Clinical Trial Protocol

Boehringer Ingelheim

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EUCT No. **Universal Trial No.**	2024-511245-18-00 U1111-1304-2287
BI Trial No.	1305-0029
BI Investigational Medicinal Product	BI 1015550, nerandomilast
Title	Relative bioavailability of two different formulations of nerandomilast and investigation of the food effect on new formulation following oral administration in healthy adult male and female subjects (an open-label, randomised, single-dose, three-way crossover trial)
Lay Title	A study in healthy people to compare 2 different formulations of nerandomilast tablets when taken with or without food
Clinical Phase	I
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]
[redacted] **Investigator**	[redacted] Phone: [redacted] Fax: [redacted]
Current Version, Date	Version 2.0, 11 April 2025
Original Protocol Date	06 May 2024

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	06 May 2024
Revision date	11 April 2025
BI trial number	1305-0029
Title of trial	Relative bioavailability of two different formulations of nerandomilast and investigation of the food effect on new formulation following oral administration in healthy adult male and female subjects (an open-label, randomised, single-dose, three-way crossover trial)
[redacted] **Investigator**	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	BI plans to develop a paediatric formulation of nerandomilast for the treatment of fibrosing interstitial lung disease in paediatric patients. This trial is conducted to compare bioavailability between the paediatric and adult tablet formulations of nerandomilast, and to evaluate a potential food effect on the paediatric formulation (1 mg film-coated tablets).
Trial objective	To investigate the *i.* relative bioavailability of paediatric and adult tablet formulation under fasted condition. *ii.* effect of food on the pharmacokinetics of paediatric formulation
Trial endpoints	Primary endpoints: AUC_{0-tz} and C_{max} of nerandomilast Secondary endpoint: $AUC_{0-\infty}$ of nerandomilast
Trial design	Randomised, open-label, single dose, three-way crossover design
Number of subjects **total entered** **on each treatment**	 15 15
Diagnosis	Not applicable
Main inclusion criteria	Healthy male and female subjects, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)

Test product	Nerandomilast film-coated tablets, 1 mg (paediatric formulation)
dose	18 mg (18 x 1 mg film-coated tablets)
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h (T1*)* Oral with 240 mL of water after a high-calorie breakfast (T2)
Reference product	Nerandomilast film-coated tablet (Formulation C1), 18 mg (adult formulation)
dose	18 mg (1 film-coated tablet)
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 10 h (R)
Duration of treatment	Single dose of each treatment (R = 1 x 18 mg film-coated tablet, fasted, T1= 18 x 1 mg film-coated tablets, fasted, T2= 18 x 1 mg film-coated tablets, fed), separated by a washout phase of at least 7 days
Statistical methods	Relative bioavailability will be estimated by the ratios of the geometric means for the comparison of interest, i.e. T1/R or T2/T1, for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period and treatment. CIs will be calculated based on the residual error from the ANOVA. The statistical model will be applied only to data that contribute to the particular comparison of interest. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration)	Approximate clock time of actual day	Event and comment	Safety laboratory [7]	PK nerandomilast	12-lead ECG	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-21 to -1			Screening (SCR)[1]	x[A]		x	x	
1/2/3 (three identical periods separated by a wash-out of at least 7 days	2 / 3 / 4	-1	-12:00	20:00	Admission to trial site[8]	x[5,8]				x[8]
		1	-1:00	07:00	Allocation to treatment[2] (visit 2 only)		x[2]		x[2]	x[2]
			- 0:30	07:30	High fat, high calorie breakfast (treatment T2 only)					
			0:00	08:00	nerandomilast administration					
			0:30	08:30			x			
			0:45	08:45			x			
			1:00	09:00			x			
			1:15	09:15			x			
			1:30	09:30			x			
			1:45	09:45			x			
			2:00	10:00	240 mL fluid intake		x			
			2:30	10:30			x			
			3:00	11:00			x			
			4:00	12:00	240 mL fluid intake, thereafter lunch[3]		x			x
			6:00	14:00			x			
			8:00	16:00	Snack (voluntary)[3]		x			
			10:00	18:00			x			
			11:00	19:00	Dinner[3]					
			12:00	20:00			x			x
		2	24:00	08:00	Breakfast (voluntary) [3], discharge from trial site		x		x	x
			34:00	18:00	Ambulatory visit		x			x
		3	48:00	08:00	Ambulatory visit		x			x
			58:00	18:00	Ambulatory visit		x[10]			x[10]
		4	72:00	08:00	Ambulatory visit		x[10]			x[10]
		5	96:00	08:00	Ambulatory visit		x[10]			x[10]
FU	5	6 to 20[9]			End of study (EoS) examination[4]	x[B]		x	x	x

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, check of vital signs, ECG, safety laboratory (including drug screening and pregnancy test in women), demographics (including determination of body height and weight, smoking status and alcohol history trial subject`s age on the day of informed consent, subject's sex at birth, and ethnicity and race), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Pharmacogenetic samples will be collected if needed.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. If several actions are indicated at the same time, the intake of meals will be the last action.
4. At the end of study (synonym for end of trial), the EoS examination includes physical examination, vital signs, ECG, safety laboratory, pregnancy test in women, recording of AEs and concomitant therapies.
5. Only urine drug screening and alcohol breath test as well as pregnancy test in women will be done at this time
6. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
7. Letters A and B define different sets of safety laboratory examinations (see Section 5.2.3)
8. The time is an approximate. The procedure is to be completed no later than 10 hours prior to drug administration.
9. Referring to last study drug administration.
10. Starting from 58h after dosing a tolerance of +/- 120 minutes is given for all procedures

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ABBREVIATIONS AND DEFINITIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ALAT	Alanin-Aminotransferase
ANOVA	Analysis of variance
ATS	American Thoracic Society
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
cAMP	Cyclic adenosine monophosphate
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study (synonym for End of Trial)
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second

FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
gMean	Geometric mean
[redacted]	[redacted]
HR	Heart rate
IB	Investigator's brochure
iCF	Intended Commercial Formulation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IPD	Important protocol deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator site file
JRS	Japanese Respiratory Society
λ_z	Terminal rate constant of the analyte in plasma
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multiple Rising Dose
PCR	Polymerase chain reaction
PDE4B	Preferential inhibitor of the phosphodiesterase
PE	Polyethylene
PF-ILDs	Progressive fibrosing interstitital lung diseases
PKS	Pharmacokinetic set
PP	Polypropylene
PPF	Pulmonary Progressive Fibrosis
PR	Pulse rate
QT interval	ECG interval from the start of the QRS complex to the end of the T wave
QTc interval	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure

SRD	Single rising dose
SUSAR	Suspected unexpected serious adverse reaction
T	Test product or treatment
TEAE	Treatment-Emergent Adverse Event
TF2	Trial Formulation 2
TMF	Trial master file
TNF-α	Tumornekrosefaktor-α
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
t_z	Time of last measurable concentration of the analyte in plasma
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal

1. INTRODUCTION

Nerandomilast (BI 1015550), a preferential inhibitor of the phosphodiesterase 4B (PDE4B) isoenzyme which hydrolyzes and inactivates cyclic adenosine monophosphate (cAMP), is being developed by Boehringer Ingelheim (BI) for the treatment of Idiopathic Pulmonary Fibrosis (IPF) and Progressive Pulmonary Fibrosis (PPF).

1.1 MEDICAL BACKGROUND

IPF and other PF-ILDs share common pathophysiologic characteristics; alveolar epithelial cell injury and subsequent dysregulated repair, characterized by excessive deposition of extracellular matrix and loss of normal parenchymal architecture and lung function (P11-07084). In IPF, fibroblasts exhibit unregulated proliferation and differentiate into myofibroblasts. The latter is considered the hallmark cell in the development and establishment of lung fibrosis (P12-03241). Several growth factors are implicated in the proliferation, migration and transdifferentiation of the fibroblast and myofibroblast pool in pulmonary fibrosis.

Nerandomilast is an oral preferential inhibitor of the PDE4B with broad anti-inflammatory and antifibrotic activities. Based on its mode of action, as well as available pre-clinical and clinical data, nerandomilast is hypothesised to have complementary activity to current therapies in IPF and other forms of progressive pulmonary fibrosis.

1.2 DRUG PROFILE

1.2.1 Residual Effect Period of Nerandomilast

The Residual Effect Period (REP) of nerandomilast is 7 days. 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 nerandomilast profile, please refer to the current Investigator's Brochure (IB) [c02094779] nerandomilast.

1.2.2 Clinical Pharmacology Profile of Nerandomilast

The PK of nerandomilast was linear over all dose groups tested in SRD and MRD studies. After oral administration, nerandomilast is rapidly absorbed with peak plasma concentrations occurring at a median tmax around 1.25 h (range between 0.5-4 h) post-dose. The gMean t1/2 was approximately 10-17 h. After single and multiple oral doses, nerandomilast exposure (Cmax and AUC0-∞) appeared to increase dose proportionally. Steady state of nerandomilast was achieved by Day 4 of bid administration. Accumulation ratio based on Cmax and AUC were 1.30 and 1.38, respectively. Administration of nerandomilast together with food did not change the exposure to a clinically relevant extent.
In the human ADME (mass balance) study (1305-0016) following a single oral dose administration of [14C]nerandomilast, the total recovery of [14C]drug-related material was on average 95.0% of the administered dose with 58.0% excreted in faeces and 36.4% excreted in urine where 11.9% was excreted unchanged as parent compound [c36151567].

Exposures are slightly higher in Asian healthy subjects (around 1.5-fold) compared to Caucasian healthy subjects, likely due to lower body weight rather than a race effect. The impact of renal or hepatic impairment on nerandomilast exposure was not substantial. Compared with healthy subjects with normal renal and hepatic function, AUC was increased by 29-37% in subjects with moderate and severe renal impairment and increased by 31% in subjects with moderate hepatic impairment Child-Pugh B (no relevant change in subjects with Child-Pugh A).
Nerandomilast is mainly metabolized by CYP3A with contributions from UGTs. Chiral inversion from administered pharmacologically active R-enantiomer to inactive S-enantiomer occurs to a small extent (11%) in human also via metabolism. Administration of nerandomilast together with a strong CYP3A4 inhibitor itraconazole increased nerandomilast AUC by 2.2-fold and Cmax by 1.3-fold. Furthermore, nerandomilast did not induce CYP3A enzyme based on the clinical DDI study with midazolam [c40607236].
Results from the Phase II trial 1305-0013 in patients with IPF showed that pre- and post-dose concentration levels of nerandomilast (measured via non-chiral bioanalytical method) were similar between patients treated with nintedanib and those not treated with any antifibrotic, suggesting nintedanib did not impact the exposure of nerandomilast. However, a 35-50% lower exposure was observed in IPF patients on background treatment with pirfenidone [c37065416].

1.2.3 Overview of Safety of Nerandomilast

Data from non-clinical studies
The toxicity profile for nerandomilast has been assessed in safety pharmacology studies, genetic toxicology studies, and repeat dose studies in the rat, minipig, and monkeys of up to 13, 26, and 39 weeks, respectively.
Vasculopathy and mortality secondary to vasculopathy are the primary findings defining the no adverse effect level (NOAEL) and lowest observed adverse effect Level (LOAEL) in the rat and minipig, respectively.
In contrast, vascular changes were not observed in a 39-week monkey study at 30 mg/kg/day, supporting the decreased sensitivity of primates to PDE4i-induced vascular changes.
Vasculopathy is a well characterized class-effect pathology associated with PDE4 inhibitors [R10-1559] and has not been demonstrated in humans administered marketed PDE4i apremilast and roflumilast

In addition, a fertility and early embryonic development (rat) and embryo-fetal development toxicity studies (rat and rabbit) were conducted. Decreased mating, fertility, and pregnancy indices were observed in male and female rats at a dose level that also level caused evidence of severe toxicity in both sexes. In rats but not in rabbits foetal loss was increased. Teratogenicity and fetotoxicity was not observed. In long-term toxicity studies in rats (26-weeks), minipig and monkeys (13-weeks) there was no microscopic evidence of changes in female reproductive organs or on male spermatogenesis. Sporadic menstrual cycle prolongation was observed in the 39-week NHP toxicology study in females at exposures corresponding to approximately ≥4- fold human exposure at 18 mg bid. Menstrual cycles were not affected in monkeys at exposures equivalent to humans.

toxicity similar to the observations made for nerandomilast with respective labellingFor more details, please refer to the current Investigator's Brochure (IB) (c02094779).

Data from clinical studies
A total of 13 clinical studies in healthy volunteers have been completed with nerandomilast. Overall, 271 healthy volunteers have been exposed to nerandomilast: 222 subjects to single-dose administration with up to 48 mg and 49 subjects to multiple administrations for up to 14 days with up to 18 mg bid.

Clinical safety in healthy subjects

Overall, nerandomilast, up to a 48 mg single-dose and 18 mg bid multiple-dose appeared to show acceptable safety and tolerability. The most common AEs were nervous system events, particularly headache, and GI events, particularly diarrhoea and abdominal pain. Overall, no clear dose-dependency in the frequency and intensity of these AEs was observed. (c02094779) No severe, serious, fatal events or suspected unexpected serious adverse reactions (SUSARs) have been reported in healthy volunteers.

In the SRD trial single doses up to 24 mg nerandomilast have been tested (54 subjects on active treatment + 16 subjects on placebo in total). AEs were reported by 27 of 70 subjects. The most frequent AE to be reported was headache in 9 subjects, followed by diarrhea in 3 subjects. A total of 9 subjects were reported with drug related AEs. [U13-1792-01]

In another trial (1305-0011) single doses of 36 mg and 48 mg nerandormilast (6 subjects on active treatment + 3 subjects on placebo in each DG) and multiple doses of 6 mg bid and 12 mg bid, administered for 11 days followed by a morning dose on the next day (8 subjects on active treatment + 4 subjects on placebo in each DG) have been tested in healthy subjects. In the SRD part AEs related to the intake of nerandomilast were reported by 3 of 12 subjects (48 mg DG only). The most frequent drug related AE was headache reported by 3 subjects. Further drug related AEs comprise diarrhoea, abdominal distension, upper abdominal pain, constipation, and nausea. [c22991937].

The trial 1305-0033 (DDI with midazolam) investigated the CYP3A induction potential of BI 1015550, which required the administration of the expected therapeutic dose (18 mg bid) over 14 days to healthy subjects. Drug related AEs were reported by 9 of 15 subjects and comprise myalgia (3 subjects), diarrhoea (2x), headache (2x), flatulence (2x) and hyperaesthesia (1x). All these AEs were of mild intensity. No relevant changes of lab values, vital signs and ECG parameters have been reported [c40607236, draft report].

Clinical safety in patients

Two clinical trials have been completed in patients with IPF:
A Phase 1c study of nerandomilast at 18 mg twice daily in patients with IPF not on background antifibrotic therapy showed similar PK to healthy volunteers along with an acceptable safety and tolerability profile. A total of 10 patients were treated with nerandomilast 18 mg bid and 5 patients were treated with placebo.

The most frequently reported AEs by system organ class were gastrointestinal disorders. Gastrointestinal disorders were more frequent in the nerandomilast group (8 patients, 80%) than in the placebo group (2 patients, 40%). On preferred term level, diarrhoea and flatulence were the most frequently reported gastrointestinal disorders; they occurred with similar incidences in both treatment groups (diarrhoea: 40% each in nerandomilast and Placebo group, flatulence: 30% in nerandomilast, 20% in placebo group). SAEs were reported for 1 patient (anal fistula and anal incontinence) that were related to a long-lasting pre-existing condition and subsequent elective surgery. No fatal events were reported (c25085412).

Treatment with nerandomilast at 18 mg twice daily in a Phase II proof-of-concept trial preserved lung function in patients with IPF over a period of 12 weeks, either as a monotherapy or on top of approved antifibrotic standard of care (nintedanib or pirfenidone). nerandomilast showed acceptable safety and tolerability in the overall study population and in the subgroups of patients without or with background antifibrotic treatment.

In this trial 97 patients were exposed to nerandomilast and 50 patients to placebo. The most frequently reported AEs were gastrointestinal disorders (32.0% in the nerandomilast group, 24.0% in the placebo group). Diarrhea was the most common AE, with a higher frequency in the nerandomilast group (23.7%) than in the placebo group (12.0%) and diarrhea was also the most common event leading to treatment discontinuation (3 patients, all in the nerandomilast group and all on background treatment with nintedanib). However, the majority of diarrhea events were mild in intensity.
AEs leading to discontinuation of trial treatment were only observed in the nerandomilast treatment group. Apart from the mentioned 3 patients with diarrhoea and 2 patients with Covid-19, all events occurred in single patients without any pattern or cluster.

Serious adverse events were reported in 10.0% of patients in the placebo group and 6.2% of patients in the nerandomilast treatment group. There were two events with fatal outcome in the nerandomilast treatment group, one patient with Covid-19 pneumonia and one patient with suspected IPF exacerbation and suspected vasculitis (the diagnosis of vasculitis could not be confirmed by the sponsor nor the independent external data monitoring committee). Risk factors were present in both fatal events.

There were no clinically relevant changes in vital signs (including body weight) and/or ECG parameters (including QTc) observed. No changes in the Columbia Suicidal Severity Rating Scale (C-SSRS) and no AEs of suicidal ideation or behaviour were reported during trial treatment (c37065416).

For a more detailed description of the nerandomilast profile, please refer to the current Investigator's Brochure (IB) (c02094779).

1.2.4 Clinical Experience with other PDE4 inhibitors

Selective PDE4 inhibitors have been approved for chronic obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbations (roflumilast), and for moderate to severe plaque psoriasis and active psoriatic arthritis (apremilast).

Roflumilast has been tested in Phase III studies for asthma and apremilast in Phase III studies for active Behcet's disease. No PDE4 inhibitor has been tested in IPF, yet.

Roflumilast
Only one PDE4 inhibitor, roflumilast (Daxas® in EU, Daliresp® in US), has received marketing authorization by regulatory agencies for a respiratory indication, COPD.
More than 5,000 patients with COPD were included in the "COPD Safety Pool" of the large roflumilast clinical development program. The most frequently reported AEs associated with the treatment with roflumilast were diarrhoea, weight loss, nausea, abdominal pain and headache followed by insomnia, dizziness and decreased appetite.
The most common AEs leading to withdrawal in approximately 14% of the patients treated with roflumilast were nausea, diarrhoea and headache. The rate of withdrawal due to AEs among patients receiving placebo was 9%.
The mechanism of weight loss, which was observed in approximately 7% of the patients receiving roflumilast, is not fully understood (R10-1555).
The SPCs of Daxas®/Daliresp®, recommend the close monitoring of patient's body weight and its cautious use in patients with previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products, which are likely to cause psychiatric events, is intended.

Apremilast
One PDE4 inhibitor for treatment of active psoriatic arthritis (Otezla®) has been approved by the FDA on March 2014, in September 2014 for moderate to severe plaque psoriasis and in July 2019 for the treatment of oral ulcers associated with Behçet's disease.
Otezla® has been evaluated in 1493 patients with active psoriatic arthritis in three randomised placebo-controlled studies (R17-1427).
The most common adverse reactions were diarrhoea, headache and nausea, followed by vomiting, upper respiratory tract infection, nasopharyngitis and abdominal pain.
The most common adverse reactions leading to discontinuation were diarrhoea (1.8%), nausea (1.8%) and headache (1.2%).

The proportion of patients with psoriatic arthritis who discontinued treatment due to any adverse reaction was 4.6% for patients taking Otezla® 30 mg twice daily and 1.2% for placebo-treated patients.
The product information of Otezla® recommends the close monitoring of patient's body weight and its cautious use in patients with history of depression and/or suicidal thoughts or behaviour (R14-1795).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Nerandomilast 18 mg film-coated tablet (Formulation C1) is currently used in two Phase 3 safety and efficacy trials in adult patients. A new formulation, 1 mg film-coated tablet, has been developed and is planned to be used in paediatric trial evaluating nerandomilast in paediatric fibrosing ILD patients. This trial is conducted to show the relative bioavailability of the 18 mg film-coated tablet of nerandomilast and 18 tablets of a new formulation of 1 mg film-coated tablets of nerandomilast. In addition, the food effect of the new formulation will be evaluated.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of paediatric formulation.

1.4.2 Risks

Subjects are exposed to risks of trial procedures and risks related to the exposure to the trial medication. An overview of trial-related risks is given in Table 1.4.2: 1.

There are no identified risks for nerandomilast, based on the toxicology program or any clinical trials conducted for this product to date. Vasculitis and foetal loss are considered as important potential risk based only on nonclinical findings (see Section 1.2.1).
The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs and from preclinical and clinical data of compounds with a comparable mode of action (see Section 1.2.3). For adverse events reported during clinical trials with nerandomilast please refer to Section 1.2.1.

Table 1.4.2: 1 Overview of trial-related risks for this trial

Possible or known risks of clinical relevance	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: nerandomilast		
Vasculitis	• Vasculopathy is an established preclinical toxicity of PDE 4 inhibitors • Vasculitis has been shown in rats and minipigs following oral administration of nerandomilast but not in monkeys • Vasculitis is listed as an important potential risk for the marketed PDE4 inhibitor apremilast • In marketed PDE4 inhibitors, vasculitis has not been identified as an adverse drug reaction in humans.	• The risk in a single dosing trial is considered to be very low. • Active vasculitis (unstable or uncontrolled) is an exclusion criterion for participants. • Close monitoring for AEs of vasculitis. • Treatment discontinuation in case of suspected vasculitis.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Reproductive toxicity: foetal loss, decreased fertility	• No teratogenicity was seen in 2 species in preclinical studies and exposure with nerandomilast via the semen is expected to be very low. • In rats, male and female fertility was potentially reduced. Long term toxicity studies with nerandomilast in rat and monkey showed no microscopic evidence of changes in female reproductive organs or male spermatogenesis. For another PDE4 inhibitor with comparable nonclinical findings, clinical data showed no effect on male fertility and sperm in humans. • In monkeys, a sporadic prolongation in menstrua cycles was observed at approximately ≥ 4-fold human exposure at 18 mg nerandomilast bid. • Fetal loss was increased in female rats treated with nerandomilast.	• Women of childbearing potential (WOCBP) need to use a highly effective method of contraception. • WOCBP taking oral contraceptives (OCs) also have to ensure the use of one barrier method during sexual intercourse with their partner, e.g., condom to account for the risk of potentially reduced efficacy of the OCs in the event of severe vomiting and diarrhoea • Pregnancy testing for WOCBP • Treatment discontinuation in case of pregnancy
Weight decrease in underweight patients (BMI < 18.5 kg/m2)	• For the marketed PDE4i apremilast and roflumilast weight loss in underweight participants is an identified important risk • Presumably caused by increased energy expenditure and causing predominately loss of body fat.	• With single dosing, the risk is considered to be negligible. • Only participants with BMI > 18.5 kg/m2 will be included.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Psychiatric disorders: • Depression and anxiety • Suicidality	For the marketed PDE4i depression is listed as side effect and they are associated with increased risk of depression with some patients reporting suicidal ideation and attempts and also with some reported cases of completed suicide.	• The risk after a single administration nerandomilast is considered very low and will be addressed by careful close clinical monitoring for AEs and increased awareness by the investigator for signs and symptoms of depression and anxiety as well as for signs and symptoms of suicidal ideation and behavior • Only participants with no relevant medical history including psychiatric disorders will be enrolled • Treatment discontinuation in case of signs for suicidality
Severe infections including, serious, opportunistic and mycobacterium tuberculosis infections	• Inhibition of the immune response due to the anti-inflammatory mode of action of nerandomilast potentially increases the risk of severe and serious infections. • Serious infections were balanced between placebo and nerandomilast in Phase II trial • Nasopharyngitis was more frequently reported under treatment with nerandomilast in Phase Ic/II but not in Phase I trials and the numbers were very small.	• This risk is considered to be low in a single dosing trial • Participants with any relevant chronic or acute infections are excluded from the trial • Treatment of infections should be initiated promptly according to standards of care

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Major Adverse Cardiovascular Events (MACE) and tachyarrhythmia	• Important potential risk for marketed PDE4 inhibitor apremilast. • In preclinical studies with nerandomilast no adverse cardiovascular findings detected. • In clinical trials with nerandomilast no relevant findings were observed.	• The risk in a single dosing trial is considered to be very low. • Only healthy subjects without relevant cardiovascular risk factors will be included
Malignancies	• Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus, theoretically decrease immune defence against malignancies.	• The risk in a single dosing trial is considered to be very low. • Participants with a recent history of malignancy within 5 years will be excluded from participation in this trial.
Gastrointestinal disorders (e.g., diarrhoea, nausea, vomiting, abdominal pain)	• Vomiting and diarrhoea are important dose-limiting side effects of marketed oral PDE-4 inhibitors. • In Phase II study nerandomilast, diarrhoea was the most frequently reported AE.	• The risk in a single dosing trial is considered to be low. • Careful monitoring and symptomatic treatment if required
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 subjects´ safety.
<u>Trial procedures</u>		
Inflammation of the wall of the vein. Injuring of a nerve while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	General risk by venipuncture for blood sampling, acceptable in the framework of trial participation.	Evaluation of the medical expertise of the trial sites is part of site feasibility assessment. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Table 1.4.2: 1 Overview of trial-related risks for this trial (cont.)

Skin irritation, redness, itching	General risk by ECG electrodes, acceptable in the framework of trial participation.	Exclusion of subjects from trial participation with known clinically relevant hypersensitivity reactions to adhesive tapes

The total volume of blood withdrawn per subject during the entire trial will not exceed the volume of a normal blood donation (500 mL). No health-related risk to healthy subjects is expected from withdrawal of this volume of blood.

1.4.3 Discussion

The nature of the target and the mechanism of action of nerandomilast is well understood. Based on its mode of action, nerandomilast is hypothesized to have complementary activity to current therapies in IPF.
In the context of the unmet medical need and anticipated benefit of nerandomilast, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is favourable.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the relative bioavailability of 1 x 18 mg of nerandomilast film-coated tablet (Formulation C1, adult formulation) compared with 18 x 1 mg of nerandomilast film-coated tablets (paediatric formulation) and the effect of food on the PK of paediatric formulation following oral administration.

2.1.2 Primary endpoints

The following pharmacokinetic parameters will be determined for nerandomilast:

- $AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)
- C_{max} (maximum measured concentration of the analyte in plasma)

2.1.3 Secondary endpoint

The following pharmacokinetic parameter will be determined for nerandomilast:

- $AUC_{0\text{-}\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

[redacted]

2.2.2.2 Safety and tolerability

Safety and tolerability of nerandomilast will be assessed based on:

- Adverse events (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- Vital signs (blood pressure, pulse rate)
- ECG

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as a randomised, open-label, three-way crossover trial in healthy male and female subjects in order to compare the test treatment 1 (T1) to the reference treatment (R) and to compare test treatment 2 (T2) to test treatment 1 (T1) .

The treatments will be

- one 18 mg nerandomilast film-coated tablet, adult formulation, administered to subjects in the fasting state (R)
- eighteen 1 mg nerandomilast film-coated tablets, pediatric formulation, administered to subjects in the fasting state (T1)
- eighteen 1 mg nerandomilast film-coated tablets, pediatric formulation, administered to subjects in the fed state (T2)

The subjects will be randomly allocated to one of the 3 treatment sequences: R-T1-T2, T1-T2-R, or T2-R-T1. There will be a washout period of at least 7 days between the treatments (referring to day 1). In each treatment period (1, 2, 3), the subject is planned to receive 1 single dose of medication (R, T1, or T2). See Figure 3.1.: 1

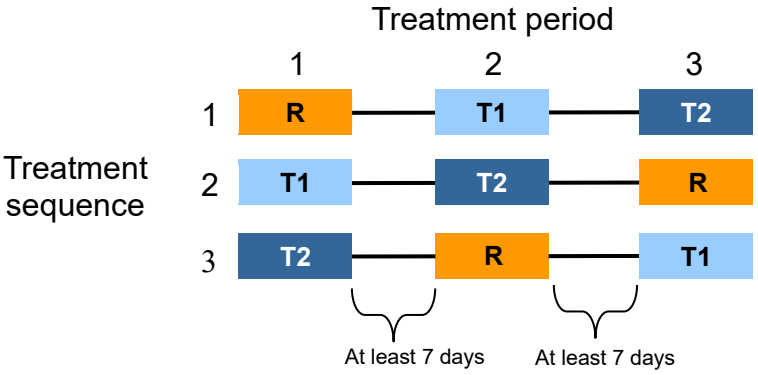

Figure 3.1: 1 Trial design

For details on the treatments, refer to Section 4.1.

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

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

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his/her own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments [R94-1529].

The open-label treatment is not expected to bias results, since the trial endpoints are derived from measurement of plasma concentrations of the analyte, which are provided by a bioanalytical laboratory that is blinded to treatment allocation.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 15 healthy male and female subjects will enter the trial. They will be recruited from the volunteers' pool of the trial site.

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

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

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. Healthy male or female subjects according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests

2. Age of 18 to 55 years (inclusive)

3. BMI of 18.5 to 29.9 kg/m^2 (inclusive)

4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

5. Either male subject, or female subject who meet any of the following criteria for a highly effective contraception from at least 30 days before the first administration of trial medication until 30 days after trial completion:

    - Use of combined (estrogen and progestogen containing) hormonal contraception that prevents ovulation (oral, intravaginal or transdermal), *plus condom*

    - Use of progestogen-only hormonal contraception that inhibits ovulation (only injectables or implants*), plus condom*

    - Use of intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)

- Sexually abstinent
- A vasectomised sexual partner who received medical assessment of the surgical success (documented absence of sperm) and provided that partner is the sole sexual partner of the trial participant
- Surgically sterilised (including hysterectomy)
- Postmenopausal, defined as no menses for 1 year without an alternative medical cause (in questionable cases a blood sample with levels of FSH above 40 U/L and estradiol below 30 ng/L is confirmatory)

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Relevant chronic or acute infections
10. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)

13. Intake of an investigational drug in another clinical trial within 60 days of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
17. Drug abuse or positive drug screening
18. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
19. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
20. Inability to comply with the dietary regimen of the trial site
21. A marked prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening
22. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
23. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
24. Male subjects with WOCBP partner who are unwilling to use male contraception (condom or sexual abstinence) from time point of first administration of trial medication until 7 days after the last administration of nerandomilast
25. For female subjects: Lactation, pregnancy, or plans to become pregnant during the trial or within 30 days after trial completion
26. For female subjects: Positive pregnancy test
27. Active vasculitis, unstable or uncontrolled within 8 weeks prior to enrolment

For restrictions of the trial, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may withdraw or may be removed from trial treatment or may 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.

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

If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, trial data will be included in the CRF and will be reported in the CTR.

Following removal or withdrawal, a complete end-of-trial examination should be performed. If the discontinuation or withdrawal occurs before the end of the REP (see Section 1.2.1), the discontinued subject should, if possible, be questioned for AEs and concomitant therapies at or after the end of the REP, in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1 Withdrawal from trial treatment

An individual subject will be withdrawn from trial treatment if:

1. The subject wants to withdraw from trial treatment. The subject will be asked to explain the reasons but has the right to refuse to answer
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, the safety of the subject cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, adverse events (AEs), or diseases)
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

If any of the following adverse events is reported, the treatment has to be discontinued:

- Severe or serious infections, opportunistic or mycobacterium tuberculosis infection
- Vasculitis
- Occurrence of malignancies other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix
- Suicidal ideation or behaviour

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

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy.

The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For reporting of pregnancy and associated events, refer to Section 5.2.6.2.3.

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

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial at any time for any of the following reasons (if reasons 4 and/or 5 are met, the trial should be discontinued immediately):

- Failure to meet expected enrolment goals overall or at a particular trial site
- The sponsor decides to discontinue the further development of the investigational products
- Deviation from GCP, or the CTP impairing the appropriate conduct of the trial
- New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment (see Section 3.3.4.1)
- More than 50% of the subjects show drug-related and clinically relevant adverse events of moderate or severe intensity in one treatment periods or if at least one drug-related serious adverse event is reported in the trial

3.3.5 Replacement of subjects

In case more than 3 subjects do not complete the trial (including subjects non- evaluable for PK), subjects may be replaced if considered necessary to reach the objective of the trial. Subjects who withdraw or are withdrawn from treatment or assessments because of a drug-related adverse event will not be replaced. The Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. The total number of replacements may not exceed 5 subjects. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment sequence as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product (T) are given below:

Substance:	nerandomilast
Pharmaceutical formulation:	film-coated tablets
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	1 mg
Posology:	18-0-0
Mode of administration:	Oral
Duration of use:	single dose

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

Substance:	nerandomilast
Pharmaceutical formulation:	film-coated tablet, formulation C1
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	18 mg
Posology:	1-0-0
Mode of administration:	Oral
Duration of use:	single dose

4.1.2 Selection of doses in the trial

18 mg bid of nerandomilast is one of the doses that is currently used in Phase 3 clinical trials. For the investigation of relative bioavailability and food effect using single dose is sufficient.

4.1.3 Method of assigning subjects to treatment groups

The randomisation scheme will be provided to the trial site in advance.

Subjects will be allocated to treatment sequences prior to the first administration of trial medication in the morning of Day 1 of Visit 2. For this purpose, numbers of the randomisation scheme will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation scheme.

Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g., due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable

For discussion of trial-associated risks and safety measurements, see Section 1.4.

The randomisation procedure is described in Section 7.4.

4.1.4 Drug assignment and administration of doses for each subject

This is a 3-way crossover trial. All subjects will receive the 3 treatments in randomised order. The treatments to be evaluated are summarised in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Unit strength	Dosage for a single application	Metabolic state	Total dose
T1 (Test 1)	nerandomilast	film-coated tablet (paediatric)	1 mg	18 tablets	Fasted	18 mg
T2 (Test 2)	nerandomilast	film-coated tablet (paediatric)	1 mg	18 tablets	Fed	18 mg
R (Reference)	nerandomilast	film-coated tablet formulation C1 (adult)	18 mg	1 tablet	Fasted	18 mg

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Administration of trial medication in two treatment periods (T1 and R) will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. Furthermore, subjects in these periods will continue to fast 4 additional hours after the dose administration.
In treatment period receiving T2, the subjects will consume a high-fat, high-calorie meal within 30 min before drug administration. The subjects must completely consume the meal prior to drug intake. The composition of the standard high-fat, high-calorie meal is detailed in Table 4.1.4: 2; this meal is in compliance with the FDA guidance 'Food-Effect Bioavailability and Fed Bioequivalence Studies' [R03-2269]. For restrictions with regard to diet, see Section 4.2.2.2.

Table 4.1.4: 2 Composition of the high-fat, high-calorie meal

Ingredients	kcal
2 chicken eggs (whole content) for scrambled eggs	192
10 g butter for frying scrambled eggs	75
35 g fried bacon	186
2 toasted slices of wheat bread	130
15 g butter for buttering toast slices	113
115 g hash brown potatoes	132
240 mL whole milk (3.5% fat)	156
Sum[1]	984

[1] The total caloric content was supplied approximately as following: 150 kcal as protein, 250 kcal as carbohydrate, and 500 to 600 kcal as fat.

Subjects will be kept under close medical surveillance until 24 h after drug administration. During the first 4 h after drug administration, subjects are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture).

The treatments will be separated by a wash-out phase of at least 6 days.

4.1.5 Blinding and procedures for unblinding

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

Table 4.1.5: 1 Blinding level of individual functions

Role/function	**Timing of receiving access to the treatment information**
Subject/Participant	As soon as treatment sequence has been assigned.
Investigator/Site Staff	The randomization scheme will be provided to the trial site prior to setup.
Sponsor trial team and data	Unblinded as requested.
Bioanalytical Staff	Persons directly involved in bioanalyses of PK samples will be blinded to trial treatments.
Pharmacokineticist/ Pharmacometrician	Unblinded as requested for analysis.

During the time a role/function is blinded according to the table above, the randomisation schemes (i.e., the treatment information) are kept restricted by the global Randomization Team per Sponsor SOP.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packing and the description of the label, refer to the ISF.

The labels will be prepared according to Regulation (EU) No 536/2014, Annex 6 omitting certain particulars with the following justifications:

- The visit number is not relevant for the label because the product will remain at the clinical site.
- The investigator name was omitted from the label because it is included on the Trial Identification Card, which will be issued to each trial participant.
- The "keep out of reach of children" statement was omitted from the label because the product will remain at the clinical site

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. The EudraCT number is indicated on the title page of this protocol as well as on the subject information and informed consent forms.

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area in accordance with the recommended (labelled) storage conditions. If necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the Clinical Research Associate (as provided in the list of contacts) is to be contacted immediately.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee
- 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

Only authorised personnel documented in the form 'Trial Staff List' may dispense investigational drugs to trial subjects. Investigational drugs are not allowed to be used outside of this protocol.

The investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the disposal of unused products.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused medication will be disposed of locally by the trial site upon written authorisation of the Clinical Trial Leader. Receipt, usage and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. In particular strong CYP3A inhibitors are restricted medication due to potential drug-drug interactions. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardised meals will be served at the times indicated in the Flow Chart. No food is allowed for at least 4 h after drug intake.

From 1 h before drug intake until lunch, fluid intake is restricted to the milk served with breakfast (see Table 4.1.4: 2), to the water administered with the drug, and an additional 240 mL of water at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3000 mL.

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

Alcoholic beverages are not permitted starting 48 h before first trial drug administration until last PK sampling of each trial period.

Poppy seeds containing products should not be consumed starting 3 days before first trial drug administration until last PK-sampling of the trial.

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

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

Smoking is not allowed during in-house confinement.

4.2.2.3 Contraception requirements

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see Section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At screening, the medical examination will include demographics, height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination.

At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination and an AE/CT questioning.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate) will be measured by a blood pressure monitor (Dinamap Pro 100, [redacted] at the times indicated in the Flow Chart, after subjects have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm, if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the times indicated in the Flow Chart after the subjects have fasted for at least 10 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters to be assessed are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

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

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A	B
Haematology	Haematocrit	X	X
	Haemoglobin	X	X
	Red Blood Cell Count/Erythrocytes	X	X
	White Blood Cells/Leucocytes	X	X
	Platelet Count/Thrombocytes (quant)	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs)/Leukocytes; Neut. Poly (segs), absol.; Neutrophils Bands/Leukocytes; Neutrophils Bands, absol.; Eosinophils/Leukocytes; Eosinophils, absol.; Basophils/ Leukocytes; Basophils, absol.; Monocytes/Leukocytes; Monocytes, absol.; Lymphocytes/Leukocytes; Lymphocytes, absol.		
Coagulation	Activated Partial Thromboplastin Time	X	X
	Prothrombin time (Quick)	X	X
	Prothrombin time – INR (International Normalization Ratio)	X	X
Enzymes	AST [Aspartate aminotransferase] /GOT, SGOT	X	X
	ALT [Alanine aminotransferase] /GPT, SGPT	X	X
	Alkaline Phosphatase	X	X
	Gamma-Glutamyl Transferase	X	X
Hormones	Thyroid Stimulating Hormone	X	--
Substrates	Glucose (Plasma)	X	X
	Creatinine	X	X
	Bilirubin, Total	X	X
	Bilirubin, Direct	X	X
	C-Reactive Protein (Quant)	X	X
Electrolytes	Sodium	X	X
	Potassium	X	X
Urinalysis (Stix)	Urine Nitrite (qual)	X	X
	Urine Protein (qual)	X	X
	Urine Glucose (qual)	X	X
	Urine Ketone (qual)	X	X
	Urobilinogen (qual)	X	X
	Urine Bilirubin (qual)	X	X
	Urine HGB (qual)	X	X
	Urine Leucocyte esterase (qual)	X	X
	Urine pH	X	X
Urine sediment (microscopic)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)		

A: parameters to be determined at Visit 1 (screening examination)
B: parameters to be determined at Visit 5(end of trial examination)

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

planned to perform these tests. Pregnancy testing in women will be performed at screening, prior to each treatment period, and as part of the end of trial examination. Drug screening will be performed at screening and prior to each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
Pregnancy test (urine)	Beta human chorionic gonadotropin (beta-HCG)

To encourage compliance with alcoholic restrictions, a breath alcohol test (e.g. AlcoTrue® M, [redacted]) will be performed prior to each treatment period, and may be repeated at any time during the trial at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at [redacted] with the exception of drug screening and pregnancy tests. These tests will be performed at the trial site using M-10/14-PDT Surestep Multiline test and Cleartest® Diagnostik HCG test, respectively, or comparable test systems. If a quantitive confirmation of the drug screening is needed this also may be performed by [redacted]

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

It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator are to 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 5.2.6.1.4).

5.2.4 Electrocardiogram

Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (CardioSoft EKG System, [redacted] at the times provided in the Flow Chart.

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

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG assessment will always precede all other trial procedures scheduled for the same time to avoid compromising ECG quality.

All ECGs will be stored electronically on the Muse CV Cardiology System ([redacted]). Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

All locally printed ECGs will be evaluated by the investigator or a designee. Abnormal findings will be reported as AEs (during the trial) or baseline conditions (if identified at the screening visit) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

ECGs may be repeated for quality reasons (for instance, due to alternating current artefacts, muscle movements, or electrode dislocation) and the repeated ECG will be used for analysis. Additional (unscheduled) ECGs may be collected by the investigator for safety reasons.

5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 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 upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

SUSAR

A suspected unexpected serious adverse reaction (SUSAR) is an untoward and unintended response to a study drug. A SUSAR should be considered as unexpected if the nature, seriousness, severity, or outcome of the reaction is not consistent with the reference safety information of the investigational drug (e.g. the investigator's brochure, or the corresponding defined local label such as the summary of product characteristics).

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 eDC system, an electronic data capture system which allows the entry of trial data at the trial site. 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 must be classified as a serious event regardless of the time since discontinuation of the trial medication 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:

- Potential severe DILI
  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:
  1. AST (aspartate aminotransferase) and/ or ALT (alanine aminotransferase) elevation ≥3x ULN and TB (total bilirubin) ≥2x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
  2. AST and/ or ALT elevation ≥3x ULN and INR ≥1.5x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
  3. AST and/ or ALT elevation ≥3x ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/ or eosinophilia (>5%), OR
  4. AST and/ or ALT elevation ≥5x ULN

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

5.2.6.1.5 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 judgment should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given trial 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
- There is an 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

Upon enrolment into a trial, the subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?'. Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A carefully written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, intensity of the event, and any treatment or action required for the event and its outcome.

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, SUSAR, AESIs, and non-serious AEs which are relevant for the reported SAE, SUSAR or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country specific reporting process will be provided in the ISF. The same timeline applies if follow-up information becomes available. On specific occasions, the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information, the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after the individual subject's end of trial, must be followed up until they have resolved, have been sufficiently characterized (e.g. 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 subject 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 Part 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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples 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 Blood sampling for pharmacokinetic analysis

For quantification of nerandomilast concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 x g to 4000 x g and 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 minutes with interim storage of blood samples and aliquots at room temperature. The time each aliquot was placed in the freezer will be documented.

Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the

analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, barcode, subject number, visit, and planned sampling time.

After analysis, the plasma samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR is archived.

[redacted]

5.4 ASSESSMENT OF BIOMARKERS

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the screening examination from each subject whose genotype has not been previously determined. Separate informed consent for genotyping will be obtained from each volunteer prior to sampling.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs. The gene sequences to be determined include known and likely functional variations of key

ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

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 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

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

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

If not stated otherwise in the Flow Chart, the acceptable deviation from the scheduled time for vital signs, AE questioning and laboratory tests will be ± 60 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs, and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters. In all periods subjects may have their dinner together.

For planned blood sampling times, refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters. Starting from 58h after dosing a tolerance of ± 120 minutes is given for all procedures.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

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

For information regarding laboratory tests (including drug and virus screening, pregnancy), ECG, vital signs, and physical examination, refer to Sections 5.2.1 to 5.2.5.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.6).

6.2.2 Treatment periods

Each subject is expected to participate in 3 treatment periods (Days -1, 1, 2, 3, 4 and 5 in each period). At least 7 days will separate drug administrations in the first, second and third treatment period.

On the evening of Day -1 of each treatment period, trial participants will be admitted to the trial site and kept under close medical surveillance for at least 24 h following drug administration.

The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

For details on time points and procedures for collection of plasma samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. AEs and concomitant therapy will be assessed continuously from obtaining subject's written informed consent until the end of trial examination.

For details on times of all other trial procedures, refer to the Flow Chart.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoS Visit.

If needed in the opinion of the investigator, additional visits may be scheduled after the EoS Visit for continued safety monitoring.

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 EoS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

The relative bioavailability of paediatric vs. adult formulation, i.e. T1 vs. R, and administering the paediatric formulation with or without food, i.e. T2 vs. T1, will be estimated by the ratios of the geometric means (T1/R respectively T2/T1), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Descriptions of additional analysis sets may be provided in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be suggested in the iPD specification file. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.1.2 Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2.2 for drug nerandomilast will be calculated according to the relevant BI internal procedures.

Plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- A predose concentration is >5% C_{max} value of that subject
- Missing samples/concentration data at important phases of PK disposition curve

Plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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

7.2.2 Primary endpoint analyses

Primary analyses

The two main objectives of this trial, see Section 2.1.1, will be analysed according to the statistical model described below. However, the statistical model will be applied only to data that contribute to the particular comparison of interest.

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: sequence, subjects within sequences, period and treatment. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed.

The model is described by the following equation:

$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm}$, where

y_{ijkm} = logarithm of response measured on subject m in sequence i receiving treatment k in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, 2, 3

s_{im} = the effect associated with the m^{th} subject in the i^{th} sequence, m = 1, 2, ..., 5

π_j = the j^{th} period effect, j = 1, 2, 3

τ_k = the k^{th} treatment effect, k = 1, 2, 3

e_{ijkm} = the random error associated with the m^{th} subject in sequence i who received treatment k in period j.

where $s_{im} \sim N(0, \sigma_B^2)$ i.i.d., $e_{ijkm} \sim N(0, \sigma_W^2)$ i.i.d. and s_{im}, e_{ijkm} are independent random variables.

Point estimates for the ratios of the geometric means (T1/R respectively T2/T1) for the primary endpoints (see Section 2.1) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T1)-log(R) respectively log(T2)-log(T1) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Further exploratory analyses

The same statistical model as stated above will be repeated for the primary endpoints but with all sources of variation ('sequence', 'subjects within sequences', 'period', 'treatment') considered as fixed effects.

In addition to the model based approach all primary endpoints will be analysed descriptively.

7.2.3 Secondary endpoint analyses

The secondary endpoint (refer to Section 2.1.3) will be calculated according to the relevant BI internal procedures and will be assessed statistically using the same methods as described for the primary endpoints (refer to Section 7.2.2).

7.2.5 Safety analyses

Safety will be analysed based on the assessments described in Section 2.2.2.2. All treated subjects (TS, refer to Section 7.2) will be included in the safety analysis. Safety analyses will be descriptive in nature and based on BI standards. No hypothesis testing is planned.

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

Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used to evaluate categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements performed or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (see Section 1.2.1) will be assigned to the respective treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

Additionally, further treatment intervals (analysing treatments) may be defined in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class, and preferred term. SAEs, AESIs (see Section 5.2.6.1), and other significant AEs (according to ICH E3) will be listed separately.

Relevant ECG findings will be reported as AEs.

Previous and concomitant therapies will be presented per treatment without consideration of treatment periods.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be highlighted in the listings.

Vital signs data will be assessed with regard to possible on-treatment changes from baseline. Baseline is defined as last measurement prior to drug administration of the respective treatment period.

7.2.6 Interim analyses

No interim analysis is planned.

7.3 HANDLING OF MISSING DATA

7.3.1 Safety

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

7.3.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant BI internal procedures.

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Subjects will be randomised to one of the 3 treatment sequences (R-T1-T2, T1-T2-R, or T2-R-T1) in a 1:1:1 ratio. The block size will be documented in the CTR.

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

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

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to enter a total of 15 subjects in the trial including up to 3 PK non-evaluable subjects, because this sample size is considered sufficient to achieve the aims of this exploratory trial. With this sample size, the following precision in estimating the ratio of geometric means (test/reference, e.g. T1/R respectively T2/T1) can be expected with 95% probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means.

The observed intra-individual coefficient of variation (gCV) for nerandomilast in previous trial 1305-0028 [c40013550] was roughly 20% for C_{max} and 7% for AUC.

For various assumptions of the gCV up to 25%, Table 7.5: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative purposes, the expected 90% confidence intervals are displayed for different values of the ratios T1/R or T2/T1 of geometric means.

Table 7.5: 1 Precision that can be expected with 95% tolerance probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T1/R or T2/T1) for different gCVs in a 3x3 crossover trial (N = 12, 15).

N	gCV [%]	Precision upper CL** / relative BA estimate	90% CI [%] of respective ratio*		
			80%	100%	150%
12	10	1.09	(73.26; 87.36)	(91.57; 109.20)	(137.36; 163.80)
12	15	1.14	(70.13; 91.25)	(87.67; 114.07)	(131.50; 171.10)
12	20	1.19	(67.17; 95.28)	(83.97; 119.10)	(125.95; 178.64)
12	25	1.24	(64.38; 99.41)	(80.47; 124.27)	(120.71; 186.40)
15	10	1.08	(74.15; 86.31)	(92.68; 107.89)	(139.03; 161.84)
15	15	1.12	(71.41; 89.63)	(89.26; 112.03)	(133.89; 168.05)
15	20	1.16	(68.80; 93.02)	(86.00; 116.28)	(129.00; 174.42)
15	25	1.21	(66.32; 96.50)	(82.90; 120.63)	(124.35; 180.94)

*Ratio of geometric means (test/reference, i.e. T1/R or T2/T1) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.
**Confidence interval limit

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper,lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious [R11-5230] using R Version 4.2.2.

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

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. As a general rule, no trial results should be published prior to finalisation of the CTR.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects and are stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the 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 a subject's participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

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

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

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

Electronic Study Documentation System:
In the [redacted] a validated electronic study documentation system (ClinBase™ or successor Trial Complete Early Phase, TCEP) is used for processing information and controlling data collected in clinical trials. In addition to its function as a procedure control system, the study documentation system serves as databases. Instead of being entered into CRFs, selected data are directly entered into the system.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

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

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

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

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of subject's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Data directly entered into ClinBase™ or successor Trial Complete Early Phase, TCEP (that is, without prior written or electronic record) are considered to be source data. The place where data are entered first will be defined in a trial specific Source Data Agreement. The data in ClinBase™ or successor Trial Complete Early Phase, TCEP are available for inspection at any time.

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents.

The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site:
The trial site(s) must retain the source and essential documents (including ISF) according to 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.

Reporting suspected unexpected serious adverse reactions (SUSARs) to the EMA will be done via E2B transmission of Individual Case Safety Reports (ICSRs) to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

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

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

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

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage 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 (e.g. 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 ICF

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ('Last Subject 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 laws of each member state.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU), so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted] under the supervision of the Principal Investigator. 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 trial activities, in order to

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

- Ensure appropriate training and information of local Clinical Trial Mangers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating trial sites

The trial medication will be provided by the [redacted]

Safety laboratory tests will be performed by the local laboratory of the trial site [redacted]

Analyses of nerandomilast concentrations in plasma will be performed at [redacted]

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

Data management and statistical evaluation will be done by BI, or a contract research organisation appointed by BI, according to BI SOPs.Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R03-2269 Guidance for industry: food-effect bioavailability and fed bioequivalence studies. In: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) 2002:1-9.

R10-1555 Daxas (roflumilast) in chronic obstructive pulmonary disease, NDA 22-522, FDA Advisory Committee briefing document presented to: Pulmonary-Allergy Drugs Advisory Committee (briefing book, April 7, 2010).http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm207376.htm (access date: 23 November 2010) ; Jersey City: Forest Research Institute; 2010.

R10-1559 Giembycz MA. Life after PDE4: overcoming adverse events with dual specificity phosphodiesterase inhibitors. Curr Opin Pharmacol 2005; 5:238-244.

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group; 2010.

R14-1795 Otezla (apremilast) tablets, for oral use (Celgene) (U.S. prescribing information, revised: 3/2014).

R17-0915 Roflumilast 500 mcg tablets (Forest Research Institute): pharmacology/toxicology NDA/BLA review and evaluation, application number: 022522Orig1s000. Source: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000PharmR.pdf (access date: 13 March 2017) ; Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 2011.

R17-0919 Otezla (apremilast) (Celgene): pharmacology/toxicology NDA/BLA review and evaluation, application number: 205437Orig1s000. Source: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205437Orig1s000PharmR.pdf (access date: 13 March 2017) ; Department of Health and Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research; 2014.

R17-1427 Otezla 10 mg, 20 mg, 30 mg film-coated tablets, Otezla 30 mg film-coated tablets (Celgene) (summary for product characteristics, manufacturer responsible for batch release, conditions or restrictions regarding supply and use, other conditions and requirements of the marketing authorisation, conditions or restrictions with regard to the safe and effective use of the medicinal product, labelling and package leaflet (first published 16/02/2015). Source: https://ec.europa.eu/health/documents/community-register/2015/20150115130395/anx _130395_en.pdf (access date: 19 April 2017); 2015.

R94-1529 Chow SC, Liu JP, editors. Design and analysis of bioavailability and bioequivalence studies. New York: Marcel Dekker Inc., 1992

9.2 UNPUBLISHED REFERENCES

c02094779 BI 1015550 - Investigator's Brochure, current version

c22991937 Safety, tolerability and pharmacokinetics of single and multiple rising oral doses of BI 1015550 in healthy subjects. 1305-0011.

c24902949 Relative bioavailability of a single oral dose of BI 1015550 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects. 1305-0015.

c25085412 Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy. 1305-0012

c36151567 A Phase I, open-label, non-randomized, single-dose, single-arm, single-period study to investigate the metabolism and pharmacokinetics of [C 14]-labelled BI 1015550 after oral administration in healthy male subjects. 1305-0016.

c37065416 A randomised, double-blind, placebo-controlled parallel group study in IPF patients over 12 weeks evaluating efficacy, safety and tolerability of BI 1015550 taken orally. 1305-0013

c40013550 Clinical Trial Report Trial 1305-0028

c40607236 The effect of multiple oral doses of BI 1015550 on metabolism of midazolam administered orally in healthy male subjects.1305-0033 [draft report]

U13-1792-01 Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1015550 in healthy male volunteers (a partially randomised, single-blinded, placebo-controlled Phase I study). 1305-0001

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		09 April 2025
EudraCT number **EU number**		2024-511245-18-00
BI Trial number		1305-0029
BI Investigational Medicinal Product(s)		BI 1015550, nerandomilast
Title of protocol		Relative bioavailability of two different formulations of nerandomilast and investigation of the food effect on new formulation following oral administration in healthy adult male and female subjects (an open-label, randomised, single-dose, three-way crossover trial)
Substantial Global Amendment due to urgent safety reasons		☐
Substantial Global Amendment		☐
Non-substantial Global Amendment		☒
Section to be changed		1. Title Page 2. Global Amendment 1 entry
Description of change		1. Clinical Trial Leader changed from [redacted] to [redacted]
Rationale for change		1. Change of CTL

Signature Page for VV-TMF-986619 v2.0

Reason for signing: Approved	Name: [redacted] Role: Verification-Paper Signature Completion Date of signature: 14-Apr-2025 05:21:31 GMT+0000

Reason for signing: Approved	Name [redacted] Role: Approver Date of signature: 14-Apr-2025 05:34:44 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Author Date of signature: 14-Apr-2025 06:25:53 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Approver Date of signature: 14-Apr-2025 10:01:57 GMT+0000

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