Clinical Trial Protocol

	Document Number:	**c30404410-03**
EudraCT No.	2019-005037-37	
BI Trial No.	1407-0041	
Investigational Medicinal Products	Otezla® (Apremilast) film-coated tablets sourced from three ICH regions (EU, US, and Japan)	
Title	Bioequivalence of three different tablet formulations of 30 mg of apremilast (EU-sourced Otezla® vs. US-sourced Otezla® vs. Japan-sourced Otezla®) administered in healthy male and female subjects in the fasted state as well as (for EU-sourced Otezla® vs. US-sourced Otezla®) in the fed state (an open-label, randomised, single-dose, five-period, ten-sequence crossover study)	
Lay Title	A study in healthy people to compare 3 different formulations of apremilast tablets taken with or without food	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on Global Amendment 2))	
Version and Date	Version: 3.0	Date: 05 November 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	03 March 2020
Revision date	05 November 2020
BI trial number	1407-0041
Title of trial	Bioequivalence of three different tablet formulations of 30 mg of apremilast (EU-sourced Otezla® vs. US-sourced Otezla® vs. Japan-sourced-Otezla®) administered in healthy male and female subjects in the fasted state as well (for EU-sourced Otezla® vs. US-sourced Otezla®) as in the fed state (an open-label, randomised, single-dose, five-period, ten-sequence crossover study)
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	I
Trial rationale	The aim of this trial is to establish bioequivalence between EU-, US- and Japan-sourced Otezla® tablet formulations to assure comparability of results from Phase III trials of BI 730357 (new oral agent for treatment of psoriasis [redacted] regardless of whether only the EU-sourced Otezla or EU- and US-sourced Otezla /Japan-sourced Otezla® have been used as an active comparator.
Trial objectives	To demonstrate bioequivalence (BE) between EU-sourced Otezla® film-coated tablets, US-sourced Otezla® film-coated tablets and Japan-sourced Otezla® film-coated tablets in the strength of 30 mg. For all tablet formulations their bioequivalence will be tested in the fasted state (BE under fasting conditions) as well as for the EU- and US-formulation in the fed state (BE under fed conditions).
Trial design	Randomised, open-label, single-dose, five-period, ten-sequence crossover design
Trial endpoints	Primary endpoints: AUC_{0-tz}, $AUC_{0-\infty}$, and C_{max} of apremilast in plasma
Number of subjects	
total entered	40 subjects
each treatment	40 subjects
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male/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 (T)	EU-sourced Otezla® (apremilast) film-coated tablet 30 mg (EU-approved)
dose	30 mg apremilast
mode of admin.	Oral administration in the fasted and in the fed state (treatments T_{fasted} and T_{fed}), all with 240 mL of water after an overnight fast of at least 10 h
Reference product (R1)	US-sourced Otezla® (apremilast) film-coated tablet 30 mg (US-licensed)
dose	30 mg apremilast
mode of admin.	Oral administration in the fasted and in the fed state (treatments $R1_{fasted}$ and $R1_{fed}$), all with 240 mL of water after an overnight fast of at least 10 h
Reference product (R2)	Japan-sourced Otezla® (apremilast) film-coated tablet 30 mg (Japan-approved)
dose	30 mg apremilast
mode of admin.	Oral administration in the fasted state (treatment $R2_{fasted}$) with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	One day (single dose) for each of the five treatments
Statistical methods	The assessment of bioequivalence will be based upon 2-sided 90% confidence intervals (CIs) for the ratios of the geometric means (test/reference) for the primary endpoints using an acceptance range of 80.00 to 125.00%. This method corresponds to the two one-sided t-tests procedure, each at a 5% significance level. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for sequence, subjects nested within sequences, period, treatment and metabolic state (fed or fasted) as well as the treatment-by-metabolic state interaction. CIs will be calculated based on the residual error from the ANOVA and quantiles from the t-distribution. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory [8]	PK_{blood} (Apremilast)	Vital signs (BP, PR)	Questioning for AEs and concomitant therapy [6]
SCR	1	-23 to -1			Screening (SCR)[1]	A		x	
1/2/3/4/5[7]	2/3/4/5/6[7]	-1	-12:00	20:00	Admission to trial site	x[5]			x
			-11:30	20:30	Snack (voluntary) [3]				
		1	-1:00	07:00	Allocation to treatment [2] (visit 2 only)	B[2]	x[2]	x[2]	x[2]
			-0:30	07:30	Start of high fat, high calorie breakfast prior to treatments T_{fed} and $R1_{fed}$				
			0:00	**08:00**	**Drug administration**				
			0:30	08:30			x		
			1:00	09:00			x		
			1:30	09:30			x		
			2:00	10:00	240 mL fluid intake		x		x
			2:30	10:30			x		
			3:00	11:00			x		
			3:30	11:30			x		
			4:00	12:00	240 mL fluid intake		x		x
			5:00	13:00	Lunch [3]		x		
			6:00	14:00			x		
			8:00	16:00			x		
			10:00	18:00	Dinner				
			11:00	19:00			x		
			15:00	23:00			x		x
		2	24:00	08:00	Breakfast (voluntary) [3], discharge from trial site	B	x	x	x
			36:00	20:00	Ambulatory visit		x		x
		3	48:00	08:00	Ambulatory visit		x		x
FU	7	5 to 11			End of trial (EoTrial) examination[4]	C		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 pregnancy test in women and drug screening), demographics (including determination of body height and weight, smoking status and alcohol history), 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 3h 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 trial visit the EoTrial examination includes physical examination, vital signs, ECG, safety laboratory (including 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. Five identical periods /visits separated by wash-out periods of at least 5 days between the administrations of apremilast.
8. Letter A, B and C define different sets of safety laboratory examinations (see Section 5.2.3)

TABLE OF CONTENTS

TITLE PAGE 1
CLINICAL TRIAL PROTOCOL SYNOPSIS 2
FLOW CHART 4
TABLE OF CONTENTS 5
ABBREVIATIONS 9
1. INTRODUCTION 12
1.1 MEDICAL BACKGROUND 12
1.2 DRUG PROFILE 13
1.2.1 Apremilast 13
1.2.2 Residual Effect Period 14
1.3 RATIONALE FOR PERFORMING THE TRIAL 14
1.4 BENEFIT - RISK ASSESSMENT 14
1.4.1 Procedure-related risks 15
1.4.2 Drug-related risks and safety measures 15
2. TRIAL OBJECTIVES AND ENDPOINTS 18
2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS 18
2.1.1 Main objectives 18
2.1.2 Primary endpoints 18
2.1.3 Secondary endpoint 18
[redacted]
2.2.2.2 Safety and tolerability 19
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION 20
3.1 OVERALL TRIAL DESIGN AND PLAN 20
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP 21
3.3 SELECTION OF TRIAL POPULATION 21
3.3.1 Main diagnosis for trial entry 21
3.3.2 Inclusion criteria 21
3.3.3 Exclusion criteria 22
3.3.4 Withdrawal of subjects from treatment or assessments 24
3.3.4.1 Discontinuation of trial treatment 24
3.3.4.2 Withdrawal of consent to trial participation 25
3.3.4.3 Discontinuation of the trial by the sponsor 25
3.3.5 Replacement of subjects 25

4. TREATMENTS 26
4.1 INVESTIGATIONAL TREATMENTS 26
4.1.1 Identity of the Investigational Medicinal Products 26
4.1.2 Selection of doses in the trial 27
4.1.3 Method of assigning subjects to treatment groups 27
4.1.4 Drug assignment and administration of doses for each subject 27
4.1.5 Blinding and procedures for unblinding 28
4.1.6 Packaging, labelling, and re-supply 28
4.1.7 Storage conditions 29
4.1.8 Drug accountability 29
4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS 29
4.2.1 Other treatments and emergency procedures 29
4.2.2 Restrictions 30
4.2.2.1 Restrictions regarding concomitant treatment 30
4.2.2.2 Restrictions on diet and life style 30
4.3 TREATMENT COMPLIANCE 30
5. ASSESSMENTS 31
5.1 ASSESSMENT OF EFFICACY 31
5.2 ASSESSMENT OF SAFETY 31
5.2.1 Physical examination 31
5.2.2 Vital signs 31
5.2.3 Safety laboratory parameters 31
5.2.4 Electrocardiogram 33
5.2.5 Other safety parameters 34
5.2.6 Assessment of adverse events 34
5.2.6.1 Definitions of adverse events 34
5.2.6.1.1 Adverse event 34
5.2.6.1.2 Serious adverse event 34
5.2.6.1.3 AEs considered ‘Always Serious’ 35
5.2.6.1.4 Adverse events of special interest 35
5.2.6.1.5 Intensity of AEs 36
5.2.6.1.6 Causal relationship of AEs 36
5.2.6.2 Adverse event collection and reporting 37
5.2.6.2.1 AE collection 37
5.2.6.2.2 AE reporting to the sponsor and timelines 37
5.2.6.2.3 Information required 38
5.2.6.2.4 Pregnancy 38
5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS 38
5.3.1 Assessment of pharmacokinetics 38
5.3.2 Methods of sample collection 38
5.3.2.1 Blood sampling for pharmacokinetic analysis 38

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S) 39
5.5 BIOBANKING 39
5.6 OTHER ASSESSMENTS 39
5.6.1 Pharmacogenomic evaluation 39
5.7 APPROPRIATENESS OF MEASUREMENTS 40
6. INVESTIGATIONAL PLAN 41
6.1 VISIT SCHEDULE 41
6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS 41
6.2.1 Screening 41
6.2.2 Treatment periods 41
6.2.3 Follow-up period and trial completion 42
7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE 43
7.1 STATISTICAL DESIGN – MODEL 43
7.2 NULL AND ALTERNATIVE HYPOTHESES 43
7.3 PLANNED ANALYSES 44
7.3.1 Primary endpoint analyses 45
7.3.2 Secondary endpoint analyses 47

[redacted]

7.3.4 Safety analyses 47
7.4 INTERIM ANALYSES 48
7.5 HANDLING OF MISSING DATA 48
7.5.1 Safety 48
7.5.2 Pharmacokinetics 48
7.6 RANDOMISATION 48
7.7 DETERMINATION OF SAMPLE SIZE 49
8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE 50
8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT 50
8.2 DATA QUALITY ASSURANCE 51
8.3 RECORDS 51
8.3.1 Source documents 51
8.3.2 Direct access to source data and documents 52
8.3.3 Storage period of records 53
8.4 EXPEDITED REPORTING OF ADVERSE EVENTS 53

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY.....53
8.5.1 Collection, storage and future use of biological samples and corresponding data 53
8.6 TRIAL MILESTONES 54
8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL 54
9. REFERENCES 56
9.1 PUBLISHED REFERENCES.....56
9.2 UNPUBLISHED REFERENCES.....58
10. APPENDICES 59
11. DESCRIPTION OF GLOBAL AMENDMENT(S) 60
11.1 GLOBAL AMENDMENT 1 60
11.2 GLOBAL AMENDMENT 2 61

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
ANOVA	Analysis of variance
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
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
BE	bioequivalence
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
cAMP	cyclic adenosine monophosphate
CI	confidence intervals
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CT Leader	Clinical Trial Leader
CTFG	Clinical Trial Facilitation Group
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
CYP	Cytochrome P450
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalogram
EoTrial	End of trial
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (US)
FSH	Follicle-stimulating hormone

FU	Follow-up
GI	gastrointestinal
GCP	Good Clinical Practice
gCV	geometric coefficient of variation
gMean	Geometric mean
[redacted]	
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
[redacted]	
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
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
MRT_{po}	Mean residence time of the analyte in the body after oral administration
PDE4	phosphodiesterase 4
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
REP	Residual effect period
[redacted]	

[redacted]

SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
T	Test product or treatment
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma

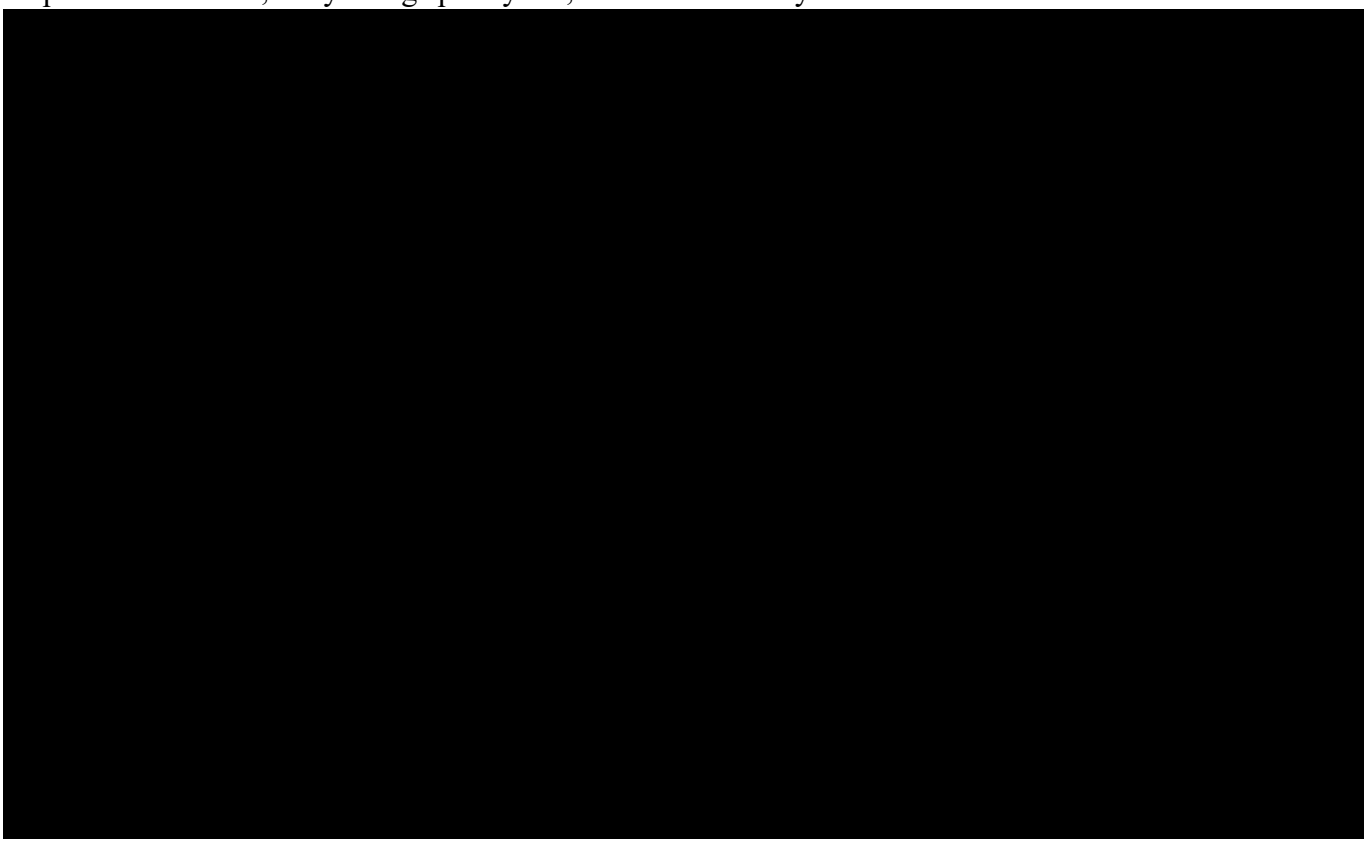
[redacted]

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
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Woman of childbearing potential
XTC	Ecstasy

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

BI 730357 is being developed for the treatment of patients with moderate to severe plaque psoriasis and is also under development for the treatment of other disease indications such as psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.



Boehringer Ingelheim (BI) intends to conduct two parallel pivotal Phase III trials designed to demonstrate the superiority of BI 730357 to apremilast (trade name Otezla®) as active comparator.

BI currently assumes that each pivotal trial will be conducted globally and plans to use apremilast (Otezla®) sourced from three ICH regions (EU, US, and Japan) as the active comparator in the planned Phase III studies of BI 730357.

Apremilast, an inhibitor of phosphodiesterase 4 (PDE4), has been approved in the US since 2014 for the treatment of patients with active psoriatic arthritis, and since 2015 for the treatment of moderate to severe plaque psoriasis. In the EU, apremilast is approved in both indications, psoriasis and psoriatic arthritis. In Japan, apremilast is approved since 2017 for the treatment of plaque psoriasis with inadequate response to topical treatment, and the treatment of psoriatic arthritis. In all tree ICH regions, the recommended maintenance dose of apremilast is 30 mg twice daily taken orally (following initial titration stating with 10 mg once daily) [R20-3168, R20-3173, R20-3422].

BI intends to use either EU-sourced Otezla® only or EU-sourced Otezla® and US-sourced Otezla® as active comparator in the planned Phase III studies for marketing authorization.

BI conducts this bioequivalence study for the 30 mg strength to demonstrate bioequivalence between EU-approved Otezla®, US-licensed Otezla® and Japan-approved Otezla® tablet formulations in order to allow bridging of the Japan-, US- and EU-sourced Otezla® drug products, i.e. the usage of either EU-approved Otezla® only, or EU-approved and US-licensed Otezla®/Japan-approved Otezla®, in the planned Phase III trials for marketing authorization.

1.2 DRUG PROFILE

1.2.1 Apremilast

Apremilast, an oral small-molecule PDE4 inhibitor, works intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of tumor necrosis factor alpha (TNF-α), interleukin (IL)-23, IL-17 and other inflammatory cytokines. Cyclic AMP also modulates levels of anti-inflammatory cytokines such as IL-10. These pro- and anti-inflammatory mediators have been implicated in psoriatic arthritis and psoriasis [R20-3173]. The specific mechanism(s) by which apremilast exerts its therapeutic action is not well defined [R20-3168].

The recommended therapeutic dose of apremilast is 30 mg taken orally twice daily, with no food restrictions. An initial dose titration over the first five treatments days helps to reduce gastrointestinal (GI) symptoms associated with initial therapy.

Apremilast is well absorbed with an absolute oral bioavailability of approximately 73%, with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2.5 hours. Apremilast pharmacokinetics are linear, with a dose-proportional increase in systemic exposure in the dose range of 10 to 100 mg daily. Co-administration with food does not alter the extent of absorption of apremilast [R20-3168, R20-3173].

Human plasma protein binding of apremilast is approximately 68%. The mean apparent volume of distribution is 87 L, indicative of extravascular distribution [R20-3168].

Apremilast is extensively metabolised by both cytochrome P450 (CYP) and non-CYP mediated pathways including oxidation, hydrolysis, and conjugation, suggesting inhibition of a single clearance pathway is not likely to cause a marked drug-drug interaction. In vitro, oxidative metabolism of apremilast is primarily mediated by CYP3A4, with minor contributions from CYP1A2 and CYP2A6. After oral administration, apremilast is the major circulating component (45%) followed by inactive metabolite M12 (39%), a glucuronide conjugate of O-demethylated apremilast. The plasma clearance of apremilast is about 10 L/hr in healthy subjects, with a terminal elimination half-life of approximately 9 hours [R20-3168, R20-3173].

Co-administration of rifampicin, a strong CYP3A4 inducer, resulted in a reduction of systemic exposure of apremilast. Therefore, the use of rifampicin and other strong CYP3A4 inducers (e.g. phenobarbital, carbamazepine, phenytoin and St. John's Wort) with apremilast is not recommended. Co-administration of apremilast with multiple doses of 600 mg

rifampicin for 15 days resulted in a decrease in apremilast area-under-the-concentration (AUC) time curve and maximum plasma concentration (C_{max}) by approximately 72% and 43%, respectively [R20-3168, R20-3173].

There was no clinically meaningful interaction between apremilast and ketoconazole, a potent CYP3A4 inhibitor. There was no pharmacokinetic interaction between apremilast and oral contraceptives containing ethinylestradiol and norgestimate, thus apremilast can be co-administered with oral contraceptives [R20-3173].

The most commonly reported adverse reactions with apremilast are GI disorders including diarrhoea (15.7%) and nausea (13.9%). These GI adverse reactions are mostly mild to moderate in severity, with 0.3% of diarrhoea and 0.3% of nausea reported as severe. These GI adverse reactions generally occur within the first 2 weeks of treatment and usually resolve within 4 weeks. The other most commonly reported adverse reactions include upper respiratory tract infections (8.4%), headache (7.9%), and tension headache (7.2%) and are mostly mild to moderate in severity [R20-3173].

The most common adverse reactions leading to discontinuation during the first 16 weeks of treatment are diarrhoea (1.7%), and nausea (1.5%) (frequencies are based on Phase III clinical studies).

For a detailed description of the apremilast profile, please refer to the to the German and European SmPC [R20-3610 and R20-3173], the US PI [R20-3168], or the Japanese SmPC [R20-3422].

1.2.2 Residual Effect Period

The Residual Effect Period (REP) of apremilast is four days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects is still likely to be present.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The aim of this trial is to demonstrate bioequivalence between EU-, US- and Japan-sourced Otezla® (apremilast 30 mg) tablet formulations to assure comparability of results from Phase III trials of BI 730357 (new oral agent for treatment of moderate to severe psoriasis and psoriatic arthritis) regardless of whether only the EU-sourced Otezla® or EU- and US-sourced Otezla® have been used as an active comparator in these trials.

In accordance with FDA guidance ‘Food-Effect Bioavailability and Fed Bioequivalence Studies’ [R03-2269] and FDA guidance ‘Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA’ [R15-4652], the bioequivalence of EU and US Otezla® (orally administered immediate release products) is to be investigated under fed conditions in addition to fasting conditions.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this bioequivalence study is without any (therapeutic) benefit for healthy subjects. Their participation, however, is of major importance for the development of BI 730357, a new oral agent for the treatment of psoriasis and psoriatic arthritis, to assure regulatory acceptance of results of Phase III trials, in which BI 730357 is compared with

apremilast. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

1.4.1 Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

ECG electrodes may cause local and typically transient skin reactions.

The total volume of blood withdrawn per subject during the entire study 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.

1.4.2 Drug-related risks and safety measures

Based on available nonclinical and clinical information about apremilast [R17-0919, R18-1249, R20-3610, R20-3168, R20-3173, R20-3422] as well the design of the trial, the sponsor (Boehringer Ingelheim) considers this trial to be ethically acceptable. Healthy subjects will not be exposed to undue risks and adverse events (AEs) in relation to the information are expected from this clinical trial. Both apremilast drug products are marketed in the US or the EU for at least 5 years, and in Japan for 3 years (trade name Otezla®).

The potential for side effects has been assessed to be minimal following single doses and thus acceptable. The planned single dose treatments (5 doses separated by at least 5 days) are expected to be well tolerated by participating subjects. This is confirmed by Phase I trials with the 30 mg single dose. For example, 24 healthy male or female (demographically matched control) subjects received a single oral dose of 30 mg of apremilast to investigate the impact of renal Impairment on the pharmacokinetics of apremilast and metabolite M12. Seven out of 24 (29%) subjects reported AEs. Of these, 5 out of 24 (21%) subjects had AEs considered possibly related to apremilast (one case each of cheilitis, nausea, vomiting, back pain, pain in the extremity, and increased blood creatinine phosphokinase). Most AEs were mild or moderate in severity and resolved without intervention [R20-0189]. In another trial, apremilast was administered as a 30 mg single dose to 21 healthy male or female subjects in order to assess the impact of rifampicin co-administration on the pharmacokinetics of apremilast. Headache and rhinitis were the more frequently reported AEs. One subject was withdrawn from the trial after the first single dose of apremilast due to an AE (influenza) [R20-0188]. Both Phase I trials in healthy subjects revealed no clinically meaningful changes in clinical laboratory parameters, vital signs, ECGs or physical examination findings.

Potential risks for subjects will be minimized and addressed by eligibility criteria, safety laboratory examinations, vital sign measurements, in-house observation periods and AE questioning.

Apremilast is associated with an increased risk of psychiatric disorders such as insomnia and depression [R20-3173]. Instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression. During 16-week treatment periods in clinical trials, depression or depressed mood was reported by 1.0% of apremilast-

treated patients with psoriatic arthritis and by 1.3% of apremilast-treated patients with psoriasis (versus 0.8% and 0.4% with placebo, respectively) [R20-3168]. In order to address these risks, although the overall incidence is low and minimized in addition by single doses of apremilast, subjects with depression, suicidal thoughts or behaviour, or clinically relevant insomnia are excluded from this clinical trial (refer to Section 3.3.3). The medical staff at the trial site will nevertheless be instructed to notify the investigator or designee of any changes in behaviour or mood and of any suicidal ideation. If after apremilast dosing a subject suffers from psychiatric symptoms assessed as clinically relevant by the investigator, or suicidal ideation or suicidal attempt is identified, subject's treatment with apremilast is to be discontinued (refer to Section 3.3.4.1).

Non-clinical and clinical safety data of apremilast support clinical trials in both sexes, including women of childbearing potential (WOCBP). Because apremilast is contraindicated during pregnancy, WOCBP have to use a highly effective birth control method until 30 days after trial completion in accordance with the recommendations of the Clinical Trial Facilitation Group (CTFG) related to contraception and pregnancy testing in clinical trials [R16-0373] (see inclusion criteria of Section 3.3.2). In addition, negative highly sensitive pregnancy tests will be required at the screening visit, prior to each administration of apremilast, and during the end of trial examination. Effects of apremilast on pregnancy included embryofoetal loss in mice and monkeys, and reduced foetal weights and delayed ossification in mice at doses higher than the currently recommended highest human dose. No such effects were observed when exposure in animals was at 1.3-fold the clinical exposure [R20-3173]. No teratogenic findings attributed to apremilast were observed in mice or monkeys. Available pharmacovigilance data with apremilast use in pregnant women have not established a drug-associated risk of major birth defects, miscarriage or adverse maternal or foetal outcomes, but these data are extremely limited [R20-3168]. The decision not to exclude WOCBP from this clinical trial is based upon relevant regulatory guidelines (e.g. ICH M3 [R09-1400], CTFG recommendations related to contraception and pregnancy testing in clinical trials [R09-1400], and Guidance for Industry on Bioavailability and Bioequivalence Studies [R15-4651]. One of their common approaches to minimize and limit the possible risk is to prevent pregnancy during the clinical trials.

Up to now, there is no reliable evidence suggesting a link between the inhibition of PDE4 and susceptibility to SARS-CoV-2 infections. Nonetheless, as with other immunomodulatory treatments, apremilast might potentially increase the risk of infections in healthy volunteers participating in clinical trials. Therefore, several risk mitigation measures (e.g., repeated laboratory tests for SARS-CoV-2 infection, exclusion of subjects with a history or findings indicative of a SARS-CoV-2 infection, close monitoring of AEs) are considered for this clinical trial. Trial conduct and protocol-defined procedures do not impose additional risk to trial participants. To address potential risks associated with operational aspects related to the participation in clinical trials in the context of the COVID-19 pandemic, different risk mitigation measures are considered based on local requirements and development of the pandemic. Any subject with suspected or diagnosed SARS-CoV-2 infection should be treated according to standard of care, and discontinuation of trial medication should be considered.

If the investigator should have any clinical concern, the safety of subjects will be of upmost importance. The Investigator has the discretion to remove subjects from the trial should there be any safety concerns, or if the subjects' wellbeing is at jeopardy.

All in all, the risk of the participating volunteers is judged to be low considering the well-known safety profile of apremilast and the planned administration of single doses. The risks involved in inclusion of females (particularly WOCBP) have been adequately assessed and can be managed safe and satisfactorily. With respect to the medical need for an effective and safe treatment of psoriasis and mediated diseases, the benefit of this trial is assessed to outweigh the potential risks.

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 demonstrate bioequivalence (BE) between EU-sourced Otezla® film-coated tablets (Test, T), US-sourced Otezla® film-coated tablets (Reference 1, R1) and Japan-sourced Otezla® film-coated tablets (Reference 2, R2) in the strength of 30 mg. All tablet formulations will be tested for bioequivalence in the fasted state (BE under fasting conditions, i.e. T_{fasted} versus $R1_{fasted}$ and T_{fasted} versus $R2_{fasted}$) as well as for the EU- and US-formulation in the fed state (BE under fed conditions, i.e. T_{fed} versus $R1_{fed}$).

2.1.2 Primary endpoints

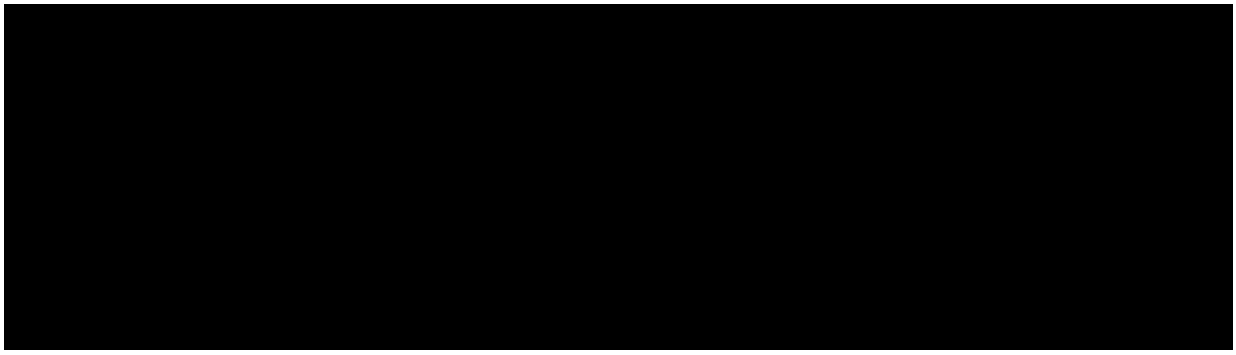
The following pharmacokinetic parameters will be determined for apremilast:

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

2.1.3 Secondary endpoint

Not applicable.

[redacted]



2.2.2.2 Safety and tolerability

Safety and tolerability of apremilast will be assessed based on:

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The study will be performed as a randomised, open-label, single-dose, five-period, ten-sequence crossover trial in healthy male and female subjects in order to compare the test treatment (T) to the reference treatments (R) under fasting and fed conditions.

All subjects will receive the following five treatments in a randomised order:

T_{fasted} (Test $_{fasted}$): One EU-sourced Otezla® film-coated tablet of 30 mg apremilast administered in the fasted state (after an overnight fasting period)

$R1_{fasted}$ (Reference 1 $_{fasted}$): One US-sourced Otezla® film-coated tablet of 30 mg apremilast administered in the fasted state (after an overnight fasting period)

T_{fed} (Test $_{fed}$): One EU-sourced Otezla® film-coated tablet of 30 mg apremilast administered in the fed state (after a high-fat, high-calorie meal)

$R1_{fed}$ (Reference 1 $_{fed}$): One US-sourced Otezla® film-coated tablet of 30 mg apremilast administered in the fed state (after a high-fat, high-calorie meal)

$R2_{fasted}$ (Reference 2 $_{fasted}$): One Japan-sourced Otezla® film-coated tablet of 30 mg apremilast administered in the fasted state (after an overnight fasting period)

The subjects will be randomly allocated to ten treatment sequences according to the five period William's design in Table 3.1: 1 below. For details, refer to Section 4.1.

Table 3.1: 1 Five period William's design

Sequence	Period				
	1	2	3	4	5
1	T_{fasted}	$R2_{fasted}$	$R1_{fasted}$	$R1_{fed}$	T_{fed}
2	$R1_{fasted}$	T_{fasted}	T_{fed}	$R2_{fasted}$	$R1_{fed}$
3	T_{fed}	$R1_{fasted}$	$R1_{fed}$	T_{fasted}	$R2_{fasted}$
4	$R1_{fed}$	T_{fed}	$R2_{fasted}$	$R1_{fasted}$	T_{fasted}
5	$R2_{fasted}$	$R1_{fed}$	T_{fasted}	T_{fed}	$R1_{fasted}$
6	T_{fasted}	$R1_{fasted}$	$R2_{fasted}$	T_{fed}	$R1_{fed}$
7	$R1_{fasted}$	T_{fed}	T_{fasted}	$R1_{fed}$	$R2_{fasted}$
8	T_{fed}	$R1_{fed}$	$R1_{fasted}$	$R2_{fasted}$	T_{fasted}
9	$R1_{fed}$	$R2_{fasted}$	T_{fed}	T_{fasted}	$R1_{fasted}$
10	$R2_{fasted}$	T_{fasted}	$R1_{fed}$	$R1_{fasted}$	T_{fed}

There will be a washout period of at least 5 days between the five treatments (administrations of apremilast).

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

For this bioequivalence trial, open-label treatment is acceptable, because the primary endpoints of this trial are pharmacokinetic endpoints derived from measurement of plasma concentrations of apremilast. These endpoints are not expected to be affected by knowledge of treatment.

Male and female subjects should be enrolled in bioequivalence trials unless there is a specific reason to exclude one sex. Female subjects should not be pregnant at the beginning of the trial and should not become pregnant during the trial [R15-4651]. The risk of WOCBP should be considered [R10-2509].

Because information on bioequivalence is required in both the fasted and fed states for the EU-sourced and the US-sourced Otezla® tablet formulation, it is acceptable to conduct a five-period, ten sequence crossover study [R10-2509].

3.3 SELECTION OF TRIAL POPULATION

It is planned that 40 healthy male and female subjects (if feasible at least 12 of each sex) will enter the study. 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 study will be performed in healthy subjects.

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 prior to admission to the study, in accordance with GCP and local legislation
5. Male subjects, or female subjects 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)
   - A vasectomised sexual partner (vasectomy at least 1 year prior to enrolment)
   - Surgically sterilised (including hysterectomy or bilateral occlusion)
   - 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. Chronic or relevant acute infections
10. History of relevant allergy or hypersensitivity (including to the trial medication or its excipients)

11. 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)
12. 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
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 12 g per day for females and 24 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 100 mL within 30 days of planned administration of trial medication or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. 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
21. Clinically relevant insomnia (e.g., difficulty falling or staying asleep at least 3 nights a week for at least 1 month, associated with daytime impairment)
22. History of depression and/or suicidal thoughts or behaviour
23. Galactose intolerance, lactase deficiency or glucose-galactose malabsorption
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 30 days after the last administration of trial medication
25. Male subject who is unwilling to refrain from donating sperm from time point of first administration of trial medication until 30 days after the last administration of trial medication
26. Subject (male or female) who is unwilling to refrain from donating blood (other than for this clinical trial) from time point of first administration of trial medication until 30 days after the last administration of trial medication
27. For female subject, positive pregnancy test, pregnancy, or plans to become pregnant within 30 days after study completion
28. For female subject, lactation
29. During COVID-19 pandemic: laboratory test indicative of an ongoing SARS-CoV-2 infection

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

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, the data will be included in the CRF and will be reported in the CTR. At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.2), 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.

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 5.2.6.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
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, 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
6. The subject suffers from psychiatric symptoms assessed as clinically relevant by the investigator, or suicidal ideation or suicidal attempt is identified

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

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

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 (no. 2 and no. 3 are mandatory discontinuation criteria):

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk-assessment.
3. Occurrence of severe non-serious adverse events considered as drug-related by the investigator in more than 25% of subjects, or occurrence of at least one drug-related serious adverse event. Moreover, the trial will be terminated if more than 50% of the subjects have drug-related and clinically relevant adverse events of at least moderate intensity.
4. Violation of GCP or the CTP impairing the appropriate conduct of the trial
5. The sponsor decides to discontinue the further development of the investigational product BI 730357

3.3.5 Replacement of subjects

In case more than 4 subjects do not complete the trial, the CT Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products will be supplied by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Name:	Otezla® 30 mg film-coated tablets
Substance:	Apremilast
Pharmaceutical formulation:	Film-coated tablet
Source:	EU commercial market
Marketing authorization holder:	[redacted]
Unit strength:	30 mg
Posology:	1-0-0
Route of administration:	Oral

The characteristics of the reference product 1 are given below:

Name:	Otezla® (apremilast) tablets
Substance:	Apremilast
Pharmaceutical formulation:	Film-coated tablet
Source:	US commercial market
Marketing authorization holder:	[redacted]
Unit strength:	30 mg
Posology:	1-0-0
Route of administration:	Oral

The characteristics of the reference product 2 are given below:

Name:	Otezla® Tablets 30 mg
Substance:	Apremilast
Pharmaceutical formulation:	Film-coated tablet
Source:	Japanese commercial market
Marketing authorization holder:	[redacted]
Unit strength:	30 mg
Posology:	1-0-0
Route of administration:	Oral

The manufacture batch numbers used will be reported in the CTR.

4.1.2 Selection of doses in the trial

The 30 mg dose selected for this trial is the standard clinical dose of apremilast taken twice daily (see Section 1.2).

4.1.3 Method of assigning subjects to treatment groups

The randomisation list 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 (Visit 2). For this purpose, numbers of the randomisation list will be allocated to the subjects by drawing lots. Subjects are then assigned to a treatment sequence according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

This trial is a 5-way crossover study. All subjects will receive the 5 treatments in randomised order. The treatments to be evaluated are outlined in Table 4.1.4: 1 below.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Formulation	Source	Unit strength	Dosage / metabolic state at administration	Total dose
T_{fasted}	Apremilast	film-coated tablet	EU	30 mg	1 film-coated tablet / fasted	30 mg
$R1_{fasted}$	Apremilast	film-coated tablet	US	30 mg	1 film-coated tablet / fasted	30 mg
T_{fed}	Apremilast	film-coated tablet	EU	30 mg	1 film-coated tablet / fed	30 mg
$R1_{fed}$	Apremilast	film-coated tablet	US	30 mg	1 film-coated tablet / fed	30 mg
$R2_{fasted}$	Apremilast	film-coated tablet	Japan	30 mg	1 film-coated tablet / fasted	30 mg

Administration of trial medication in three treatment periods (treatments T_{fasted}, $R1_{fasted}$, and $R2_{fasted}$) will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. 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, if correct dosage cannot be ensured otherwise.

In two treatment periods (treatments T_{fed} and $R1_{fed}$), the subjects will start to consume a high-fat, high-calorie meal 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 on Food-Effect Bioavailability and Fed Bioequivalence Studies [R03-2269] and the EMA

Guideline on the Investigation of Bioequivalence [R10-2509]. 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 5 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 (administrations of apremilast) will be separated by a wash-out phase of at least five days.

4.1.5 Blinding and procedures for unblinding

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

Emergency envelopes will not be provided, because the dose of trial medication is known to investigators and subjects.

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 local law and the principles of Good Manufacturing Practice.

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

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 (ICF).

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 local clinical monitor (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 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 medication to trial subjects. The trial medication must be administered in the manner specified in the CTP.

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 CT 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 except for hormonal contraceptives. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed within 3 days before each admission to trial site, in order to avoid false-positive results in the drug screen.

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 5 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), 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.

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 the end of trial examination.

Alcoholic beverages are not permitted from 2 days before each administration of trial medication until after the last PK sample of each trial period is collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before until 24 h after each administration of trial medication.

Smoking is not allowed during in-house confinement while admitted to 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.

If female subjects of child-bearing potential are included in the trial, highly effective contraception is to be maintained throughout the course of the trial until 30 days after trial completion (see Section 3.3.2 for the definition of highly effective measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study 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 (results not mandatory to be entered into CRF or to be reported), relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) 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 9 h. For retests, at the discretion of the investigator or designee, overnight fasting is not required.

The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF, Section 10.

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[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count/Erythrocytes	X	X	X
	White Blood Cells/Leucocytes	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	X
Automatic WBC differential, absolute	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Neut. Poly (segs); Neut. Poly (segs), absol.; Neutrophils Bands; 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	X	--	X
	Prothrombin time – INR (International Normalization Ratio)	X	--	X
Enzymes	AST [Aspartate transaminase] /GOT, SGOT	X	X	X
	ALT [Alanine transaminase] /GPT, SGPT	X	X	X
	Alkaline Phosphatase	X	X	X
	Gamma-Glutamyl Transferase	X	X	X
	Creatine Kinase [CK]	X	--	X
	Creatine Kinase Isoenzyme MB [only if CK is elevated]	X	--	X
Hormones	Thyroid Stimulating Hormone	X	--	--
Substrates	Glucose (Plasma)	X	X	X
	Creatinine	X	X	X
	Bilirubin, Total	X	X	X
	Bilirubin, Direct	X	X	X
	Protein, Total	X	X	X
	C-Reactive Protein (Quant)	X	X	X
	Cholesterol, total	X	--	X
	Triglyceride	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
Urinalysis [2] (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 RBC/Erythrocytes (qual)	X	--	X
	Urine WBC/Leucocytes (qual)	X	--	X
	Urine pH	X	--	X
Urine sediment [2]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

1 A, B and C are different sets of laboratory values. The Flow Chart details at which time point which set is to be investigated.

2 Microscopic examination if erythrocytes, leukocytes, nitrite or protein are abnormal in urine

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, it is planned to perform these tests during screening only. 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/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)
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 study 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 HCG-K20 test, respectively, or comparable test systems.

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

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 study 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 modified by Mason and Likar (hips and shoulders instead of ankles and wrists).

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 (at screening) 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 or not considered related to the medicinal product.

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
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based 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

5.2.6.1.3 AEs considered 'Always Serious'

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

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

The latest list of 'Always Serious AEs' can be found in the eDC system, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

For this trial, depression, mood changes, suicidal ideation, and suicidal behaviour/attempt are considered as AESIs.

5.2.6.1.5 Intensity 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 the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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 as well as the time of onset, end time, and intensity of these events. 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:
    - 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 or trial database 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 AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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 assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.6.2.4 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.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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 apremilast plasma concentrations, 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 venepuncture with a metal needle.

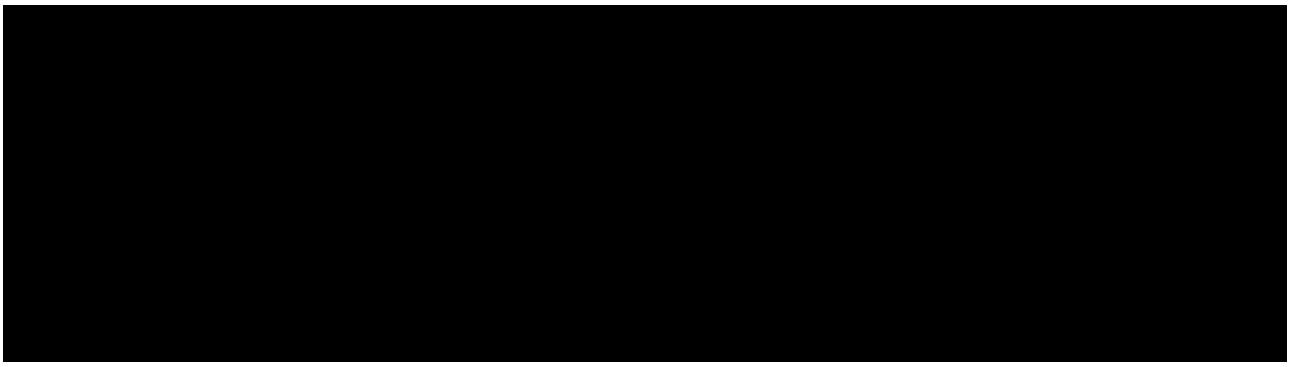
The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and

stored in polypropylene tubes. If (depending on method development and validation results) an additive should be required in order to stabilize the analyte, details will be described in a Lab Manual.

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 60 min, with interim storage of blood samples in ice water or on ice. 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 -70°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 -70°C or below until analysis.

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

The study samples will be discarded after completion of the clinical trial but not later than 5 years after the CTR is archived.



5.4 ASSESSMENT OF BIOMARKER(S)

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 pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Sections 2.1.2, 2.1.3, 2.2.2.1, and 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.

The acceptable deviation from the scheduled time for vital signs and laboratory tests will be ± 45 min.

If scheduled in the Flow Chart at the same time as a meal, blood sampling and measurement of vital signs have to be done first. Furthermore, if several measurements including venepuncture are scheduled for the same time, venepuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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.

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 study.

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

Genotyping will be performed in those volunteers whose genotypes have not been previously determined (for details, see Section 5.3).

6.2.2 Treatment periods

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

On evening of Day -1 of each treatment period, study 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 study 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 5.3 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the end of trial examination.

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 Sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

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 EoTrial 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 STATISTICAL DESIGN – MODEL

The main objective of this trial is to establish the bioequivalence of 30 mg of EU-sourced Otezla® film-coated tablets (Test, T) compared with 30 mg of US-sourced Otezla® film-coated tablets (Reference 1, R1) and 30 mg of Japan-sourced Otezla® film-coated tablets (Reference 2, R2) following oral administration on the basis of the primary pharmacokinetic endpoints, as listed in Section 2.1.2 and 2.1.3.

Relative bioequivalence will be tested in the fasted state (T_{fasted} versus $R1_{fasted}$ versus $R2_{fasted}$) as well as in the fed state (T_{fed} versus $R1_{fed}$). The trial is designed to allow intra-subject comparisons and will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints.

[redacted]

The assessment of safety and tolerability is a further objective of this trial, and will be evaluated by descriptive statistics for the parameters specified in Section 2.2.2.2.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Although there are multiple primary endpoints, an alpha adjustment is not needed because it is required that all primary endpoints meet the equivalence criterion as described below simultaneously. Therefore, a one-sided alpha of 5% will be used for testing.

The assessment of bioequivalence of 30 mg of EU-sourced Otezla® compared with 30 mg of US-sourced Otezla® under fed conditions (T_{fed} versus $R1_{fed}$) and 30 mg of EU-sourced Otezla® compared with 30 mg of US-sourced Otezla® and 30 mg of Japan-sourced Otezla® under fasted conditions (T_{fasted} versus $R1_{fasted}$ versus $R2_{fasted}$) will be based upon two-sided 90% confidence intervals (CIs) for the ratio of the geometric means ($T_{fed}/R1_{fed}$, $T_{fasted}/R1_{fasted}$, and $T_{fasted}/R2_{fasted}$, respectively) for the primary endpoints using an acceptance range of 80.00 to 125.00%. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following hypotheses are tested:

Null hypothesis H_0 (Inequivalence): $\mu_T - \mu_R \leq -\delta \quad or \quad \mu_T - \mu_R \geq \delta$

where μ_T and μ_R are the means of the log-transformed endpoint for the test and reference treatments, respectively, and δ is the bioequivalence limit that defines the acceptance range on the logarithmic scale.

Alternative hypothesis H_a (Equivalence): $-\delta < \mu_T - \mu_R < \delta$,

with T referring to the test treatment in fasted or fed state and R to the reference treatment in fasted or fed state.

In this trial, the bioequivalence limit δ is ln(1.25). By back-transforming (exponentiating), this translates to an acceptance range of 80.00 to 125.00% for the ratio of the geometric means ($T_{fed}/R1_{fed}$ or $T_{fasted}/R1_{fasted}$, $T_{fasted}/R2_{fasted}$, respectively) for endpoints on the original scale.

The rejection of the null hypothesis at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_T - \mu_R$ in the acceptance range (-δ, δ).

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study 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 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.

Further details will be given in the Trial statistical analysis plan (TSAP).

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the TSAP, IPVs will be identified no later than in the Report Planning Meeting, and the IPV categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2 for EU-sourced Otezla®, US-sourced Otezla®, and Japan-sourced Otezla® will be calculated according to the relevant Standard operating procedure (SOP) of the Sponsor (001-MCS-36-472).

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.

Relevant 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 is 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).

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.

If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead.

7.3.1 Primary endpoint analyses

Primary analyses

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, treatment and metabolic state (fed or fasted) as well as the treatment-by-metabolic state interaction. 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:

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

y_{ijklm} = logarithm of response measured on subject m in sequence i receiving treatment k under metabolic state l in period j,

μ = the overall mean,

ζ_i = the i^{th} sequence effect, i = 1, …, 10

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

π_j = the j^{th} period effect, j = 1, …, 5

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

γ_l= the l^{th} metabolic state, l= 1 (fed), 2 (fasted)

φ_{kl}=the k^{th} treatment effect (k=1, 2, 3) in the the l^{th} metabolic state (l=1 (fed), 2 (fasted))

e_{ijklm} = the random error associated with the m^{th} subject in sequence i who received treatment k for metabolic state l in period j.

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

Point estimates for the ratios of the geometric means ($T_{fed}/R1_{fed}$, $T_{fasted}/R1_{fasted}$, and $T_{fasted}/R2_{fasted}$) 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 $\log(T_{fed})$-$\log(R1_{fed})$, $\log(T_{fasted})$-$\log(R1_{fasted})$ and $\log(T_{fasted})$-$\log(R2_{fasted})$ 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.

Bioequivalence is considered established if the 90% confidence intervals of the geometric means for the primary endpoints are contained in the pre-defined acceptance range, see Section 7.2.

[redacted]

[redacted]

7.3.2 Secondary endpoint analyses

Not applicable.

[redacted]

7.3.4 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 planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between first trial medication intake and end of REP (see Section 1.2.2) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. In case of two or more treatments, the follow-up will be summarized according to the previous treatment. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before final 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 in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and follow-up intervals).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, 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.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as values defined as possibly clinically significant will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

Relevant ECG findings will be reported as AEs.

The TSAP will provide further details.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

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

7.6 RANDOMISATION

Subjects will be randomised to one of the 10 treatment sequences in equal numbers. The block size will be documented in the CTR.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system 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 list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

The sample size for this trial was determined using assumptions on the intra-individual variability of the primary endpoints based on the relative bioavailability trial CC-10004-CP-022 and food-effect trial CC-10004-BA-002 both reported by the European Medicines Agency in the Assessment Report for Otezla® [R18-1250]. For C_{max} the geometric coefficient of variation (gCV) was estimated to be about 23% in CC-10004-CP-022 and about 28% in CC-10004-BA-002, while for AUC_{0-tz} the gCV was about 8% and 20%, respectively.

A sample size of 40 subjects is needed to achieve 90% power to reject both one-sided null hypotheses for C_{max} each at the 5% level of significance in favor of bioequivalence.

Due to the high correlation between the primary endpoints, only C_{max} will be considered for power calculations. Using a sample size of 40 subjects (4 per sequence group), the power to reject both one-sided null hypotheses for one parameter each at the 5% level of significance in favour of bioequivalence is displayed in Table 7.7: 1, under various assumptions for the T/R ratio. To account for the uncertainty of the assumed gCV, a range of gCVs around 26% is also presented.

Table 7.7: 1 Power for concluding bioequivalence (acceptance range 80-125%) based on a geometric coefficient of variation around 26% and for different expected ratios of geometric means (T/R) in a five-period, ten-sequence crossover trial (N=40, 4 per sequence)

	Ratio[%]*						
gCV[%]	**92.5**	**95**	**97.5**	**100**	**102.5**	**105**	**107.5**
20	94.7	98.7	99.7	>99.9	99.8	98.9	96.0
26	81.1	91.0	96.0	97.5	96.1	91.7	83.6
28	76.0	87.0	93.2	95.1	93.3	87.8	78.7

*Ratio of geometric means (T/R) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

From the above table, a sample size of 40 will yield approximately 90% power to conclude bioequivalence for an assumed gCV of 26%, if the ratio is not more than 5% different from the ratio of 100%, which reflects no difference in exposure. In addition, this sample size still provides more than 80% power, if the ratio is not more than 7.5% different from 100% under the assumption of a gCV of 26% in both cases.

The calculations were performed as described in 'Using SAS Proc Power to perform model-based power analysis for clinical pharmacology studies [R20-3405] using SAS version 9.4.

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.

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 archiving 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.

For subjects enrolled during the COVID-19 pandemic: In addition to the study specific informed consent, separate written consent will be obtained for testing on SARS-CoV-2 infection.

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

ClinBase™
In the [redacted] – the validated ClinBase™ system is used for processing information and controlling data collected in clinical studies. In addition to its function as a procedure control system, ClinBase™ serves as data base. 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.

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: sex, 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™ (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™ 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.

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.

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

Personalised treatment data may be given to the 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, biobanking and future use of biological samples and clinical data, in particular

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

Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

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

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for 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 EC/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 patient (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.

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 managers (CT Managers), Clinical Research Associates, 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 apremilast concentrations in plasma will be performed under the responsibility of the [redacted] at suitable contract research organisations.

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 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

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.

R09-1400 European Medicines Agency (EMEA). ICH topic M3 (R2) non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals: step 4: note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (June 2009, CPMP/ICH/286/95). http://www.emea.europa.eu; 2009

R10-2509 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on the investigation of bioequivalence (London, 20 January 2010, doc. ref.: CPMP/EWP/QWP/1401/98 rev. 1/corr). http://www.emea.europa.eu; 2010.

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R16-0373 Recommendations related to contraception and pregnancy testing in clinical trials (final version - 2014-09-15). http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-about_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf (access date: 2 February 2016); Clinical Trial Facilitation Group (CTFG), Head of Medicine Agencies (HMA); 2014.

R17-0919 Otezla (apremilast) (Celgene): pharmacology/toxicology NDA/BLA review and evaluation, application number: 205437Orig1s000. 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.

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R20-3610 Otezla 10 mg, 20 mg, 30 mg Filmtabletten (Amgen), Zusammenfassung der Merkmale des Arzneimittels (SmPC), April 2020.

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R20-0189 Liu Y, Zhou S, Assaf M, Nissel J, Palmisano M. Impact of renal impairment on the pharmacokinetics of apremilast and metabolite M12. Clin Pharmacol Drug Dev 2016; 5(6): 469-479.

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R20-3405 Sung P. Using SAS Proc Power to perform model-based power analysis for clinical pharmacology studies. https://www.pharmasug.org/cd/papers/SP/SP05.pdf (access date: 19 October 2020); PharmaSUG; 2010.

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		16 April 2020
EudraCT number		2019-005037-37
BI Trial number		1407-0041
BI Investigational Medicinal Products		Otezla® (Apremilast) film-coated tablets sourced from two ICH regions (EU and US)
Title of protocol		Bioequivalence of two different tablet formulations of 30 mg of apremilast (EU-sourced Otezla® vs. US-sourced Otezla®) administered in healthy male and female subjects in the fasted state as well as in the fed state (an open-label, randomised, single-dose, four-period, four-sequence crossover study)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1) 3.3.4.3 2) 5.2.6.1.4 3) 5.2.6.1.4
Description of change		1) Specification, which of the reasons mandatory lead to discontinuation of the trial. Limitation of severe non-serious adverse events considered as drug-related by the investigator to 25% of the subjects (refer to reason no. 3). 2) Definition of AESIs (depression, mood changes, suicidal ideation, and suicidal behaviour/attempt) 3) BI 730357 was specified as the investigational product whose development could be discontinued (refer to reason no. 5).
Rationale for change		1) Required by Competent Authority and IEC 2) Recommended by Competent Authority and IEC 3) Clarification by Sponsor

11.2 GLOBAL AMENDMENT 2

Date of amendment		05 November 2020
EudraCT number		2019-005037-37
BI Trial number		1407-0041
BI Investigational Medicinal Products		Otezla® (Apremilast) film-coated tablets sourced from three ICH regions (EU, US, and Japan)
Title of protocol		Bioequivalence of three different tablet formulations of 30 mg of apremilast (EU-sourced Otezla® vs. US-sourced Otezla® vs. Japan-sourced Otezla®) administered in healthy subjects in the fasted state as well as (for EU-sourced Otezla® vs. US-sourced Otezla®) in the fed state (an open-label, randomised, single-dose, five-period, ten-sequence crossover study)

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		1) Title page, CTP synopsis, Flow chart, Sections 1.1, 1.3, 1.4.2, 2.1.1, 3.1, 3.2, 3.3, 4.1.1, 4.1.4, 6.2.2, 7.1, 7.2, 7.3, 7.6, and 7.7 2) Sections 1.4.2, 3.3.3, and 8.1 3) Sections 1.1, 1.2.1, 1.4.2, 4.1.1, and 9.1 4) Section 5.3.2.1
Description of change		1) Adaption of CTP title, trial design, sample size, randomization, and statistical evaluation 2) Addition of potential drug risk with respect to SARS-CoV-2 infection, addition of safety measures and exclusion criterion no. 29 3) Updating of marketing authorization holder and references in the text 4) Removal of further methodological investigations
Rationale for change		1) Extension of the bioequivalence comparison to include the Japanese Otezla formulation under fasting conditions 2) Consideration of the current COVID-19 pandemic 3) Revised Otezla® SmPC/Prescribing Information 4) Not applicable for this clinical trial

APPROVAL / SIGNATURE PAGE

Document Number: c30404410 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-03

Title: Bioequivalence of three different tablet formulations of 30 mg of apremilast (EU-sourced Otezla® vs. US-sourced Otezla® vs. Japan-sourced Otezla®) administered in healthy male and female subjects in the fasted state as well as (for EU-sourced Otezla® vs. US-sourced Otezla®) in the fed state (an open-label, randomised, single-dose, five-period, ten-sequence crossover study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	09 Nov 2020 08:54 CET
Author-Clinical Trial Leader		09 Nov 2020 10:47 CET
Approval-Clinical Pharmacokinetics		09 Nov 2020 14:34 CET
Approval-Therapeutic Area [redacted]		09 Nov 2020 19:02 CET
Verification-Paper Signature Completion		10 Nov 2020 11:17 CET
Approval-Team Member Medicine		11 Nov 2020 17:48 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed