entered on each treatment	• 14 patients on BI 1265162 20µg bid including 3 adolescent patients • 14 patients on BI 1265162 50µg bid including 3 adolescent patients • 14 patients on BI 1265162 100µg bid including 3 adolescent patients • 28 patients on BI 1265162 200µg bid including 6 adolescent patients
Diagnosis	Cystic Fibrosis
Main in- and exclusion criteria	Inclusion criteria 1. Male or female patients / 12 years of age or older at screening; 2. Documented diagnosis of cystic fibrosis including: • positive sweat chloride ≥ 60 mEq/L, by pilocarpine iontophoresis or • a genotype with 2 identifiable mutations consistent with cystic fibrosis accompanied by one or more clinical features with cystic fibrosis phenotype; 3. FEV_1 ≥ 40% and ≤ 90% of predicted values at screening and predose at Visit 2. 4. Women of childbearing potential must be willing and able to use highly effective methods of birth control Exclusion criteria 1. Evidence of acute upper or lower respiratory tract infection within 4 weeks prior to randomisation based on investigator's judgement; 2. Pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics or oral corticosteroids within 4 weeks prior to randomisation.
Test product(s)	BI 1265162
dose	20, 50, 100 and 200 µg bid
method and route of administration	Inhalation via the Respimat®
Comparator product(s)	Placebo
dose	Not applicable
method and route of administration	Inhalation via the Respimat®
Duration of treatment	4 weeks
Statistical methods	The primary objective is to demonstrate proof of concept with respect to a non-flat dose response curve and define a suitable dose range for BI 1265162 regarding efficacy and safety for further pivotal testing in Phase III. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered. An efficacy interim analysis will be conducted on the first 28 patients included in the placebo and BI 1265162 200µg bid arms once they will have completed the 4-week treatment period.

(***) After the individual patient's end of the trial the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, please see section.5.2.6.2.1.
(****) Only for patients who can legally consent. Requires separate informed consent for sputum and DNA Biobanking. Whole blood for DNA biobanking sample will be collected on Day 1 only (Visit 2), and if not possible on day 1, this sample may also be collected at a later visit.
Spontaneous sputum will be collected on Day 1, Day 29 and Follow-up Visit.

1 Site staff should contact the patients by phone/text/email to remind them to inhale the drug at the appropriate times on the day before the clinic visit.

2 Blood sampling for serum electrolytes to be performed before and 5 min (+5 min) after study drug inhalation. In case of early treatment discontinuation, blood sampling for serum electrolytes will be performed once at anytime during the early EoT visit.

3 A laboratory kit to conduct blood sampling by local laboratory/doctor/health care provider for serum potassium by central laboratory will be used. This kit will be provided to the patient at Visit 3. Blood sampling can be performed anytime.

4 Patients will qualify for N_2MBW test if demonstrating a FEV1 > 60% of predicted values at screening and are able to complete the N_2MBW test at Visit 2. When a patient fails N_2MBW test at visit 2 for quality reasons, the patient should not complete the N_2MBW test at visit 4

5 Pregnancy testing will be performed locally to all women of childbearing potential and to female adolescents who have reached menarche, even irregular, using the urine pregnancy test kits supplied by the central laboratory. Serum pregnancy test is required in case of positive urine test.

6 It is also possible to perform this visit at site if more appropriate for patient.

FLOW CHART FOR N_2MBW TEST

Visits	Timepoints
1	NA
2 Day 1	Predose
3 Day 8	NA
4 EoT Day 29	Predose
In case of early EoT	Anytime
5 FUP Day 36	NA

Only for patient with FEV1 > 60% of predicted values at screening and who are able to complete the N_2MBW test at V2

FLOW CHART FOR PULMONARY FUNCTION TEST

Visits	Timepoints [min post dose]
1	No bronchodilator washout required
2 Day 1	Predose
	5-20
	60-120
3 Day 8	Predose
	5-20
	60-120
4 EoT Day 29	Predose
	5-20
	60-120
In case of early EoT	Anytime
5 FUP Day 36	Anytime

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eCRF	Electronic Case Report Form
ED	Effective Dose
eDC	Electronic Data Capture
ENaC	Epithelial Sodium Channel
EoT	End of Treatment
ES	Enrolled Set
EudraCT	European Clinical Trials Database
FC	Flow Chart
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FUP	Follow Up
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HA	Health Authority
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IPD	Important Protocol Deviation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
K	Potassium
LCI	Lung Clearance Index
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
Na	Sodium
NCA	Non-Compartmental Analysis
N_2MBW	N_2 Multiple Breath Washout
N_2MBWS	N_2 Multiple Breath Washout Set

For a graphical presentation of the trial, see Figure 3.1:1 below.

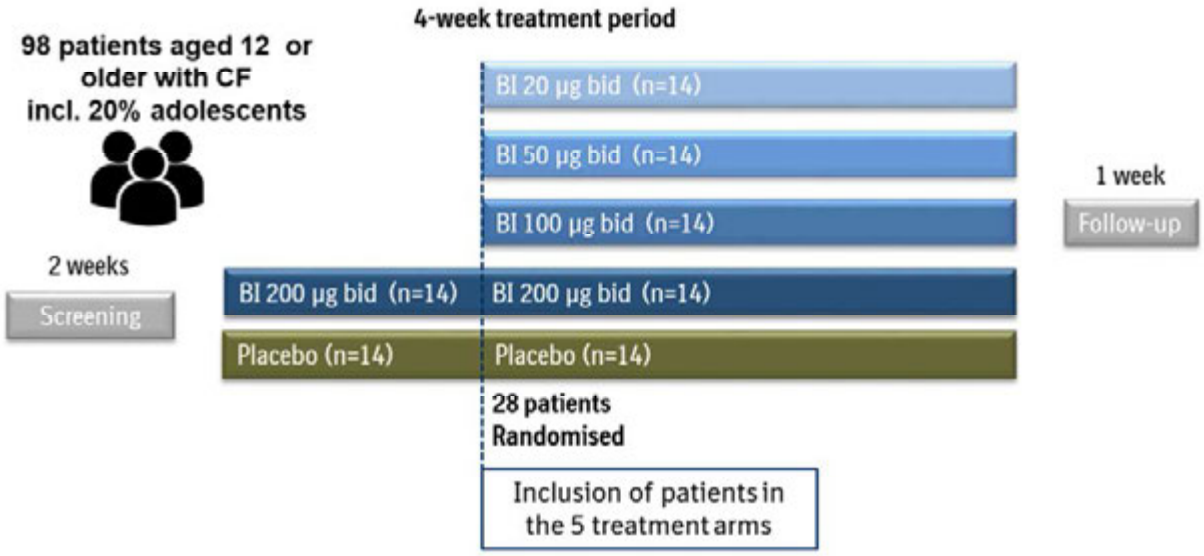


Figure 3.1.1 Trial Design

In addition, in order to prevent the exposure of further patients in case of insufficient efficacy, an efficacy interim analysis will be conducted on the first 28 patients exposed to placebo or BI 1265162 200µg bid. Please refer to Section 7.4 for further details.

Patient recruitment will not be stopped during the conduct of the interim analysis and this efficacy interim analysis is not correlated with the periodic safety data reviews that will be performed by the independent DMC.

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

Since the initial pulmonary defect in CF is airway obstruction, FEV_1 is the recommended primary endpoint for assessing the efficacy of a new drug in patients with CF [R12-2800]. Due to its mechanism of action, a 4-week treatment period is considered sufficient to evaluate the indirect effects of BI 1265162 on trough FEV_1.

A parallel group, randomized, double-blind and placebo controlled trial is considered the most appropriate design to assess efficacy and safety of four doses of BI 1265162.

The rationale for the BI 1265162 dose selection is described in Section 4.1.2.

In order to prevent the exposure of further patients in case of insufficient efficacy, patients will be first randomised to either the highest dose of BI 1265162 or placebo. An interim efficacy analysis will be conducted on the first 28 patients exposed to either placebo or the highest dose of BI 1265162. As described in Section 3.1 and 7.4, depending on the results of the interim analysis, the trial may be stopped.

The 1-week follow-up period is considered to be sufficient, as previous studies with BI 1265162 have shown that the majority of the drug, measured in the systemic circulation, is excreted from the body within 1 week.

As described in Section 8.7, a data monitoring committee (DMC), which is independent of the sponsor, will be established to assess the progress of the clinical trial, including safety reviews at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial. The DMC will also be in charge of allowing enrolment of adolescent patients in the trial. Further details are provided in the DMC charter.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A sufficient number of patients with cystic fibrosis will be screened from approximately 40 trial sites to ensure the randomisation of 98 patients including 21 adolescents (12 to 17 years of age).
It is expected that 2 to 3 patients will be randomised at each trial site. If enrolment is delayed, additional sites may be recruited. The number of adolescent patients to be included in each treatment arm should be as follows:

- Placebo: at least 6 adolescents
- 2x10µg (i.e. 20µg bid) of BI 1265162: at least 3 adolescents
- 2x25µg (i.e. 50µg bid) of BI 1265162: at least 3 adolescents
- 2x50µg (i.e. 100µg bid) of BI 1265162: at least 3 adolescents
- 2x100µg (i.e. 200µg bid) of BI 1265162: at least 6 adolescents

Reasons for screening failures will be collected in the eCRF. The re-screening of patients will be permitted in circumstances where safety is not compromised and in which the patient becomes eligible. In such case, the patient should be declared as a screening failure in the eCRF and IRT with their original patient number. Upon re-screening, a new patient number will be assigned by the IRT. The old patient number, with which the patient failed screening, will be recorded in the eCRF. The current approved version of the information sheet and consent form should be signed again.
In case of pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics or oral corticosteroids prior to the randomisation visit, the patient should be declared as a screening failure and a re-screening may be considered when the patient becomes eligible again.

Re-testing for eligibility criteria is only to be performed for a laboratory test that has been cancelled by the central laboratory (e.g. for specimen not received or received beyond stability) or for a laboratory result thought to be a spurious result based on previously available laboratory results. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit windows in order to avoid protocol window violations.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
  If a patient becomes pregnant during the trial, the trial medications will need to be stopped and patient will be followed up until birth or otherwise termination of pregnancy. The data of the patient will be collected and reported in the clinical trial report until patient last visit and that any events thereafter will be reported in the BI Pharmacovigilance database. Please refer to Section 5.2.6.2.3 for detailed information on event reporting in case of pregnancy.
- The patient has a confirmed level of serum potassium of > ULN in non-haemolysed blood.
  Each result of elevated serum potassium level > ULN should be confirmed, either by a second measurement or by presence of clinical symptoms. At least one measurement should be performed by central laboratory. If second measurement is required and if blood sampling for central laboratory cannot be done in a reasonable timeframe according to investigator´s judgement, confirmation of serum potassium level can be evaluated by local laboratory.

An individual patient may be considered to be withdrawn from trial treatment if:

- The patient is not consistently taking a concomitant chronic CF medication. Changes in concomitant treatment required due to medically valid reasons will be permitted as judged by the investigator.
- The patient experiences more than one acute upper or lower respiratory tract infection or pulmonary exacerbation. In this case, a documented discussion should take place between investigator and sponsor to determine how to proceed.
- The patient has repeatedly shown to be non-compliant with trial medication intake (below 80% or above 120%).

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and Section 6.2.3.
For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

Dispensation of the appropriate medication kits will occur at Visit 2. The patient will receive one Respimat® medication kits and one reserve Respimat® inhaler. Medications will be dispensed by the investigator, study coordinator or pharmacist, depending on the site structure. The reserve kit allows the patient the flexibility of not having to return to the clinic immediately to replace a lost or malfunctioning Respimat® inhaler. In the event that the patient may need additional extra Respimat® inhalers and cartridges due to rescheduled visits, inhaler loss or malfunction, these will be supplied on an 'on demand' basis. Dispensing of these extra Respimat® inhalers will also be managed via the IRT.

4.1.4.2 Training and Priming of the Respimat® inhaler

Patients will receive training on the use of the Respimat® inhaler at Visit 1 to familiarize themselves with assembling, priming and using the inhaler. Training will be repeated at Visit 2 and 3 where observance of the inhalation procedure will occur.

Each newly assembled Respimat® inhaler needs to be primed prior to first time use. The inhaler should be primed by actuating it until an aerosol is visible, plus three additional actuations. All priming actuations should be directed to the ground and priming should NOT take place in the same room where the patient is inhaling trial medication or in the room where PK blood samples are taken or being processed. On the PK sampling days, should priming of a new Respimat® inhaler be required, it should be performed by site personnel, and not by the patient. Gloves must be worn and discarded immediately after the priming to avoid contamination of the PK samples to be taken and processed subsequently (see also Section 5.3.2).

4.1.4.3 Study medication administration

At Visit 2, the first dose of study medication will be self-administered in the clinic. The clock time of the end of second inhalation will be captured on the source documents and in the eCRF. At all subsequent visits, medication will also be self-administered in the clinic and the clock time of the end of inhalation will be captured.
The utmost care should be taken to ensure that during the treatment period, the study medication is not taken prior to coming to the site for a visit. In case the patient would take the study medication in the morning of the clinic visit, the trial visit should be re-scheduled the day after.

Study Medication administration at home:
Twice a day, each morning (other than clinic visit days) and each evening, medication will be self-administered by the patient. The patient will inhale two puffs of study medication from the assigned Respimat® inhaler. Patients should be encouraged to take their study medication at approximately the same time each morning and each evening after all other (inhaled) CF treatments. If a dose is missed for more than 4 hours, the next dose should be taken as planned. If the evening dose is missed on the day prior to a clinic visit, the visit should be rescheduled the day after. A glass of water can be taken after the trial drug inhalation, if needed.

5.1.3 Cough and Sputum Assessment Questionnaire (CASA-Q©)

The Cough and Sputum Assessment Questionnaire (CASA-Q©) will be completed at the time points indicated in the Flow Chart. The CASA-Q should be administered at the start of the clinic visit, after the CFQ-R, prior to any other tests or procedures. The questionnaire will be paper-based and available in the local language (provided in the ISF).

5.1.4 N_2 Multiple Breath Washout test (LCI)

N_2 Multiple Breath Washout (N_2MBW) measurements will be carried out at the timepoints indicated in the Flow Chart, and only in qualified patients. Patients will qualify for N_2MBW test if demonstrating a FEV1 > 60% of predicted values at screening and are able to complete the N_2MBW test at Visit 2.

LCI will be assessed using a standardised washout recording system with 100% medical grade oxygen as to washout the tracer gas, nitrogen. N_2MBW measurements will be centrally reviewed.

N_2MBW tests will be conducted with the patient in a seated position. A suitable nose clip must be used and the subject has to maintain a tight mouthpiece seal. Three technically acceptable N_2MBW runs according to the ERS/ATS consensus statement for acceptability criteria have to be performed during relaxed tidal breathing of the subject [R15-1327]. The lung clearance index (LCI), of these N_2MBW runs will be recorded. LCI, are measures of ventilation homogeneity.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination and chest examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, cardiovascular system, abdomen, extremities, and skin.

Chest examination will be performed at the time points specified in the flowchart.

Measurement of height and body weight will be performed at the time points specified in the flowchart. In order to get comparable body weight values, it should ideally be performed in the following way:

- after bladder voiding
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flowchart, prior to blood sampling and prior to the pre-dose PFT measurement. This includes systolic and diastolic

blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the flowchart.
Overall, approximately 80 mL of blood will be collected throughout the trial, to evaluate patient safety, PK and for optional biobanking. For PK, each sample will require approximately 4 ml.
All analyses will be performed by a central laboratory, the respective reference ranges will be provided in Laboratory Manual in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

Pregnancy testing will be performed locally to all women of childbearing potential and to female adolescents who have reached menarche, even irregular, using the urine pregnancy test kits supplied by the central laboratory. Immediately after the result of a pregnancy test is known, the pregnancy test kit will be discarded at the site. In case of positive result, a serum pregnancy test will be performed by the central laboratory. The results of the test must therefore be documented in the source documents available at the site for future verification by the CRA.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

Laboratory reports will be provided through the central laboratory web-based system. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the eDC system.

The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

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

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

1. A confirmed elevation of serum potassium > upper limit of normal (ULN) in non-haemolysed blood (see definition in Section 3.3.4)

2. Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC 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.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood samples for pharmacokinetic analysis will be collected at the time points indicated in the Flow Chart for PK blood sampling.

The date and exact clock time of drug administration and of sampling times have to be recorded and documented in the eCRF by the investigator or designated site-personnel. The actual sampling times will be used for determination of pharmacokinetic parameters. These samples may also be used for metabolite determination or for further methodological investigation if required. 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.

5.3.2 Methods of sample collection

The planned PK analyses will require blood sampling at the time points indicated in the Flowchart. Correct, complete and legible documentation of drug administrations and blood sampling times as well as adequate handling and identification of PK samples are mandatory to obtain data of adequate quality for the PK analysis.

In order to allow the sample identification, the sample tube labels should list at a minimum the following information: BI trial number, patient number, visit and planned sampling time or planned sampling time interval.
All samples will be stored at about -20°C or below and be shipped on dry ice. Further details to the information provided in the following chapters on sample collection, preparation of plasma aliquots, sample handling, and shipping are provided in the laboratory manual.

5.3.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of analyte plasma concentrations, blood will be taken from an antecubital or forearm vein into a blood drawing tube that contains potassium EDTA–anticoagulant at the times indicated in the flow chart.
During the whole trial, a maximum of 40 mL of blood per person will be drawn for PK purposes.Plasma samples will be obtained by centrifugation. Sample aliquots will be stored at the trial site and at the logistics CRO until shipment and at the analytical laboratory until analysis.
First and second sample aliquots are to be shipped separately.
For further details please refer to laboratory manual.

5.3.3 Analytical determinations

BI 1265162 concentrations in plasma will be determined by validated a 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.

5.3.4 Pharmacokinetic and Pharmacokinetic – pharmacodynamic relationship

The following PK parameters will be determined if feasible through a population PK approach:

- $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N)
- $C_{pre,N}$ (predose concentration measured for dose N)
- $AUC_{0\text{-}t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

A non-compartmental (NCA) PK analysis may be undertaken on Day 8 if the data allows. The following parameters may be calculated;

- $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N)
- $C_{pre,N}$ (predose concentration measured for dose N)
- $AUC_{0\text{-}t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

For both methods of PK analysis, additional PK parameters may be generated if warranted by the data.

Using appropriate population methodology, the relationship between BI 1265162 dose, systemic exposures and outcome (e.g. clinical outcomes such as FEV_1, LCI, AEs and/or safety labs) will be investigated using a population PK/PD approach. The details will be documented in the population PK, PK/PD SAP, and the resulting data will be reported separately outside of the Clinical Study Report for this study. The results from a NCA analysis, if undertaken, along with listings of the plasma concentration-time data will be included in the study report.

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

3. AE and concomitant therapy collection
4. Physical examination / vital signs/body weight
5. ECG
6. N_2MBW test
7. Pulmonary Function Tests prior to dosing
8. Training on Respimat® inhaler
9. Laboratory tests including serum electrolytes
10. PK pre-dose
11. Trial medication intake
12. Serum electrolytes tests 5 min post inhalation
13. PK blood sampling 5 min post inhalation
14.
15. PK blood samplings

Laboratory testing including serum electrolytes can be conducted also prior to N_2MBW testing according to site´s preference.
PK pre-dose sample should be taken within 60 minutes prior to dosing.

With regards to the optional biobanking, blood drawing can be performed with other blood drawings for safety laboratory tests. Sputum collection can be performed at anytime but after the questionnaire administration.

Additional details regarding visit procedures are provided below.

6.2.1 Screening period

Screening Period
No trial procedure is allowed unless the appropriate consent and assent are in place. Consent and assent must be obtained prior to the screening visit procedures.

Visit 1 is the beginning of the screening period. The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient when Visit 1 is performed. Once Visit 1 procedures are complete and laboratory results are received, inclusion/exclusion criteria must be reviewed. If the patient meets inclusion/exclusion criteria, he/she should be contacted to schedule Visit 2.

If the patient does not meet inclusion/exclusion criteria, the patient must be recorded in eCRF as a screen failure. Patient must be registered as a screen failure in IRT.

Baseline Conditions
Any pre-existing medical conditions considered as relevant by the investigator, excluding the indication of the trial, are recorded into the eCRF in the appropriate page. This concern all active pathology, chronic disease or recurrent event.

Medical History:
All relevant medical histories according to the investigator judgement have to be captured in the eCRF.

- N_2 multiple breath washout set (N_2MBWS): The N_2MBWS includes all subjects in the treated set, who provided at least one pair (baseline and end of treatment) of evaluable measures of the N_2MBW parameter.

- 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 7.3.5 of the CTP. 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 deviations (IPDs) will be identified no later than in the Blinded Report Planning Meeting (BRPM) and pre-defined in the TSAP.

7.3.1 Primary endpoint analyses

The analyses for PoC and dose-finding will be performed using multiple comparison and modelling techniques (MCPMod) [R10-1424] whereby several possible dose response models (patterns) will be evaluated, while keeping full control of the type I error at 5%, one-sided) to identify the best-fitting model or subset of models.
To account for the repeated nature of the data and the covariates in the nature, a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) will be carried out comparing the change from baseline in trough FEV_1 percent predicted at 4 weeks of treatment.

The primary analysis will be performed on the Treated Set. The analysis will include the fixed, categorical effects of treatment at each visit, age (adolescents vs. adults) and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The statistical model will be as follows:

$$y_{ijkm}=\beta_j S_i+\tau_{jk}+\phi_m+e_{ij}$$
$$e_{ij} \sim N_Z(0, \sum)$$

y_{ijkm} = response variable for subject i in age stratum m at visit j receiving treatment k
β_j = coefficient of baseline effect at visit j
S_i = the baseline measurement of subject i, i=1,2,…
τ_{jk} = the effect of treatment k at visit j, j=1,2 and k=1,2,…,5
ϕ_k= the effect of age stratum (adolescents vs. adults), k=1, 2
e_{ij} = the random error associated with the j_{th} visit of the i_{th} subject. Errors are independent between subjects.
$\sum$ = unstructured covariance matrix

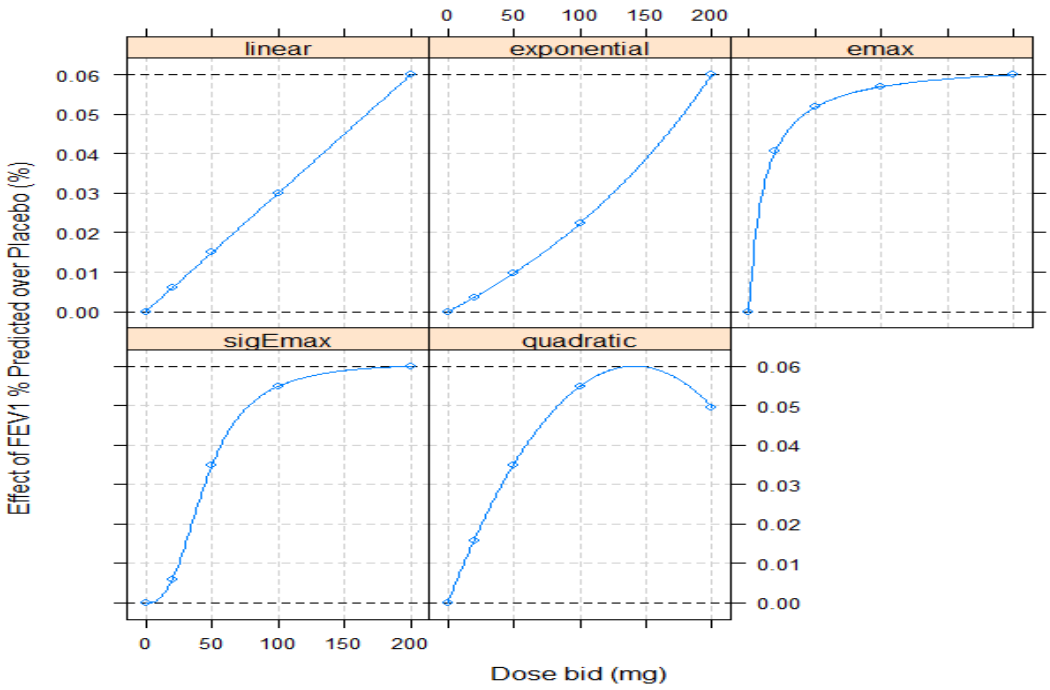
The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

The MMRM analysis will be carried out in SAS and covariate-adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit and used for MCPMod analysis.

For PoC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. The following models will be considered for this analysis: linear, exponential, Emax, SigEmax and quadratic.

The model assumptions and resulting graphs were selected to cover both plausible and a diverse range of dose response patterns. These are shown in Figure 7.3.1:1. The parameters for each model shape are listed in Table 7.3.1:1.

Figure 7.3.1:1 Shape of the considered dose response patterns for the MCPMod Analysis



I error will not be protected for these comparisons the resulting confidence intervals and p - values will be considered as nominal or descriptive statistics.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

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 summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients 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 and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Using a sparse population PK approach that jointly analyses the combined data from this study along with that from the previous studies in healthy volunteers, the following pharmacokinetic parameters will be determined if feasible for each subject.

-
- $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N)
- $C_{pre,N}$ (predose concentration measured for dose N)
- $AUC_{0\text{-}t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

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 patients 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 patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will periodically evaluate safety data.
While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. The DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as required by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor (TCM), 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,

R15-4955 Clunes MT, Boucher RC, Virtual Lung Group. Cystic fibrosis: the mechanisms of pathogenesis of an inherited lung disorder. Drug Discov Today Dis Mech 4 (2), 63 - 72 (2007)

R15-5856 Riordan JR et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 245 (4922), 1066 - 1073 (1989)

R16-1992 Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, Boeck K de, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, ratjen F, Rowe SM, Waltz D, Boyle MP, TRAFFIC Study Group, TRANSPORT Study Group Lumacaftor-ivacaftor in patients with cysticfibrosis homozygous for Phe508del CFTR. N Engl J Med 373 (3), 220 - 231 (2015)

9.2 UNPUBLISHED REFERENCES

Not applicable.

FLOW CHART

During trial visit, the sequence in which specific assessments are performed is important. The sequence of procedures at each visit (where applicable) should be as defined in Section 6.2.

Trial Periods	**Screening**	**Randomised Treatment**				**Follow-up**
Visit	**1**	**2**	**3**	**Ambulatory Visit[6]**	**4 EoT****	**5 FUP**
Days calculated from Day 1	-14	1*	8	15	29	EoT plus 7 days
Time window for visits	±3 days	none	±3 days	±3 days	±3days	+3days
Informed consent	X					
Demographics	X					
Medical history	X					
Physical examination	X				X	X
Chest examination	X	X	X		X	
Height	X					
Body weight		X			X	
Vital signs	X	X	X		X	X
Laboratory tests	X	X	X		X	
Serum electrolytes tests	X	X[2]	X[2]		X[2]	X
Serum K^+ test				X[3]		
Pregnancy test[5]	X	X	X		X	X
12 lead-ECG	X	X	X		X	
Review of in-/exclusion criteria	X	X				
Randomisation		X				
Dispense trial drugs		X				
Administer trial drugs		X	X		X	
Collect trial drugs					X	
Optional biobanking (sputum, blood)****		X			X	X
PK Sampling[1]		X	X		X	X
Pulmonary Function Tests (PFTs)	X	X	X		X	X
Dispense patient diary		X				
Patient diary review			X		X	
CASA-Q		X	X		X	
CFQ-R		X			X	
N_2 Multiple Breath Washout (N_2MBW)[4]		X			X	
Respimat® inhaler training	X	X	X			
Phone contact				X		
All Aes/SAEs/AESIs***	X	X	X	X	X	X
Compliance check			X		X	
Concomitant therapy	X	X	X	X	X	X
Completion of patient participation						X

(*) Day of Randomisation / Day of first intake of randomised medication

(**) Patients who discontinue trial treatment prematurely should come to the clinic as soon as possible for an early End of Treatment Visit. Study procedures will be the same as for V4/EoT except for PK blood sampling, serum electrolytes and PFTs. Those assessments will be performed once at anytime during the EoT visit. Follow-up (FUP) visit should take place one week after the early End of Treatment Visit

FLOW CHART FOR PK BLOOD SAMPLING

Visits	Timepoints [hrs post dose]
2 Day 1	Pre-dose
	5 min (+5 min)
3 Day 8	Pre-dose
	5 min (+5 min)
	30 min (+/- 15 min)
	1 h(+/- 15 min)
	4 h (+/- 30 min)
4 EoT Day 29	Pre-dose
	Post-dose (anytime with a preference around 5-15 minutes post-dose)
In case of early EoT	Anytime
5 FUP Day 36	Anytime

NOAEL	No Observable Adverse Effect Level
OPU	Operative Unit
PFT	Pulmonary Function Test
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
RA	Regulatory Authority
REP	Residual Effect Period
RS	Randomised Set
SAE	Serious Adverse Event
SRD	Single Rising Dose
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
TCM	Trial Clinical Monitor
TS	Treated Set
t_{max}	Timepoint of Maximum Plasma Concentration
ULN	Upper Level of Normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-center, multinational, randomised, double-blind, placebo-controlled, parallel group dose-ranging trial of BI 1265162 inhaled from the Respimat® inhaler in patients with CF.

The study consists of a 2-week screening period, a 4-week, randomised treatment period, and a 7-day follow-up period.

Patients will be enrolled (screened) in the trial once the appropriate informed consent and assent (if applicable) have been given. Patients who successfully complete the screening visit and still meet the inclusion/exclusion criteria at Visit 2 will be randomised. After the completion of the treatment period or in case of early discontinuation, patients will be evaluated for an additional 7 days.
Overall, each patient's participation in the trial is estimated to last a total of approximately 7 weeks.
The patient's participation is concluded when they have undergone the last planned visit (i.e. Follow-up Visit).

As described in the Figure 3.1.1 below, patient randomisation in the trial will start to either 200µg bid of BI 1265162 or placebo. Once 28 patients are allocated to these two arms (14 patients in each arm), the remaining patients will be randomised to the additional doses of BI 1265162 (20, 50 and 100µg bid) as well as 200µg bid and placebo with 14 patients per treatment arm.
As a result, patients will be distributed in a 2:1:1:1:2 ratio to receive twice daily via the Respimat® inhaler either:

- Placebo, or
- 2x10µg (i.e. 20µg bid) of BI 1265162, or
- 2x25µg (i.e. 50µg bid) of BI 1265162, or
- 2x50µg (i.e. 100µg bid) of BI 1265162, or
- 2x100µg (i.e. 200µg bid) of BI 1265162.

Furthermore, patient recruitment in the trial will start with adult patients only. Enrolment of adolescent patients will be based on periodic reviews of adult patient safety data. Those safety data reviews allowing the recruitment of adolescent patients will be performed by an independent Data Monitoring Committee (DMC). The independent DMC will decide when adolescent patients can be enrolled and inform the Sponsor accordingly.

Randomisation will be stratified by age (<18 years old and ≥ 18 years old at day of randomisation) in order to ensure that approximately 20% of adolescent patients are randomised per treatment group (i.e., at least 3 adolescents in the 20µg, 50µg and 100µg bid of BI 1265162 groups and at least 6 adolescents in the 200µg bid of BI 1265162 and placebo groups).

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Adult and adolescent (12 to 17 years of age) patients diagnosed with CF and who comply with eligibility requirements may qualify for participation in this trial.

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

1. Male or female patients, 12 years of age or older at screening;
2. Documented diagnosis of cystic fibrosis including:
    - positive sweat chloride ≥ 60 mEq/L, by pilocarpine iontophoresis OR
    - genotype with 2 identifiable mutations consistent with cystic fibrosis accompanied by one or more clinical features with cystic fibrosis phenotype;
3. Patients able to perform acceptable spirometric manoeuvres according to American Thoracic Society (ATS) standards;
4. $FEV_1 \geq 40\%$ and $\leq 90\%$ of predicted* values at screening and predose at Visit 2;
5. Women of childbearing potential (WOCBP) [1] must be willing and able to use highly effective methods of birth control per ICH M3 (R2) that result in a failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient (or patient's legal guardian) information;
6. Signed and dated written informed consent and assent in accordance with ICH Harmonized Guideline for Good Clinical Practice (GCP) and local legislation prior to admission in the trial.

*Global Lung Initiative (GLI) lung function reference equations [R15-0845].

3.3.3 Exclusion criteria

1. Evidence of acute upper or lower respiratory tract infection within 4 weeks prior to randomisation based on investigator's judgement;
2. Pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics or oral corticosteroids within 4 weeks prior to randomisation;

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Furthermore, based on the interim analysis to be conducted on the first 28 patients included, the trial may be stopped as defined in Section 3.1 and Section 7.4.

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

The patients will be given a patient specific paper diary in which they will record the date and time he/she took the doses of trial medication for the 3 days preceding the clinic visits. Time of administration means the end of the second inhalation.

If the current used Respimat® inhaler is locked, lost or malfunctions, the patient must assemble and prime the reserve Respimat® inhaler at home.

4.1.4.4 Respimat® malfunctioning

Any Respimat® inhaler that has been reported as malfunctioning by a patient or a patient's legal representative or investigator will be returned to BI for investigation. See the ISF for specific instructions.

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.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

The randomisation codes will be provided to Bioanalytics prior or during the study to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients and to analyse the PK data on an ongoing basis. The project pharmacometrician and trial pharmacokineticist will also be given access to the randomisation code, along with preliminary BI 1265162 concentration data during the study to allow the PK, PK/PD modelling to be started from at least 53 evaluable patients. This will also allow minimizing the time from database lock to obtaining the final PK modelling results. If required, and draft PK data is available, this can be supplied to the DMC upon request. This data, including the randomisation codes, will be kept separate and securely in a manner not to unblind any members of the medical team or team personnel interacting with the study sites or investigators.

The interim analysis to be performed on the primary efficacy endpoint once 28 patients have completed 4 weeks of treatment will be conducted by a Sponsor team independent from the trial team. The randomisation codes will be provided to this team who will keep those separate and securely in a manner not to unblind any members of the medical team or team personnel interacting with the study sites or investigators.

The randomisation codes will also be provided to the independent DMC in case unblinded data review is required by any of the DMC members. This data including the outputs of the unblinded analysis will not be communicated to the Sponsor. Please refer to Section 8.7 for further details.

Table 5.2.3:1 Safety laboratory tests

Panel	Parameters to be tested
Hematology	Hematocrit Hemoglobin Erythrocyte count Total and differential leucocyte count Platelet count
Serum Chemistry	Albumin Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-glutamyltranspeptidase (GGT) Alkaline phosphatase (AP) Lactic dehydrogenase (LDH) Total bilirubin Direct bilirubin Indirect bilirubin Protein (total) Creatinine (IDMS standardised Jaffe Method) Urea Uric acid Glucose
Serum electrolytes	Potassium Sodium Chloride Inorganic phosphorus Calcium
Serum pregnancy test	β-HCG (only for female patients in case of positive urine pregnancy test)

The estimated glomerular filtration rate (eGFR) will be calculated according to:

- Bedside/interim Schwartz formula for patients below 18 years of age
  eGFR (mL/min/1.73 m^2) = 0.413 x height / Serum creatinine (mg/dL)

- CKD/EPI formula for adult patients
  eGFR (mL/min/1.73 m^2) = 141 x $\min(S_{Cr}/\kappa, 1)^{\alpha}$ x $\max(S_{Cr}/\kappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if Black]

S_{Cr} = standardized serum creatinine (mg/dL)
κ = 0.7 (females) or 0.9 (males)

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send the BI SAE form.

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

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Both adults and adolescents will be included in this trial. However, sputum and DNA biobanking will be performed only in patients who can legally consent.
Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Banked samples may be analysed in the future to further understand, for example, the mechanistic of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

5.5.1 Methods and timing of sample collection

Sampling will be performed at the time points specified in the Flow Chart.

Whole blood (DNA) banking:
Approximately 8.5mL blood will be drawn into a PAXgene Blood DNA tube.
DNA extracted from the original whole blood sample will be stored at the Sponsors' site. All other sample types will be stored at an external biobanking facility contracted by the Sponsor.
Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual

Spontaneous sputum
For all biospecimens collected, detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

The primary and secondary endpoints related to pulmonary function tests are standard assessments for the efficacy evaluation of an inhaled drug in cystic fibrosis.
The secondary PK endpoints outlined in Section 2.1.3 are standards PK parameters to assess drug exposure.

Assessments performed to assess the safety of the trial drug (ECG, physical examination, vital signs and safety laboratory tests) are also standard assessments for such kind of clinical trial.

Efficacy measurements based on N_2MBW test have proven to be valuable assessments of the small airway function and the distribution of ventilation among lung regions in patients with cystic fibrosis.

6. INVESTIGATIONAL PLAN

For investigational sites where patients below 18 years of age will be enrolled, trial visits should take place at a location within the clinical site that has a child-friendly infrastructure (e.g. an environment that is familiar to the patients, the setting is physically appropriate, if desired by the patient, parent(s)/legal guardian are allowed to stay with them during the trial procedures). Furthermore, site-personnel should be knowledgeable and skilled in dealing with the paediatric population and its age-appropriate needs.

6.1 VISIT SCHEDULE

Patients should make every attempt to complete the visits as specified in the Flow Chart (FC) and within the applicable visit windows. Investigators should encourage patient treatment compliance and adherence to protocol specific activities.

Patients who discontinue study medication prematurely will undergo the procedures for an early treatment discontinuation and a follow up visit as outlined in the FC.

Rescheduling visits:
A visit may be rescheduled within the acceptable visit window, due to:

- lack of bronchodilator(s) washout compliance, or
- no intake of study medication on the evening preceding the visit, or
- intake of study medication at home in the morning of the visit.

All deviations from the planned visit schedule will be documented. If any visit has to be re-scheduled, subsequent visits should follow the original visit schedule (calculated from Visit 2).

If bronchodilator(s) washout restrictions are not adhered to, the visit will be rescheduled once. The importance of adherence to washout requirements should be discussed and documented.

If a dose of study medication is missed on the day prior to a clinic visit with PK, the patient should contact the site for instructions and to determine if the visit should be rescheduled.

If a patient mistakenly takes trial medication in the morning of a visit where blood samples are drawn for PK assessment, the visit should be re-scheduled to the next day reminding the patient about the expected conditions.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart.

During trial visit, the sequence in which specific assessments are performed is important.

The sequence of procedures at each visit (where applicable) should be as follows:

1. CFQ-R questionnaire
2. CASA-Q questionnaire

At the end of Visit 1, patients who remain eligible for randomisation, should be reminded of bronchodilator(s) washouts and restrictions pertinent to Visit 2.

6.2.2 Treatment period(s)

For patients eligible to be randomised, assessments should be performed as mentioned in the Flow Chart and the respective protocol sections.

Randomisation Visit (Visit 2)
Eligible patients will be randomised by using the IRT system; all visit assessments should have been completed prior to this, and before the first intake of study medication. Patients will be trained on correct use of the Respimat® inhaler. First dose of trial drugs will be administered in the clinic (Day 1).

For patients who are on a stable regimen of inhaled cycling antibiotics, the Visit 2 should occur on the Day 1 of an "On-cycle" (+/- 1 or 2 days); whatever the antibiotic is. For patients cycling different antibiotics, the Visit 2 should occur on the Day 1 of a new antibiotic cycle.

A patient diary will be dispensed at Visit 2. Patients should be instructed to use the diary to record the date and time of administration of study medication for the 3 days preceding the clinic visits. Time of administration means the end of the second inhalation.

Next clinic visits will be scheduled after 1 and 4 weeks of treatment (Visit 3 and 4). For detailed description of the trial procedures at each visit and dispensing schedule, please refer to the Flow Chart.

In between clinic visits, serum potassium will be measured for safety monitoring. A laboratory kit to perform blood sampling by local laboratory/doctor/heatlh care provider will be provided to the patient at Visit 3 for measurement by central laboratory. The patient should be instructed to use the patient diary to record the date and time of the blood drawing. A phone contact with the patient will be required to check any adverse event and any concomitant medications. It is also possible to perform this serum potassium sampling at site if more appropriate for patient.

To ensure consistent and correct dosing, at each visit patients will be re-trained on use of the Respimat® inhaler.

6.2.3 Follow up period and trial completion

A follow-up (FUP) Visit should be planned 1 week after last trial drug administration. For detailed description of the trial procedures at the FUP Visit, please refer to the Flow Chart.

The FUP visit will be required for all patients, even those who discontinue treatment early. If laboratory tests were not completed at the end of treatment visit, they should be done at follow up.

Table 7.3.1:1 Parameter(s) in each Model depicted above

Model	**Pre-specified parameters**
Emax	ED_{50} = 25.555556 (90% of the maximum effect is achieved at 100 µg b.i.d.)
Sigmoidal Emax	ED_{50} = 50, h=3 (50% of the maximum effect is achieved at 45 µg b.i.d. and 90% of the maximum effect is achieved at 100 µg b.i.d.)
Linear	No assumption needed
Exponential	δ =300 (20% of the maximum effect is achieved at 60 µg b.i.d.
Quadratic	δ = -.003333 (50% of the maximum effect is achieved at 40 µg b.i.d. and 90% of the maximum effect is achieved at 100 µg b.i.d.)

PoC is established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship over trough FEV_1 percent predicted at 4 weeks for each of the candidate dose response models with a contrast test controlled for the family–wise type I error rate at one sided α = 5%.

If PoC is established, the statistically significant (best fitting) model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters from the data. The average model will be determined and will be used to refit the data and generate the new estimates.

The target dose(s) can be estimated from the average model by incorporating information on the minimum clinically relevant effect and accounting for safety.

Pairwise comparisons of BI 1265162 doses to placebo (90% confidence intervals (CI) and p-values) based on the mixed effects model will be reported. These are further, descriptive analyses of the primary endpoint to supplement the MCPMod analysis, which is the primary analysis.

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of age (< 18 years old and ≥ 18 years old), the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-age-by-visit term. A descriptive p-value of treatment effect homogeneity at Week 4 will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

7.3.2 Secondary endpoint analyses

The linear mixed effects model described above will be used to analyse the secondary endpoints including LCI, CFQ-R and CASA-Q scores. 90% confidence intervals and p-values will be provided for the comparison of each dose of BI 1265162 to placebo. Since type

Depending on the resulting data, additional pharmacokinetic parameters might be calculated as appropriate. Parameters such as age, weight, BMI may be used as covariates to investigate the pharmacokinetics fully in the current adult and patient population.

The results from the population analysis will be reported separately outside of the current Clinical Trial Report (CTR).

A non-compartmental (NCA) PK analysis may be undertaken on Day 8 if the data allows. The following parameters may be calculated;

- $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N)
- $C_{pre,N}$ (predose concentration measured for dose N)
- $AUC_{0\text{-}t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

The results from a NCA analysis, if undertaken, along with listings of the plasma concentration-time data will be included in the study report.

7.4 INTERIM ANALYSES

An interim futility analysis will be conducted on the primary efficacy endpoint once 28 patients in the placebo and BI 1265162 200µg bid arms have completed the 4-week treatment period. Additional details of the interim analysis will be specified in the TSAP.

7.5 HANDLING OF MISSING DATA

No imputation will be applied while the MMRM will use all available data. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

7.6 RANDOMISATION

Patient randomisation will start with only adult patients to either 200 µg bid of BI 1265162 or placebo in a 1:1 ratio. As soon as 28 patients are allocated to these two treatment arms, the remaining patients will be allocated to the other doses of BI 1265162 as well as the highest dose and placebo in a 1:1:1:1:1 ratio (14 patients per treatment arm).
As a result, patients will be distributed to one of the five treatment groups in a 2:1:1:1:2 ratio.

Randomisation will be stratified by age (< 18 years old and ≥ 18 years old).

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

- 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 BI 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.

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, a PFT central reading services, a N_2MBW test central reading services and an IRT vendor will be used in this trial. Details will be provided in the dedicated Manuals, available in the ISF.

10. APPENDICES

Not applicable.