Clinical Trial Protocol

	Document Number:	**c31693972-02**
EudraCT No. **EU Trial No.**	2019-003853-27	
Boehringer Ingelheim (BI) Trial No.	1405-0008	
BI Investigational Medicinal Product(s)	BI 1323495	
Title	Safety, tolerability, pharmacokinetics, and pharmacodynamics of different oral doses of BI 1323495 versus placebo in patients with non-cystic fibrosis bronchiectasis (randomised, double-blind, placebo-controlled, parallel group trial)	
Lay Title	A study in patients with non-cystic fibrosis bronchiectasis to test how well different doses of BI 1323495 are tolerated and how BI 1323495 affects biomarkers of inflammation	
Clinical Phase	Phase Ic	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted]	
Version and Date	**Version: 2.0**	**Date: 22 Apr 2021**
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	17 Sep 2020
Revision date	22 Apr 2021
BI trial number	1405-0008
Title of trial	Safety, tolerability, pharmacokinetics, and pharmacodynamics of different multiple oral doses of BI 1323495 versus placebo in patients with non-cystic fibrosis bronchiectasis (randomised, double-blind, placebo-controlled, parallel group trial)
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial conducted in 2 countries
Clinical phase	Phase Ic
Trial rationale	After establishing safety and tolerability in healthy volunteers, the trial is intended to confirm the safety and tolerability of multiple doses of BI 1323495 in a population of patients with non-cystic fibrosis bronchiectasis (nCFB), and to assess the inhibition of neutrophil elastase (NE) in blood and sputum.
Trial objective(s)	The main objectives of this trial are to compare safety and tolerability of different doses of BI 1323495 with placebo and to assess pharmacodynamics of BI 1323495 in sputum and in blood as well as early signs of clinical efficacy of BI 1323495 in patients with nCFB.
Trial endpoints	Primary endpoint: The safety and tolerability of BI 1323495 will be assessed based on the occurrence of drug-related adverse events. Secondary endpoints: • Change from baseline to week 12 in absolute NE activity in sputum • Change from baseline to week 12 in neutrophil cell count in sputum • Change from baseline to week 12 in NE activity in whole blood after stimulation with zymosan, normalized to neutrophil cell counts • Change from baseline to week 12 in post-bronchodilator forced expiratory volume in one second (FEV1)
Trial design	Multicentre, randomised, double-blind (patient and investigator blinded), placebo-controlled, parallel group trial over 12 weeks treatment
Total number of patients randomised	36 patients in Parts A and B
Number of patients on each treatment	• 9 patients on placebo (in total in Parts A and B) • 9 patients on BI 1323495 30mg bid in Part A • 18 patients on BI 1323495 150 mg qd in Part B
Diagnosis	Proven and documented diagnosis of bronchiectasis not related to cystic fibrosis
Main in- and exclusion	• 18 years to 80 years (inclusive), male and female (not of

criteria	childbearing potential) subjects • Clinical history consistent with nCFB and proven and documented diagnosis of bronchiectasis by CT and dilated airways compatible with bronchiectasis at initial diagnosis • Regular daily sputum producers with a history of chronic expectoration who are able to provide a valid sputum sample during screening (SCR) • Sputum neutrophil elastase positive based on point-of-care test (NEATstik® score ≥ 6 or equivalent) assessment at baseline • UDP-glucuronosyltransferase 2B17 (UGT2B17) extensive metabolizer (EM) (genotypes *1/*1 or *1/*2) • Stable regimen of standard nCFB treatment allowed • No concomitant diagnosis of pulmonary disease other than bronchiectasis, chronic obstructive pulmonary disease (COPD), or asthma
Test product(s)	BI 1323495 film-coated tablets (tablet strengths 10 and 50 mg)
dose	In Part A: 60 mg daily (30 mg bid). In Part B: 150 mg qd
mode of administration	Oral (p.o.) within 30 minutes of a meal containing a fat component
Comparator product(s)	Matching placebo
dose	Not applicable
mode of administration	Oral (p.o.) within 30 minutes of a meal containing a fat component
Duration of treatment	84 days: In Part A, 83 days twice daily (bid) and single dose on day 84; in Part B, 84 days once daily (qd)
Statistical methods	The primary and secondary endpoints will be evaluated using descriptive statistics.

MAIN FLOW CHART

Trial Periods	**Screening[1]**	**Run-in (Baseline - BSL)**		**Randomised Treatment Period**									**Follow-up (FUP)**
Visit[2]	**1**	**2a BSL**	**2b BSL**	**3[3]**	**4[15]**	**5**	**6 PK Day**	**7[16]**	**8**	**9a**	**9b**	**10 EoT / early EoT[4]**	**11 FUP / EoS**
Week	**-4**	**-1**		**0**	**1**	**2**	**4**	**6**	**8**	**11**		**12**	**14**
Day	**-27**	**-6**	**-2**	**1**	**8**	**15**	**29**	**43**	**57**	**78**	**82**	**84**	**98**
Time window for visits (days)	**+14**	**+2**	**+1**	**±0**	**±3**	**±3**	**±3**	**±3**	**±3**	**+3**	**+1**	**+3**	**±4**
Informed consent	**X**												
Demographics	**X**												
Medical history including Smoking status and alcohol history	**X**												
Testing for UGT2B17 genotype	**X**												
Physical examination	**X**			**X**			**X**					**X**	**X**
Height (only at V1)**/ body weight**	**X**			**X**			**X**					**X**	**X**
Vital signs: pulse rate (PR), blood pressure (BP), aural body temperature	**X**			**X**		**X**	**X**		**X**			**X**	**X**
Laboratory tests (blood/urine)	**X[13]**			**X**		**X**	**X**	**X**	**X**			**X**	**X**
12-Lead Electrocardiogram (ECG) (single ECG, may be repeated by investigator judgement)	**X**			**X**		**X**	**X**		**X**			**X**	
Pregnancy test in women (serum S / urine U)	**X (S)**			**X (U)[5]**					**X (U)[5]**			**X (U)[5]**	
Concomitant therapy	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Review of in-/exclusion criteria	**X**	**X**	**X**	**X**									
Randomisation				**X**									

Trial Periods	**Screening[1]**	**Run-in (Baseline - BSL)**		**Randomised Treatment Period**									**Follow-up (FUP)**
Visit[2]	**1**	**2a BSL**	**2b BSL**	**3[3]**	**4[15]**	**5**	**6 PK Day**	**7[16]**	**8**	**9a**	**9b**	**10 EoT / early EoT[4]**	**11 FUP / EoS**
IRT call/notification[12]	X			X		X	X		X			X	
Administer trial drugs at site[6]				X			X						
Dispense trial drugs for home[6]				X		X	X		X				
PK blood sampling (see Sample and Assessment Flow Chart)				X		X	X					X	
Lung questionnaires (QoL-B; SGRQ; CASA-Q)			X						X			X	
Sputum (collected at site)[7, 14]	X[17]	X	X	X		X	X		X	X	X	X	X
24h Sputum (collected at home)[8]				X			X					X	
Murray sputum colour chart			X	X								X	
NEATstik® (NE determination)		X	X									X	
Blood sample for biomarkers, pharmacodynamic (PD)			X	X		X	X		X			X	X
Zymosan stimulation in whole blood			X	X		X	X		X			X	X
Cotinine test			X	X		X	X		X			X	X
Serum banking sample (optional)[9]			X	X		X	X		X			X	X
Urine banking sample (otional)[9]			X										
Pulmonary Function Test (PFT)[10]	X		X			X			X			X	X
All AEs/SAEs/AESIs[11]	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check (medication)						X	X		X			X	
Completion of patient participation													X

1. Informed consent needs to be signed before any procedure related to this trial is performed (before or at Visit 1).
2. Timing of sampling and assessments: see Sample and Assessment Flow Chart.
3. Day of Randomisation / Day of first intake of randomised medication.
4. Patients who discontinue trial treatment prematurely should undergo an early End of Treatment (EoT) visit as soon as possible (study procedures will be the same as for Visit 10 (EoT) except no treatment will be administered). Follow up Visit (End of Study (EoS)) will be 14 days +/- 4 days thereafter.
5. Serum pregnancy test is to be performed if urine test positive and no Investigational Medicinal Product (IMP) to be given until negative result confirmed.
6. Following first drug administration in Part A, evening and morning dose should be taken with a 12 h time interval (e.g. 20:00 h and 08:00 h) approximately at the same time each day during the treatment phase, within a time window of +/- 1 hour. In Part B, the once-daily dose should be taken approximately at the same time each morning during the treatment phase. Drug should be taken 15-30 min after food intake including a fat component (like yogurt, milk, cheese or sausage). As an exemption, at Visit 3 and Visit 6, drug administration will happen at the site outside the normal schedule. Patients will then go back to their usual evening/morning interval (Part A) or once-daily interval (Part B), respectively. At Visit 3, patient will receive a reserve kit in case medication gets lost or the patients comes back to the next visit after more than 2 weeks. The morning drug administration date/time is collected on the eCRF for all Visits 3 to 10 (except Visit 4).
7. [redacted]
8. Sputum containers for 24h sputum collection will be provided to the patient at Visit 2b, Visit 5 and Visit 9b.
9. Collection of biobanking samples is optional and requires a separate informed consent form (ICF).
10. If treated with bronchodilators, wash-out of 24 hours for qd long acting, 12 hours for bid long acting, and 8 hours for short acting bronchodilators should be observed before pulmonary function tests. Screening PFT would also be accepted without wash-out in case consent was only signed on the same day.
11. After the EoS visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and relapse of existing cancer, trial treatment related adverse events (AEs), serious adverse events (SAEs) and trial treatment related adverse events of special interest (AESIs) of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.
12. Screening has to be registered in the Interactive Response Technology (IRT) at time of informed consent to trigger initial medication supply to the site.
13. Polymerase Chain Reaction (PCR) Test on SARS-CoV-2 to be performed only at Screening.
14. Left over volume of sputum samples may be used for optional biobanking see Section 5.5.
15. Visit 4 will be conducted as a phone call with the patient.
16. Visit 7 will be conducted as a phone call and blood for safety lab will be collected at a local lab or by a flying nurse.
17. Sputum collection for check of inclusion criterion #7

SAMPLE AND ASSESSMENT FLOW CHART

Visit	Day Window	Planned time (relative to last drug administration [h:min][1]	Approximate clock time of actual day [h:min][1]	Event and comment	Safety laboratory	12-lead ECG[2], Vital signs	PK_{blood}[3]	Blood for PD readouts	Biobanking sample	Lung questionnaires[4]	Sputum collection[5]	Pulmonary function test[6]	24 h Sputum	Murray colour chart	NEATstik®
V1	-27 +14		08:00	Screening visit											
			08:30	Safety	X[7]	X									
			09:00	Sputum collection for inclusion check							X				
			11:00	Pulmonary function								X			
V2a	-6 +2		09:00	Sputum collection incl NEATstik®							X				X
V2b	-2 +1		08:00	Blood PD, serum and urine banking[8]				X	X						
			08:30	Questionnaires						X					
			09:00	Sputum collection incl Murray chart and NEATstik®							X			X	X
			11:00	Pulmonary function								X			
V3	1	-02:30	08:00	Hand over of 24h sputum collected at home, safety, baseline PK and blood PD, serum banking[8]	X[7]	X	X	X	X				X		
		-02:00	08:30	Sputum collection incl. Murray chart							X			X	
		00:00	**10:30**	**First drug administration**											
		06:00	16:30	Safety	X	X									
		06:30	17:00	Discharge from trial site[9]; at home: **Follow daily drug posology[10]**											
V5	15 ±3		08:00	Drug intake at home. At site: safety, blood PD, PK, serum banking[8]	X	X	X	X	X						
			09:00	Sputum							X				
			11:00	Pulmonary function								X			

Visit	Day Window	Planned time (relative to last drug administration [h:min][1]	Approximate clock time of actual day [h:min][1]	Event and comment	Safety laboratory	12-lead ECG[2], Vital signs	PK_{blood}[3]	Blood for PD readouts	Biobanking sample	Lung questionnaires[4]	Sputum collection[5]	Pulmonary function test[6]	24 h Sputum	Murray colour chart	NEATstik®
V6	29 ±3	-1:30	08:00	**No drug intake at home**. At site: safety, trough PK, blood PD, hand over of 24h sputum collected at home, serum banking[8]	X	X	X	X	X				X		
		-0:30	08:30	Sputum collection							X				
		0:00	**10:30**	**Drug administration at site**											
		1:00	11:30	PK			X								
		2:00	12:30	PK			X								
		4:00	14:30	PK			X								
		6:00	16:30	Safety, PK, Blood PD	X	X	X	X							
			17:00	Discharge from trial site[9]; at home: **Follow daily drug posology**[10]											
V7	43 ±3		8:00	Safety blood collected at a local lab or by a flying nurse	X										
V8	57 ±3		08:00	Safety, blood PD, serum banking[8]	X	X		X	X						
			08:30	Questionnaires						X					
			09:00	Sputum collection							X				
			11:00	Pulmonary function								X			
V9a	78 +3		08:00	Sputum collection							X				
V9b	82 +1		08:00	Sputum collection							X				
V10	84 +5		08:00	**Last drug administration at home; EoT site visit:** Hand over of 24h sputum collected at home, safety, blood PD, PK, serum banking[8]	X	X	X	X	X				X		
			08:30	Questionnaires						X					
			09:00	Sputum collection incl. Murray chart, NEATstik®							X			X	X

Visit	Day Window	Planned time (relative to last drug administration [h:min][1]	Approximate clock time of actual day [h:min][1]	Event and comment	Safety laboratory	12-lead ECG[2], Vital signs	PK_{blood}[3]	Blood for PD readouts	Biobanking sample	Lung questionnaires[4]	Sputum collection[5]	Pulmonary function test[6]	24 h Sputum	Murray colour chart	NEATstik®
			11:00	Pulmonary function								X			
V11	98 ±5		08:30	Safety, blood PD, serum banking[8]	X	X[11]		X	X						
			09:00	Sputum collection							X				
			11:00	Pulmonary function								X			

1. The time is approximate; a deviation from the scheduled time of the day of ± 120 minutes is acceptable. The relative time deviations from time of administration should be kept as minimal as possible and should be below ± 15 minutes for PK measurements. The exact time of sample collection should be collected in electronic Case Report Form (eCRF).
2. ECG recordings are performed as single ECGs (no central ECG lab). The ECG recording may be repeated by investigator judgment for medical or quality reasons.
3. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of blood samples and visits as long as the total blood volume taken does not exceed 500 mL per subject.
4. Self-reported outcome questionnaires include: Quality of Life Questionnaire-Bronchiectasis, QOL-B; St. George's Respiratory Questionnaire, SGRQ; Cough and sputum assessment questionnaire, CASA-Q. Questionnaires should be done in a quiet place prior to the lung-related visit procedures.
5. Sputum collection should occur during a 2h timeframe with active breathing techniques. Study nurse / physiotherapist needs to be available to support patient in performing active cycle of breathing technique in case of difficulties producing sputum. Next step will be Oscillating Positive Expiratory Pressure (OPEP), if despite breathing technique still no sputum is being produced. Patients who produce an adequate sputum sample do not have to undergo these supportive measures. In case no adequate sputum sample is produced spontaneously, induction of sputum with isotonic, or subsequently hypertonic saline is mandatory. If sputum samples do not meet the quality criteria as directly assessed at the site, re-sampling at the next day is generally possible.
6. If treated with bronchodilators, wash-out of 24 hours for qd long acting, 12 hours for bid long acting, and 8 hours for short acting bronchodilators should be observed before pulmonary function tests.
7. Including urine drug screening and alcohol breath test
8. Collection of biobanking samples is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research.

9. Discharge is not mandatory and always at discretion of the investigator. Patient in-house stay may be extended at any time if deemed clinically necessary. The subjects are only allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.
10. Following first drug administration in Part A, evening and morning dose should be taken with a 12 h time interval (e.g. 20:00 h and 08:00 h) approximately at the same time each day during the treatment phase, within a time window of +/- 1 hour. In Part B, the once-daily dose should be taken approximately at the same time each morning during the treatment phase. Drug should be taken 15-30 min after food intake including a fat component (like yogurt, milk, cheese or sausage). As an exemption, at Visit 3 and Visit 6, drug administration will happen at the site outside the normal schedule. Patients will then go back to their usual evening/morning interval (Part A) or once-daily interval (Part B), respectively.
11. At V11, only Vital Signs need to be assessed

TABLE OF CONTENTS

ABBREVIATIONS

A1AT	Alpha-1 antitrypsin
ABPA	Allergic Bronchopulmonary Aspergillosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area under the Curve
BCRP	Breast Cancer Resistance Protein
BE	bronchiectasis
BI	Boehringer Ingelheim
bid	bis in die (twice daily)
BP	Blood Pressure
BSL	Baseline
CA	Competent Authority
CASA-Q	Cough and Sputum Assessment Questionnaire
CatC	Cathepsin C
CF	Cystic Fibrosis
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CK-MB	Creatine Kinase Isoenzyme MB
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus-associated disease 2019
$C_{pre,N}$	Predose concentration of the analyte in plasma immediately before administration of the Nth dose
CRA	Clinical Research Associate
CRO	Clinical Research Organization

CRP	C-Reactive Protein
CT	Computed Tomography
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CXCR1	C-X-C motif chemokine receptor 1
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DMARDS	Disease-modifying Anti-rheumatic Drugs
[redacted]	[redacted]
DV	Deviation
e. g.	exempli gratia (for example)
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Effective Dose
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EM	Extensive Metabolizer(s)
EoS	End of Study
EoT	End of Treatment
ERS	European Respiratory Society
FDA	U.S. Food and Drug Administration
FEV1	Forced Expiratory Volume in one second
FSH	Follicle Stimulating Hormone
FUP	Follow-up
[redacted]	[redacted]
g	gram
GCP	Good Clinical Practice
gCV	Geometric Coefficient of Variation
GFR	Glomerular Filtration Rate

GGT	Gamma-Glutamyl Transferase
GLDH	Glutamate Dehydrogenase
GLI	Global Lung Initiative
GLP	Good Laboratory Practice
gMean	Geometric mean value
GMP	Good Manufacturing Practice
gRT	global Randomisation Team
GSH	Glutathione
h	hour(s)
hERG	human Ether-à-go-go-Related Gene
HIV	Human Immunodeficiency Virus
i. e.	id est (that is)
i. v.	intravenous
IB	Investigator's Brochure
IC_{50}	Concentration at which 50% Inhibition of Target Occurs
IC_{90}	Concentration at which 90% inhibition of target occurs
IC_{95}	Concentration at which 95% inhibition of target occurs
ICF	Informed Consent Form
iCS	Inhaled Corticosteriods
IEC	Independent Ethics Committee
IgG	Immunglobulin G
IGRA	interferon gamma release assay
IL-1β	Interleukin-1ß
IL-8	Interleukin-8
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
iPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
kg	kilogram
LABA	Long Acting Beta Agonists

LAMA	Long Acting Muscarinic Agonists
LC-MS/MS	liquid chromatography tandem mass spectrometry
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	milligram
min	minute(s)
mL	millilitre
mm	minute(s)
MMRM	Mixed Model for Repeated Measurements
MoA	Mode of Action
MRD	Multiple Rising Dose
mRNA	Messenger ribonucleic acid
NA	Not applicable
nCFB	Non-Cystic Fibrosis Bronchiectasis
NE	Neutrophil Elastase
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
NSAID	Non-Steroidal Anti-Inflammatory Drug
NTM	Nontuberculous Mycobacteria
OATP1B1	Organic anion transporting polypeptide 1B1
OPEP	Oscillating Positive Expiratory Pressure
OPU	Operating Unit
p.o.	per os (oral)
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PFT	Pulmonary Function Test
P-gp	P-Glycoprotein
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PLS	Papillon-Lefèvre syndrome
PM	Poor Metabolizer(s)
PR	Pulse Rate
PR3	proteinase 3

qd	once daily (quaque die)
QOL-B	Quality of Life Questionnaire - Bronchiectasis
$R_{A,Cmax}$	Accumulation ratio for C_{max} at steady state versus after the first dose
$R_{A,AUC\tau}$	Accumulation ratio for AUC_{τ} at steady state versus after the first dose
RBC	Red Blood Cell Count
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
RS	Randomised Set
SAE	Serious Adverse Event
SCR	Screening
SCS	Screened Set
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
SP-D	Surfactant-Protein D
SRD	Single Rising Dose
SS	Steady State
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Timepoint of Maximum Plasma Concentration
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UDP	Uridine diphosphate
UGT2B17	UDP-glucuronosyltransferase 2B17
UGT2B7	UDP-Glucuronosyltransferase 2B7
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
WBC	White Blood Cells
WOCBP	Woman of Childbearing Potential
$\lambda_{z(,ss)}$	Terminal rate constant in plasma

1. INTRODUCTION

BI 1323495 is an oral, reversible inhibitor of neutrophil elastase (NE) under clinical development in chronic lung diseases with neutrophilic inflammation of the lower airways as a main feature, such as COPD, cystic fibrosis (CF), and nCFB.

1.1 MEDICAL BACKGROUND

There is a high unmet medical need in chronic lung diseases with neutrophilic airway inflammation as a main feature, such as non-cystic fibrosis bronchiectasis (nCFB).

nCFB is a chronic lung disease caused by a number of pathological insults and characterised by predominantly neutrophilic inflammation. Proteases released by neutrophils, such as neutrophil elastase, cause structural damage to the airways. This leads to irreversibly dilated airways, mucus gland hyperplasia, and impaired mucus clearance, and results in a vicious cycle of recurrent severe infections and further airway damage [P13-15562]. About 50 to 70 per 100,000 are affected by nCFB [R19-3085, R20-1159]. Patients with nCFB typically suffer from chronic cough, sputum production, frequent respiratory infections and impaired lung function. They have a substantial burden due to frequent pulmonary exacerbations that cause hospital stays and unscheduled outpatient visits, and a significant morbidity, and are associated with increased mortality [R19-3087, R19-3082, P19-09060, R20-2791]. There is a high medical need for the development of drugs targeting the neutrophilic inflammation of nCFB, as currently there are no approved pharmacological therapies for nCFB. Current pharmacological management options centre around as-needed antibiotics to treat pulmonary exacerbations and off-label administration of bronchodilators, and/or inhaled corticosteroids.

Under pathophysiological conditions, dysfunctional activation of neutrophils leads to release of neutrophil serine proteases, such as neutrophil elastase (NE), that are not adequately inhibited by endogenous anti-proteases. This leads to inflammation, excessive proteolysis of the lung connective tissue, damage to the airways [R19-3378, R19-3084, R19-3080, R16-2239], increase mucus production in lung epithelial cells [R17-2928], and delay of the resolution phase of chronic lung inflammation [R17-2929]. Of note, NE proteolytic activity as well as extracellular matrix turnover markers have been associated with disease severity and clinically relevant outcomes in this disease [R18-3321]. Inhibition of NE by an orally available inhibitor is expected to result in reduced distal airway destruction related to damage to pulmonary elastin and other extracellular matrix proteins, in anti-inflammatory [R17-2929], as well as in anti-mucus hypersecretory effects [P02-06423, R17-2928].

1.2 DRUG PROFILE

In this trial, the investigational medicinal product BI 1323495, an inhibitor of NE, will be administered. The sections below summarize the drug profile of BI 1323495. For details, refer to the current version of the Investigators's Brochure (IB) [c21238478-05].

1.2.1 Mode of action

BI 1323495 is a highly selective and reversible inhibitor of the enzymatic activity of neutrophil elastase (NE). NE is produced and stored in neutrophil granules and released in large quantities after activation. Excess activity of NE in the lung of COPD patients results in the degradation of several extracellular matrix proteins, an increased activation of other proteases (e.g. MMP9), and further inactivation of endogenous protease inhibitors (e.g., TIMP1, elafin). This leads to the destruction of alveolar septa and hence emphysema development, as well as potentiation and propagation of inflammation. By inhibiting NE, BI 1323495 is expected to slow the development of emphysema.

In CF, NE is known to impair antibacterial defense by cleavage of C-X-C motif chemokine receptor 1 (CXCR1), CD14, and CD16 on neutrophils and to promote bacterial persistence by crippling normal host opsonophagocytotic mechanisms [R18-3357]. The same processes are assumed to contribute to impaired antibacterial defense in nCFB. BI 1323495 is expected to reduce the deleterious effects of NE in the highly inflamed airways. This will result in a reduction in airway inflammation and its associated tissue destruction, in improved mucociliary clearance, as well as in improved bacterial killing capacity of neutrophils in the airways. Together, these effects are expected to result in a reduction in the frequency and severity of pulmonary exacerbations that are a hallmark of both nCFB and CF. The benefits of this therapeutic approach are assumed to be independent of concomitant therapies of a patient.

1.2.2 Data from non-clinical and toxicology studies

1.2.2.1 Non-clinical pharmacology

Due to sequence differences between human and other species' NE, compounds targeting the S1 pocket are expected to show a different activity on the isolated human enzyme compared to other species. Therefore, the inhibition of isolated NE derived from different species (mouse, rat, dog, cynomolgus monkey) by BI 1323495 was measured. Half maximal inhibitory concentrations (IC_{50}) are summarized in the following table.

Table 1.2.2.1: 1 Comparison of potency between mouse, rat, cynomolgus monkey, and human

Molecular potency (IC_{50})	**Nanomolar (nM)**
Mouse	21
Rat	16
Cynomolgus monkey	3
Human	**0.4**

BI 1323495 exhibits > 4000x selectivity versus the related neutrophil serine proteases Cathepsin G (CatG) and proteinase 3 (PR3) and has no activity against 44 tested unrelated receptors, transporters, and enzymes up to a concentration of 10 µM. BI 1323495 inhibits NE in plasma from zymosan-stimulated human blood with an IC_{50} of 1 nM and inhibits the degradation of insoluble elastin by human NE.

The *in-vivo* activity of BI 1323495 was measured in an NE-induced lung damage model in mice. In this model, the intratracheal application of human NE results in a specific acute lung injury, which was attenuated by BI 1323495 in a dose-dependent manner with an effective dose at 50% reduction (ED_{50}) of 1.9 mg/kg.
BI 1323495 inhibited hERG (human Ether-à-go-go-Related Gene) current with an IC_{50} of 80 µM. The cardiovascular and central nervous systems were unaffected. In rats, a transient increase in mean respiratory rate (30-90 min postdose) of 26-59 % and minute volume (30-90 min and 180 min postdose) of 15-27 % was observed at 900 mg/kg compared to vehicle-treated control animals.

1.2.2.2 Non-clinical pharmacokinetics

Plasma protein binding of BI 1323495 was low and similar in all investigated animal species and humans with bound fractions ranging between 47.4 % and 59.6 %. Based on quantitative whole-body autoradiography in rats, distribution from whole blood into tissues was moderate. The half-lives in ocular tissues and skin were very similar to half-lives in plasma. BI 1323495 was metabolized in vitro in human hepatocytes by glucuronidation by UDP-Glucuronosyltransferase 2B7 (UGT2B7) and UGT2B17 and via various phase I biotransformations by Cytochrome P450 (CYP) 3A4. Non-enzymatic formation of a cysteine adduct was observed. The in vitro ratio of metabolism via glucuronidation to oxidation was in the range of 7:1 to 2:1. The predominant metabolite in rat plasma after oral administration was an oxidative metabolite in male rat. In female rats the cleavage product of BI 1323495 glutathione (GSH) conjugate was the predominant metabolite in plasma. These gender-related differences were also observed in excreta with respect to formation of sulfate conjugate that was observed only in female faeces.

The main route of elimination was via faeces (90 % and 88 % of the oral and intravenous dose, respectively). Urinary excretion was also relevant following oral administration (4 % of the dose in male rats and 10.5 % of the dose in female rats) and intravenous administration (6.7 % of the dose in males and 7.8 % of the dose in females).

1.2.2.3 Drug interactions

BI 1323495 is not expected to inhibit hepatic CYP 1A1, 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 up to a maximum plasma concentration (C_{max}) of 87µM.

The induction potential of BI 1323495 was investigated on messenger ribonucleic acid (mRNA) level. Based on these results, BI 1323495 has the potential to induce CYP3A4 at $C_{max,ss}$ levels of 20 nM, CYP2C8 at 191 nM, CYP2B6 at 369 nM, and CYP2C9 at 678 nM. Based on current PK results of the multiple rising dose (MRD) trial, geometric mean value (gMean) $C_{max,ss}$ levels of the 30 mg bid dose are ~100 nM, but at a higher dose, $C_{max,ss}$ is predicted to increase to up to 447 nM for 300 mg BI 1323495 bid. However, a midazolam arm was included into the MRD trial for dose groups ≥ 70 mg bid BI 1323495 to investigate the induction potential in humans. A microdose of midazolam (75 µg) was administered orally at day -1 before start of treatment with BI 1323495 (reference) and at day 11 (test).

No signs of induction of CYP3A4 was detected within the 70 mg bid BI 1323495 based on Midazoam and its metabolite 1-OH Midazolam. The results for dose groups above 70 mg are not yet available (data on file). Hence co-administration of drugs that are sensitive substrates of CYP3A4, including hormonal contraceptives are at the moment allowed for doses ≤ 70 mg bid BI 1323495.

In vitro assessment showed that BI 1323495 has the potential to inhibit the gastrointestinal transporters P-Glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) at single doses higher than 32 mg and 120 mg, respectively. In addition, the renal transporter MATE2-K may be inhibited at exposures higher than 0.12µM. There is also a likelihood that the hepatic transporter organic anion transporting polypeptide 1B1 (OATP1B1) may be inhibited at doses higher than 150 mg of BI 1323495.

1.2.2.4 Toxicology

The toxicology program of BI 1323495 to date includes repeat-dose toxicity trials up to 13 weeks in Wistar rats and cynomolgus monkeys, the complete standard battery of genotoxicity trials, and the in vitro phototoxicity assay. Pivotal trials were performed in compliance with GLP (Good Laboratory Practice). General and safety pharmacology trials included in vitro hERG potassium channel trials, cardiovascular assessments in conscious cynomolgus monkeys, effects on the central nervous system and respiratory system in rats.

The 4- and 13-week trials resulted in no observed adverse effect levels (NOAEL) in rat or cynomolgus monkey of 300 and 200 (males)/600 (females) mg/kg/day or 250 and 300 mg/kg/day, respectively. The associated mean exposures combined for males and females from the 4-week trials were 33,000 and 54,700 nM (C_{max}) and 179,000 and 471,000 nM·h (area under the curve (AUC)0-24), respectively. At higher exposures above the NOAEL, BI 1323495 was associated with findings in the liver and kidneys in the rat in the 4-week study while only kidney findings were confirmed in the 13-week rat study, showing reversibility within 8 weeks of recovery. Changes in the immune system were seen in the monkey at the NOAEL and below. They were mild in extent and reversible.

Based on these non-clinical toxicology assessments, exposure caps not to be exceeded in human trials were set to 1,900 nM and 11,500 nM*h for C_{max} and AUC0-24, respectively. These exposure boundaries were defined to provide safety factors of 16 and 10 to the C_{max},ss of 30,900 nM and AUC0-24,ss of 115,000 nM*h, respectively that were observed at the NOAEL in rats in the 4 week toxicity study at 300 mg/kg, when – as the most conservative approach – the lower exposure observed in female rats were taken as reference.

For a detailed description of the non-clinical toxicology of BI 1323495, please refer to the current Investigator's Brochure (IB) [c21238478-05].

1.2.3 Data from clinical studies

At the time of preparing this trial protocol, three Phase I trials with administration of single doses of BI 1323495 to healthy male volunteers have been completed.

The single-rising dose trial 1405-0001 was the first-in-man trial. Trial 1405-0007 investigated the relative bioavailability of single doses of BI 1323495 once administered in the fasted state and once administered following a high-fat, high-calorie meal. Trial 1405-0009 investigated the drug-drug interaction (DDI) with the strong CYP3A / P-gp inhibitor itraconazole.

Two clinical trials are completed and are in the reporting phase at the time of completing CTP amendment no 1: The multiple-rising dose trial 1405-0002 assessed the safety and tolerability as well as CYP3A4 induction potential of multiple twice daily (bid) or once daily (qd) doses of BI 1323495 in healthy subjects. Trial 1405-0015 assessed the effect of single doses of BI 1323495 on various transporter proteins in healthy male subjects.

1.2.3.1 Clinical pharmacokinetics

BI 1323495 exposure levels were found to be associated with a genetic polymorphism of uridine diphosphate (UDP)-glucuronosyltransferase 2B17 (UGT2B17). This metabolizing enzyme glucuronidates BI 1323495, predominantly in enterocytes, but also in the liver. Two common alleles exist: The *1 allele contains the full enzyme-encoding sequence which is, however, completely deleted in the *2 allele. Hence, *2/*2-homozygous individuals do not express UGT2B17 and do not glucuronidate BI 1323495 via this pathway (poor metabolizers, PMs). Carriers of at least one *1 allele are extensive metabolizers (EMs). In EMs, BI 1323495 is glucuronidated upon intestinal absorption and eliminated during the first passage through the liver/bile system. As the orally administered dose is only partially absorbed as the non-glucuronidated parent molecule, systemic exposure levels are low. In PMs, in contrast, most of the orally administered dose of BI 1323495 is absorbed non-glucuronidated, resulting in higher systemic exposures. After the first-pass metabolism, the same pharmacokinetic properties apply to all genotypes. The effect of this UGT2B17 polymorphism on the exposure of other drugs predominantly metabolized via this enzyme has been described [R19-1806]. The UGT2B17 polymorphism is unequally distributed among different ethnic groups. In Caucasian populations, the *2/*2 genotype is present in less than 15%, whereas in Asian populations, the *2/*2 genotype predominates (>80% of the population) [R19-1805].

In the single rising dose (SRD) trial 1405-0001, AUCs and C_{max} were increased in PMs, compared with EMs [c26492551]. gMean plasma exposure increased in a less than dose-proportional manner. Multiple plasma concentration peaks were observed in the profiles of nearly all subjects treated. The terminal half-life was similar over all dose groups, except for being longer in the 600 mg dose group.

The most prominent metabolites within the 200 mg dose group of the SRD in UGT2B17 *1/*1 and *1/*2 subjects, were the glucuronide of BI 1323495 (CD 7545) and an oxidative metabolite (M517(1)). In UGT *2/*2 subjects, only minor amounts of the glucuronide (CD 7545) were found in plasma. Comparable exposure of oxidative metabolites was found in both groups. Minor amounts of an additional oxidated and glucuronidated metabolite were additionally identified.

In clinical trial 1405-0002, the pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 1323495 were investigated. Preliminary PK data of the 10 mg, 30 mg,

70 mg, 120 mg, and 150 mg bid dose levels in Extensive Metabolizers, and the 10 and 30 mg bid dose levels in Poor Metabolizers are shown in Table 1.2.3.1: 1.

Pharmacokinetics after multiple doses in UGT2B17 Extensive Metabolizers (EMs)

The exposure to BI 1323495, based on C_{max} and AUC at steady state, increased less than dose-proportionally from 10 to 30 mg bid and from 70 to 120 mg bid. However, the exposure to BI 1323495 increased more than dose-proportionally from the 30 to 70 mg bid dose. This over-proportional increase was caused by an increase in accumulation from 2-fold based on AUC in the 30 mg bid DG to ~3.5-fold for doses ≥ 70 mg bid. The exposure to BI 1323495 was comparable between 70 mg bid and 150 mg bid. This was interpreted to be caused by usage of a higher tablet strength (150 mg) with unfavourable dissolution properties. The exposure at steady state of 120 mg administered once daily was between the exposure of 30 and 70 mg given twice daily, as the accumulation ratio was lower as for the bid treatments. The exposure values in UGT2B17 EMs showed considerable inter-individual variability. Preliminary PK results do not indicate an obvious effect of gender on the pharmacokinetics of BI 1323495. No obvious effects of genotype (*1/*1 versus *1/*2 EMs) on the pharmacokinetics of BI 1323495 was observed in the completed dose groups.

Pharmacokinetics after multiple doses in UGT2B17 Poor Metabolizers (PMs)

The inter-individual variability was considerably lower in PMs as compared to EMs. Exposure to BI 1323495 at steady state was approximately ~3- to 5-fold higher based on Cmax and AUC in PMs as compared to EMs. The accumulation ratios at 10 mg bid and 30 mg bid were comparable between both PMs and EMs at the same dose level. However, the exposure after the first dose of 30 mg in PMs was twice as high as the one after the first dose of 70 mg bid DG in EMs. At 30 mg bid in PMs, less high accumulation was observed than in the higher dose groups in the EMs. This suggests that UGT2B17 metabolism plays a role in the unexpectedly high accumulation behavior in EMs. Steady state exposure upon 30 mg bid DG in PMs was comparable to the one observed with 70 mg bid in EMs. For further details refer to the IB (c21238478-05).

Based on a preliminary Pop PK model analysis that includes pharmacokinetic data from the SRD (1405-0001) and food effect (1405-0007) trials and preliminary data from the MRD (1405-0002) trial, sex was not a statistically significant covariate, meaning that females so far did not show relevant higher exposure as compared to male volunteers (1405-0002 data on file).

Table 1.2.3.1: 1 Preliminary selected gMean PK parameters of BI 1323495 at steady state in healthy volunteers under fed conditions in UGT2B17 EMs (genotypes *1/*2, *1/*1) and UGT2B17 PMs (*2/*2) in trial 1405-0002 (data on file)

		$C_{max,ss}$ [nmol/L]	RA_{Cmax}	$AUC_{\tau,ss}$ [nmol·h/L]	$RA_{AUC\tau}$
	N	**gMean (gCV%)**	**gMean (min-max**	**gMean (gCV%)**	**gMean (min-max)**
UGT2B17 EMs (*1/*2, *1/*1)					
10 mg bid	9	37.5 (49.6)	1.59 (0.914 – 2.45)	237 (60.9)	2.00 (1.47 – 2.84)
30 mg bid	8	64.4 (78.7)	1.06 (0.684 – 1.99)	475 (86.2)	1.96 (1.14 – 2.47)
70 mg bid	8	281 (48.0)	2.31 (1.44 – 6.06)	2500 (59.4)	3.56 (2.18 – 6.37)
120 mg bid	9	362 (77.7)	2.38 (1.62 – 2.92)	2850 (69.3)	2.98 (2.21 – 3.71)
150 mg bid	8	265 (46.0)	2.55 (1.71 – 7.57)	2080 (41.6)	3.45 (1.96 – 7.70)
120 mg qd		164 (48.7)	1.32 (0.828-2.68)	1960 (56.2)	1.50 (1.02-2.64)
UGT2B17 PMs (*2/*2)					
10 mg bid	5	109 (27.7)	1.59 (0.914 – 2.45)	740 (22.4)	1.71 (1.28 – 2.26)
30 mg bid	6	300 (32.6)	1.06 (0.684 – 1.99)	2380 (28.1)	1.81 (1.47 – 2.26)

In the food effect trial 1405-0007, administration of 100 mg BI 1323495 together with a high-fat, high-calorie meal increased the exposure 2.4-fold and 1.7-fold based on C_{max} and AUC, respectively, versus fasted conditions. The maximum plasma concentrations were reached earlier in the fed state (median timepoint of maximum plasma concentration (t_{max}) 2.00) as compared to the fasted state (median t_{max} 3.52 h). The food effect was not different in poor metabolizers as compared to extensive metabolizers.

The DDI trial 1405-0009 investigated the effects of multiple doses of itraconazole – a strong CYP3A4 and P-gp inhibitor – on the relative bioavailability of a single dose of 10 mg BI 1323495 in EMs. Itraconazole caused a modest increase in exposure to BI 1323495 in gMean $AUC_{0-\infty}$ and C_{max} of ~1.7-fold and ~1.4-fold, respectively. Therefore, concomitant treatment with strong CYP3A4 / P-gp inhibitors should be avoided in EMs. In PMs, the effect of CYP3A4 / P-gp inhibition has not yet been assessed.

In a DDI trial (1405-0015) the effects of a single dose of 300 mg BI 1323495 on the PK of Rosuvastatin (10 mg) and Dabigatran (75 mg) were tested in 14 healthy subjects each. Rosuvastatin is a sensitive substrate of BCRP and OATP1B1, while Dabigatran is a sensitive substrate for P-gp. Co-administration with BI 1323495 increased the C_{max} (1.14-fold) and AUC (1.05-fold) of Rosuvastatin only slightly, with the upper boundary of the 90% confidence interval (CI) within or only slightly above (Cmax) above 125%. Co-administration with BI 1323495 increased the AUC (1.09-fold) and Cmax (1.08-fold) of dabigatran only slightly with the upper boundary of the 90% CI still within 125%. Hence, BI 1323495 appears not to have a clinically relevant effect on BCRP, OATP1B1 and P-gp (c33366190-01).

1.2.3.2 Clinical Pharmacodynamics

In human single and multiple rising dose studies, *ex-vivo* peripheral blood enzymatic activity of NE following zymosan-induced release of enzyme-containing granules was quantified as a marker of the pharmacodynamic effect (direct target engagement). Enzymatic activity was calculated as percent inhibition from individual baseline values corrected for neutrophil count for each time point.

In the SRD trial 1405-0001, after fitting an Emax model to plasma concentration against % inhibition of NE, IC50, IC90, and IC95 values were estimated to 3.6 nM, 33 nM, and 69 nM, respectively, with a maximum inhibition of 100% achieved (c26492551).

c26492551In the MRD trial 1405-0002, peripheral blood NE activity was evaluated only in the extensive metabolizers (EMs). Based on a preliminary evaluation, all subjects achieved a maximum % inhibition of at least 90% in doses higher than 10 mg bid. In Table 1.2.3.2: 1, % inhibition of NE (at trough and after dosing) is summarized per dose level.

Table 1.2.3.2: 1 Preliminary assessment of peripheral blood % inhibition of NE (at trough and after dosing at steady state) in healthy volunteers that are UGT2B17 EMs (genotypes *1/*2, *1/*1) in trial 1405-002 (data on file)

		% inhibition of NE (at trough)		% inhibition of NE (after dosing)	
		N	**Median (Range)**	**N**	**Median (Range)**
	Placebo	16	-3.1 (-41.3 – 36.6)	17	-9.1 (-41.4 – 36.9)
BID dosing					
	10 mg	8	81.0 (61.2 – 94.5)	8	90.0 (85.4 – 95.4)
	30 mg	8	91.8 (80.4 – 93.4)	8	95.1 (90.0 – 99.0)
	70 mg	8	98.5 (96.4 – 99.5)	7	98.6 (97.4 – 99.7)
	120 mg	9	98.0 (96.8 – 99.1)	9	98.7 (98.4 – 99.6)
	150 mg	8	97.3 (95.0 – 99.0)	8	98.3 (93.6 – 99.8)
QD dosing					
	120 mg	9	93.1 (86.1 – 95.4)	9	98.0 (95.0 – 98.3)

1.2.3.3 Clinical safety

In the single-rising dose trial 1405-0001, 48 healthy male subjects received single oral doses of BI 1323495 of 10 mg to 600 mg, and 15 were administered placebo. The observed exposures did not reach the exposure safety caps of AUC_{0-24} (11,500 nM*h) and C_{max} (1,900 nM) – even not on an individual level – that had been predefined based on animal toxicity data. BI 1323495 was well tolerated, with no clinically relevant changes in safety lab, ECG, and vital signs observed. Treatment-emergent Adverse Events (AEs) were reported in 16 of the 48 subjects (33.3%) treated with BI 1323495 and 2 of the 15 subjects (13.3%) treated with placebo. Investigator-defined drug related AEs were reported for 11 (22.9%) of the 48 subjects dosed with BI 1323495 and 1 (6.7%) of the 15 subjects dosed with placebo. Most frequent drug related AEs were headache, reported by 6 (12.5%), and diarrhea, reported by 2 (4.2%). There was no relationship between the occurrence of AEs and dose. 3 AEs in subjects receiving BI 1323495 were judged as moderate in intensity, all other AEs were classified as mild. No severe or serious AEs were reported. Among the subjects receiving single doses of BI 1323495, 7 were UGT2B17 *2/*2 homozygous. Of these 7 subjects, 3 reported AEs (42.9%), which included one case of mild transient elevation of alanine aminotransferase (ALT) and glutamate dehydrogenase (GLDH) in a subject having received a single dose of 300 mg.

In the food effect trial 1405-0007, 12 healthy male subjects received single oral doses of BI 1323495 of 100 mg under fasted and fed (high calorie, high fat meal) conditions. Of these, 11 subjects completed the trial according to trial protocol.
During the study, 5 AEs were observed in 5 subjects while on treatment. One on-treatment AE of headache was considered drug-related. No serious AEs or other significant AEs were reported. One severe AE of influenza led to discontinuation and was not considered drug related.

In the DDI trial 1405-0009, a total of 14 healthy male subjects were administered single doses of 100 mg, once alone and once in combination with itraconazole. AEs were reported in 6 of the 14 subjects (42.9%) treated with BI 1323495. Investigator-defined drug related AEs were reported for 2 (14.3%) of the 14 subjects, both diarrhea and occurring while treated with BI 1323495 in combination with itraconazole. No severe or serious AEs were reported.

MRD trial 1405-0002 investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple bid oral doses of BI 1323495 in healthy subjects that are UGT2B17 EMs or PMs. One additional dose group with 120 mg qd oral doses of BI 1323495 in UGT2B17 EMs was also conducted. The following represents a summary of the clinical safety data of 6 dose groups in EMs and 2 dose groups in PMs. In the six completed EM dose groups, 27 male healthy subjects and 18 female healthy subjects (not of child-bearing potential or using adequate contraception methods) received multiple bid doses of BI 1323495 of 10 mg, 30 mg, 70 mg, 120 mg, or 150 mg over 10.5 days, and 6 male healthy subjects and 3 female healthy subjects received multiple qd doses of 120 mg BI 1323495 over 11 days. In the two completed PM dose groups, 6 male healthy subjects and 5 female healthy subjects received multiple twice daily doses of BI 1323495 of 10 mg or 30 mg over 10.5 days. 22 (16 males, 6 females) healthy EM or PM subjects received placebo.

Two subjects in the 120 mg bid dose group and one subject in the 150 mg bid dose group had AUC exposures exceeding the pre-defined exposure cap of AUC0-24 (11,500 nM*h); no subject exceeded the predefined exposure cap for Cmax (1,900 nM). One subject in the 70 mg dose group had increased blood pressure, and one subject in the 150 mg dose group had a prolongation of the QTcB interval, both considered drug related by the investigator. In the other subjects, multiple bid or qd doses of BI 1323495 were associated with no clinically relevant changes in safety lab, ECG, and vital signs observed. No deaths or serious AEs were reported in this trial. Any AEs were reported in 42 (65%) of the 65 subjects treated with BI 1323495, and 11 (50%) of the 22 subjects treated with placebo.

Investigator-defined drug-related AEs were reported for 12 (18.5%) of 65 subjects treated with BI 1323495 and 1 (4.5%) of 22 subjects receiving placebo. Headache of mild intensity was the most frequently reported drug related AE (by 6 subjects treated with BI 1323495). Abdominal pain was reported by 3 subjects treated with BI 1323495, the furthergastrointestinal events abdominal pain diarrhea and flatulence each in 2 subjects treated with BI 1323495 and CK elevation was reported for 1 subject. No other drug related AEs were reported in more than one subject treated with BI 1323495. One subject in the placebo group had an AE of severe intensity (abdominal discomfort) that was considered related. One EM subject in the 30 mg dose group had an AE of severe intensity (headache; not considered related to study medication). All other reported AEs were of mild or moderate

intensity. Overall, three AEs led to treatment discontinuation: One each in the EM dose groups 30 mg bid (nausea/vomiting, moderate, not considered related), 70 mg bid (blood pressure increased, moderate, considered related), and 150 mg bid (electrocardiogram QT prolonged, mild, considered related). There was no apparent relationship of the occurrence of AEs with dose. An overview on AEs judged related by the investigator is presented in Table 1.2.3.3: 1. In summary, multiple doses of BI 1323495 investigated so far in clinical trials with healthy subjects were safe and well tolerated.

Table 1.2.3.3: 1: Drug-related AEs reported in MRD trial 1405-0002

System Organ Class Preferred Term	Placebo	BI 1323495									
		Extensive metabolizers (EMs)						Poor metabolizers (PMs)		Total on BI 1323495	Total on treatment
		10 mg bid	30 mg bid	70 mg bid	120 mg bid	150 mg bid	120 mg qd	10 mg	30 mg		
Number of subjects, N (%)	22 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	5 (100)	6 (100)	65 (100)	87 (100)
Total with any drug related AEs	1 (4.5)	2 (22.2)	3 (33.3)	1 (11.1)	2 (22.2)	4 (44.4)	0 (0)	0 (0)	1 (16.7)	11(16.9)	12 (13.8)
Gastrointestinal disorders/											
Abdominal discomfort	1 (4.5)										1 (1.1)
Abdominal pain	1 (4.5)					1 (11.1)			1 (16.7)	2 (3.1)	3 (3.4)
Abdominal pain (upper)						1 (11.1)				1 (1.5)	1 (1.1)
Diarrhea			1 (11.1)			1 (11.1)				2 (3.1)	2 (2.3)
Flatulence			1 (11.1)			1 (11.1)				2 (3.1)	2 (2.3)
Investigations/											
Blood pressure increased				1 (11.1)						1 (1.5)	1 (1.1)
CK elevation					1 (11.1)					1 (1.5)	1 (1.1)
Electrocardiogram QT prolonged						1 (11.1)				1 (1.5)	1 (1.1)
Electrocardiogram PR shortened					1 (11.1)					1 (1.5)	1 (1.1)
Nervous system disorders/											
Headache		1 (11.1)	3 (33.3)	1 (11.1)		1 (11.1)				6 (9.2)	6 (6.9)
Syncope		1 (11.1)								1 (1.5)	1 (1.1)

In the ongoing DDI study 1405-0015, 14 healthy male subjects were administered single doses of rosuvastatin, and of BI 1323495 300 mg in combination with rosuvastatin. Any AEs were reported in 5 of the 14 subjects (35.7%) while treated with BI 1323495 and rosuvastatin, and in 4 of the 14 subjects (28.6%) while treated with rosuvastatin alone. Investigator-defined drug related AEs were reported for 2 (14.3%) of the 14 subjects, both while treated with rosuvastatin alone. No severe or serious AEs were reported.

1.2.4 Residual Effect Period

The Residual Effect Period (REP) of BI 1323495 is assumed to be 7 days, equivalent to 5 times the half-life of 30 h (at the highest dose group of the SRD trial, 600 mg). This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

For a more detailed description of the drug profile of BI 1323495, please refer to the current IB [c21238478-05].

1.3 RATIONALE FOR PERFORMING THE TRIAL

In this trial, for the first time the effects of multiple doses of BI 1323495 will be assessed in patients. The main purpose of the trial is to investigate whether the targeted pharmacodynamic effect of inhibition of neutrophil elastase (NE) activity is achieved with one or more dose levels that are associated with favourable pharmacokinetic, safety, and tolerability profiles over a 12 week treatmen period. This will be done in a population of nCFB patients that are UGT2B17 EMs.

Whilst BI 1323495 has the potential for development in several inflammatory airway diseases, nCFB patients were selected to be the study population, as their condition represents an inflammatory state characterized by accumulation of neutrophils and high NE activity in sputum. Furthermore – as one of the hallmarks of the disease – nCFB patients regularly produce a sufficient volume of spontaneous sputum which therefore can be collected non-invasively [R18-3321]. nCFB patients will be selected that have detectable NE activity in sputum at baseline [R19-3080, R19-3083]. A 12 week trial is considered an adequate duration to allow the assessment of safety/tolerability and the quantification of the inhibitory effect on NE activity in sputum, to assess further inflammatory and tissue-destruction biomarkers, and to collect data on clinical outcomes.

Results of this trial are intended to provide the basis for a planned further clinical development of BI 1323495 for patients with COPD, CF, and/or nCFB. Particularly, the results will help to define an appropriate dosing regimen for future studies with this compound.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g., to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Patients with nCFB receiving the NE inhibitor BI 1323495 that participate in this 'first-in-patient' trial may have a transient direct medical benefit from participation, as a treatment duration of 12 weeks is not expected to have a permanent impact on the long-term course of their disease. However, the NE pathway is anticipated to have an important role in nCFB, as sputum NE activity was found to be a biomarker of disease severity and future risk of exacerbations in patients with bronchiectasis [R18-3321], and patients will be selected that have elevated NE activity in sputum indicating that the targeted pathway is active.
Considering the study duration of 12 weeks, inhibition of NE activity may result in modulation of clinical efficacy endpoints. Some benefit in symptoms (e.g., sputum volume, cough, mucus plugging), quality of life, and lung function might be expected with administration over 12 weeks.
In patients treated with placebo, no benefit is expected beyond the general benefits of regular medical assessment during participation in a clinical trial. All participants will have a close safety monitoring of their health status throughout the trial.

The major expected benefit is that results from the 1405-0008 trial will guide further clinical development activities of the NE inhibitor BI 1323495, such as Phase II and III studies for treatment of patients with COPD, CF, and/or nCFB. As a high proportion of patients with bronchiectasis have a concomitant diagnosis of COPD [R19-3085], such nCFB patients might especially benefit from further clinical development of BI 1323495.

1.4.2 Risks

Factors of risk may derive from particular knowledge (or the lack thereof) regarding the mode of action (MoA), the nature of the target, findings in animal models / non-clinical safety studies, findings from clinical studies, or drug-induced liver injury, and are referenced in detail in the latest version of the Investigator's Brochure of BI 1323495 [c21238478-05].

Table 1.4.2:1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: BI 1323495		
Infection	A mildly increased risk of bacterial infection has been reported in patients with Papillon-Lefèvre syndrome (genetic deficiency for Cathepsin C, the enzyme activating NE in neutrophil precursor cells in the bone marrow). These patients have life-long complete deficiency of active neutrophil serine proteases (NE, Cathepsin G, Proteinase 3). No elevated risk of infection was reported in previous clinical studies with other inhibitors of NE.	Exclusion of patients with relevant immunodeficiency or receiving immunomodulatory medication, or of patients having an acute infection. Requirement of vaccination against Streptococcus pneumoniae in accordance with national vaccination recommendations. Regular clinical and laboratory monitoring for infection.
Effects on the liver	Non-clinical toxicity studies at exposures high above those expected in humans revealed effects on the liver, indicated by increases in liver enzymes (aspartate aminotransferase (AST), ALT or GLDH) and an increase in total bilirubin in rats, accompanied by biliary hyperplasia in female rats in the 4 week studies. These findings were not seen in the 13-week toxicity studies although male rats achieved high exposures. The drug exposure was much higher in these animals than those expected in man.	Subjects with clinically relevant impairment of liver function, based on laboratory assessment regarding liver aminotransferases, alkaline phosphatase (AP), gamma glutamyl transferase, bilirubin, serum albumin, and International Normalized Ration (INR), are excluded from participation in this trial. Liver aminotransferases, alkaline phosphatase, gamma-glutamyl transferase, as well as total and direct bilirubin are monitored as part of the standard safety laboratory assessments.

Table 1.4.2:1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Effects on the kidneys	At exposures high above those expected in humans, effects on the kidneys were observed in 2- and 4-week non-clinical toxicity studies. These were accompanied by increases in creatinine levels and changes in blood urea. In the 13-week study, tubular degeneration was seen in male rats at the highest dose tested but recovered fully within the 8 week recovery period. In the cynomolgus monkey toxicology studies no effects on the kidney were seen.	Patients with a clinically relevant, at least moderate impairment in kidney function will be excluded from participation in this trial. Serum creatinine, urea, and electrolyte levels will be assessed and Glomerular Filtration Rate (GFR) be estimated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation as part of the safety laboratory assessments.
Coagulation pathway	In rats, an increase in fibrinogen (not considered toxicologically relevant) was observed. A reduction in platelet counts was observed in both rats and cynomolgus monkeys at exposures high above those expected in humans. This was accompanied by minor increases in prothrombin time in male rats. No bleeding events occurred.	Patients with a known coagulopathy or abnormal coagulation laboratory parameters at screening, or patients who within 10 days prior to administration of trial medication used any drug that could inhibit coagulation will be excluded, except for low-dose acetylsalicylic acid (aspirin) and NSAID. Platelet count, prothrombin time and activated partial thromboplastin time (aPTT) will be measured as part of the standard safety laboratory assessments and concomitant drugs that inhibit platelet aggregation or coagulation will be prohibited.

Table 1.4.2:1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Reproductive system	The risk to embryo-fetal development has not yet been assessed, and no data are available from its use in pregnant or breastfeeding women.	Women of child-bearing potential are excluded from participating in this trial, which also includes women that are pregnant or breastfeeding. Men able to father a child must be willing and able to use highly effective methods of birth control.
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.
Trial procedures		
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	- close clinical monitoring for AEs - selection of experienced sites and site staff
Lung function measurements (FEV1)	Risks and discomforts associated with lung function testing may include shortness of breath, dizziness, or headache during the breathing tests.	- close clinical monitoring for AEs - selection of experienced sites and site staff

Table 1.4.2:1 Overview over trial related risks (cont'd)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Other risks		
Placebo	If the patient is randomised to receive a placebo, no clinical benefit from treatment with study medication is expected.	Study medication will be administered add-on to standard of care, ensuring that no relevant treatments are being withheld from patients.
Risk related to Pandemic situations COVID-19 (Coronavirus-associated disease 2019)	Travelling to site, being at site for assessments, increased infection risk for lung function testing	Instead of site visits at Day 8 and Day 43, phone visits will be conducted. A flying nurse and local safety lab structure will be used to maintain control of safety of a patient and at the same time avoid risk of SARS-CoV-2 exposition at site. To evaluate and implement the option of sputum collection at patient's home as a fall-back scenario. Possible modifications in pandemic situation as described in Section 6.1 and in Appendix 10.4.

1.4.2.1 Risk related to the COVID-19 pandemic

Patients with chronic respiratory diseases, such as non-CF bronchiectasis, are generally assumed to be at a higher risk of experiencing severe COVID-19, although this has not been seen clinically to date. A systematic evaluation of the risk for this particular patient population has currently not yet been published. An overview [R20-2485] of a limited number of cases reported in several national CF patient registries indicates no relevant increased risk for patients with cystic fibrosis, which shares many pathophysiological and clinical features with non-CF bronchiectasis (such as, e.g., mucus plugging of the airways and chronic colonization with pathogenic bacteria).

A theoretical risk of treatment with BI 1323495 and the associated suppression of NE activity may be an increase in the probability of contracting COVID-19 or of experiencing severe disease in case of such an infection, either by the virus itself or secondary bacterial infection. A thorough assessment has been conducted to evaluate whether the mechanism of action of

BI 1323495 to inhibit NE may suggest such an increased risk. The key aspects of the assessment are summarised below. The full written documentation of this assessment (BI 1323495: Benefit-Risk assessment in context of COVID-19 infection) will be filed in the Trial Master File (TMF).

NE is an important component of the innate immune system, targeting proteins and virulence factors of various bacteria and thereby helping to fend off bacterial infections. However, it is only one among a large number of antimicrobial mechanisms of which neutrophils make use to kill bacterial pathogens. A specific role for neutrophils in the protection agains viral pathogens is not assumed.

The phenotype of patients with Papillon-Lefèvre syndrome (PLS), who completely lack functional neutrophil serine proteases (including NE) due to complete deficiency for Cathepsin C, is well described. No increased risk of viral infections has been reported in PLS patients. Likewise, no such risk has been documented in previous clinical trials in healthy subjects or in patients with respiratory diseases, including non-CF bronchiectasis, upon treatment with inhibitors of NE or inhibitors of the mechanistically related cathepsin C (CatC) (referenced in the Investigator's Brochure [c21238478-05]). Therefore, suppression of NE activity upon treatment with BI 1323495 is not expected to be associated with an increased risk of acquiring an infection with a viral pathogen targeting the airways, e.g., SARS-CoV-2, nor of a particularly severe clinical presentation in case of such an infection.

Currently available evidence does also not suggest an increased risk of secondary bacterial infection in case of COVID-19 upon treatment with BI 1323495. Suppression of NE represents a limited intervention into the overall armamentarium available to neutrophils to control bacterial infections. Furthermore, high levels of active NE have even been reported to impair antibacterial defense by cleavage of CXCR1, CD14, or CD16 on neutrophils, and by cleavage of opsonins from target bacteria, thereby impairing phagocytosis. Consistent with these considerations, studies investigating the effects of CatC or NE inhibitors in healthy subjects or patients with various respiratory diseases, including non-CF bronchiectasis, have not revealed an increased risk of bacterial infections, nor of aggravated clinical courses of influenza infections, or complications thereof by secondary bacterial infections.

NE inhibition by treatment with BI 1323495 is not expected to affect the benefit/risk ratio of a COVID-19 vaccine, and vice versa. A decision regarding vaccination of a subject participating in trial 1405-0008 must be taken based on an individual benefit-risk assessment by the investigator after thorough discussion with the subject. This assessment is to consider the approved label of the respective vaccine according to its summary of product characteristics as well as the provisions given in the CTP, including the time point when the vaccination should be given or a potential delay of the vaccination or the study treatment.

Based on these considerations, the benefit/risk assessment for the administration of BI 1323495 to patients with non-CF bronchiectasis remains unaltered also in face of the COVID-19 pandemic.

Risk mitigation:

Despite no increased risk of SARS-CoV-2 infection – or of a more severe COVID-19 disease in case of such an infection – is assumed upon treatment with BI 1323495, an individual withdrawal criterion that treatment with BI 1323495 is to be discontinued in case of laboratory-confirmed COVID-19 infection has been defined. General protective measures to limit the risk of acquiring a SARS-CoV-2 infection, e.g., wearing gown, mask, and gloves; social distancing, etc., will be taken care of by each site in accordance with local/regional/national regulations.

1.4.3 Discussion

The BI 1323495 preclinical and clinical data, the clinical information from competitor compounds with the same MoA, as well as the implemented safety measures in this study, establish an acceptable risk profile to allow dosing of nCFB patients over 12 weeks.

The trial may only demonstrate efficacy in an exploratory fashion, and any direct benefit to patients receiving active treatment may be limited to a transient improvement of symptoms. However, the selected patient population and trial duration may allow detecting an early efficacy signal. Considering the medical need for the development of an effective treatment to slow the progression of airway inflammation and subsequent disease worsening, the Sponsor considers that the potential long-term benefits for patients with nCFB and other respiratory diseases associated with high levels of neutrophilic airway inflammation (COPD, CF) support the clinical development of BI 1323495.

Potential risks for the subject in relation to the current COVID-19 pandemic situation have been evaluated. With regard to study treatment, no relevant negative impact is expected on the patients' health condition (e.g., increased susceptibility to viral / secondary bacterial infections, immune suppression, or impaired lung function). The number of scheduled site visits represents the minimum required for achieving the study goals. Appropriate cautionary measures will be set up at each site to minimize risk of infection with SARS-CoV-2 due to trial-related procedures. For the very unlikely case that despite all implemented measures a COVID-19 case occurs in a trial subject while in the study, a withdrawal criterion in case of laboratory-confirmed COVID-19 disease has been defined. The local/regional/national pandemic situation will be continuously evaluated while the study is ongoing, and – if needed – changes to the situation will be addressed by amendments to the Clinical Trial Protocol (CTP) to implement additional risk mitigation measures.

A periodic safety review will be conducted to ensure the safety and wellbeing of trial participants.

In summary, based on these considerations, the benefit/risk assessment for the administration of BI 1323495 to nCFB patients is considered to remain positive also in face of the current COVID-19 pandemic.

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 compare safety and tolerability of different doses of BI 1323495 with placebo in patients with nCFB based on the proportions of patients with drug-related adverse events after 12 weeks of different doses of BI 1323495 or placebo on an on-treatment basis.

The secondary objective is to assess pharmacodynamics of BI 1323495 in sputum and in blood as well as early signs of clinical efficacy of BI 1323495, mainly focused on the change from baseline to week 12 in NE activity in sputum for each treatment, assuming that patients remain on treatment for 12 weeks without the use of prohibited medication (for details refer to Section 4.2).

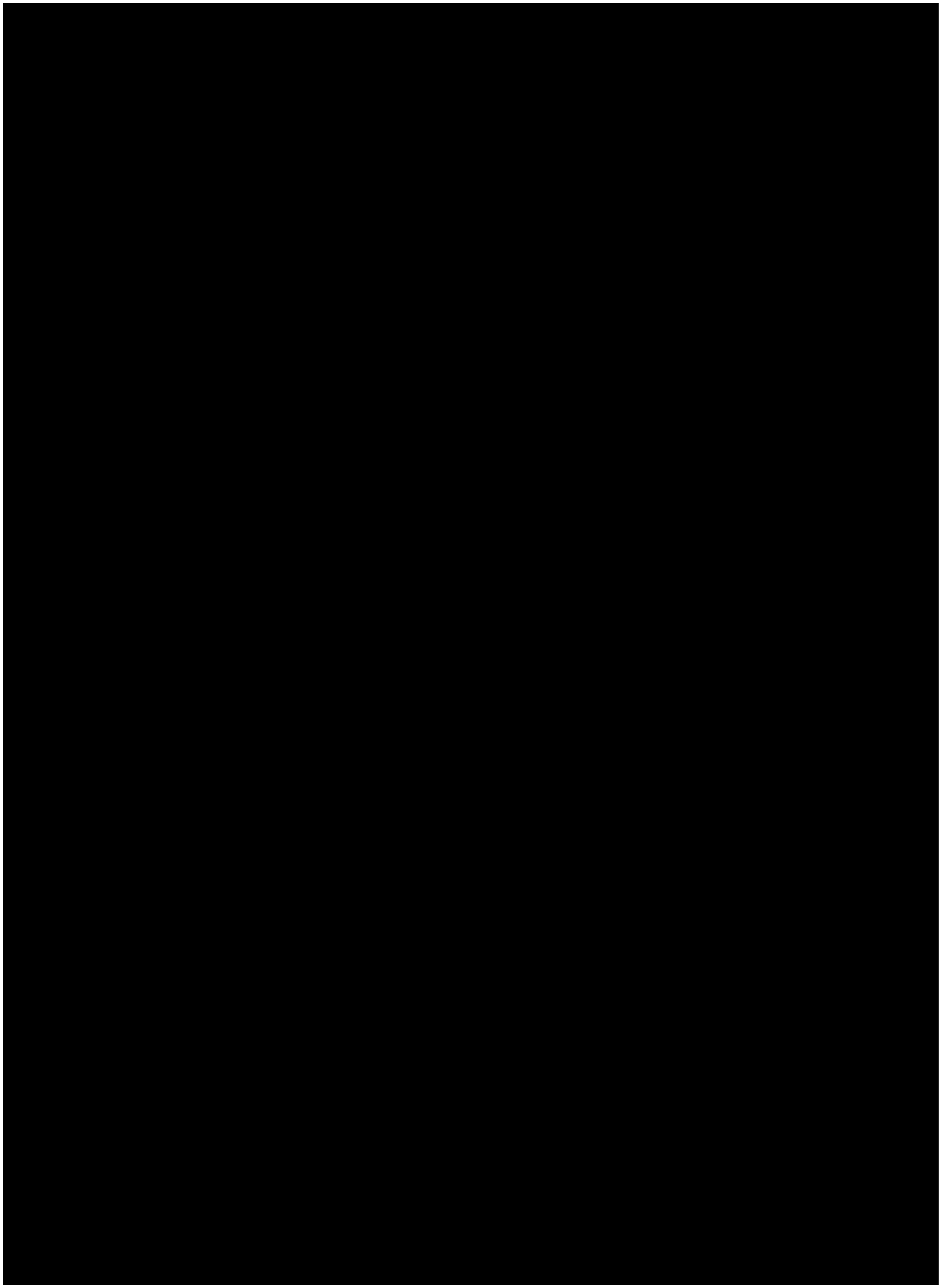
2.1.2 Primary endpoint(s)

The safety and tolerability of BI 1323495 will be assessed based on the occurrence of drug-related adverse events after 12 weeks of treatment. The timeframe for the primary endpoint is from the first drug administration until end of the REP (Section 1.2.4) after the last drug administration.

2.1.3 Secondary endpoint(s)

The following secondary endpoints will be determined:

- Change from baseline to week 12 in absolute NE activity in sputum
- Change from baseline to week 12 in neutrophil cell count in sputum
- Change from baseline to week 12 in NE activity in whole blood after stimulation with zymosan, normalized to neutrophil counts
- Change from baseline to week 12 in absolute post-bronchodilator forced expiratory volume in one second, FEV1



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This Phase Ic trial consists of two trial parts (Part A and Part B). Each part is designed as multi-centre randomised, placebo controlled parallel study investigating different doses of BI 1323495 (orally, bid or qd) in patients with nCFB. Patients and investigators will remain blinded during the entire trial, the sponsor will be unblinded (for details refer to Section 4.1.5).

In both trial parts, the study consists of a 2 to 4 week screening period including a 1 week baseline period, a 12 weeks randomised treatment period, and a 2 week follow-up period. Overall, each patient's participation in the trial is estimated to last a total of approximately 16-18 weeks.

As described in Figure 3.1: 1 below, patients will be enrolled (screened) in the trial (Visit 1) once the appropriate informed consent has been given. Determination of UGT2B17 genotype will be performed at screening to assess the eligibility of a patient to this trial that only allows participation of EMs (expected to constitute >85% in the Caucasian population). A point-of care assay (NEATstik®, [redacted]) will be used to select patients with high sputum NE activity at baseline (NEATstik® score ≥ 6). During the baseline period (Visits 2a, b and Visit 3 before treatment), patients have to donate two to three valid sputum samples.

At Visit 3, patients who successfully completed the screening visit and baseline period and still comply with the in- and exclusion criteria and have been clinically stable during the previous run-in period, will be randomised and allocated to treatment.

Subsequent visits (Visits 4, 5, 6, 7, 8, 10) primarily address safety, tolerability, and pharmacodynamics of BI 1323495, with an additional focus on pharmacokinetics of BI 1323495 at steady state (Visit 6). The last treatment week (Visits 9a and b and Visit 10 = End of Treatment) will again focus on the collection of two to three valid sputum samples to assess pharmacodynamics of BI 1323495.

After the completion of the 12 week treatment period, or in case of early treatment discontinuation, patients will be followed up for an additional 2 weeks. The patient's participation is concluded when they have undergone the last planned visit (i.e. Visit 11 = Follow-up Visit = end of study visit, EoS). No overnight stationary visits are planned unless preferred by the patient or required by the investigator for operational reasons.

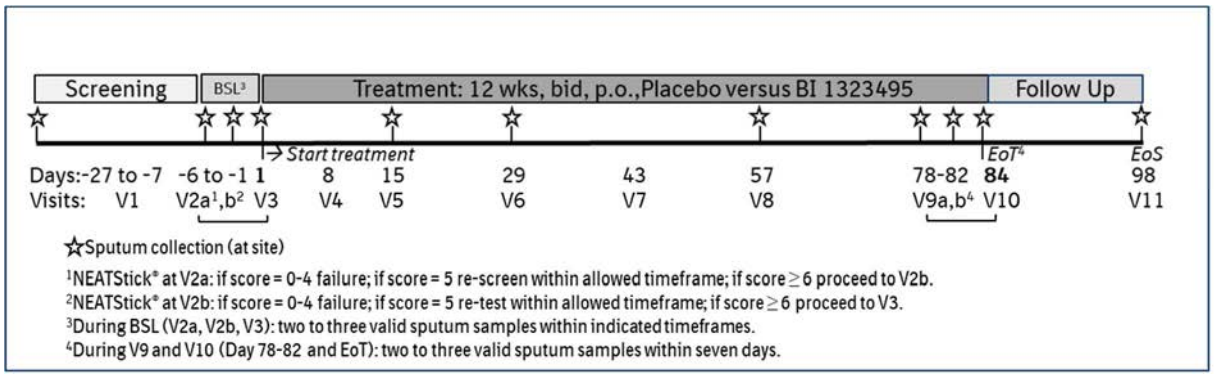


Figure 3.1: 1 Schematic overview of the trial periods and visit schedule

As described in Figure 3.1:.2 below, the trial consists of two trial parts, Part A and Part B. In Part A, patients will be randomised to receive either 30 mg bid BI 1323495 or placebo bid. This dose was confirmed to be safely tolerated upon an assessment of clinical safety during an earlier stage of the healthy volunteer multiple-rising dose trial 1405-0002. The sponsor will review available safety data periodically throughout the trial.

Part B will start if the following conditions are fulfilled: 1) the active dose for Part B has been defined; and 2) periodic safety review up to this point has not revealed any concerns. Completion of Part A is not a prerequisite to start Part B. In Part B, patients will be randomised to receive either 150 mg qd of BI 1323495 or placebo qd. Doses up to 150 mg bid (total daily dose: 300 mg BI 1323495) were tolerated safely in the healthy volunteer multiple-rising dose trial 1405-0002.

It is planned to include, in total, 36 patients with non-CF bronchiectasis in trial Parts A and B: 12 patients in Part A (3:1 randomisation, active:placebo) and 24 patients in Part B (3:1 randomisation, active:placebo).

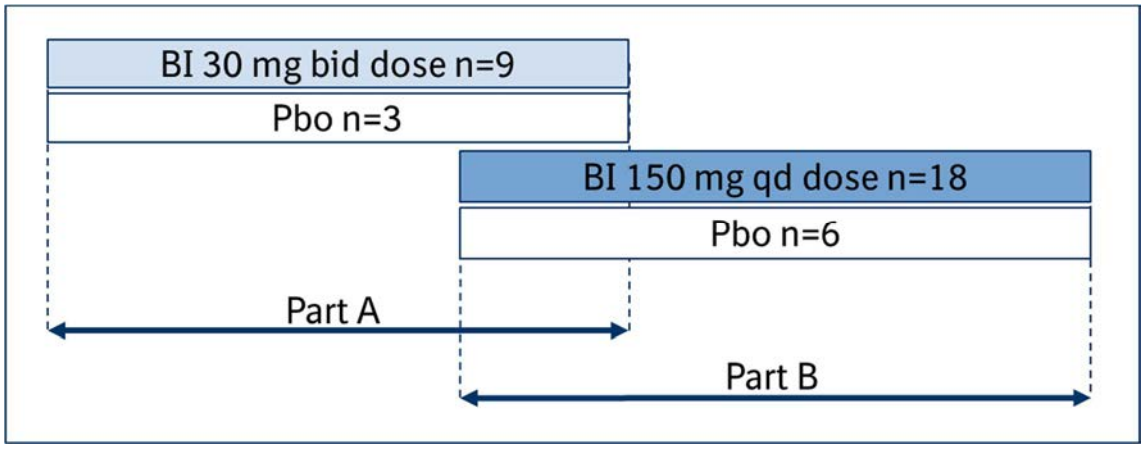


Figure 3.1: 2 Overview of trial design

An unscheduled safety review meeting can be requested anytime by the Principal Investigator (or an authorised deputy) or the sponsor of the study (for instance, due to occurrence of any unforeseen adverse events).

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

Since this trial evaluates BI 1323495 for 12 weeks (compared to 10.5 days – for bid dose groups, or 11 days – for the qd dose group in the healthy volunteer MRD trial) and for the first time in a patient population up to a higher age, safety and tolerability is the recommended primary objective for assessing a new drug in patients with nCFB. Due to its mechanism of action, a 12-week treatment period is considered sufficient to evaluate the PK and PD, and to potentially obtain an early sign of clinical efficacy of BI 1323495. A 2-week follow-up period without treatment is considered to be sufficient, as this covers twice the residual effect period during which BI 1323495 exposures are expected to return to not quantifiable levels and pharmacodynamic effects (inhibition of NE) are expected to have fully reversed.

Each trial part has a parallel-group, randomised, double-blind and placebo-controlled design as this is considered the most appropriate design to assess safety and efficacy of different doses of BI 1323495. In this trial, a double-blind (patient and investigator blinded, sponsor unblinded - for details refer to Section 4.1.5) concept was chosen to reduce the bias with regard to treatment-dependent effects as much as possible. Due to a close safety monitoring, this approach is considered acceptable for patients. A placebo group is included in order to control for safety, tolerability, and pharmacodynamic effects of the trial medication.

Only UGT2B17 extensive metabolizers will be included in this study to reduce PK variability. A dose of 30 mg bid BI 1323495 has been shown to be safely tolerated and was associated with a median level of >90% inhibition of NE at trough in blood of a healthy volunteer population of UGT2B17 EMs. Of note, in addition, according to preliminary pharmacometric simulations, a dose of 30 mg bid is predicted to remain within the exposure boundaries defined based on the results of the non-clinical toxicity studies even in UGT2B17 PMs who are expected to have BI 1323495 exposures exceeding those in EMs. Therefore, this dose level might be compatible later in clinical development with a mixed population of both PMs and EMs (beyond the scope of this trial). As such, this dose could be a therapeutic dose for EMs and PMs alike.

Total daily doses exceeding the dose of 150 mg qd to be investigated in Part B were confirmed to be safe and tolerated in the MRD trial in healthy volunteers, and at 150 mg qd it is not expected that exposures in individual patients may exceed exposure boundaries that were predefined based on the NOAEL in animal toxicity studies. This dose is expected to achieve the maximal pharmacodynamic effect. A dose associated with a pharmacodynamic effect approaching complete suppression of NE activity in blood is considered important as previous trials with other NE inhibitors have failed to achieve a high level of NE suppression in the airways despite adequate suppression in blood.

Based on information collected during the conduct of Parts A and B of this trial, it may be decided by the sponsor that important additional insights could be obtained from an additional part to introduce a third (intermediate or lower) dose level. This may be addressed in a subsequent substantial amendment.

The start of each trial part is chosen to efficiently evaluate the overall trial objectives given the staggered availability of data from the MRD trial 1405-0002 and represents a careful and safety conscious approach to the treatment of nCFB patients with BI 1323495. Periodic analyses of trial data (for details see Section 7.2.7) will provide valuable results based on the actual study population.

A total sample size of up to 36 patients, with N=12 in Part A and N=24 in Part B, is considered sufficient to assess the main objectives of this exploratory trial.

The final analysis of this trial will be based on data from all trial parts, resulting in a sample size of possibly 9 - 18 patients per treatment group. Data from patients treated with placebo from both trial parts will be pooled for the purpose of comparison with the two active treatment groups. The potential risk for bias due to combined analysis is thereby seen as low, as the unblinded periodic analysis results will not be shared with the staff at trial sites. Also, the time lag between the investigations of a specific treatment group from one trial part to the other is not expected to introduce bias in the data.

The overall feasibility of the trial is considered given, as experienced investigators will be selected that have both, access to nCFB patients as well as sputum handling proficiency.

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 nCFB will be screened from approximately 10 to 15 sites in two countries. nCFB patients who are regular daily producers of sputum with detectable NE activity levels will be the study population as 1) bronchiectasis (BE) represents an inflammatory state characterized by accumulation of neutrophils and associated proteases in the airways, and 2) a sufficient volume of spontaneous sputum can reproducibly be collected. It is expected that 2 to 5 patients will be randomised at each trial site. If enrolment is delayed, additional sites may be recruited.

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 is expected to become eligible as the screening failure was due to a transient, potentially reversible, condition. 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 and the already determined UGT2B17 genotype copied from the old eCRF. The current approved version of the information sheet and consent form should be signed again. One re-screening per patient will be allowed.

In case of pulmonary exacerbation requiring use of i.v./oral/inhaled antibiotics or hospitalization 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 if compared to 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 was randomised in error (does not meet all inclusion criteria or meets one or more exclusion criteria before randomisation), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

The key in- and exclusion criteria were selected to allow the enrolment of the preferred target population, i.e., patients of a broad age range that have clinically stable nCF bronchiectasis with regular daily sputum production and detectable NE activity in sputum. Eligibility will be confirmed at screening and baseline. The screening for detectable NE activity is considered crucial to reduce the potentially high variability in regard to sputum NE activity and ensure a trial population in which a treatment response to NE inhibition can be expected [R19-3080].

Concomitant maintenance treatment for the management of nCFB is allowed, except for strong CYP 3A4 inhibitors (a specified list of not-allowed comedications will be provided in ISF).

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

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

1. 18 years to 80 years (inclusive) at the time of informed consent signature, male and female (not of childbearing potential) subjects.
   For ‘female not of childbearing potential’ at least one of the following criteria must be fulfilled:
   - Permanently sterile (permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy; tubal ligation is not a method of permanent sterilisation)
   - Postmenopausal, defined as at least 1 year of spontaneous amenorrhea without an alternative medical cause (in questionable cases a blood sample with Follicle Stimulating Hormone (FSH) above 40 U/L and estradiol below 30 ng/L is confirmatory).

Men must be vasectomised with documented absence of sperm or use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after the last administration of trial medication if their sexual partner is a woman of childbearing potential (WOCBP).
2. Clinical history consistent with nCFB (cough, chronic sputum production and/or recurrent respiratory infections) and proven and documented diagnosis of bronchiectasis by computed tomography (CT) scan including dilated airways compatible with bronchiectasis at initial diagnosis. Bronchiectasis of various etiologies will be allowed, with exclusion criteria as below.
3. Vaccination against Streptococcus pneumoniae in accordance with national vaccination recommendations.
4. Signed and dated written informed consent prior to admission to the study, in accordance with Good Clinical Practice (GCP) and local legislation.
5. FEV1 ≥ 30 % predicted (post-bronchodilator) at Screening Visit 1.
6. Stable (i.e., no dose change) regimen of standard nCFB treatment (including – but not limited to – hypertonic inhalation solutions, mucolytics, Long Acting Muscarinic Agonists (LAMA)/ Long Acting Beta Agonists (LABA) / inhaled corticosteriods (iCS), oral antibiotic maintenance regimen, and physiotherapy), if applicable, administered at least for 4 weeks prior to Screening Visit 1 and throughout the run-in period.
7. Regular daily sputum producers with a history of chronic expectoration who are able to provide a typical bronchiectasis sputum sample at Screening Visit 1.
8. Sputum neutrophil elastase positive based on point of care test (NEATstik® score ≥ 6) assessment at Visit 2a and Visit 2b.
9. Subjects genotyped as UGT2B17 extensive metabolizers prior to randomisation, i.e., carrying at least one functional allele of the UGT2B17 gene (*1/*1 or *1/*2).

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR, or ECG) and/or laboratory value and/or any evidence of a concomitant disease assessed as clinically relevant by the investigator.
2. Concomitant diagnosis of pulmonary disease other than bronchiectasis, COPD, or asthma.
3. A current diagnosis of CF, primary immunodeficiency, active ABPA (Allergic Bronchopulmonary Aspergillosis) (defined by receipt of corticosteroids, anti-fungal treatment or monoclonal antibody treatment), or alpha-1 antitrypsin (A1AT) deficiency as underlying disease.
4. A history or current immunodeficiency or are currently being treated (or are planned to be treated) with immunomodulatory drugs (except for iCS or low-dose oral corticosteroids), including disease-modifying anti-rheumatic drugs (DMARDs), and/or Immunglobulin G (IgG) treatments. Other medication that is excluded will be provided in the ISF. On the day of the site visit with lung function measurement, no bronchodilators should be used until after completion of lung function assessment (see restrictions in Section 4.2.2.1).

5. Any acute infections defined as infections requiring antibiotic therapy, or Upper Respiratory Tract Infection (URTI). Are currently being treated (or are planned to be treated) for a nontuberculous mycobacterial (NTM) lung infection or tuberculosis.
6. A history of invasive pneumococcal disease.
7. Inhaled antibiotic treatment or cycling oral antibiotic treatment with changed dose regimen 4 weeks prior to Screening Visit 1.
8. A treatment for a pulmonary exacerbation 4 weeks prior to Screening Visit 1.
9. Systemic corticosteroids at >10°mg/day prednisolone equivalent within 4 weeks prior to Screening Visit 1.
10. History and/or presence of tuberculosis or positive result for interferon gamma release assay (IGRA) (i.e., QuantiFERON TB-Gold); positive results for Hepatitis B antigen, Hepatitis C antibodies and/or human immunodeficiency virus (HIV) 1 antigen or HIV1/2 antibodies.
11. Any documented active or suspected malignancy or history of malignancy including lung cancer within 5 years prior to Screening Visit 1, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
12. Current smokers or or ex-smokers who stopped smoking less than three months ago or are not willing to maintain nicotin-abstinence during the trial if stopped smoking more than three months ago.
13. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled, i.e. any condition that, in the investigator's opinion, makes the patient an unreliable trial participant.
14. Alcohol abuse (consumption of more than 20 g per day for females and 30 g per day for males) and/or drug abuse in the opinion of the investigator or positive drug screening.
15. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial.
16. Recent significant hemoptysis (≥300 mL or requiring blood transfusion) in the preceding 4 weeks before Screening Visit 1 (and during the run-in period).
17. Intake of an investigational drug in another clinical trial within 60 days, or within 5 half-lives of the investigational drug (whichever is longer), of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered.
18. Major surgery (major according to the investigator's assessment) performed within 6 weeks prior to randomisation or planned within 3 months after screening, e.g. hip replacement.
19. Current or history of relevant kidney, urinary tract diseases or abnormalities (e.g. nephrolithiasis, hydronephrosis, acute or chronic nephritis, renal injury, renal failure), according to investigator judgement.
20. Estimated glomerular filtration rate (eGFR) according to CKD-EPI formula < 60 mL/min at Screening Visit 1.
21. Known clinically relevant impairment of liver function or clinically relevant laboratory abnormality at the Screening Visit 1 regarding liver aminotransferases, alkaline phosphatase, gamma glutamyl transferase, bilirubin, serum albumin, as judged by the investigator.
22. Known coagulopathy or abnormal coagulation laboratory parameters at screening, or subjects who, within 10 days prior to administration of trial medication, used any drug

that could reasonably inhibit coagulation, except for low-dose acetylsalicylic acid (aspirin) or NSAID.
23. Laboratory confirmed SARS-CoV-2 infection (PCR positive) within 4 weeks prior to Screening Visit 1.
24. Household contact with an individual with confirmed SARS-CoV-2 infection within 4 weeks prior to Screening Visit 1.
25. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.

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") with very different implications; 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 eCRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2).

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). The subject shows an elevation of AST and/or ALT ≥3-fold upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
- The subject experiences an infection with SARS-CoV-2 (as confirmed by PCR Test, see Section 5.2.3) or an infection other than pulmonary exacerbation which requires systemic antibiotic treatment.In case a patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment (see Section 4.2.2), it will be decided on a case-by-case basis after consultation with the Sponsor whether or not discontinuation of trial treatment is required.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and Section 6.2.3.

Additional patients may be recruited, if early treatment discontinuation is due to non-safety related reasons (e.g. unable to continue protocol defined visits due to personal reason), or due to COVID-19 given the prevalence of the coronavirus in the community. In all cases, recruitment of additional patients should only occur if the patient discontinued treatment prior to week 12, and must first be discussed and agreed upon with the sponsor.

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, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

- Failure to meet expected enrolment goals overall or at a particular trial site.
- New efficacy or safety information, toxicological findings or serious adverse events invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
- Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
- The sponsor decides to discontinue the further development of the investigational product.

Further follow up of patients affected will occur as described in Section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of patients

Patients with premature treatment discontinuation will not be replaced as all safety data captured from treated patients will be evaluated. In certain cases of premature treatment discontinuation, the recruitment of additional patients may be considered, see Section 3.3.4.1 for details.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products used in this trial, BI 1323495 and placebo, are manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

Film-coated tablets of 2 dosage strengths and matching placebo tablets were developed for oral administration: 10°mg (14 x 6.8 mm oval) and 50°mg (11 x 5.5 mm oval.

Table 4.1.1: 1 Test product BI 1323495

Substance:	BI 1323495
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg or 50 mg
Posology:	bid for 12 weeks in Part A and qd for 12 weeks in Part B
Method and route of administration:	Oral, as tablets

Further details are given in the Investigator's Brochure [c21238478-05].

Matching placebo tablets have been developed, containing mannitol, microcrystalline cellulose, and magnesium stearate.

Table 4.1.1: 2 Placebo

Substance:	No substance (placebo)
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	No strength, matched to active test drug
Posology:	bid for 12 weeks in Part A and qd for 12 weeks in Part B
Method and route of administration:	Oral, as tablets

The clinical trial supplies will be provided in blisters. The tablets should be handled according to the labelled storage instructions and shelf life.

4.1.2 Selection of doses in the trial and dose modifications

The 30 mg bid dose of BI 1323495 is a confirmed safe and tolerated dose after multiple dosing in healthy volunteers and could potentially be a therapeutic dose that is applicable for both, EMs and PMs, and will thus be tested in Part A. In the MRD trial 1405-0002, with 30 mg bid in EMs, median trough NE inhibition at steady state exceeded 90% which is considered a PD effect size potentially associated with a clinical benefit if maintained long term (Table 1.2.3.2: 1). The 150 mg qd dose of BI 1323495 selected for Part B was based on safety/tolerability data from higher dose groups of the healthy volunteer MRD study and is anticipated to reach the maximal safely achievable PD effect. This dose was selected to ensure that exposures will not exceed a gMean value that was observed and safely tolerated in the MRD trial 1405-0002, and to not exceed exposure boundaries that were predefined based on animal toxicity studies (see Section 1.2.2.4). Doses will be administered with food containing a fat component.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 3:1 ratio at visit 3 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the respective dose group of the active substance.

Trial medication will be dispensed in a double-blinded manner to patients. That means, investigators and patients will not know if a patient is assigned to BI 1323495 or placebo.

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

Treatment	Substance	Formulation	Unit strength	Dosage	Total daily dose
Part A	BI 1323495	Tablet, film coated	10 mg	3 tablets bid	60 mg
Part B	BI 1323495	Tablet, film coated	50 mg	3 tablets qd	150 mg

Subjects should take the study drug while in a standing or sitting position, as an oral dose together with about 240 mL of water. Drug should be taken 15-30 min after food intake including a fat component (like yogurt, milk, cheese or sausage).
Following first drug administration in Part A, evening and morning dose should be taken with a 12 h time interval (e.g. 20:00 h and 08:00 h) approximately at the same time each day during the treatment phase, within a time window of +/- 1 hour. In Part B, the once-daily dose should be taken approximately at the same time each morning during the treatment phase. Missed dose(s) will not be replaced.

As an exemption, at Visit 3 and Visit 6, drug administration will happen at the site outside the normal schedule for practical reasons to accomplish assessments. Patients will then return to their usual evening/morning interval (Part A) or thertheir usual morning interval (Part B), respectively.

All patients will be dispensed the trial medication consisting in total of 7 medication kits. Dispensing will be done during the trial stepwise via the IRT system at Visit 3, Visit 5, Visit 6 and Visit 8. During the above-mentioned visits, 1 medication kit will be assigned by the IRT system. At Visit 6 and Visit 8, 2 kits will be dispensed to cover the 4 weeks duration until EoT visit. In addition, a patient will receive 1 kit as a reserve at Visit 3 in case medication gets lost or the patients comes back to the next visit after more than 2 or 4 weeks, respectively.
The kits will be used for treating the patient at visits at the site and at the respective time points at home in between site vists.

During the COVID-19 pandemic, physical visits to the sites may need to be cancelled to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment, and trial medication may be shipped to the patient's home if acceptable according to local laws and regulations (for more details see Section 6.1).

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The table below summarizes the masking /blinding level of individual functions involved in the trial.

Table 4.1.5.1: 1 Blinding of functions involved in the trial

Role/function	**Timing of unblinding/receiving access to the treatment information (including rationale)**
Patients	Blinded until data ready for final analysis.
Investigator/Site Staff	Blinded until data ready for final analysis.
Sponsor (incl. clinical trial/project team), and database	After individual patient has been allocated to treatment. Periodic safety review and descriptive analyses of selected PK and PD endpoints will be performed during the trial conduct (see Section 7.2.7). The release of the treatment information at the individual time points will be documented accordingly.
Bioanalytical Staff	As requested for analysis of bioanalytical samples.

During the time a role/function is blinded, the randomisation schemes and medication kit lists (i.e. the treatment information) are kept restricted by the global Randomisation Team (gRT) per Sponsor Standard Operating Procedure (SOP).

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 eCRF 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.

Prior to completion of treatment allocation in each trial part, an in dividual patient unblinding by the sponsor may occur, in case during the periodic safety review an AESI or any other relevant AE has occurred, that needs a more detailed investigation and is crucial for continuation or modification of the trial.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated Clinical Research Organization (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 Clinical Research Associate (CRA) (as provided in the list of contacts) must be contacted immediately.

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

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

All concomitant therapies will be recorded (including time of intake on study days) on the appropriate pages of the eCRF.

The use of certain medications, e.g. listed under the exclusion criteria (Section 3.3.3) is restricted during the trial. Details with regard to its use are provided in the ISF.

Drugs that are strong inhibitors of CYP3A4 have to be avoided for Part B, since a modest effect of the strong CYP3A4 inhibitor itraconazole on the PK of BI 1323495 in UGT2B17 EMs has been observed (see Section 1.2.3.1).

Excluded concomitant medications that might be of relevance in the population of this trial are provided in the ISF, including a detailed list of strong CYP3A4 inhibitors.

If treated with bronchodilators, wash-out of 24 hours for qd long acting, 12 hours for bid long acting, and 8 hours for short acting bronchodilators should be observed before pulmonary function tests.

4.2.2.2 Restrictions on vaccinations

Live or live-attenuated vaccine should be avoided during the trial. Vaccination against COVID-19 should have been completed (administration of both doses for those vaccinations in which two injections separated by several weeks are required) at least 4 weeks prior to screening. In case a patient, during his/her participation in this trial, is being offered COVID-19 vaccination, this is considered – in principle – possible. Vaccination reactions (such as fever, chills, fatigue, pain or swelling at the injection site) have frequently been reported during the first 48 hours after vaccination against COVID-19. Therefore, vaccination should occur at least 48 hours prior to a study visit, and the time of its administration should be carefully documented on the concomitant medication page of the eCRF, to avoid 1) potential interference of a vaccination reaction with study procedures and data collection, and 2) to facilitate the differentiation of potentially vaccination-associated AEs from potentially IMP-related AEs.

4.2.2.3 Restrictions on diet and life style

Drug should be taken 15-30 min after intake of food including a fat component like yogurt, milk, butter, cheese, or sausage. On PK day at Visit 6, a meal with a fat component will be provided by the site prior to drug administration.

Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until after the last PK sample is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed during in-house confinement.

For more details on food effects please refer to Section 1.2.3.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first administration of trial medication until the end of trial examination.

4.2.2.4 Contraception requirements

Trial participation is allowed for male and female (not of childbearing potential) subjects.

For 'female not of childbearing potential' at least one of the following criteria must be fulfilled:

- Permanently sterile (permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy; tubal ligation is not a method of permanent sterilisation)
- Postmenopausal, defined as at least 1 year of spontaneous amenorrhea without an alternative medical cause (in questionable cases a blood sample with FSH above 40 U/L and estradiol below 30 ng/L is confirmatory).

Men must be vasectomised with documented absence of sperm or use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after the last administration of trial medication if their sexual partner is a woman of childbearing potential (WOCBP).

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

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 Spirometry (PFT)

Pulmonary function will be assessed using standardised spirometry equipment which will be provided centrally with supplies of pre-calibrated disposable flow sensors. These sensors meet International Organization for Standardization (ISO) 26782 standards, but with a maximum permissible accuracy error of ±2.5%, in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Technical Statement [R20-2419]. As such there is no need to conduct daily calibration prior to use. Only these spirometers are to be used for this trial. Spirometry performance will be centrally overread.

Description of COVID-19 precautionary measures upon conduct of spirometry testing will be provided in the ISF.

Spirometry will be conducted with the subject in a seated position. It is preferable that the same trained individual performs the PFTs for a given subject. The best of three efforts will be defined as the highest FEV_1 obtained on any of three blows meeting the 2019 ATS/ERS criteria (with a maximum of eight attempts). Predicted normal values will be calculated according to GLI (Global Lung Initiative).

On days of clinic visits, patients must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Patients should also avoid cold temperatures, environmental smoke, dust, or areas with strong odours (e.g. perfumes). If treated with bronchodilators, patients should not take their daily bronchodilator inhalation until after completion of the spirometry.

At Visit 1, the PFT should be started 11:00 am as outlined in the Flow Chart. At each following site visit, PFT will always start at approximately the same time of the day.

Post-bronchodilator (salbutamol (albuterol)) testing:

Following the completion of three acceptable pre-bronchodilator forced expiratory manoeuvers, salbutamol (albuterol) will be administered to each subject. After a gentle and incomplete expiration, a dose of approximately 100 µg of salbutamol (albuterol) is inhaled in one breath to total lung capacity. The breath is held for 5 – 10 sec before the subject exhales. Four separate doses (total dose approximately 400 µg) are delivered at approximately 30 sec intervals (this dose ensures that the response is high on the salbutamol (albuterol) dose - response curve). Three to five additional, acceptable post-bronchodilator force expiratory manoeuver tests are recorded 15 – 30 minutes after the last dose of salbutamol (albuterol) is inhaled.

During the study, a central quality control center will receive the data of spirometry measurements electronically to ensure that the sites maintain the same standard throughout the study. The central quality center will review the spirometry measurement data and report to the sponsor on data quality and, if required, actions to be taken.

Further instructions regarding FVC measurements will be provided in the ISF.

5.1.2 24h-sputum weight

Patients will be asked to collect spontaneous sputum into a pre-weighted container at home over 24 hours and seal it in the collection container on days before hand-over of 24 hour sputum is indicated in the Flow Chart. The collection of the sputum has to be done over the 24 hours preceeding the handover at the site. At the site the sputum weight will be determined. More details about the procedure will be provided in the ISF.

5.1.3 Patient Reported Outcomes

Patient questionnaires will be completed at the time points indicated in the Flow Chart. Questionnaires will be completed in random order by the patient alone in a quite room. The questionnaire will be paper-based and available in the local language (provided in the ISF).

- **Quality of Life Questionnaire-Bronchiectasis, QOL-B**

The Quality of Life-Bronchiectasis (QOL-B), a self-administered, patient-reported outcome measure assessing symptoms, functioning and health-related quality of life for patients with non-cystic fibrosis (CF) bronchiectasis, contains 37 items on 8 scales (Respiratory Symptoms, Physical, Role, Emotional and Social Functioning, Vitality, Health Perceptions and Treatment Burden).

Details of the QOL-B are provided in Appendix 10.1.1.

- **St. George's Respiratory Questionnaire, SGRQ**

The SGRQ [R96-0686] is designed to measure health impairment in patients with COPD. It is divided into two parts. Part 1 produce the Symptoms score, and Part 2 the Activity and Impacts scores. A Total score is also produced.

Part 1 (Questions 1 to 8) covers the patient's recollection of their symptoms over a preceding period that may range from 1 month to 1 year. It is not designed to be an accurate epidemiological tool; its purpose is to assess the patient's perception of their recent respiratory problems. The original version was validated using a 12-month recall period. A 3-month recall period has been used very satisfactorily. In summary, the 3-month and 1-year versions provide the best properties, with no specific advantages to either.

Part 2 (questions 9 to 16) addresses the patients' current state (i.e. how they are these days). The activity score just measures disturbances to patient's daily physical activity. The Impacts score covers a wide range of disturbances of psycho-social function. Validation studies

showed that this component relates in part to respiratory symptoms, but it also correlates quite strongly with exercise performance (6-minute walk test), breathlessness in daily life (MRC breathlessness score) and disturbances of mood (anxiety and depression). The Impacts score is, therefore, the broadest component of the questionnaires, covering the whole range of disturbances that respiratory patients experience in their lives.

Details of the SGRQ are provided in Appendix 10.1.2.

- **Cough and sputum assessment questionnaire, CASA-Q**

The CASA-Q is a self-administered questionnaire that assesses cough and sputum based on their frequency, severity, and impact on daily activities in the previous 7 days. The CASA-Q contains four domains: cough symptoms, cough impact, sputum symptoms, and sputum impact. Each domain contains three to eight items, each of which is answered in five categories from “never” to “always” for frequency and from “not at all” to “a lot/extremely” for intensity.

Details of the CASA-Q are provided in Appendix 10.1.3.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

Measurement of height and body weight will be performed at the time points specified in the Flow Chart.

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 Flow Chart, prior to blood sampling.

This includes systolic and diastolic blood pressure (BP) and pulse rate (PR) (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 and exclusionary laboratory tests in Table 5.2.3: 2. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.
Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. 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 ISF). 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

Functional lab group	**Test name**
Haematology	Haematocrit Haemoglobin Red Blood Cell Count/Erythrocytes (RBC) Reticulocyte count Reticulocytes/Erythrocyte White Blood Cells/Leucocytes (WBC) Platelet Count/Thrombocytes (quant)
Automatic WBC differential, relative (per Leukocytes) and absolute	Neutrophils Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time – INR (International Normalized Ratio) Fibrinogen
Enzymes	Aspartate aminotransferase (AST/GOT) Alanine aminotransferase (ALT/GPT) Alkaline Phosphatase [AP] Gamma-Glutamyl Transferase (GGT) Creatine Kinase (CK) Creatine Kinase Isoenzyme MB (CK-MB), if CK is elevated

Table 5.2.3: 1 Safety laboratory tests (cont'd)

Functional lab group	Test name
Substrates	Creatinine GFR/ CKD-EPI Total bilirubin Direct bilirubin Total protein Albumin C-Reactive Protein (CRP) Uric Acid Urea Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Chloride Calcium
Urinalysis	Urine nitrite (qual) Urine protein (qual) Urine glucose (qual) Urine ketone (qual) Urobilinogen (qual) Urine bilirubin (qual) Urine leucocyte esterase (qual) Urine blood (qual) Urine RBC/erythrocytes Urine WBC/leucocytes Urine pH

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which are planned during screening only, but may be repeated as required. The results will not be entered in the eCRF/database and will not be reported in the Clinical Trial Report (CTR). Pregnancy testing in women will be performed at screening, prior to treatment start, and as part of the end of study examination. Drug screening will be performed at screening and prior to treatment start. Cotinine will be assessed at different time points and results will be transferred to the database.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Cotinine Methadone Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qual) Hepatitis B core antibody (qual) Hepatitis C antibodies (qual) HIV-1 and HIV-2 antibody (qual)
Immunology*	Interferon-ɣ release assay to tuberculosis (qualitative), e.g. QuantiFERON®-TB-Gold Test
Molecular Diagnostics	PCR test for detection of SARS-CoV-2 according to official local/national recommendations

*Test results already available for a subject do not have to be repeated, if assessment took place within 4 weeks before randomisation

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

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. 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 or 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”

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

The latest list of "Always Serious AEs" can be found in the electronic Data Capture (eDC) system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.
Cancers of new histology and relapse 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".**

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

- an elevation of AST (Aspartate Aminotransferase) 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 ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure 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 eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (the End of Study (EoS) visit):
  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 on the eCRF.

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. 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.
Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (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 Studies 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.

5.2.6.2.4 Exemptions to SAE reporting

No exemptions are defined.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for pharmacokinetic analysis

The planned PK analyses of BI 1323495 and its metabolite CD 7545 will require blood sampling at the time points indicated in the Flow Chart. 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, matrix and planned sampling time.

After completion of the trial, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites). However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

5.3.2.2 Sputum sampling for pharmacokinetic analysis

Spontaneous sputum will be collected as indicated in the Flow Chart. In case no adequate sputum sample is produced spontaneously, induction of sputum with isotonic, or subsequently hypertonic saline is mandatory. If sputum samples do not meet the quality criteria as directly assessed at the site, re-sampling at the next day is generally possible.

Whether the BI 1323495 and CD 7545 concentrations in sputum will be measured depends on the amount of sputum expectorated at the clinical sites as the measurements for the secondary endpoints in sputum take precedence over PK analysis (further details will be provided in the lab manual). Hence, it might be that not at all visits with sputum collection PK samples are taken.

Correct, complete and legible documentation of drug administrations and sputum sampling times as well as adequate handling and identification of sputum PK samples are mandatory to obtain data of adequate quality for the sputum PK analysis.

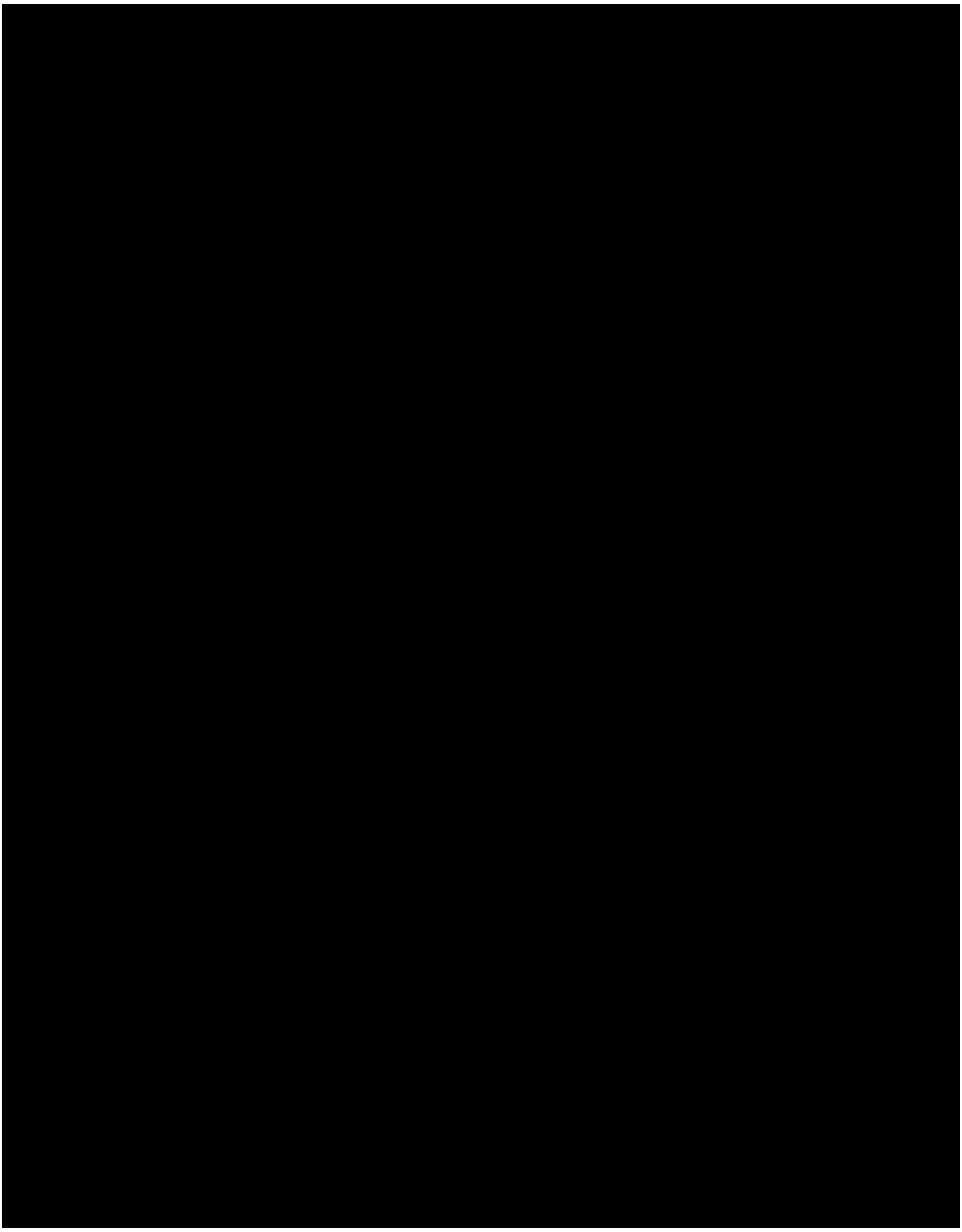
In order to allow the sputum sample identification, the sample tube labels should list at a minimum the following information: BI trial number, patient number, visit, matrix and planned sampling time.

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

The left over sputum samples will be transferred to the biobank after completion of these analysis but no later than 5 years after signature of the CTR (see Section 5.5).

[redacted]

[redacted]



[redacted]

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

5.5.1 Methods and timing of sample collection

Approximately 60 mL blood will be drawn per patient for serum banking and spot urine will be collected at timepoints indicated in the Flow Chart.

In addition left over sputum volume (see Section 5.3.2.2 and 5.4) will be used for banking purposes.
Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.

5.6 OTHER ASSESSMENTS

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters

in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The study scheme, including all visits, is shown in Section 3.1, Figure 3.1: 1.

Screening Visit 1 will be done at least 7 days prior to Baseline (BSL) Visit 2a. During BSL (V2a, V2b, V3), there will be a minimum of two and up to three valid sputum samples within indicated timeframes. The End of Treatment (EoT) Visit 10 will be done 12 weeks after randomisation. Prior to EoT, during V9 and V10, i.e. Day 78-82 and EoT, two to three valid sputum samples will be obtained within seven days.

The acceptable time windows for screening, for measurements and assessments are provided in the main Flow Chart and are also described in the Section 6.2 below.

The Sample and Assessment Flow Chart provides sputum, PK and PD details for timing of sampling as well as conduct of lung function meassurements and questionnaires. Planned blood sampling times should be adhered to as closely as possible.

The acceptable deviation from the scheduled time for vital signs, ECG, PK and laboratory tests will be ± 15 min. The exact times of trial visit assessments and measurements outside the permitted time windows will be documented in the eCRF.

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

In exceptional circumstances during COVID-19 pandemic, when it is impossible to conduct study visits at the study site, study visits may be performed at patient's home or remotely (via telephone and/or internet based means of communication). Visits may also be performed as a hybrid of home and remote visit. All home/remote visits need to be discussed with and authorised by the sponsor's trial team. The trial team's decision will be based on a thorough benefit-risk evaluation.

The procedures performed during a home/remote visit may be adjusted as compared to a regular visit, as detailed in Appendix 10.4

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Screening Period

After having been informed about the trial, all subjects will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study.
At screening, the medical examination will include demographics, height and body weight, smoking and alcohol use, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, aural body temperature), 12-lead ECG, pregnancy testing, laboratory tests (including UGT2B17 genotyping), sputum collection, lung function and a physical examination. For information regarding physical examination, vital signs, laboratory tests and ECG refer to Sections 5.2.1, 5.2.2, 5.2.3 and 5.2.4.

Genotyping for UGT2B17 will be performed in all trial patients (for details, see Section 5.4). The Screening Visit 1 can cover a period of up to 4 weeks, e.g. to wait for laboratory results, or if washout of certain restricted medication is required (see Section 4.2.2.1).

During the baseline period (Visits 2a, b and Visit 3 before treatment), patients have to donate two to three valid sputum samples.

6.2.2 Treatment period

After Visit 3 with first drug administration, patients will visit the site after 2, 4, 8, 11 and 12 weeks. Visit 4 after 1 week of treatment start will be conducted as a phone call with the patient. At Visit 7, 6 weeks after treatment start, the patient will be contacted via phone, and blood collection for safety laboratory will be done via a local lab or a flying nurse.

Following first drug administration in Part A, the evening and the morning dose should be taken with a 12 h time interval (e.g. 20:00 h and 08:00 h) approximately at the same time each day during the treatment phase, within a time window of +/- 1 hour. In Part B, the once-daily dose should be taken approximately at the same time each morning during the treatment phase. Drug should be taken 15-30 min after food intake including a fat component (like yogurt, milk, cheese or sausage). As an exemption, at Visit 3 and Visit 6, drug administration will happen at the site outside the normal schedule. Patients will then go back to their usual evening/morning interval (Part A) or once-daily interval (Part B), respectively. On PK day at Visit 6, patients will stay at site for the reason of medical surveillance.

The provided time according the Sample and Assessment Flow Chart is approximate; i.e. a deviation from the scheduled time of the day of ± 120 minutes is acceptable. The relative time deviations from time of administration should be kept as minimal as possible and should be below ± 15 minutes for PK measurements on PK days. The exact time of sample collection should be collected in electronic Case Report Form (eCRF). Patient questionnaires will be completed by the patient alone in a quite room.

Sputum collection should occur during a 2h timeframe with active breathing techniques or equivalent manouvres, if necessary. Study nurse / physiotherapist needs to be available to support patient in performing active cycle of breathing technique in case of difficulties producing sputum. Next step will be Oscillating Positive Expiratory Pressure (OPEP), if despite breathing technique still no sputum is being produced. Patients who produce an adequate sputum sample do not have to undergo these supportive measures. In case no

adequate sputum sample is produced spontaneously, induction of sputum with isotonic, or subsequently hypertonic saline is mandatory. If sputum samples do not meet the quality criteria as directly assessed at the site, re-sampling at the next day is generally possible. An instruction on sputum handling will be provided to the site in the ISF.

If treated with bronchodilators, wash-out of 24 hours for qd long acting, 12 hours for bid long acting, and 8 hours for short acting bronchodilators should be observed before pulmonary function tests.
The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart.

AEs and concomitant therapy will be assessed continuously from screening until the end ofstudy.

6.2.3 Follow-up period and trial completion

End of Study assessments must be conducted at least 7 days after the last trial drug intake, i.e. after the REP for BI 1323495.
For AE assessment, laboratory tests, recording of ECG and vital signs, sputum collection, lung function and physical examination during the End of Study Visit, see Section 5.2.
Patients who discontinue treatment before the end of the planned treatment period should also undergo the EoT Visit, at least 7 days after the last trial drug intake.

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

Male subjects with 'women of childbearing potential' (WOCBP) partner will be reminded to use male contraception (condom or sexual abstinence) during the trial until 30 days after the last administration of trial medication.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary objective of this trial is stated in Section 2.1 and the associated endpoint will be evaluated using descriptive statistics.

The secondary endpoints, see Section 2.1, will be assessed using descriptive analysis. If considered valueable, an inferential analysis will be performed in an exploratory fashion, i.e. no hypothesis is stated and no adjustment for multiplicity will be applied.

[redacted]

7.1 NULL AND ALTERNATIVE HYPOTHESES

The study is exploratory in nature and no confirmatory testing will be performed. Hence no null and alternative hypotheses are defined. Any confidence intervals or p-values provided are to be interpreted in the perspective of the exploratory character of the study. A justification of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum, and maximum) or frequency tables will be presented where appropriate.

Analysis sets
Statistical analyses will be based on the following analysis sets:

- Screened set (SCS): This patient set includes all patients that signed informed consent. The SCS will be used for disposition.
- Randomised Set (RS): This patient set includes all randomised patients. The RS will also be used for disposition.
- Treated set (TS): The treated set includes all patients who were randomised and received at least one dose of study drug. The treatment assignment will be determined based on the first actual treatment the patients received. The TS will be used for safety analyses and evaluation of biomarker and clinical assessments.
- [redacted]

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the Domain Deviation (DV). Protocol deviations will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.2 Primary endpoint analyses

The primary endpoint, see Section 2.1.2, will be derived according to BI standards and the proportion of patients with at least one drug-related AE per treatment group will be derived. The analysis will be based on the TS and will be descriptive in nature.

7.2.3 Secondary endpoint analyses

The analysis of the secondary endpoints, see Section 2.1.3, will be based on the TS.
Data from of all timepoints except those that were sampled within 15 days after the end of an exacerbation will be included in the analysis.

The 'baseline' and 'after 12 weeks' value of parameters that are measured more than once for these time points, see Sample and Assessment Flow Chart, will be derived as the mean of the available valid samples at each of these time points.

The change from baseline of NE activity in sputum at the different visits (X) is calculated as:
cfb in NE activity at Visit X = NE activity at Visit X – NE activity at baseline.

For the derivation of the change from baseline of NE activity in blood, the NE activity in blood at each visit will first be normalized to neutrophil counts [redacted]
and then the change from baseline is determined analog to the NE activity in sputum above.

The secondary endpoints will be primarily analysed by descriptive statistics and graphical representations across all visits.

[redacted]

[redacted]

[redacted]

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

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, see Section 1.2.4. 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.

Clinically relevant abnormal findings in ECG will be reported either as baseline condition (at screening) or otherwise as AEs.

[redacted]

7.2.7 Interim Analyses

No formal interim analysis will be performed and no interim report is to be written.

A periodic unblinded safety review will be conducted by the sponsor to monitor safety and tolerability. Therefor descriptive and graphical presentations of the primary endpoint and further safety assessments will be created.

[redacted]

7.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

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

Secondary biomarker endpoints
No imputation will be applied [redacted]

[redacted]

7.4 RANDOMISATION

In trial Part A (N=12), patients will be randomised in a 3:1 ratio to receive either 30 mg bid BI 1323495 or placebo bid. In Part B (N=24), patients will be randomised in a 3:1 ratio to receive either 150 mg qd of BI 1323495 or placebo qd.

The randomisation of patients to the treatment groups will be performed via an interactive response technology (IRT).

BI will arrange for the randomisation, 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 (CTR). Access to the codes will be controlled and documented

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory trial, it is planned to include a total of 36 treated patients in Part A (N=12) and B (N=24). The planned sample size is not based on a power calculation. In Part A and B combined, 9 patients in total will receive placebo, 9 patients will receive 30 mg bid BI 1323495 and 18 patients will receive 150 mg qd. The selected sample size per dose group is considered sufficient to explore safety and tolerability of BI 1323495 [redacted]

[redacted]

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 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 finalisation 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-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

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

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

eCRFs 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 should be traceable (audit trail).

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

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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 eCRF, 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 eCRF 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. U.S. Food and Drug Administration (FDA)). They may review all eCRFs 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

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
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"). **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 periodic unblinded safety review will be conducted by the sponsor to monitor safety and tolerability. Therefor descriptive and graphical presentations of the primary endpoint and further safety assessments will be created.

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 web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), 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 Clinical Trial Managers (CT Managers), 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 central spirometry service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual, the Spirometry Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Quality of Life Questionnaire-Bronchiectasis, QOL-B

Table 10.1.1: 1 Quality of Life Questionnaire-Bronchiectasis, QOL-B

QOL-B QUALITY OF LIFE QUESTIONNAIRE - BRONCHIECTASIS

Understanding the impact of your illness and treatments on your everyday life can help your doctor monitor your health and adjust your treatments. For this reason, we have developed a quality of life questionnaire specifically for people who have bronchiectasis. Thank you for your willingness to complete this questionnaire.

Instructions: The following questions are about the current state of your health, as you perceive it. This information will allow us to better understand how you feel in your everyday life.

Please answer all the questions. There are **no** right or wrong answers! If you are not sure how to answer, choose the response that seems closest to your situation.

Demographics *Please fill-in the information or check the box indicating your answer.*

A. What is your date of birth?
Date ☐☐/☐☐/☐☐☐☐
Mo Day Year

B. What is your gender?
☐ Male ☐ Female

C. During the **past week**, have you been on vacation or out of school or work for reasons **NOT** related to your health?
☐ Yes ☐ No

D. What is your current marital status?
☐ Single/never married
☐ Married
☐ Widowed
☐ Divorced
☐ Separated
☐ Remarried
☐ With a partner

E. Which of the following best describes your racial background?
☐ Caucasian
☐ African American
☐ Hispanic
☐ Asian/Oriental or Pacific Islander
☐ Native American or Native Alaskan
☐ Other (please describe) _____
☐ Prefer not to answer this question

F. What is the highest grade of school you have completed?
☐ Some high school or less
☐ High school diploma/GED
☐ Vocational school
☐ Some college
☐ College degree
☐ Professional or graduate degree

G. Which of the following best describes your current work or school status?
☐ Attending school outside the home
☐ Taking educational courses at home
☐ Seeking work
☐ Working full or part time (either outside the home or at a home-based business)
☐ Full time homemaker
☐ Not attending school or working due to my health
☐ Not working for other reasons/ Retired

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Table 10.1.1: 1 Quality of Life Questionnaire-Bronchiectasis, QOL-B (cont'd)

QOL-B QUALITY OF LIFE QUESTIONNAIRE - BRONCHIECTASIS

Section I. Quality of Life *Please check the box indicating your answer.*

During the past week, to what extent have you had difficulty:	A lot of difficulty	Moderate difficulty	A little difficulty	No difficulty
1. Performing vigorous activities, such as gardening or exercising	☐	☐	☐	☐
2. Walking as fast as others (family, friends, etc.)	☐	☐	☐	☐
3. Carrying heavy things, such as books, groceries, or shopping bags	☐	☐	☐	☐
4. Climbing one flight of stairs	☐	☐	☐	☐

During the past week, indicate how often:	Always	Often	Sometimes	Never
5. You felt well	☐	☐	☐	☐
6. You felt tired	☐	☐	☐	☐
7. You felt anxious	☐	☐	☐	☐
8. You felt energetic	☐	☐	☐	☐
9. You felt exhausted	☐	☐	☐	☐
10. You felt sad	☐	☐	☐	☐
11. You felt depressed	☐	☐	☐	☐

Are you currently on any treatments (such as oral or inhaled medications, PEP or Flutter® device, chest PT, or Vest) for bronchiectasis?

☐ Yes ☐ No (Go to Question 15 on the next page)

Please circle the number indicating your answer. Please choose only one answer for each question.

12. To what extent do your treatments for bronchiectasis make your daily life more difficult?
    1. Not at all
    2. A little
    3. Moderately
    4. A lot

13. How much time do you currently spend each day on your treatments for bronchiectasis?
    1. A lot
    2. A moderate amount
    3. A little
    4. Almost none

14. How difficult is it for you to fit in your treatments for bronchiectasis each day?
    1. Not at all
    2. A little
    3. Moderately
    4. Very

Continue to Next Page

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Table 10.1.1: 1 Quality of Life Questionna)ire-Bronchiectasis, QOL-B (cont'd)

QOL-B **QUALITY OF LIFE QUESTIONNAIRE - BRONCHIECTASIS**

Please circle the number indicating your answer. Please choose only one answer for each question.

15. How do you think your health is now?
    1. Excellent
    2. Good
    3. Fair
    4. Poor

Please select a box indicating your answer.

Thinking about your health during the past week, indicate the extent to which each sentence is true for you.

	Completely true	Mostly true	A little true	Not at all true	
16. I have to limit vigorous activities, such as walking or exercising	☐	☐	☐	☐	
17. I have to stay at home more than I want to	☐	☐	☐	☐	
18. I am worried about being exposed to others who are sick	☐	☐	☐	☐	Doesn't apply ☐
19. It is difficult to be intimate with a partner (kissing, hugging, sexual activity)	☐	☐	☐	☐	
20. I lead a normal life	☐	☐	☐	☐	
21. I am concerned that my health will get worse	☐	☐	☐	☐	
22. I think my coughing bothers others	☐	☐	☐	☐	
23. I often feel lonely	☐	☐	☐	☐	
24. I feel healthy	☐	☐	☐	☐	
25. It is difficult to make plans for the future (vacation, attending family events, etc.)	☐	☐	☐	☐	
26. I feel embarrassed when I am coughing	☐	☐	☐	☐	

Please circle the number or check the box indicating your answer.

During the past week:

27. To what extent did you have trouble keeping up with your job, housework, or other daily activities?
    1. You have had no trouble keeping up
    2. You have managed to keep up but it's been difficult
    3. You have been behind
    4. You have not been able to do these activities at all

	Always	Often	Sometimes	Never
28. How often does having bronchiectasis get in the way of meeting your work, household, family, or personal goals?	☐	☐	☐	☐

Continue to Next Page

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Table 10.1.1: 1 Quality of Life Questionnaire-Bronchiectasis, QOL-B (cont'd)

QOL-B QUALITY OF LIFE QUESTIONNAIRE - BRONCHIECTASIS

Section II. Respiratory Symptoms *Please check the box indicating your answer.*

Indicate how you have been feeling during the past week:	A lot	A moderate amount	A little	Not at all
29. Have you felt congestion in your chest?	☐	☐	☐	☐
30. Have you been coughing during the day?	☐	☐	☐	☐
31. Have you had to cough up mucus?	☐	☐	☐	☐

32. Has your sputum been mostly: ☐ Clear ☐ Clear to yellow ☐ Yellowish-green ☐ Brownish-dark ☐ Green with traces of blood ☐ Don't know

How often during the past week:	Always	Often	Sometimes	Never
33. Have you had shortness of breath with greater activity, such as housework or yardwork?	☐	☐	☐	☐
34. Have you been wheezing?	☐	☐	☐	☐
35. Have you had chest pain?	☐	☐	☐	☐
36. Have you had shortness of breath when talking?	☐	☐	☐	☐
37. Have you woken up during the night because you were coughing?	☐	☐	☐	☐

Please be sure you have answered all the questions.

THANK YOU FOR YOUR COOPERATION!

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10.1.2 St. George's Respiratory Questionnaire, SGRQ

Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE
ENGLISH FOR THE UNITED STATES

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you the most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please check one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ (cont'd)

St. George's Respiratory Questionnaire
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) *one box for each question*:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had wheezing attacks:	☐	☐	☐	☐	☐

5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?

Please check (✓) *one*:
- more than 3 times ☐
- 3 times ☐
- 2 times ☐
- 1 time ☐
- none of the time ☐

6. How long did the worst respiratory attack last?
(Go to Question 7 if you did not have a severe attack)

Please check (✓) *one*:
- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?

Please check (✓) *one*:
- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day was good ☐
- every day was good ☐

8. If you wheeze, is it worse when you get up in the morning?

Please check (✓) *one*:
- No ☐
- Yes ☐

USA / US English version 2

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Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ (cont'd)

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your respiratory condition?

Please check (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problems ☐

If you have ever held a job:

Please check (✓) *one*:

- My respiratory problems made me stop working altogether ☐
- My respiratory problems interfere with my job or made me change my job ☐
- My respiratory problems do not affect my job ☐

Section 2

These are questions about what activities usually make you feel short of breath <u>these days</u>.

For each statement please check (✓) *the box* that applies to you *these days*:

	True	False
Sitting or lying still	☐	☐
Washing or dressing yourself	☐	☐
Walking around the house	☐	☐
Walking outside on level ground	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or other physical activities	☐	☐

USA / US English version 3

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Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ (cont'd)

St. George's Respiratory Questionnaire
PART 2

Section 3

These are more questions about your cough and shortness of breath <u>these days</u>.

	For each statement please check (✓) *the box* that applies to you *these days*: True	False
Coughing hurts	☐	☐
Coughing makes me tired	☐	☐
I am short of breath when I talk	☐	☐
I am short of breath when I bend over	☐	☐
My coughing or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

These are questions about other effects that your respiratory problems may have on you <u>these days</u>.

	For each statement, please check (✓) *the box* that applies to you *these days*: True	False
My cough or breathing is embarrassing in public	☐	☐
My respiratory problems are a nuisance to my family, friends or neighbors	☐	☐
I get afraid or panic when I cannot catch my breath	☐	☐
I feel that I am not in control of my respiratory problems	☐	☐
I do not expect my respiratory problems to get any better	☐	☐
I have become frail or an invalid because of my respiratory problems	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.

	For each statement, please check (✓) *the box* that applies to you *these days:* True	False
My treatment does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My treatment interferes with my life a lot	☐	☐

USA / US English version 4

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Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ (cont'd)

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your respiratory problems.

For each statement, please check (✓) *the box* that applies to you ***because of your respiratory problems***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time to do it	☐	☐
I walk slower than other people my age, or I stop to rest	☐	☐
Jobs such as household chores take a long time, or I have to stop to rest	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	☐	☐

Section 7

We would like to know how your respiratory problems <u>usually</u> affect your daily life.

For each statement, please check (✓) *the box* that applies to you ***because of your respiratory problems***:

	True	False
I cannot play sports or do other physical activities	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do household chores	☐	☐
I cannot move far from my bed or chair	☐	☐

USA / US English version 5

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Table 10.1.2: 1 St. George's Respiratory Questionnaire, SGRQ (cont'd)

St. George's Respiratory Questionnaire

Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):

Going for walks or walking the dog

Doing activities or chores at home or in the garden

Sexual intercourse

Going to a place of worship, or a place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

It does not stop me from doing anything I would like to do ☐

It stops me from doing one or two things I would like to do ☐

It stops me from doing most of the things I would like to do ☐

It stops me from doing everything I would like to do ☐

Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.

USA / US English version 6

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10.1.3 Cough and sputum assessment questionnaire, CASA-Q

Table 10.1.3.: 1 Cough and sputum assessment questionnaire, CASA-Q

Cough And Sputum Assessment Questionnaire (CASA-Q)

- With this questionnaire, we would like to learn from you how your cough and your phlegm affect your day-to-day life.
- Please read each question carefully.
- Answer as best as you can without the help from anyone by marking the box that best corresponds to your answer (☒ or ☑).
- There are no right or wrong answers.
- All of the information you provide will be kept confidential.
- This questionnaire will take about 10 minutes to complete.

CASA-Q – US English version – v4.0

Table 10.1.3.: 1 Cough and sputum assessment questionnaire, CASA-Q (cont'd)

Cough

The following questions ask about your cough. Please try to think only about your cough when answering these questions.

1. Over the last 7 days, how much did you cough when you woke up in the morning?

Not at all	A little	Somewhat	Quite a bit	A lot
☐1	☐2	☐3	☐4	☐5

2. Over the last 7 days, how often did you cough during the day?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

3. Over the last 7 days, how often did you have coughing bouts?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

4. Over the last 7 days, how often were you tired after coughing?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

5. Over the last 7 days, how often did coughing make you short of breath?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

CASA-Q – US English version – v4.0

Table 10.1.3.: 1 Cough and sputum assessment questionnaire, CASA-Q (cont'd)

6. Over the last 7 days, how annoyed were you by your cough?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. Over the last 7 days, how often did you avoid going to public places because of your cough (for example, movie theaters, restaurants, etc)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

8. Over the last 7 days, how often were your usual activities interrupted by your cough (for example, driving, hobbies, working around the house)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

9. Over the last 7 days, how often did your cough interrupt your conversations with others (for example, phone conversations and face-to-face)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

10. Over the last 7 days, how often did your cough wake you up, prevent you from falling asleep or falling back to sleep?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

CASA-Q – US English version – v4.0

Table 10.1.3.: 1 Cough and sputum assessment questionnaire, CASA-Q (cont'd)

11. Over the last 7 days, how often were you uncomfortable about bothering other people while coughing?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

Phlegm

The following questions ask about your phlegm. Please try to think only about your phlegm when answering these questions.

12. Over the last 7 days, how thick was your phlegm?

Not at all	Slightly	Somewhat	Quite	Extremely
☐1	☐2	☐3	☐4	☐5

13. Over the last 7 days, how often did you bring up phlegm?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

14. Over the last 7 days, how often did your phlegm make it difficult for you to breathe?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

15. Over the last 7 days, how difficult was it for you to bring up phlegm?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

CASA-Q – US English version – v4.0

Table 10.1.3.: 1 Cough and sputum assessment questionnaire, CASA-Q (cont'd)

16. Over the last 7 days, how often did you feel uncomfortable about bothering other people while bringing up phlegm?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

17. Over the last 7 days, how annoyed were you by your phlegm?

Not at all	A little	Somewhat	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

18. Over the last 7 days, how often did your phlegm interfere with your ability to speak?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

19. Over the last 7 days, how often did your phlegm prevent you from going to public places (for example, movie theaters, restaurants, etc)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

20. Over the last 7 days, how often did you have to interrupt your usual activities to get rid of your phlegm (for example, driving, hobbies, working around the house)?

Never	Rarely	Sometimes	Often	Always
☐1	☐2	☐3	☐4	☐5

Thank you for your help.

CASA-Q – US English version – v4.0

10.2 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable

10.3 TRIAL BIOMARKER PLAN

Not applicable

10.4 VISIT MODIFICATION IN EXCEPTIONAL CIRCUMSTANCES

INITIAL / STANDARD	MODIFIED or ADDED
Face-to-face patient visit performed by a physician/under the responsibility of a physician on site.	Phone call or home visit performed by the investigational site physician/under the responsibility of the investigational site physician to ensure the wellbeing of a patient and to collect at least: Adverse Events and Concomitant Treatments.
Regular on-site safety lab test using central lab kits: • Haematology, Biochemistry, Electrolytes, Coagulation, Urinalysis as per Flow Chart. • At visits indicated in the Flow Chart, safety lab samples can be collected at local labs by using central lab kits)	• The results of the lab tests are to be reported and transferred to the investigator, who has to ensure medical review and proper documentation. • Decision whether to continue BI 1323495 treatment should be made based on an individual risk assessment for that individual patient and weigh up the benefits of an extended lab interval to maximum 2 weeks (3 weeks at the end of the treatment period) versus an interruption of treatment. The sponsor shoud be contacted for a joint decision. • Medical decision has to be documented in patient's source notes.
Dispensation of study treatment on site	• Site to patient IMP shipments • Patients must consent to providing contact details for shipping purposes • Patients should retain all unused IMP and packaging and return it when they are able to return to the site.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 Apr 2021
EudraCT number **EU number**		2019-003853-27
BI Trial number		1405-0008
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability, pharmacokinetics, and pharmacodynamics of different oral doses of BI 1323495 versus placebo in patients with non-cystic fibrosis bronchiectasis (randomised, double-blind, placebo-controlled, parallel group trial)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, Flowcharts, 2.1, 3.2, 4.1, 6.2, 7.4, 7.5
Description of change		Additional information and requirements for dosing of Part B, 150 mg qd in the morning was added
Rationale for change		Implementation of dosing for Part B
Section to be changed		Flowchart
Description of change		Explanation of visit procedures in more detail
Rationale for change		Correction. Visit 3 is no PK day, documentation of IMP administration in eCRF, timepoints of zymosan stimulation, compliance check of IMP only
Section to be changed		1.2.3, 4.2.2
Description of change		Due to new results being available from SRD study 1405-0001 and MRD study 1405-0002, updated information is added to this protocol, i.e. to substantiate the 150 mg qd dosing in Part B and to add new safety information
Rationale for change		Add addition PK and PD data
Section to be changed		1.4.2, 4.2.2
Description of change		Added that requirement of vaccination against Streptococcus pneumoniae should be in accordance with national vaccination recommendations. Added that BI 1323495 is not expected to affect the benefit/risk ratio of a COVID-19 vaccine
Rationale for change		Add information to Streptococcus p. and Covid-19

		vaccination
Section to be changed		3.3.2 Inclusion Criteria
Description of change		Specify that vaccination against Streptococcus pneumoniae is required in accordance with national vaccination recommendations
Rationale for change		Correction of wording for Streptococcus p. vaccination
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Exclusion Criterion #11 specified, and Exclusion Criterion #25 added
Rationale for change		Specify the patient population in more detail with respect to suspected malignancy or history of malignancy and history of allergy/hypersensitivity to trial medication
Section to be changed		4.15, 7.2.7
Description of change		Addition of unblinding possibility after an individual patient has been allocated to a treatment instead after completion of a trial part
Rationale for change		Specify blinding procedure
Section to be changed		5.2.3 Safety laboratory
Description of change		Manual differentials removed and Urinalysis specified
Rationale for change		Manual differential White Blood Counts are not required to be tested in this trial setting. Some parameters for urinalysis described in more detail
Section to be changed		[redacted]
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability, pharmacokinetics, and pharmacodynamics of different oral doses of BI 1323495 versus placebo in patients with non-cystic fibrosis bronchiectasis (randomised, double-blind, placebo-controlled, parallel group trial)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area [redacted]	[redacted]	26 Apr 2021 10:09 CEST
Approval-Team Member Medicine		26 Apr 2021 11:18 CEST
Author-Trial Clinical Pharmacokineticist		26 Apr 2021 11:47 CEST
Author-Trial Statistician		26 Apr 2021 12:14 CEST
Approval-Clinical Trial Leader		27 Apr 2021 09:07 CEST
Approval-Clinical Trial Leader		27 Apr 2021 12:37 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed