratory sample on Day -7 to -3<br>2) First laboratory samples taken on Day 1 moved from 7.45 am to 6 am and footnote 4 replaced by 24<br>3) Footnote 2 added to pre dose PK sampling at Day 1<br>5) Dosing time changed from 7.45 am to 8 am and move from 8 am to 7.45 am of pre-dose safety laboratory samples and PK samples<br>6) Addition of evening calls |
| **Rationale for change** | | 1) To correct an omission<br>2) To allow more time to perform the assessments<br>3) To correct an omission<br>4) To correct an omission<br>5) To be consistent with timepoints at every visit<br>6) To secure the study drug compliance |
| | | |
| **Section to be changed** | | Abbreviations |
| **Description of change** | | Adjustment of abbreviations list |
| **Rationale for change** | | To fit the abbreviations actually used into the protocol |
| | | |
| **Section to be changed** | | Section 3.1.2 |
| **Description of change** | | Deletion of the mention of the need to have 20 CF subjects for a review |
| **Rationale for change** | | No dose escalation meeting will be performed based |

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| | | on CF subjects data then no reason to be mentioned in this section. |
| | | |
| **Section to be changed** | | Section 3.2 |
| **Description of change** | | Maximum wash out period between treatment period 1 and 2 for CF subjects decreased from 8 to 6 weeks |
| **Rationale for change** | | To limit the length of this wash out period |
| | | |
| **Section to be changed** | | Section 3.3.2 |
| **Description of change** | | Inclusion criteria 3 for every population: Change of timeframe to obtain the progesterone measurement |
| **Rationale for change** | | To align with the change of timeframe globally |
| | | |
| **Section to be changed** | | Section 3.3.3 |
| **Description of change** | | Exclusion criteria 11: Change of timeframe for the first safety laboratory sample taken at Visit 2 |
| **Rationale for change** | | To align with the change of timeframe globally |
| | | |
| **Section to be changed** | | Section 3.3.3 |
| **Description of change** | | Exclusion criteria 13: and changed to or for the timepoint of assessment of pre dose ECGs |
| **Rationale for change** | | To ensure not to enter any patient with a potential pre-existing ECG abnormality |
| | | |
| **Section to be changed** | | Section 3.3.4 |
| **Description of change** | | 1) Maximum wash out period between treatment period 1 and 2 for CF subjects decreased from 8 to 6 weeks.<br>2) Addition of the request that the site contacts the sponsor in case of patient's withdrawal indicating the reason of discontinuation. |
| **Rationale for change** | | 1) To limit the length of the wash out period.<br>2) To ensure the sponsor is informed in a timely manner. |
| | | |
| **Section to be changed** | | Section 4.1.2 |
| **Description of change** | | 1) Deletion of a sentence defining safety margin for the starting dose (100µg).<br>2) Correction of the dose group of healthy volunteers which has to be evaluated before starting CF part. |
| **Rationale for change** | | 1) To delete unnecessary information as already included in section 2.3.2.<br>2) To correct a mistake. |
| | | |
| **Section to be changed** | | Section 4.3 |
| **Description of change** | | Retraining of the patient needed in case he/she has a |

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| | | compliance over 120% instead of 100%. |
| **Rationale for change** | | To align with other part of the CTP. |
| | | |
| **Section to be changed** | | Section 5.1.3 |
| **Description of change** | | Indication of PK parameters which will be determined at Day 7 for CF subjects. |
| **Rationale for change** | | To clarify the objective of the PK sampling done at Day 7 for CF subjects. |
| | | |
| **Section to be changed** | | Footnote Table 5.3.7: 1 |
| **Description of change** | | |
| **Rationale for change** | | To correct a mistake |
| | | |
| **Section to be changed** | | Section 5.3.7 |
| **Description of change** | | 1) Indication that the safety samples which are expected to be performed locally in addition to central laboratory are serum electrolytes<br>2) Deletion of reference to section 10 as this pointed to the section 10 of the CTP when this refers to section 10 of the ISF. |
| **Rationale for change** | | 1) To clarify which samples have to be analysed locally<br>2) To correct a mistake |
| | | |
| **Section to be changed** | | Section 5.3.8 |
| **Description of change** | | Deletion of the mention that all ECG will be centrally evaluated |
| **Rationale for change** | | To clarify that all ECGs will be collected centrally but that screening ones will not be evaluated by the vendor. |
| | | |
| **Section to be changed** | | Section 5.3.9 |
| **Description of change** | | |
| **Rationale for change** | | To correct an omission and make the explanation clearer. |
| | | |
| **Section to be changed** | | Section 5.3.10.2 |
| **Description of change** | | Deletion of a mention that a sentence can be deleted |
| **Rationale for change** | | To correct a missing adaptation from the protocol template |
| | | |
| **Section to be changed** | | |
| **Description of change** | | |

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| **Rationale for change** | | 1) To allow more flexibility to the sites and allow them to stick to their usual practices.<br>2) To clarify that a different container will be used per sampling interval. |
| | | |
| **Section to be changed** | | Section 5.5.1 Biobanking (header) |
| **Description of change** | | Header deleted |
| **Rationale for change** | | Only extended storage of sample is proposed in the protocol and not biobanking properly then the header is not applicable |
| | | |
| **Section to be changed** | | Section 6.2.2 |
| **Description of change** | | Washout period for CF patient changed from 14 days to 30 days as minimum |
| **Rationale for change** | | To align on changes done in revision 2 (omission here |
| | | |
| **Section to be changed** | | Section 7.4, Section 4.1.5, Section 3.1.3 and Statistical Methods Part within Synopsis |
| **Description of change** | | Added different timepoints for final analyses of part 1 (HV) and part 2 (CF) depending on their completion. |
| **Rationale for change** | | To enhance further project planning. |
| | | |
| **Section to be changed** | | Section 7.4 |
| **Description of change** | | Added blinded interim analysis of BA data from CF subjects |
| **Rationale for change** | | To enhance planning of upcoming Phase II trial. |
| | | |
| **Section to be changed** | | Appendix 10.1 |
| **Description of change** | | Instruction for use of Respimat® adapted to the test drug used in this study |
| **Rationale for change** | | As the dose of study drug is higher than with other drug inhaled with Respimat®, the instructions for use have been adapted to ask for a daily priming. |
| | | |
| **Section to be changed** | | |
| **Description of change** | | |
| **Rationale for change** | | |

| | | |
|---|---|---|
| **Number of global amendment** | | 6 |
| **Date of CTP revision** | | 06 September 2017 |

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|---|---|---|
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | | |
| **To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval** | | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | X | |
| | | |
| | | |
| **Section to be changed** | | 3.3.2 Inclusion criteria #7 Part 2 |
| **Description of change** | | In the c criteria, deletion of be as written twice. |
| **Rationale for change** | | To correct a typo. |
| | | |
| **Section to be changed** | | 3.3.4 Removal of Subject from therapy or assesment |
| **Description of change** | | Clarification of the type of antibiotics which have to be stopped prior to re start of treatment period 2. |
| **Rationale for change** | | To clarify the use of antibiotics during the trial. |
| | | |
| **Section to be changed** | | 3.3.4.1 Discontinuation of the trial |
| **Description of change** | | In the second potential reason for discontinuation, the timing of the baseline ECG for treatment Period 2 has been changed from Day –3 to -1 to Day 1. |
| **Rationale for change** | | To correct a typo. |
| | | |
| **Section to be changed** | | 4.2.2.1 Restrictions regarding concomitant treatment |
| **Description of change** | | 1) Clarification on the permitted use of oral/injected antibiotics if not prescribed for exacerbation or infection and in a chronic way.<br>2) Visit 2 changed into Visit 3 in the section for inhaled antibiotics and clarification of restart for treatment period 2. |

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| **Rationale for change** | | 1) To clarify that the use of oral/injected antibiotics is only excluded in the case of exacerbation or infection but not when use chronically.<br>2) To correct a typo and clarify when the treatment has to be restarted. |
| | | |
| **Section to be changed** | | 4.2.2.2 Medication restrictions for all lung function testing |
| **Description of change** | | Deletion of mention of Day 7 for a visit where serial PFTs occur. |
| **Rationale for change** | | To correct a typo, no PFT +2hr on Day 7. |
| | | |
| **Section to be changed** | | 4.2.2.3 Restrictions on diet and life style |
| **Description of change** | | Clarification of the restrictions related to diet. |
| **Rationale for change** | | To clarify the fact that dietary supplement are allowed as used as replacement in the case of CF patients. Other dietary restrictions have also been clarified to fulfil study requirements. |

| | | |
|---|---|---|
| **Number of global amendment** | | 7 |
| **Date of CTP revision** | | 09 November 2017 |
| **EudraCT number** | | 2016-001504-31 |
| **BI Trial number** | | 1363.2 |
| **BI Investigational Product(s)** | | BI 443651 |
| **Title of protocol** | | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects. |
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | X | |
| **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** | | Flowchart II - header |
| **Description of change** | | 1) Planned time relative to drug intake of the day added.<br>2) Deletion of columns bodyplethysmography and sputum collection. |
| **Rationale for change** | | 1) To be clearer for the investigators.<br>2) Cancellation , bodyplethysmography and sputum collection to restrict the burden for the patients to what is only necessary for safety monitoring.<br><br>Body plethysmography is no longer required as no relevant changes in any of the lung function parameters was observed in healthy volunteers at any timepoints. |

| | | |
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| | | |
| **Section to be changed** | | Flowchart II – deletion of several lines |
| **Description of change** | | 1) Deletion of several assessments during main clinic visits (Day 1, Day 7 and Day 14) as PFT post dose after +2 hr) Removal of PK samples with the exception of predose, 30 and 45 minutes postdose on Days1 and 14, predose and 30 min postdose on Day 7 and sample at EOS and ECGs after +30 min (Day 1).<br>2) Replacement of intermediate on-site visits by twice daily phone contact with patients as well as during wash-out/follow up period.<br>3) Vital signs measurements at +5min cancelled on Day 1 and Day 14. |
| **Rationale for change** | | 1) To limit the length of on-site visits for the patients as these assessments are considered as no longer required. And burden of PK sampling<br>2) To limit the number of in-clinic visits and then the burden for the patients while maintaining an appropriate safety monitoring of the patients.<br>3) Not feasible because of the requirement to have a minimum of 5 min rest in supine position. |
| | | |
| **Section to be changed** | | Flowchart II – addition of time windows |
| **Description of change** | | Allowance of time windows for Day 7 (+/- 2 days), Day 14 (- 1/+ 3 days), Day 23 (+/- 2 days), Day 30 (+/- 5 days). |
| **Rationale for change** | | To allow more flexibility for the patients to come on site. |
| | | |
| **Section to be changed** | | Flowchart II – changes in footnotes |
| **Description of change** | | 1) Deletion of footnotes (8, 10, 11), adaptation of some others (2, 22).<br>2) changes in footnotes 5 and 24. |
| **Rationale for change** | | 1) To meet the changes implemented in the flowchart in this amendment.<br>2) to correct a mistake (5) or to avoid misunderstanding (24) |
| | | |
| **Section to be changed** | | Sections 2.1, 2.2, 5.1.2, 5.1.3, 5.4.2.3, 6.2.3 |
| **Description of change** | | All PK sampling times removed with the exception of predose, 30 and 45 minutes postdose on Days 1 and 14, predose and 30 minutes postdose on Day 7 and EOS PK sample. This resulted in removal of PK parameters for CF patients, as they no longer can be calculated. The PK concentrations will be listed by time point along with descriptive statistics will be provided. The CF dose normalised concentration data will be shown graphically with the HV PK data |

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| | | to investigate whether systemic exposures are similar or different in the two different populations. |
| **Rationale for change** | | To reduce PK burden on CF patients. |
| | | |
| **Section to be changed** | | Section 2.3.1 Procedure related risks |
| **Description of change** | | Change of maximum volume of blood taken. |
| **Rationale for change** | | As the number of PK points decreases in the CF part, the maximum volume of blood is taken in the HV part and is then lower than initially mentioned. |
| | | |
| **Section to be changed** | | Section 3.3.3 Exclusion criteria |
| **Description of change** | | Change in exclusion criteria #16 to limit this criteria to concomitant medication not clearly allowed in the table 4.2.2.1:1 |
| **Rationale for change** | | To clarify that oral antibiotic as Azythromycin are allowed as prophylactic treatment despite their long half-life. |
| | | |
| **Section to be changed** | | Section 4.1.5.1 Blinding |
| **Description of change** | | Clarification of a sentence explaining that analyses of part I will not have an impact conduct of part II. |
| **Rationale for change** | | It is clarified that the term conduct in that sentence refers to randomisation, blinding and analyses of the primary endpoint. That is there is no conflict for this amendment. |
| | | |
| **Section to be changed** | | Section 4.2.2.2 Medication restriction for all lung function testings |
| **Description of change** | | Change of wording and timing for PFTs. |
| **Rationale for change** | | Due to the decrease of the number of PFT assessments, the wording has been reviewed. |
| | | |
| **Section to be changed** | | Section 4.2.2.3 Restrictions on diet and lifestyle. |
| **Description of change** | | Addition of “excess” in the sentence refraining CF patients from their alcoholic consumption. |
| **Rationale for change** | | To be more realistic and allow a reasonable alcoholic intake during the course of the study. |
| | | |
| **Section to be changed** | | Section 5.3.5 Body Plethysmography |
| **Description of change** | | Deletion of the mention of Flowchart II or subjects |
| **Rationale for change** | | Body plethysmography will no more be performed for CF subjects then correction required. |
| | | |
| **Section to be changed** | | Section 5.3.6 CF control during the trial |
| **Description of change** | | Few corrections in the “telephone visits” subsection to be clear that there will have twice daily calls when the patient will not have an in-clinic visit. |

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| **Rationale for change** | | To be online with the twice a day phone call planning. |
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| **Section to be changed** | | Table 5.3.7: 1 Routine laboratory tests |
| **Description of change** | | 1) Addition of the mention of HV patients only for the manual differential white blood cell count of polymorphnuclear neutrophils. |
| **Rationale for change** | | 1) To correct a mistake. |
| | | |
| **Section to be changed** | | |
| **Description of change** | | |
| **Rationale for change** | | |
| | | |
| **Section to be changed** | | Section 7.1.1 Objectives, |
| **Description of change** | | |
| **Rationale for change** | | |
| | | |
| **Section to be changed** | | Section 7.4 Interim analyses |
| **Description of change** | | Removed analyses of PK data from CF subjects by trial pharmacometrician |
| **Rationale for change** | | This is not needed any longer due to reduced PK sampling in Part 2. |
| | | |
| **Section to be changed** | | Section 9.2 Unpublished references |
| **Description of change** | | Some references deleted and some others added. |
| **Rationale for change** | | To support the changes of the CTP. |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c09013915** **Technical Version Number:8.0**

**Document Name:** clinical-trial-protocol-version-08

**Title:** A Phase Ib, multicenter, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects.

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Trial Statistician | | 13 Nov 2017 09:17 CET |
| Approval-Team Member Medicine | | 13 Nov 2017 09:20 CET |
| Approval-Therapeutic Area | | 13 Nov 2017 10:04 CET |
| Author-Trial Clinical Monitor | | 13 Nov 2017 10:42 CET |
| Approval-Clinical Pharmacokinetics | | 13 Nov 2017 18:09 CET |
| Verification-Paper Signature Completion | | 15 Nov 2017 10:40 CET |

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|---|---|---|