Clinical Trial Protocol

	Document Number:	**c23936559-02**
EudraCT No. **EU Trial No.**	2019-000261-21	
BI Trial No.	1399-0003	
BI Investigational Medicinal Product(s)	BI 1265162	
Title	A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat® inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis – BALANCE – CF™ 1	
Lay Title	A 4-week study to test different doses of BI 1265162 in adolescents and adults with cystic fibrosis using the Respimat® inhaler – BALANCE – CF™1	
Clinical Phase	Phase II	
Trial Clinical Monitor	Tel: Fax:	
Coordinating Investigator		
Status	Final Protocol (Revised Protocol based on global amendment 1)	
Version and Date	**Version: 2.0**	**Date: 18 Nov 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	08 March 2019
Revision date	18 November 2019
BI trial number	1399-0003
Title of trial	A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat® inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis – BALANCE – CF™1
Coordinating Investigator	
Trial site(s)	Multi-centre trial conducted in approximately 10 countries
Clinical phase	II
Trial rationale	Dose ranging to determine the optimal dose to be evaluated in the phase III program.
Trial objective(s)	The primary objective of this trial is to assess the efficacy, safety and pharmacokinetics of twice daily inhaled doses of 20 µg, 50 µg, 100µg and 200 µg of BI 1265162 delivered by Respimat® inhaler versus placebo in adult and adolescent patients with cystic fibrosis.
Trial endpoints	Primary endpoint: • Change from baseline in percent predicted trough FEV_1 after 4 weeks of treatment Secondary endpoints: • Change from baseline in Lung Clearance Index (LCI) assessed by N_2MBW procedure after 4 weeks of treatment • Change from baseline in CFQ-R total score after 4 weeks of treatment • Change from baseline in CASA-Q (4 separate sub-scores) after 4 weeks of treatment • Percentage of patients with treatment-emergent Adverse Events (AE) up to Day 36 • $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N) • $C_{pre,N}$ (predose concentration measured for dose N) $AUC_{0-t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)
Trial design	Randomised, double-blind, placebo-controlled and parallel group design over 4 weeks.
Total number of patients randomised	98 patients including 21 adolescent patients
Number of patients	• 28 patients on placebo including 6 adolescent patients

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.

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

(***) 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 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

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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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ASL	Airway Surface Layer
AST	Aspartate Transaminase
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
β-HCG	Beta-Human Chorionic Gonadotropin
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CASA-Q	Cough and Sputum Assessment Questionnaire
CF	Cystic Fibrosis
CFQ-R	Cystic Fibrosis Questionnaire Revised
CFTR	Cystic Fibrosis Transmembrane conductance Regulator
CI	Confidence Interval
Cl	Chlorure
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CML	Clinical Monitor Local
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DNA	DeoxyriboNucleic Acid
ECG	Electrocardiogram

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

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

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Cystic Fibrosis (CF) is an inherited disease of the exocrine glands, primarily affecting the gastrointestinal and respiratory systems and characterized by exocrine pancreatic insufficiency and abnormally high sweat electrolytes. CF is a life-threatening disease affecting approximately 30,000 children and adults in the United States and more than 70,000 worldwide. CF is an inherited autosomal recessive trait (i.e., an individual must inherit two defective CF genes – one from each parent – to have CF). The gene responsible for the disease encodes a membrane-associated protein called the cystic fibrosis transmembrane conductance regulator (CFTR) and is located on the long arm of chromosome 7 [R15-5856]. The gene defect causes the body to produce abnormally thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections.

In addition, evidence suggests a role for the epithelial sodium channel (ENaC) in the pathogenesis of CF that exacerbates the dehydration of mucus, which becomes thickened, tenacious and adherent, and leads to collapsed cilia and poor mucus clearance [R15-4955].

Standard therapy for CF patients, adult and paediatric, includes various CFTR modulators alone or in combination, antibiotics, airway clearance techniques and devices, pancreatic enzymes and nutritional supplements, and drugs such as dornase alfa (Pulmozyme®), ibuprofen and, most often, inhaled bronchodilators.

In CF, inhibition of ENaC is anticipated to modify the abnormal electrolytic exchange across the cell membrane, by specifically reducing sodium uptake and water absorption in the airways, thus counteracting dehydration of the mucus. This should translate to improved mucociliary clearance and pulmonary function (especially FEV_1). A decrease in static mucus would be expected to reduce bacterial colonisation of the lower airways, which could cause fewer exacerbations and hospitalisations. As a result, the patient would experience a relief of clinical symptoms and a better quality of life.

1.2 DRUG PROFILE

1.2.1 The Respimat® Inhaler

BI 1265162 is administered with the Respimat® inhaler from an aqueous solution in a cartridge, which is inserted into the inhaler prior to first use. Several solutions with different drug substance concentrations have been developed for use in clinical studies, including a placebo solution.

The Respimat® Inhaler generates a soft mist (without the use of propellants) which is released over a period of approximately 1.5 seconds. The drug formulation contains disodium edetate as a stabilizer and as a multi-dose inhaler and solution; it contains the antimicrobial preservative benzalkonium chloride. Both excipients have been reported to induce bronchospasms in some patients. However, the concentrations of disodium edetate and benzalkonium chloride in the BI 1265162 Respimat® formulation are well below the amounts

for which bronchospasm has been reported with nebulised solutions [P05-08465] and are already widely used in Spiriva Respimat® for the treatment of asthma and COPD, Spiolto and Combivent Respimat® for the treatment of COPD.

1.2.2 BI 1265162

Mode of action/pharmacology
BI 1265162 is a potent inhibitor of the epithelial sodium channel (ENaC)

Key pharmacokinetic characteristics

Drug interactions

Based on the plasma BI 1265162 concentrations observed in the single rising dose study in man, no drug interaction is predicted in man.

Residual Effect Period

Data from toxicology studies

Data from clinical studies

For a more detailed description of BI 1265162 profile, please refer to the current Investigator's Brochure (IB).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Because CF is an inherited disease, there is no preventative treatment. Even though new disease modifying therapies have been approved, there is still a need for symptomatic treatment that works in conjunction with existing medications to reduce the risk of CF-related exacerbations, improve the quality of life and prolong patient survival.

One particular unmet medical need in CF is for a safe and effective muco-active medication. In comparison to marketed mucolytic therapies, an ENaC inhibitor would be expected to have additional effects as a result of its direct influence on mucus hydration.
Indeed, an ENaC inhibitor does not act directly on mucus but by inhibiting the ENaC which is highly upregulated in CF, it modifies the abnormal electrolytic exchange across the cell

membrane. ENaC represents a new target in CF and is part of a physiological pathway that complements CFTR in the regulation of the fluid volume and composition of the airway surface layer (ASL), a key factor in determining the potential of mucociliary clearance. This could result in potential synergy between CF treatments targeting the two mechanisms.

Historically, CF has been considered a paediatric disease, becoming symptomatic at a young age. However, newer treatments and improved disease management allow patients to live into adulthood. The underlying aetiology, a genetic defect in the CFTR gene, remains the same irrespective of the age. The clinical manifestations of the disease are similar in children and adults, while the main cause of death in both populations is pulmonary insufficiency.

This trial will evaluate the efficacy and safety of several doses of BI 1265162 in adolescents (12-17 years of age) and adults with CF. This trial aims to determine the optimal dose to be evaluated in the phase III program.

Rationale for the N_2 Multiple Breath Washout (N_2MBW) test

Lung Clearance Index (LCI) based on N_2MBW test is a valuable endpoint to explore the small airway function and the distribution of ventilation among lung regions, aspects of lung function which are not captured by spirometry. N_2MBW test is a very sensitive test which requires experienced site staff and can only be performed in patients with less impaired lung function.

1.4 BENEFIT - RISK ASSESSMENT

The nature of the target and the mechanism of action of BI 1265162 are well understood and ENaC inhibition is a well-established target for systemic potassium sparing diuretics such as amiloride. The mechanism has been studied in multiple animal species as well as in clinical trials of up to 6 months duration via the inhaled route. The mechanism is not pleiotropic, does not have any amplification properties and will not bypass normal physiological control mechanisms. The tissue distribution of the target is well characterized and the adverse effect profile of the on target effect of inhibition is well known.

The established functions of ENaC fit to its involvement in the pathogenesis of Cystic Fibrosis and effects demonstrated in rats and sheep are expected to translate into effects in man.

Patients who will be randomised in the placebo group may have a higher probability of treatment failure, i.e. no improvement of the lung function. However, BI 1265162 will be assessed on top of standard CF therapies. Therefore, the patients randomised in the placebo group will still be treated as per the standard clinical practice. The severity of CF is determined by a combination of factors including the CFTR mutation, so the underlying cause of disease does not alter with age. In addition, the expression and function of ENaC is not considered to differ between the age groups. Therefore, the mechanism of action and the dose of BI 1265162 are anticipated to be the same in adults and paediatrics. It is expected that BI 1265162 will have a similar effect on mucociliary clearance and pulmonary function in all age groups, this is why adolescent patients aged 12 or older will be included in this phase II trial. However, patient recruitment will start with adult patients only. The enrolment of adolescents will be allowed by an independent Data and Monitoring Committee (DMC), based on periodic safety adult data reviews (please refer to the DMC charter for further details).

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators for all investigational products. Therefore, this trial will define procedures for the timely detection, evaluation, and follow-up of laboratory alterations in

selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.6, adverse events of special interest.

Some improvements are expected in CF patients after a 4-week exposure, especially on lung function and symptoms. The risks of the study procedures themselves are, in general, similar to what the patient population in question routinely experiences with the treatment/management of their disease.

Overall, the expected potential benefits for CF patients outweigh potential risks and justify exposure to BI 1265162 in this trial, at the selected doses twice daily over 4 weeks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to assess the efficacy, safety and pharmacokinetics of twice daily inhaled doses of 20 µg, 50 µg, 100µg and 200 µg of BI 1265162 delivered by Respimat® inhaler versus placebo in adolescents and adult patients with cystic fibrosis.

2.1.2 Primary endpoint(s)

The primary endpoint to assess efficacy of BI 1265162 is the change from baseline in percent predicted trough Forced Expiratory Volume in 1 Second (FEV_1) after 4 weeks of treatment. Trough FEV_1 is defined as measurement performed within 30 minutes prior to dosing.

2.1.3 Secondary endpoint(s)

The secondary endpoints of this trial are:

- Change from baseline in Lung Clearance Index (LCI) assessed by N_2 Multiple Breath Washout (N_2MBW) procedure after 4 weeks of treatment
- Change from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) total score after 4 weeks of treatment
- Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) (4 separate sub-scores) after 4 weeks of treatment
- Percentage of patients with treatment-emergent Adverse Events (AE) up to Day 36
- Ct,N (concentration of the analyte in plasma at time t following dose N)
- Cpre,N (predose concentration measured for dose N)
- AUC0-t,N (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

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).

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

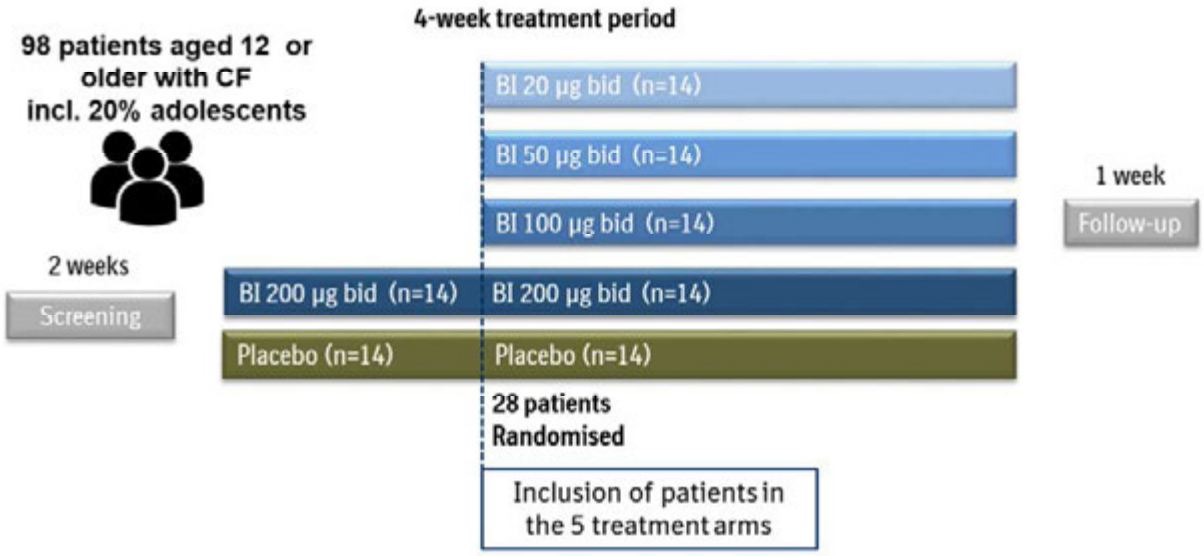

Figure 3.1.1 Trial Design

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.

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.

3. Patients with history of Acute Tubular Necrosis (ATN);
4. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or *in situ* carcinoma of uterine cervix;
5. Patients unable to inhale trial drug in an appropriate manner from the Respimat® inhaler based on investigator's judgement;
6. Patients who have started a new chronic medication for CF within 4 weeks of randomisation;
7. Patients who have previously received a lung transplant or patients who are currently on a waiting list to receive a lung transplant;
8. Patients with a significant history of allergy/hypersensitivity (including medication allergy) which is deemed relevant to the trial as judged by the investigator or with a known hypersensitivity to trial drug or its components. "Significance" in this context refers to any increased risk of hypersensitivity reaction to trial medication;
9. Any clinically significant laboratory abnormalities at screening as judged by the investigator, or any of the following:
   - Potassium > upper limit of normal (ULN) in non-haemolysed blood
   - Abnormal renal function defined as estimated Glomerular Filtration Rate (eGFR) < 60ml/min/1.73m²
   - Abnormal liver function, defined by serum level of either alanine transaminase (ALT), aspartate transaminase (AST) or total bilirubin ≥ 3 x upper limit of normal (ULN)
10. Clinically significant disease or medical condition other than CF or CF-related conditions that, in the opinion of the investigator, would compromise the safety of the patient or the data quality. This includes significant haematological, hepatic, renal, cardiovascular and neurologic disease. Patients with diabetes may participate if their disease is under good control prior to screening;
11. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled;
12. Previous randomisation in this trial;
13. Currently enrolled in another investigational device or drug trial, or less than 30 days or six half-lives (whichever is greater) since ending another investigational device or drug trial(s), or receiving other investigational treatment(s);
14. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial;
15. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent"); please see sections 3.3.4.1 and 3.3.4.2 below.
Every effort should be made to keep the patients in the trial. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

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.

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).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by BI.

Chronic CF medications are not considered as part of the clinical trial supplies and therefore will not be provided by BI.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are as shown below.

Table 4.1.1:1 Test product 1

Substance:	BI 1265162
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10µg per actuation
Posology:	2 inhalations twice a day
Method and route of administration:	Oral inhalation via Respimat® inhaler

Table 4.1.1:2 Test product 2

Substance:	BI 1265162
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	25µg per actuation
Posology:	2 inhalations twice a day
Method and route of administration:	Oral inhalation via Respimat® inhaler

Table 4.1.1:3 Test product 3

Substance:	BI 1265162
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50µg per actuation
Posology:	2 inhalations twice a day
Method and route of administration:	Oral inhalation via Respimat® inhaler

Table 4.1.1:4 Test product 4

Substance:	BI 1265162
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100µg per actuation
Posology:	2 inhalations twice a day
Method and route of administration:	Oral inhalation via Respimat® inhaler

Table 4.1.1:5 Test product 5

Substance:	Placebo
Pharmaceutical formulation:	Inhalation solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Not applicable
Posology:	2 inhalations twice a day
Method and route of administration:	Oral inhalation via Respimat® inhaler

4.1.2 Selection of doses in the trial and dose modifications

In this trial, the doses of 20 µg, 50 µg, 100 µg and 200 µg bid of BI 1265162 will be compared to placebo. The medication will be inhaled twice daily during four weeks, using the Respimat® inhaler. Each dose will consist of two inhalations; therefore the 20 µg dose will consist of two inhalations of 10 µg, the 50 µg dose will consist of two inhalations of 25 µg, the 100 µg dose will consist of two inhalations of 50 µg and the 200 µg dose will consist of two inhalations of 100µg.

The doses selected were based on the previous SRD and MRDstudies in healthy volunteers (please refer to the Investigator Brochure for further details). The doses were selected in order to cover the expected therapeutic range (50 µg to 200 µg) and a sub-therapeutic dose (20 µg) which is required for a proper modeling of the dose response shape. With these selected doses, sufficient information should be gathered to select a safe and effective dose to be assessed in Phase III pivotal studies.

4.1.3 Method of assigning patients to treatment groups

As described in Section 3.1, 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).

The assignment will occur in a blinded fashion via Interactive Response Technology (IRT). The IRT will assign the appropriate medication number based on the treatment sequence. The randomisation code will be controlled and documented. All instructions for use of the IRT system will be described in a user guide/manual which will be available in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

4.1.4.1 Drug assignment and Dispensing of medication

Patients who qualify for randomisation will be randomly assigned by the IRT to one of the treatment groups listed below.

Table 4.1.4: 1 Dosage and treatment schedule for the treatment period

Total Daily Dose (µg)	Visit 2
	4 weeks
40 (20 µg bid)	2x10 µg twice a day
100 (50 µg bid)	2x25µg twice a day
200 (100 µg bid)	2x50µg twice a day
400 (200µg bid)	2x100µg twice a day
Placebo	2 puffs twice a day

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.

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.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator 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 participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal 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 sponsor must be contacted immediately. Please refer to the ISF for further details.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, 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,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, 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 medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient 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

Four doses of BI 1265162 will be assessed on top of CF standard therapies.
There are no specific emergency procedures defined in this trial.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

BI 1265162 will be assessed as add-on therapy to standard of care and thus, patients will remain on their current treatment(s). It is recommended that patients remain on a stable CF medication regimen from 4 weeks prior to randomisation through Week 4 or, if applicable, through the Follow-up Visit, with the exception of bronchodilators (see below).

Stable medication regimen is defined as the current medication regimen for CF that the patient has been following for at least 4 weeks before Day 1 (randomisation).

In terms of physiotherapy, there are no restrictions in the morning of study visits. If physiotherapy is scheduled in the morning of study visits, it has to be performed in the same fashion as on Day 1.

Patients who are using a bronchodilator must have their spirometry (except the one at screening) and N_2 Multiple Breath Washout measurements performed according to the guidelines provided below:

- Withhold short–acting β2-agonist (e.g. albuterol) or anticholinergic bronchodilators (e.g., Atrovent) for more than 4 hours before the assessments,
- Withhold twice-daily long–acting bronchodilators (e.g. salmeterol) for more than 12 hours before the assessments,
- Withhold once-daily long–acting bronchodilators (e.g. tiotropium) for more than 24 hours before the assessments.

Patients who require bronchodilation prior to inhaling hypertonic saline solution (according to investigator´s judgement) should withheld the use of hypertonic saline solution in line with

the instructions for bronchodilators. Consistency of any withholding decisions across visits is required.

In case a patient forgets to withhold bronchodilator(s) intake (and hypertonic saline solution intake if applicable) in the morning of clinic visits, the study visit has to be re-scheduled the day after.

For patients who are on a stable regimen of inhaled cycling antibiotics, the Day 1 visit (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 Day 1 visit (Visit 2) should occur on the Day 1 of a new antibiotic cycle.

Acute exacerbations should be treated according to best standard practice, and decision to interrupt BI 1265162 left to investigator's judgment.

All concomitant medications will be recorded on the appropriate pages of the eCRF.

4.2.2.2 Restrictions on diet and life style

Patients should only follow the CF dietary recommendations provided by the investigational site staff.

Lifestyle restrictions for PFT and N_2MBW test:
The patient must refrain from strenuous activity and smoking for at least 2 hours prior to pulmonary function testing (forced spirometry) and N_2MBW measurement (if applicable).

4.2.2.3 Contraception requirements

Women of childbearing potential must maintain a highly effective method of contraception throughout the course of trial and for a period of at least 2 weeks after the last trial drug intake.
Contraception methods meeting these criteria are defined as:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomized sexual partner (with appropriate post-vasectomy documentation of that absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the WOCBP CT participant)
- Sexual abstinence: Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

Contraception of male trial participants and female partners of male trial participants is not required.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all used and unused trial medication including partially used or empty Respimat® inhalers, packages and reserve kit with them when attending visits.

Based on the Respimat® dose counter indicating the remaining number of available actuations, treatment compliance will be calculated as shown in the formula below.

Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actuations actually taken} \times 100}{\text{Number of actuations which should have been taken}}$$

Note: 2 actuations (inhalation) per dose, twice a day (after priming)
If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Pulmonary Function Testing (FEV_1

FEV_1 will be assessed using standardised spirometry equipment which will be supplied to all participating sites at trial initiation. Only these spirometers are to be used for this trial. Spirometry performance will be centrally reviewed. Spirometry equipment will be provided centrally with supplies of pre-calibrated disposable flow sensors. These sensors demonstrate variability within the required standards of +/-3% determined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [P05-12782].As such there is no need to conduct daily calibration prior to use.

For each patient, pulmonary function testing will always start at approximately the same time of day. Spirometry will be conducted while the patient is in a seated position. It is preferable that the same trained individual performs the PFTs for a given patient. The best of three efforts will be defined as the highest FEV_1 each obtained on any of three blows meeting the ATS/ERS criteria (with a maximum of eight attempts). FEV_1 will be measured at the timepoints indicated in Flow Chart. Spirometry results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading.

Spirometry predicted values will be based on the Global Lung Initiative (GLI) 2012 lung function reference equations [R15-0845].

5.1.2 Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The CFQ-R is a disease specific instrument that measures health related quality of life.

For adolescents and adults (patients 14 years old and older), the questionnaire consists of 50 items in four sections.

For children ages 12 and 13 there is a self-report format consisting of 35 items as well as a version for parents/caregivers consisting of 44 items. In case a patient would turn 14 years old during the trial participation, the same version of the questionnaire should be used at Visit 2 and for the subsequent visits to ensure an appropriate comparison of the results.

The CFQ-R will be completed at the time points indicated in the Flow Chart.

The CFQ-R should be administered at the start of the clinic visit, prior to any other tests or procedures. The CFQ-R will be paper-based and available in the local language (provided in the ISF).

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.

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)

α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based 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).

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.

5.2.6.2.3 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.

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.

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

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

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.

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.

Trial completion

The trial completion eCRF page has to be filled-in when the patient has terminated the trial.

The end of the trial is:

- At the end of the FUP visit for patients who have completed the trial on treatment as planned;
- After the early end of treatment (EOT) and follow-up Visits, if a patient prematurely withdrawn from treatment.

Patients who prematurely discontinued trial medication

Patients who prematurely discontinue study drug (refer to Section 3.3.4) before the planned end of treatment at Visit 4, should come to the clinic as soon as possible after last drug intake for an early EOT Visit. The reason for premature trial drug discontinuation must be documented in the eCRF. For detailed description of the trial procedures at this visit, please refer to the Flow Chart. Then a Follow-up Visit should take place 7 days after the early EOT Visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a Phase II, randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat® inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis.

The primary objectives of this trial is to assess the efficacy, safety and pharmacokinetics of twice daily inhaled doses of 20 µg, 50 µg, 100µg and 200 µg of BI 1265162 delivered by Respimat® inhaler versus placebo in adolescents and adult patients with cystic fibrosis.

The primary trial objective includes demonstration of proof of concept (PoC) with respect to a non-flat dose response curve based on percent predicted trough FEV_1, characterization of the dose-response relationship within the therapeutic range, and selection of the optimal dose for phase III development. For this purpose, the primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response curve comparing change from baseline in trough FEV_1 percent predicted at 4 weeks in the placebo and the BI 1265162 dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 1265162 over placebo.
The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided α of 5%). The pre-specified models and their parameters used for this test are outlined in Section 7.3.1.

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.

- 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

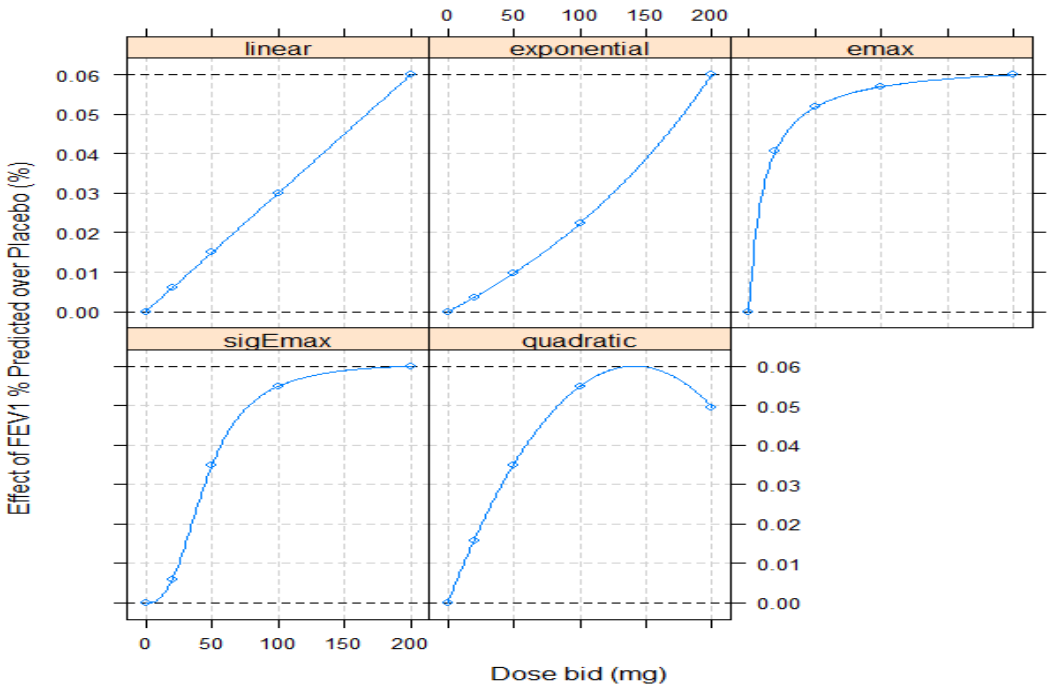

Table 7.3.1:1 Parameter(s) in each Model depicted above

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

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)

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.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the following assumptions:

- the primary endpoint "change from baseline in trough FEV_1 % predicted at Week 4" is normally distributed
- one-sided significance level $\alpha = 5\%$ (for MCP-Mod analysis)
- mean treatment difference (the highest dose of BI 1265162 vs placebo) is 6% (for interim analysis only)
- true maximum treatment effect size of BI 1265162 versus placebo is 6% (for MCP-Mod analysis)
- standard deviation is 8% [R16-1992]
- pre-specified candidate models listed in Section 7.3.1 (for MCP-Mod analysis).

Table 7.7.1 shows the probability of Continue the trial after interim analysis in case of no treatment effect and overall type I error rate (probability of Continue after interim analysis and Succeed at final analysis in case of no treatment effect) for different cut-offs. Probability of Continue is 32.3% at cut-off 1.5% in case of no treatment effect, and overall Type I error rate is controlled under 5% for all cut-offs.

Table 7.7.2 shows probability of Continue the trial after interim analysis in case of true treatment effect and overall power (probability of Continue and Succeed in case of true treatment effect) for different cut-offs and assumed true models. Probability of Continue is > 91% and overall power is ≥80% for cut-off ≤ 1.5% for all true candidate monotone shapes.

With a cut-off value ranging from 1% to 2% to continue the trial after the interim analysis, a sample size of 12 evaluable patients in each of the placebo arm and the highest dose arm at interim analysis, and additional 12 evaluable patients in each of five arms for final analysis will guarantee overall power >79.8% for all true candidate monotone shapes; and overall type I error is also controlled below 5%.

Table 7.7:1 Overall Type I error based on 12 evaluable patients per treatment arm (Placebo and the highest dose of BI 1265162)

Cut-off	Probability of continue	Probability of continue and succeed at final analysis
0	50.0%	4.8%
1%	38.0%	4.5%
1.5%	32.3%	4.3%
2%	27.0%	4.1%
3%	17.9%	3.5%

Table 7.7:2 Probability of Continue in case of true treatment effect and overall power based on 12 evaluable patients per treatment arm (5 treatment arms)

Cut-off	Probability of continue				
	Linear	Exponential	Emax	SigEmax	Quadratic
0	96.7%	96.7%	96.7%	96.7%	93.6%
1%	93.7%	93.7%	93.7%	93.7%	88.7%
1.5%	91.6%	91.6%	91.6%	91.6%	85.5%
2%	89.0%	89.0%	89.0%	89.0%	81.8%
3%	82.1%	82.1%	82.1%	82.1%	72.6%

Cut-off	Probability of continue and succeed				
	Linear	Exponential	Emax	SigEmax	Quadratic
0	84.0%	84.0%	84.7%	88.0%	76.22%
1%	82.5%	82.6%	83.2%	86.3%	74.1%
1.5%	81.3%	81.5%	82.0%	84.9%	72.4%
2%	79.8%	79.9%	80.4%	83.0%	70.22%
3%	75.2%	75.3%	75.7%	77.8%	64.3%

In order to ensure 12 evaluable patients per arm with primary endpoint data for interim analysis, at least 14 patients per arm will be randomised (total 28).

In order to ensure additional 12 patients per group are evaluable for final analysis, at least 14 patients will be randomised per treatment group (total 70). Overall, 98 patients will be randomised in the trial.
This calculation has been performed using R software, version 3.2.2.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a 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 patients, and is stored in the ISF.

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 patient participation in the trial, written informed consent must be obtained from each patient (or the patient’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/parent(s)/legal guardian-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient/parent(s)/legal guardian information must be given to each patient or the patient’s legally accepted representative.

For adolescents, the patient will be provided with an age-adapted information sheet where his/her assent will be collected according to the regulatory and legal requirements of the participating country. The refusal of an adolescent to participate must be accepted independently of the consent of his/her parent(s)/legal guardian.

For patients who may legally consent during the trial participation (turning to the age of legal consent in the participating country), written informed consent must be obtained to confirm the patient's willingness to pursue trial participation.

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual patients 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 patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data must be traceable (audit trail).

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

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

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

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient'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 patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT 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 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,

- 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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9.2 UNPUBLISHED REFERENCES

Not applicable.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 NOVEMBER 2019
EudraCT number **EU number**		2019-0001261-21
BI Trial number		1399-0003
BI Investigational Medicinal Product(s)		BI 1265162
Title of protocol		A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat® inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title page Synopsis
Description of change		Administrative change
Rationale for change		To add trial name 'BALANCE-CF™1'
Section to be changed		Title page
Description of change		Trial Clinical Monitor
Rationale for change		Personal change
Section to be changed		Synopsis Section 2.1.3 Secondary endpoints
Description of change		Change (C_{max} replaced by C_t) and clarification in PK parameters to be measured as secondary endpoint
Rationale for change		Updated PK parameter list is more in line with the sparse sampling that is planned at various visits
Section to be changed		Synopsis
Description of change		Inclusion criteria 3 corrected to : FEV1 ≥ 40% and ≤ 90% of predicted values at screening **and predose at Visit 2**.
Rationale for change		To align with inclusion criterion in section 3.3.2
Section to be changed		Synopsis Section 3.3.2 Inclusion Criteria and 3.3.3 Exclusion criteria
Description of change		Adaptation of inclusion criterion 5 and exclusion criteria 15 to allow recruitment of WOCBP using

		adequate contraception
Rationale for change		Inclusion of WOCBP using adequate contraception allowed in all countries following availability of EFD study data in new IB
Section to be changed		Synopsis Section 3.3.3 Exclusion criteria
Description of change		Addition of new exclusion criteria 15: Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
Section to be changed		Section 3.3.3 Exclusion criteria
Section to be changed		Flowchart
Description of change		Removal of trial drug collection at V3
Rationale for change		To align with section 4.1.4.1.
Section to be changed		Flowchart & Footnote 5 Section 5.2.3 Safety laboratory parameters
Description of change		Addition of pregnancy tests
Rationale for change		Addition of Pregnancy Testing for female patients who have reached menarche, even irregular, required due to allowed recruitment of Women of Childbearing Potential
Section to be changed		Synopsis Section 3.3.3 Exclusion criteria
Description of change		Removal of exclusion criteria 15 to allow recruitment of WOCBP
Rationale for change		Inclusion of WOCBP allowed in all countries following availability of EFD study data in new IB
Section to be changed		Flowchart for PK blood sampling Flowchart for Pulmonary Function Test
Description of change		Timing of flowchart for PK updated with unit of timepoints Flowchart for N_2MBW test added
Rationale for change		Clarification on procedures to be performed in the study
Section to be changed		Flowchart –footnote (**) Flowchart –footnote 2 Flowchart for PK blood sampling Flowchart for Pulmonary Function Test
Description of change		Details of procedures to be performed in case of early treatment discontinuation were added. 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
Rationale for change		Clarification on procedures to be performed in case

		of early treatment discontinuation
Section to be changed		Flowchart –footnote (****) Section 5.5 BIOBANKING
Description of change		Restriction of sputum and DNA biobanking to patients who can legally consent only.
Rationale for change		Clarification
Section to be changed		Flowchart & footnote 2 Section 5.2.3 Safety laboratory parameters
Description of change		Addition of monitoring of 3 new electrolytes
Rationale for change		To implement more standard electrolyte analysis
Section to be changed		Flowchart - footnote 2
Description of change		Addition of time window for serum electrolyte test
Rationale for change		To allow flexibility
Section to be changed		Flowchart footnote 6 Section 6.2.2 Treatment period(s)
Description of change		Possibility to perform ambulatory visit at site if more appropriate for patient
Rationale for change		To add flexibility
Section to be changed		Section 1.3 RATIONALE FOR PERFORMING THE TRIAL

Section to be changed		Section 1.4 BENEFIT - RISK ASSESSMENT
Description of change		Addition of data related to embryo-fetal development toxicity studies and update on contraception requirement for this trial
Rationale for change		Change due to update of recent IB
Section to be changed		Section 3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Specification that age to be used for stratification of randomisation is age at day of randomisation
Rationale for change		Clarification
Section to be changed		Section 3.3.2 Inclusion criteria 5
Description of change		update to include contraception of WOCBP and to remove contraception of male participant
Rationale for change		To update contraception requirements according to IB update
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		Addition of new exclusion criteria 15: Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
Rationale for change		To follow update of recent IB
Section to be changed		Section 3.3.4.1 discontinuation of trial treatment
Description of change		Addition of pregnancy as case of trial discontinuation

Rationale for change		Inclusion of WOCBP allowed in all countries
Section to be changed		Section 3.3.4.1 discontinuation of trial treatment
Description of change		Addition of requirements for confirmation of elevated value of potassium:Each result of elevated serum potassium level > ULN should be confirmed, meaning either by a second measurement either by presence of clinical symptoms.
Rationale for change		Clarification
Section to be changed		Section 4.1.4.2 Training and priming of the respimat® inhaler
Description of change		Addition of restriction for priming of the Respimat® inhaler
Rationale for change		To avoid any contamination of PK samples
Section to be changed		Section 4.1.4.3. study medication administration
Description of change		Clarification on timing of study medication intake in relation to other CF treatments Addition of recommendation in case of missed dose: If a dose is missed for more than 4 hours, the next one should be taken as planned.
Rationale for change		Clarification
Section to be changed		Section 4.1.4.3. study medication administration Section 6.1 Visit schedule
Description of change		No need to reschedule visit if only morning dose is missed on the day preceding the visit
Rationale for change		Clarification
Section to be changed		Section 4.2.2.2 Restrictions regarding concomitant treatment
Description of change		Patients who are using hypertonic saline solution just after using bronchodilator on regular basis should also follow the same washout period than period required for the bronchondilator. In case of the washout of hypertonic saline solution cannot be followed by the patient according to investigator's judgement, then the patient should inhale in the hypertonic saline solution in the same manner at each visit during the study
Rationale for change		To take in consideration hypertonic saline solution as possible CF concomitant treatment
Section to be changed		Section 5.1.1 Pulmonary Function Testing (FEV1
Description of change		Removal of calibration of spirosphere
Rationale for change		Daily Calibration prior to use not needed with this type of material
Section to be changed		Section 5.2.3 Safety laboratory parameter
Description of change		Specification of total blood volume collected
Rationale for change		Clarification

Section to be changed		Section 5.2.6.1.4 Adverse events of special interest
Description of change		Elevation of serum potassium > upper limit of normal (ULN) in non-haemolysed blood should be confirmed to be considered as AESI
Rationale for change		Clarification
Section to be changed		Section 5.3.1 Assessment of pharmacokinetics
Description of change		Maximum storage time for PK samples for additional evaluations added
Rationale for change		Clarification
Section to be changed		Section 5.3.2.1 Plasma sampling for pharmacokinetic analysis
Description of change		Maximum blood volume for PK samples corrected
Rationale for change		Correction
Section to be changed		Section 5.3.4 pharmacocinetic – pharmacodynamics relationship Section 7.3.5. pharmacokinetic and pharmacodynamics analyses
Description of change		More detail added regarding data analysis using population PK and noncompartmental PK analysis
Rationale for change		Clarification
Section to be changed		Section 6.2 details of trial procedures at selected visits
Description of change		Section updated with only mandatory requirements on sequence of procedures
Rationale for change		To allow flexibility
Section to be changed		Section 6.2.2 treatment period(s)
Description of change		Ambulatory visit can be performed at site if more appropriate for the patient
Rationale for change		Clarification
Section to be changed		Section 7.3
Description of change		Add data analysis set
Rationale for change		Clarification
Section to be changed		Section 7.3.1
Description of change		Modify the layout of statistical model and point out the analysis set for primary endpoint
Rationale for change		Update the typo in the statistical model and add the analysis set used for primary analysis
Section to be changed		Section 5.5.6.2.2
Description of change		SAE reporting update
Rationale for change		SAEs may be submitted to BI by means other than Fax

11.2 GLOBAL AMENDMENT 2

Date of amendment		

EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
Global Amendment due to urgent safety reasons		☐
Global Amendment		☐
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c23936559 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		18 Nov 2019 15:29 CET
Approval-Team Member Medicine		18 Nov 2019 17:42 CET
Approval-Biostatistics		19 Nov 2019 15:35 CET
Author-Trial Clinical Pharmacokineticist		19 Nov 2019 17:25 CET
Approval-Therapeutic Area		20 Nov 2019 08:45 CET
Verification-Paper Signature Completion		20 Nov 2019 10:30 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed