Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c27983101-03**
BI Trial No.	1407-0037	
BI Investigational Medicinal Product(s)	BI 730357	
Title	Partially-blind, randomized, parallel group, placebo and active comparator-controlled Phase I clinical trial to evaluate the photosensitivity potential of BI 730357	
Lay Title	Evaluation of photosafety of BI 730357 compared to placebo and the known photosensitizing agent ciprofloxacin	
Clinical Phase	Phase I	
Clinical Trial Leader	[redacted] Tel.: [redacted]	
Principal Investigator	[redacted] Tel: [redacted]	
Version and Date	**Version: 3.0**	**Date: 01 Apr 2020**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	27 Sep 2019
Revision date	01 Apr 2020
BI trial number	1407-0037
Title of trial	Partially-blind, randomized, parallel group, placebo and active comparator-controlled Phase I clinical trial to evaluate the photosensitivity potential of BI 730357
Principal Investigator	[redacted]
Trial site	[redacted]
Clinical phase	Phase I
Trial rationale	To evaluate photosafety of BI 730357
Trial objective(s)	The objective of this trial is to evaluate the photosensitivity potential of BI 730357 compared to placebo and a mild photosensitizer ciprofloxacin as positive control, assessed by the Photosensitivity Index (PI), changes in MED, erythema, and local skin reactions following exposure to UVA and UVB radiation. In addition, the relationship between the photosensitivity response and pharmacokinetics of BI 730357 may be evaluated.
Trial endpoints	<u>The primary endpoints are:</u> • Phototoxicity index at 24 h under condition 1 • Phototoxicity index at 24 h under condition 2 <u>The secondary endpoints are:</u> • Phototoxicity index at 10 min under condition 1 • Phototoxicity index at 1 h under condition 1 • Phototoxicity index at 10 min under condition 2 • Phototoxicity index at 1 h under condition 2 • Minimum Erythema Dose (MED) percent change from baseline at 10min, 1h, and 24h measured under condition 1 and condition 2 All endpoints are applicable for both treatment parts.
Trial design	This is a partially blind, randomized, parallel group, placebo-controlled study conducted in two treatment arms. Treatment Part A will be conducted according to a randomized,

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	double blind, placebo-controlled design to assess the photosensitivity potential, safety, tolerability, and pharmacokinetics of multiple doses of BI 730357. Subjects will be randomized in a 3:1 manner to receive BI 730357 or placebo. Subjects will receive 400mg QD of BI 730357 or placebo over 8 days, or 300 mg BID of BI 730357 or placebo over 7 days with a single dose on day 8. Separate randomizations will be carried out for 400 mg QD/placebo and 300 mg BID/placebo. Photosensitivity assessments will occur at baseline and following the last dose of either BI 730357 or placebo. Treatment Part B will be conducted according to an open-label, observer-blinded design to assess the photosensitivity potential of ciprofloxacin (a mild photosensitizer) as a positive control. Subjects will receive 500 mg ciprofloxacin twice-daily starting on Day 3 through to the morning of Day 8. Photosensitivity assessments will occur at base line and following the last dose of ciprofloxacin.
Total number of subjects randomised	Approximately 84 subjects will be enrolled to allow for at least 74 completed subjects
Number of subjects on each treatment	36 subjects in Part A for 400 mg QD 36 subjects in Part A 300 mg BID 12 subjects in Part B
Diagnosis	Healthy volunteers
Main in- and exclusion criteria	Healthy male and female subjects as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening; aged ≥18 to ≤55 years, with a BMI range: ≥18 to ≤ 35 kg/m Fitzpatrick skin type I, II, or III Fitzpatrick Skin Type Description: I Always burns easily, never tans II Always burns easily, tans minimally III Burns moderately, tans gradually
Test product(s)	BI 730357 100 mg tablets
dose	400mg once daily 300mg twice daily
mode of	p.o.

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administration	
Comparator product(s)	Placebo matching BI 730357
dose	Not applicable
mode of administration	p.o.
Comparator product(s)	Ciprofloxacin
dose	500mg twice daily
mode of administration	p.o.
Duration of treatment	BI 730357 tablets or matching placebo over 8 days Ciprofloxacin over 5.5 days
Statistical methods	A mixed model for repeated measures on Phototoxicity index (PI) values will be utilized for the analysis of primary and secondary endpoints. The model will include treatment (BI 730357, Placebo, ciprofloxacin), time (10min, 1h, 24h, 48h, and 72h), and treatment-time interaction as fixed effects and subject as a random effect. Adjusted means and differences in PI and 90% CIs for the contrasts of interest (i.e. BI 703357 – placebo at 24h) will be calculated from the model. The analysis will be carried out separately for condition 1 and condition 2 Descriptive statistics will be tabulated for all endpoints.

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FLOW CHART TREATMENT A 400 MG QD

Day	Planned time [h:min]	Approx. time [h:min]	Event and comment	Drug administration	Laboratory[1]	UVB/UVA irradiation	Photosensitivity assessment[4]	[redacted]	Physical Exam	12-lead ECG[3]	Vital signs [3]	AE/Concomitant Medication
-28 to -3			Screening		X				X	X	X	X
-3						X[4]	X[6]					X
-2						X[7]	X[5]					X
-1			Admission		X	X[8]	X[5]		X	X	X	X
1	-1:00	7:00	Predose/ Randomization				X[7]					X
	0:00	8:00		X								
	4:00	12:00										X
2	24:00	8:00		X								X
3	48:00	8:00		X								X
4	72:00	8:00		X								X
5	96:00	8:00		X								X
6	120:00	8:00		X								X
7	144:00	8:00		X								X
8	168:00	8:00		X	X							X
	169:00	9:00										
	170:00	10:00				X						
	170:10	10:10					X					
	171:00	11:00					X					
	172:00	12:00										
	174:00	14:00										
	180:00	20:00										
9	192:00	8:00										X
	194:00	10:00					X					
10	216:00	8:00										X
	218:00	10:00					X					
11	240:00	8:00							X	X	X	X
	242:00	10:00	Discharge				X					
15			EOT[2]		X				X	X	X	X

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FLOW CHART TREATMENT A 300 MG BID

Day	Planned time[9] [h:min]	Approx. time [h:min]	Event and comment	Drug administration	Laboratory[1]	UVB/UVA irradiation	Photosensitivity assessment[4]	[redacted]	Physical Exam	12-lead ECG[3]	Vital signs[3]	AE/Concomitant Medication
-28 to -3			Screening		X				X	X	X	X
-3						X[4]	X[6]					X
-2						X[7]	X[5]					X
-1			Admission		X	X[8]	X[5]		X	X	X	X
1	-1:00	7:00	Predose/ Randomization				X[7]					X
	0:00	8:00		X								
	1:00	9:00										
	2:00	10:00										
	3:00	11:00										
	4:00	12:00										X
	6:00	14:00										
	8:00	16:00										
	10:00	18:00										
	12:00	20:00		X								
2	24:00	8:00		X								X
	36:00	20:00		X								
3	48:00	8:00		X								X
	60:00	20:00		X								
4	72:00	8:00		X								X
	84:00	20:00		X								
5	96:00	8:00		X								X
	108:00	20:00		X								
6	120:00	8:00		X								X
	132:00	20:00		X								
7	144:00	8:00		X								X
	156:00	20:00		X								
8	168:00	8:00		X	X							X
	169:00	9:00										
	170:00	10:00				X						

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Day	Planned time[9] [h:min]	Approx. time [h:min]	Event and comment	Drug administration	Laboratory[1]	UVB/UVA irradiation	Photosensitivity assessment[4]	[redacted]	Physical Exam	12-lead ECG[3]	Vital signs[3]	AE/Concomitant Medication
	170:10	10:10					X					
	171:00	11:00					X					
	172:00	12:00										
	174:00	14:00										
	180:00	20:00										
9	192:00	8:00										X
	194:00	10:00					X					
10	216:00	8:00										X
	218:00	10:00					X					
11	240:00	8:00							X	X	X	X
	242:00	10:00	Discharge				X					
15			EOT[2]		X				X	X	X	X

1 For the laboratory tests performed at each particular visit refer to the Tables: 5.2.3:1 and 5.2.3:2
for Photosensitivity assessments refer to the section 5.1.

2 Patients who discontinue trial treatment prematurely-should undergo the End of Treatment (EOT) visit 7 days thereafter.

3 Measurements of vital signs (BP; PR; BT) and ECG should precede blood sampling

4 Photosensitivity assessment on day -2/-1 will be performed 10 (+/-2) min, 1h (+/-5min), 24h (+/-10min) after irradiation

5 Preliminary estimation of MED

6 Outpatient irradiation and baseline MED testing for Irradiation Condition 1 and Irradiation Condition 2 will occur on Day -2. Two areas of the back will be defined for irradiation, followed by MED assessments at 10 ±2 minutes, 1 hour ±5 minutes (Day -2) and at 24 hours ±10 minutes (Day -1) post irradiation.

7 Baseline irradiation for Irradiation Condition 3 will occur on Day -1 with baseline inflammatory responses assessed at 10 ±2 minutes, 1-hour ±5 minutes (Day -1) and at 24 hours ±10 minutes (Day 1) post Day -1 irradiation.

8 Preliminary MED irradiation will be performed on Day -3 with confirninng evaluation on Day -2.

9 Planned time relative to the drug administration

10 [redacted] samples should be taken before drug administration

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FLOW CHART TREATMENT B

Day	Planned time [h:min]	Approx. time [h:min]	Event and comment	Drug administration	Laboratory[1]	UVB/UVA irradiation	Photosensitivity assessment	Physical Exam	12-lead ECG[4]	Vital signs [4]	AE/Concomitant Mediation
-28 to -3			Screening		X			X	X	X	X
-3						X[4]	X[6]				X
-2						X[7]	X[5]				X
-1			Admission		X	X[8]	X[5]	X	X	X	X
1	0:00	8:00	Randomization				X[7]				X
2	24:00	8:00									X
3	48:00	8:00		X							X
		20:00		X							
4	72:00	8:00		X							X
		20:00		X							
5	96:00	8:00		X							X
		20:00		X							
6	120:00	8:00		X							X
		20:00		X							
7	144:00	8:00		X							X
		20:00		X							
8	168:00	8:00		X	X						X
	170:00	10:00				X					
	170:10	10:10					X				
	171:00	11:00					X				
9	192:00	8:00									X
	194:00	10:00					X				
10	216:00	8:00									X
	218:00	10:00					X				
11	240:00	8:00						X	X	X	X
	242:00	10:00	Discharge				X				
15			EOT[2]		X			X	X	X	X

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1 For the laboratory tests performed at each particular visit refer to the Tables: 5.2.3:1 and 5.2.3:2
for Photosensitivity assessments refer to the section 5.1.

2 Patients who discontinue trial treatment prematurely-should undergo the End of Treatment (EOT) visit 7 days thereafter.

3 Measurements of vital signs (BP; PR; BT) and ECG should precede blood sampling

4 Photosensitivity assessment on day -2/-1 will be performed 10 (+/-2) min, 1h (+/-5min), 24h (+/-10min) after irradiation

5 Preliminary estimation of MED

6 Outpatient irradiation and baseline MED testing for Irradiation Condition 1 and Irradiation Condition 2 will occur on Day -2. Two areas of the back will be defined for irradiation, followed by MED assessments at 10 ±2 minutes, 1 hour ±5 minutes (Day -2) and at 24 hours ±10 minutes (Day -1) post irradiation.

7 Baseline irradiation for Irradiation Condition 3 will occur on Day -1 with baseline inflammatory responses assessed at 10 ±2 minutes, 1-hour ±5 minutes (Day -1) and at 24 hours ±10 minutes (Day 1) post Day -1 irradiation.

8 Preliminary MED irradiation will be performed on Day -3 with confirming evaluation on Day -2.

9 Planned time relative to the drug administration

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AS	Ankylosing spondylitis
AST	Aspartate Aminotransferase
[redacted]	
b.i.d.(BID)	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BP	Blood Pressure
CA	Competent Authority
CI	Confidence Interval
[redacted]	
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment

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EoTrial	End of Trial
EudraCT	European Clinical Trials Database
FC	Flow Chart
FOT	Fully Outcourced Trial
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
HIV	Human Immunodeficiency Virus
i.v.	intravenous
IB	Investigator's Brochure
IC	Inhibitory Concentration
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma-Release-Assay
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MED	Minimum Erythema Dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose
NOAEL	No Adverse Effect Level
OPU	Operative Unit
p.o.	per os (oral)
PK	Pharmacokinetics
PR	Puls Rate
PsA	Psoriatic Arthritis

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PsO	Plaque Psoriasis
QD (q.d.)	Once daily
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SC	Steering Committee
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	
TMF	Trial Master File
ULN	Upper Level of Normal
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Retinoic acid-related orphan receptor γt (ROR) γt is a nuclear hormone receptor/transcription factor expressed in Th17 cells and in distinct subsets of lymphoid cells including natural killer (NK) cells, innate lymphoid cells (ILCs), and γδT cells. Upon cell activation, in response to multiple activation signals including cytokines and T cell receptor engagement, RORγt regulates the transcription of IL-17A, IL-17F, IL-22 genes, and of the IL-23 receptor gene. Emerging clinical science indicates a pivotal role for the Th17 axis in the pathogenesis of psoriasis (PsO) and other immunologically-mediated diseases. By blocking RORγt-mediated transcription of pro-inflammatory cytokines and IL-23R, and consequently their downstream signaling, RORγt antagonism could prove efficacious in the treatment of Th17-mediated diseases.

1.2 DRUG PROFILE

Boehringer Ingelheim (BI) is developing the new chemical entity (NCE), ROR γt antagonist BI 730357, for the treatment of patients with plaque PsO, and other disease indications (e.g., psoriatic arthritis (PsA), ankylosing spondylitis (AS), axial spondyloarthritis (axSpA), Crohn's disease (CD), and non-alcoholic steatohepatitis (NASH).

Mode of action

BI 730357 binds in the ligand-binding domain (LBD) of ROR γt and inhibits co-activator peptide recruitment, thereby bloking the RORγt-mediated transcription of pro inflammatory cytokines, and of IL-23R.

Residual Effect Period

The Residual Effect Period (REP) of BI 730357 is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies and toxicology studies

Relevant non-clinical pharmacology, PK, and toxicology study results are summarized below.

BI 730357 was profiled in cellular assays in primary human cells central to the pathogenesis underlying PsO, PsA, and axSpA. BI 730357 provided consistent potency across all stimuli,

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cell types, and animal species tested, including in whole blood conditions. BI 730357 provided substantial inhibition of disease-relevant biomarker and histology reads in mechanistic preclinical *in vivo* mouse models of inflammation. The anticipated human therapeutic exposure for BI 730357 was determined based on the effective plasma concentration required to reduce the tissue level of IL-17 by 80% in an IL-23 induced minicircle mouse model (c09228382 Current version, n00250111 Current version]. The data showed that 80% inhibition of tissue IL-17A mRNA at trough is required for maximal inhibition (>80%) of the histology endpoints. The trough exposure was normalized using the mouse whole blood IC50.

Translating to humans using human whole blood IC50, the required trough for maximum effect on histology endpoints for BI 730357 is 140 nM.

BI 730357 demonstrated good off-target selectivity; exhibited low-level inverse-agonism against RORα, low-level antagonism against hLXRα and low-level agonism activity against hPXR. No activity on RORβ was detected. No other off-target activities were detected.

The disposition of BI 730357 in rat, dog, and minipig is characterized by low clearance and moderate volume of distribution. Moderate-to-high oral bioavailability was observed across species. The plasma protein binding was high across all tested species (mouse, rat, dog, and human), and there was no preferential partitioning into red blood cells. Biliary excretion or fecal excretion was the major route of elimination of [14C]-BI 730357-derived radioactivity in rat and dog. In a quantitative whole body autoradiography study in pigmented rats, [14C]-

BI 730357-derived radioactivity was moderately distributed to tissues. Tissue-to-blood exposure ratios of radioactivity into melanin-containing tissues of the ocular bulb was moderate to high.

In human hepatocyte incubations, approximately 90% of the metabolism of BI 730357 occurs via oxidation by CYP3A4 to an N-oxide metabolite (CD 6975). As such, concomitant medications that are inhibitors or inducers of CYP3A may cause clinically significant changes in BI 730357 exposure. Furthermore, data from in vitro studies indicate that

BI 730357 may cause clinically relevant induction of CYP1A2 and CYP2B6 and inhibition of hepatic P-glycoprotein (P-gp) and renal MATE1 or MATE2-K. In addition, inhibition of intestinal BCRP in humans is also possible at oral BI 730357 doses > 22 mg.

The toxicity profile of BI 730357 has been assessed in safety pharmacology, genetic toxicity, embryo-fetal development, and repeat dose toxicity studies up to 26- and 39-weeks in rat and dog, respectively. In general, BI 730357 appears to be well tolerated at clinically-relevant plasma exposure in toxicity studies. BI 730357 revealed no evidence of teratogenicity in embryo-fetal development studies in rats and rabbits. In the repeat dose studies up to 26- and

39-weeks in rats and dogs, there were no effects on male or female reproductive organs.

BI 730357 is considered non-genotoxic. Based on long half-lives of radioactivity in dermal tissues and results from an *in vitro* and *in vivo* phototoxicity assay, BI 730357 has phototoxicity potential.

In summary, non-clinical BI 730357 safety data demonstrated an acceptable profile to support clinical trials in males and females, including women of childbearing potential

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(WoCBP). Human exposures up to those achieved at the no observed adverse effect level (NOAEL) of 5 mg/kg/day in the 4- and 13- weeks dog studies (C_{max} 6,660 nM, and AUC_{0-24} 127,400 nM•h in males and females combined) are considered safe for dosing up to 13 weeks in clinical trials. For clinical trials that exceed 13 weeks duration, human exposures up to those achieved at the NOAEL of 1 mg/kg/day in the 39-weeks dog study (C_{max} 1210 nM, and AUC_{0-24} 22,100 nM•h in males and females combined) are considered safe.

The nonclinical safety package supports long-term administration of BI 730357 to human subjects, including WoCBP.

Data from clinical trials

Two clinical trials have been performed in healthy volunteers.

66 male adult subjects receiving BI 730357 in the Single Rising Dose study 1407.1.

Safety evaluations included physical examination, vital signs, ECG, laboratory tests, and adverse events (AEs). AEs, which generally reflected commonly-occurring events of short duration, and were mostly mild or moderate in severity, were distributed without discernible trend among recipients of placebo and rising dose levels of BI 730357. No serious AEs (SAEs) were reported.

Phase Ib trial 1407-0002 evaluated MRD of BI 730357 ranging from 25 mg to 400 mg, administered as film-coated tablets to healthy male adult subjects aged 18 to 45 years.

83 subjects entered into the trial; each group of 12 subjects was randomized (9 active: 3 placebo) into one of 4 sequential dose groups under fasting conditions (25 mg, 50 mg, 100 mg, 200 mg), and into one of 3 sequential dose groups under fed conditions (50 mg, 200 mg, and 400 mg). Comparison of the mean BI 730357 plasma concentrations indicated that exposure was related to dose, such that exposures increased with increasing dose. When BI 730357 was administered to subjects in the fed state, higher

BI 730357 plasma levels and exposures were observed, with a delayed peak in concentrations compared to fasted conditions. Median t_{max} values ranged from 1.00 to 2.75 h in the fasted state and increased to 2.55 to 4.00 h in the fed state. Concentrations following multiple dosing appeared to be approximately double those following a single dose, with no relevant difference seen between 2 and 4 week profiles. Subjects were evaluated for safety (physical examination, ECG and laboratory studies, AEs, and SAEs) and PK during once daily study drug treatment for 14 days (dose groups up to 100 mg) or 28 days (200 mg and 400 mg dose groups), and for approximately one week after completion of treatment. Safety data indicate that with respect to the kind, incidence and severity of the AEs, there were no notable differences among dose groups. The most frequently reported AEs were headache in 26.5% and diarrhea in 10.8% of subjects, of subjects across BI 730357 dose groups. No SAEs were reported during the trial. ECG recordings, clinical laboratory evaluation, and vital signs showed no clinically-relevant changes compared to baseline. Overall, administration of BI 730357 to healthy male subjects at doses up to 400 mg for up to 28 days was well tolerated.

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A phase II trial (1407-0030) in patients with moderate-to-severe chronic plaque psoriasis is ongoing, 178 patients were included and randomized in a blinded manne to receive 25 mg, 50 mg, 100 mg, or 200 mg of BI 730357, or placebo, *q.d.*, under fasted conditions, for 24 weeks. Primary analysis data from trial 1407-0030 demonstrate that PsO patients had higher exposure (up to 2.1 fold) compared to those of healthy volunteers in 1407-0002. Moreover, the exposures in PsO patients appear to be increasing with increasing dose, up to the highest (200 mg) dose evaluated, in a close to dose- proportional manner.

Administration of BI 730357 to patients with moderate-to-severe plaque PsO at doses up to 200 mg for at least 12 weeks has been well tolerated. Through Week 12, the overall frequency of patients with at least 1 treatment emergent adverse events (TEAE) was 50.6% for patients receiving BI 730357 (range 47.5% to 53.8%, vs. 55.0% of placebo recipients). The most commonly reported AEs, by preferred term, were “upper respiratory tract infection” (10.1%, range 2.5% to 15.4%, vs. 15.0% among placebo recipients), “nasopharyngitis” (6.3%, range 5.0% to 7.7%, vs. 0% among placebo recipients), and “headache” (3.2%, range 0% to 5.1%, vs. 0% among placebo recipients). ECG recordings, laboratories, and vital signs showed no clinically-relevant changes compared to baseline.

The non-clinical BI 730357 safety data together with the safety data from the two trials in healthy volunteers (HV) and patients in plaque psoriasis demonstrated an acceptable profile to support clinical trials in males and females, including WoCBP. These data justify the oral dose of 400 mg BI 730357, taken once daily and 300 mg BI 730357 taken twice daily, over 8 days in healthy male and female volunteers. It is anticipated that higher mean BI 730357 exposures as expected with 300 mg dosed b.i.d. under fed conditions for 8 days will not exceed the NOAEL thresholds observed in 13 weeks general toxicity studies.

For a more detailed description of the profile of BI 730357 please refer to the current Investigator’s Brochure (IB) (c09228382).

Ciprofloxacin

CIPRO is a fluoroquinolone antibacterial indicated to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

The absolute bioavailability of ciprofloxacin when given as an oral tablet is approximately 70% with no substantial loss by first pass metabolism.

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Steady-state C_{max} and AUC of Ciprofloxacin following administration of multiple oral doses to healthy subjects are 2.97 and 13.7 mcg•hr/mL respectively. When CIPRO Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour.

For a more detailed description of the profile of Ciprofloxacin please refer to the ciprofloxacin hydrochloride tablet U.S. prescribing information (R19-2246 and R19-3127).

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1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 730357 is being developed for the treatment of patients with moderate-to-severe PsO, and other disease indications (e.g., psoriatic arthritis (PsA) axSpA, CD, and NASH) where there remains an unmet medical need.

Preclinical data indicate that BI 730357 has phototoxicity potential.

The current trial is being performed to assess the photosafety of BI 730357 compared to placebo and the known photosensitizing agent ciprofloxacin in healthy volunteers.

Safety data provided by this trial will support further clinical development program of BI 730357 in patients with diverse indications.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Participation in this trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance to the development of BI 730357 and may help to generate future benefit for larger groups of patients with many disease indications.

1.4.2 Risks

The subjects are exposed to the risks related to the exposure to the trial medication and the risks of the trial procedures.

Drug-related risks and safety measures

BI 730357

The pharmacological effects of BI 730357 are dose dependent, and no evidence for prolonged or irreversible effects has been observed.

As described in Section 1.2, the non-clinical BI 730357 safety data together with the safety data from trials in healthy volunteers (HV) and patients with plaque PsO demonstrated an acceptable profile to support clinical trials in males and females, including WoCBP.

Since preclinical data indicate that BI 730357 has phototoxicity potential, subjects in this trial will be kept in the clinic on all dosing days up until completion of photosensitivity assessments 72 hours after last dose and not allowed to expose themselves to the direct sunlight. Additionally, subjects will be advised to apply protection measures up to the end of trial visit, as described in section 4.2.2.2 .

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Preclinical data indicate that BI 730357 has DDI potential. During the trial, drugs or foods which are known strong or moderate inhibitors or inducers of CYP3A4, or drugs which are sensitive substrates of CYP1A2 or CYP2B6 will be prohibited. Additionally, substrates of

P-gp are also to be excluded during the trial BI 730357 is confirmed as a sensitive cytochrome P450 (CYP) 3A substrate, based on clinical drug-drug interaction (DDI) evaluation with itraconazole, a CYP3A inhibitor, in trial 1407-0014. Drugs or foods that are known CYP3A inhibitors or strong or moderate CYP3A inducers should not be co-administered in clinical trials with BI 730357. Based on *in vitro* data, BI 730357 could potentially induce CYPs 1A2, 2B6, 2C8, 2C9, or 2C19 in human. Substrates of CYPs 1A2, 2B6, 2C8, 2C9, or 2C19 for which a reduction in exposure could present a potential patient risk should not be given together with BI 730357. Additionally, based on *in vitro* data, BI 730357 may inhibit a number of transporters in human; based on the magnitudes of the *in vitro* inhibition, it is recommended that sensitive substrates of P-gp, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1, and MATE2-K that have narrow therapeutic windows should be avoided (refer to Appendix 10.1).

As with other immune-targeted therapies, impaired host defence is a theoretical target-related toxicity, potentially resulting in increased risk of infection and/or malignancy. Subjects with latent TB infection or TB disease, also subjects with HBV, HCV, HIV or any other clinically relevant bacterial or fungal infections will be excluded at screening.

Risk to subjects will also be minimized in this trial by implementing conservative eligibility criteria.

Homozygous, but not heterozygous RORC knockout mice have a high incidence of T cell lymphoma, thought to originate in the Thymus. While the translatability of the knockout phenotype to pharmacological RORγ antagonism and to humans is unknown, this raises the hypothetical concern for clinical T cell lymphoma risk. The exact cause of T cell lymphomas in RORC knockout mice is not fully understood, but changes in homeostasis in the thymus, such as thymocyte apoptosis and proliferation, are thought to play a role. AEs and SAEs consistent with malignancy, and specifically those representing lymphoma, will be carefully monitored and evaluated as well as monitoring of peripheral blood lymphocyte subsets will be integrated into this clinical trial.

An *in vivo* phototoxicity study in rats was conducted in pigmented rats. No cutaneous reactions indicative of phototoxic response were seen at 10 mg/kg/day, which corresponded to mean C_{max} and AUC_{0-24} values of 4,520 nM and 35,200 nM•h, respectively. No ophthalmic changes indicative of phototoxicity were seen up to 30 mg/kg/day, which corresponded to a mean C_{max} and AUC_{0-24} values of 13,500 nM and 107,000 nM•h, respectively.

Dose 400 mg BI 730357 planned to be tested in this study was administered once daily over a period of 4 weeks in the MRD study 1407-0002. The pharmacokinetic parameters observed in this study - AUC_{0-24} [nmol*h/L] 15,600 ($AUC_{\tau,ss}$ [nmol*h/L] 35,500) and C_{max} [nmol/L] 1320 ($C_{max,ss}$ [nmol/L] 2210) indicate that the plasma concentrations and exposures, which might be achieved in this study, are lower than those observed in *in vivo* phototoxicity study in rat where the phototoxic responses have been seen.

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Ciprofloxacin

The most frequently reported adverse reactions, from clinical trials of all formulations, all dosages, all drug therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhoea (1.6%), liver function tests abnormal (1.3%), vomiting (1%), and rash (1%).

Changes in laboratory parameters while on CIPRO are listed below:

Hepatic -Elevations of ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, serum bilirubin.

Hematologic-Eosinophilia, leukopenia, decreased blood platelets, elevated blood platelets, pancytopenia.

Renal-Elevations of serum creatinine, BUN, crystalluria, cylindruria, and hematuria have been reported.

Other changes occurring were: elevation of serum gammaglutamyl transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes, and leucocytosis.

Fluoroquinolones, including CIPRO, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. These adverse reactions include:

- Tendinitis and Tendon Rupture
- Peripheral Neuropathy
- Central Nervous System Effects
- Exacerbation of Myasthenia Gravis
- Other Serious and Sometimes Fatal Adverse Reactions
- Hypersensitivity Reactions
- Hepatotoxicity
- Serious Adverse Reactions with Concomitant Theophylline
- Clostridium difficile Associated Diarrhea
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Photosensitivity/Phototoxicity
- Development of Drug Resistant Bacteria

These reactions can occur within hours to weeks after starting CIPRO. Patients of any age or without pre-existing risk factors have experienced these adverse reactions. These events may be severe and generally occur following the administration of multiple doses.

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As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by Sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety (see also section 5.2.6.1.4).

Special precautions

The following safety measures will be applied in order to minimize the risk for healthy volunteers:

- Dose selection is based on a sound preclinical package, and safety, tolerability and PK data from MRD administration of BI 730357 up to 400 mg in healthy volunteers and preliminary safety data for up to 200 mg in patients with plaque psoriasis.
- Dose duration of 500 mg of ciprofloxacin bid over 5.5 days is a standard, well tolerated clinical dose
- Individual stopping rules as described in section 3.3.4.1 will be applied.
- UV-light protection measures as described in section 4.2.2.2 will be required until the end of study visit.
- The subjects will be kept in a Phase I unit during trial medication administration until completion of photosensitivity assessments 72 hours after last dose for safety evaluations. A careful clinical examinations will be performed during the trial, before the subjects are discharged from the clinic, and at the end of trial visit.
- Adverse events, body temperature, vital signs, ECGs and safety laboratories will be monitored at different time points during the trial. During the safety follow-up period all AEs, regardless of relatedness, will be collected up to 7 days after the last administration of trial medication.

Procedure-related risks

Blood sampling by venepuncture or through an indwelling venous catheter may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

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

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Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential (WoCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or foetus to the investigational drug, WoCBP must agree to the requirements for pregnancy testing and contraceptive methods described in this protocol. There are no specific contraceptive requirements for male participants.

Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
<u>Investigational Medicinal Products:</u>		
• Drug-induced liver injury (DILI)	• Rare but severe event, thus under constant surveillance by Sponsors and regulators.	• Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. • Drug interruption or discontinuation if applicable.
• Infection and/or malignancy	• Impaired host defence typical for immune-targeted therapies	• Subjects with latent TB infection or TB disease at screening will be excluded. • Patients with HBV, HCV or HIV infection will be excluded. • AEs and serious adverse events (SAEs) consistent with malignancy or infections are to be evaluated.
• Phototoxicity potential	• Long persistence of BI 730357 in dermal tissues. • Known phototoxicity potential of Ciprofloxacin	• Apply protection measures such as sunscreen and sunglasses during therapy and up to 7 days after last drug exposure. Prohibition of treatment with ultraviolet light or medications with known phototoxicity potential up to 7 days after last drug exposure.

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Potential risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Products:		
• Hypersensitivity	• General precautions	• Subjects with known hypersensitivity to investigational drugs will be excluded at screening. • Discontinue investigational drugs immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.
• Prolongation of the QT Interval	• Known potential of Ciprofloxacin	• Subjects with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes will be excluded at screening.
Trial procedures		
• Inflammation of the wall of the vein. Injuring of a nerve while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	• General risk, acceptable in frame of the study participation	• Evaluation of the medical expertise of the trial sites is part of site feasibility assessment

1.4.3 Discussion

The nature of the target and the mechanism of action of BI 730357 as well as of Ciprofloxacin are well understood.

In the context of the unmet medical need and anticipated benefit of BI 730357, the benefit-risk evaluation of the compounds, based upon preclinical and clinical information available to date, is considered favourable and healthy subjects in this trial will not be exposed to undue

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safety risks in relation to the important information expected from this trial as a basis for further clinical development of BI 730357.

Considering the medical need of the development of a better tolerated and more effective oral treatment for patients with PsO and other Th17-mediated diseases, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

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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 evaluate the photosensitivity potential of BI 730357.

All endpoints are applicable for both treatment parts.

2.1.2 Primary endpoint(s)

The primary endpoints are:
- Phototoxicity index at 24 h under condition 1
- Phototoxicity index at 24 h under condition 2

Where condition 1 is full range solar UVB/UVA exposures and Condition 2 is UVA exposure only. Refer to Section 5.1 for the details of photosensitivity assessments and these conditions.

Refer to Section 7.2.2 for the endpoint definitions

2.1.3 Secondary endpoint(s)

- Phototoxicity index at 10 min under condition 1
- Phototoxicity index at 1 h under condition 1
- Phototoxicity index at 10 min under condition 2
- Phototoxicity index at 1 h under condition 2
- MED percent change from baseline at 10min, 1h, and 24h measured under condition 1 and condition 2

Where conditions 1 and 2 are described above in Section 2.1.2.

Refer to Section 7.2.3 for the endpoint definitions.

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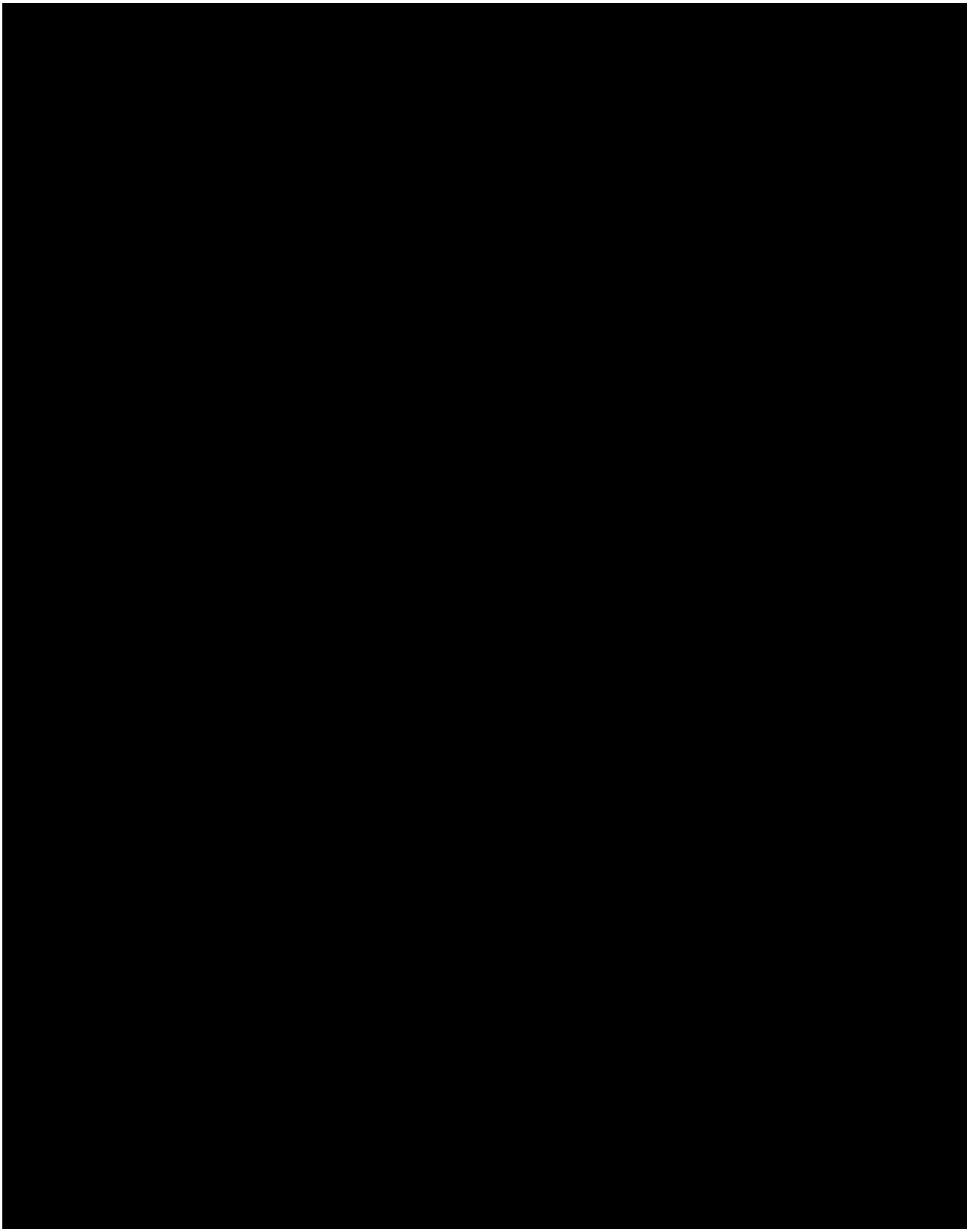

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The trial will be performed as partially-blind, randomized, parallel group, placebo and active comparator controlled Phase I clinical trial in healthy male and female subjects aged ≥18 to ≤55 years in order to evaluate the photosensitivity potential of BI 730357 compared to placebo and active comparator, and to assess the relationship between the photosensitivity response and pharmacokinetics of the BI 730357. The subjects will be randomized to one of the two treatments parts (Treatment Part A or Treatment Part B).

In total, approximately 84 healthy male and female subjects (36 subjects each dose group in Treatment A; 12 subjects in Treatment B) are planned to be randomized in this trial to allow for at least 74 completed subjects.

Treatment A will be conducted according to a randomized, double blind, placebo-controlled design to assess the photosensitivity potential, safety and tolerability, and pharmacokinetics of multiple doses of BI 730357. Subjects will be randomized in a 3:1 manner to receive BI 730357 or placebo.

Subjects will receive 400mg of BI 730357 or placebo once daily over 8 days, or 300 mg of BI 730357 or placebo twice daily over 7 days with a single dose on day 8, in order to reach pharmacokinetic steady state;

Light exposure will occur 2 hours (+/-10 min) after the last dose of either IP or placebo, and on-treatment photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) will be performed at 10 minutes, and 1, 24, 48, and 72 hours after irradiation.

Treatment B will be conducted according to an open-label, observer-blinded design to assess the photosensitivity potential of ciprofloxacin (a mild photosensitizer) as a positive control.

Subjects will receive 500 mg ciprofloxacin starting on the morning of Day 3. Twelve (12) hours later, subjects received their second dose of 500 mg ciprofloxacin. Subjects continued a twice-daily dosing regimen through to the morning of Day 8 to ensure they reached pharmacokinetic steady state.

Light exposure will occur on Day 8 at 2 hours (+/-10 min) post-dose, and on-treatment photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) were performed at 10 minutes, and 1, 24, 48, and 72 hours after irradiation.

This trial will have a screening period of up to 28 days including preliminary photosensitivity assessment on Day -3. Eligible subjects will undergo base line photosensitivity assessment starting after irradiation on day -2 10 min, 1h, 24 hours after irradiation, and will be admitted to the clinical site on Day -1.

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Subjects confirmed eligible will be dosed on Day 1 and be resident until the Day 11. All subjects will remain in the clinic until day 11. The subject will then return to the clinic for ambulatory visit approx. 7 days after the last drug administration for safety follow up (e.o.t.).

Additionally, all AEs, regardless of relatedness, will be collected until 7 days after the administration of trial medication. Adverse events not fully resolved at the End of Trial visit will be followed until recovery or in case of persistency, sufficient characterization has been achieved and the investigator and medical monitor agree to not pursue them further.

For details for treatments to be administered refer to Section 4.1.

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

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

This is an approximately 8 weeks Phase I trial in healthy volunteers consisting of the two treatment parts.

The design of this clinical photosensitivity study followed the general concepts of ICH S10 (a recently published international guideline on “Photosafety Evaluation of Pharmaceuticals”), and included ciprofloxacin as a positive control (R19-2247).

Three distinct exposure conditions were included to account for seasonal and regional differences in human exposure to sunlight.

A two-layer randomization process will be employed:

Allocation to the Study part: Subjects will be randomly allocated to part A or part B in a 3:1 ratio in an open-label manner. Randomization numbers defining subject allocation to study part will be assigned in ascending, sequential order to eligible subjects.

Treatment Part A will be conducted according to a randomized, double blind, placebo-controlled design.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety. Treatment Part A group will consist of 36 subjects in 400 mg QD group and 36 subjects in 300 mg BID group, with each group having 27 on active treatment and 9 on placebo.

The treatment will be blinded throughout the whole trial, to minimize any bias that could be introduced by knowledge of the treatment by either the investigator or the subject.

Treatment Part B will be conducted according to an open-label, observer-blinded design to assess the photosensitivity potential of ciprofloxacin (a mild photosensitizer) as a positive control.

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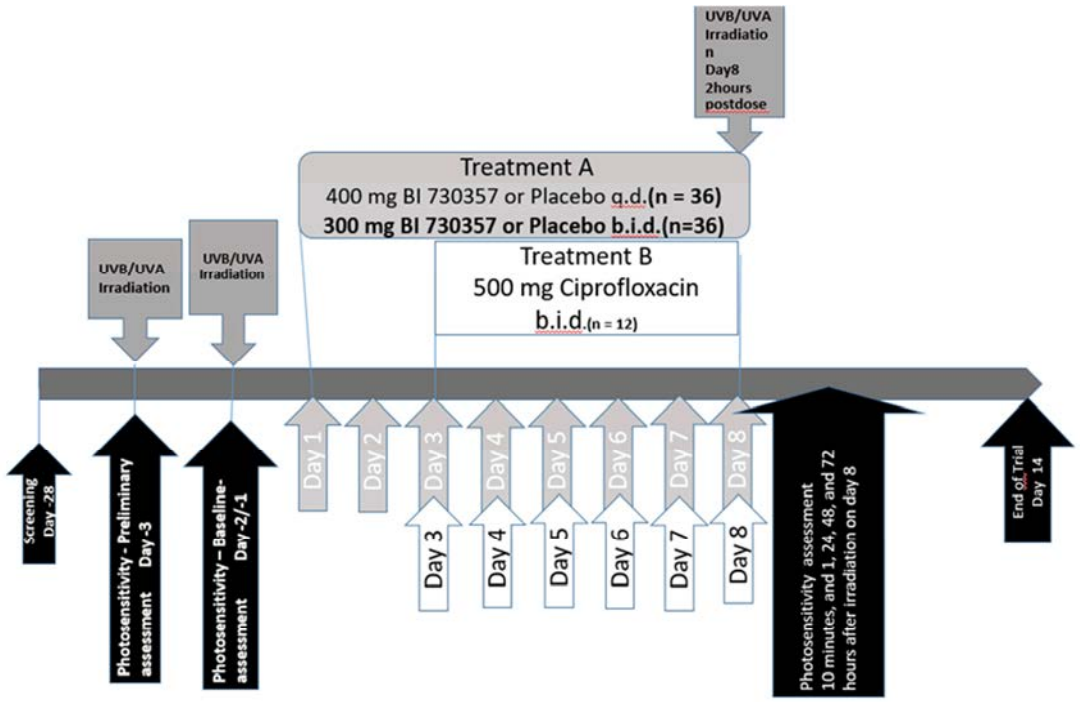
12 subjects will receive 500 mg ciprofloxacin b.i.d. over 5 days with a single dose on the 6th day.

The open-label treatment is not expected to bias the photosafety results, since the trial endpoints derived from the photosensitivity assessments will be provided by an observer performing skin evaluations which is blinded to treatment allocation.



3.3 SELECTION OF TRIAL POPULATION

It is planned that in total up to 84 healthy male and female subjects will enter the trial.

Subjects who prematurely discontinue the trial due to any reason may be replaced to ensure sufficient number complete the trial. Thus the planned number of subjects entered may exceed a total of 84. 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 Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

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

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3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy male and female subjects.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Healthy male and female subjects according to the assessment of the Investigator, based on a complete medical history, physical examination (including dermatological skin type assessment), vital signs (blood pressure, pulse rate), 12-lead ECG, and clinical laboratory tests
2. 18 to 55 years old
3. BMI 18 to 35 kg/m (incl.)
4. Fitzpatrick skin type I, II, or III:
   - I Always burns easily, never tans
   - II Always burns easily, tans minimally
   - III Burns moderately, tans gradually
5. No ultraviolet exposure of the test areas 4 weeks prior to baseline photo testing
6. Normal skin response during preliminary photo testing.
7. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
8. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Tubal ligation is NOT a method of permanent sterilisation.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

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3.3.3 Exclusion criteria

1. Any finding in the medical examination (including blood pressure, pulse rate or ECG) deviating from normal and judged as clinically relevant by the Investigator.
2. Any laboratory value outside the reference range that the Investigator considers to be of clinical relevance.
3. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders or any evidence of a concomitant disease judged as clinically relevant by the Investigator.
4. Major surgery (major according to the investigator's assessment) performed within 10 weeks prior to randomisation or planned within 2 months after screening.
5. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
6. Active skin disorders on the back where photosensitivity testing will be performed.
7. Subjects who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
8. Subjects not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the subject an unreliable trial participant).
9. Currently enrolled in another investigational device or drug trial, or less than 30 days (or 5 half-lives (whichever longer)) since ending another investigational drug trial.
10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients).
12. History of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterials.
13. History of hypersensitivity to sunlight or artificial source of intense light, especially UV light.
14. Chronic or acute infections which are of relevance in the opinion of the Investigator.
15. Positive result for HIV, HBV, and hepatitis C (Hep C) at screening.
16. History of TB or positive finding in IGRA.
17. Unwillingness/inability to refrain from intake of alcoholic beverages from 48 hours prior to the trial medication administration and until Day 7 post trial medication administration.
18. Positive drug screening.
19. Blood donation of more than 500 mL within 30 days prior to administration of trial medication or intended donation during the trial.
20. Intention to perform excessive physical activities within 4 days prior to administration of trial medication or contact sport during the entire trial and unwilling to avoid vigorous exercise for 7 days post dosing.

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21. Inability to comply with dietary regimen of trial site.
22. Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2.
23. Received a live vaccination within 12 weeks prior to randomisation (visit 2), or any plan to receive a live vaccination during the conduct of this trial.
24. Subjects with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes.

3.3.4 Withdrawal of patients 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.

Every effort should be made to keep the subjects in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful subjects' selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the subject files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

- The subject wants to discontinue trial treatment, without the need to justify the decision.
- 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.
- The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment listed in section 4.2.2 and appendix 10.1
- The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- During the course of treatment the subject experiences any clinically significant adverse event (including laboratory abnormalities). The physician may discontinue subjects at any time based on his or her clinical judgment.

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

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

For all participants, the reason for withdrawal from trial treatment (e.g., AE) must be recorded in the CRF. These data will be included in the trial database and reported.

In case some subjects do not complete the trial, the clinical trial lead together with the clinical project lead and the trial statistician will decide if and how many subjects will be replaced. A replacement subject will be assigned to the same treatment as the subject he/she replaces.

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 overall or at a particular trial site at any time for the following reasons:

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

Further follow up of subjects affected will occur as described in section 6.2.3.

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

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 730357, Placebo to match BI 730357.
Ciprofloxacin.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	100 mg
Posology:	QD over 8 days, or BID over 7 days with a single dose on day 8
Method and route of administration:	Per os

Table 4.1.1:2 Test product 2

Substance:	Placebo to match BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	NA
Posology:	QD over 8 days, or BID over 7 days with a single dose on day 8
Method and route of administration:	Per os

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Table 4.1.1:3 Comparator drug

Substance:	Ciprofloxacin
Pharmaceutical formulation:	Film-coated tablet
Source:	[redacted]
Unit strength:	500 mg
Posology:	BID over 5 days from day 3 with a single dose on day 8
Mode of administration:	Per os

4.1.2 Selection of doses in the trial and dose modifications

The dose of 400 mg BI 730357 QD or 300 mg BID for this trial are selected on the basis of the PK and safety data obtained in the SRD and MRD trials 1407.0001 and 1407-0002, preliminary PK and safety data obtained in patients with plaque psoriasis in the ongoing 1407.30 study, combined with the preclinical data (see section 1.1), are intended to cover the highest therapeutic dose range (including safety margin) chosen for the future clinical development of BI 730357 in diverse indications.

In the SRD trial, single dose levels up to 800 mg and in the MRD trial, multiple dose levels up to 400 mg were well tolerated in healthy volunteers, and doses up to 200mg were well tolerated in plaque psoriasis patients.

Blinded photosafety data will be evaluated by the independent Investigator and BI medical team after completion of the 400 mg BI 730357 or placebo QD treatment.

If no photo-safety concerns have been observed in the Treatment A group,300 mg BI 730357 or placebo BID will be conducted.

The Ciprofloxacin dose selected in this trial reflects the standard clinical dose with acceptable safety profile. Ciprofloxacin was chosen as the positive control based on its property as mild photosensitizer (R 19-2246, R 19-3127).

4.1.3 Method of assigning subjects to treatment groups

After the assessment of all in- and exclusion criteria, each eligible subject will be first randomly allocated to part A 400 mg QD or part B in a 3 : 1 ratio, where Part A is initially set of patients who will either receive BI 730357 400mg QD or placebo.

Randomization list for this first step randomization process will be provided by BI to the dedicated staff.

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Consequently, subjects allocated to the treatment Part A will be randomised according to a randomisation plan in a 3:1 ratio following the double blind design, which reflects the ratio of subjects receiving BI 730357 to placebo on Day 1.

Additionally, 12 subjects allocated to the treatment Part B will be assigned to receive Ciprofloxacin treatment.

A second set of 36 patients will be enrolled to either receive BI 730357 300mg BID or placebo. These patients will be randomized using the same double blind design and procedures as described for Part A above (for BI 730357 400mg QD or placebo) and randomized in a 3:1 ratio to BI 730357 300mg BID or placebo. Randomization list for this set of patients will also be provided by BI to the dedicated staff.

The appropriate medication number will be assigned and documented in the CRF.

4.1.4 Drug assignment and administration of doses for each patient

The trial medication will be administered to the subjects as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee. To ensure a dosing interval of 24 and 12 hours for treatment group Part A and 12 hours in treatment Part B, the administration of trial medication should take place at the same time every day within a deviation of no more than +/-15 min. A standard continental breakfast (table 4.1.4:1) should be taken after blood sampling and before the study drug administration (the safety laboratory samples will be taken as the first morning sample from all subjects after at least 6 hours fast prior). The consumption of the continental breakfast will occur within 30 minutes prior to dosing and can occur as for Days 2 -Days 8 before PK samples are collected. A light morning snack can be consumed in the mornings if dosing occurs after 11 am. Further, subjects will consume a snack within 30 minutes prior to their evening dosing.

The medication phase will be followed by a 7 day follow-up and wash-out period.

Table 4.1.4: 1 Composition of the standard continental breakfast as an example

Ingredients	kcal
1 bread roll	164
15 g butter	113
1 slice of Gouda cheese (approximately 40g)	146
1 slice of meat (approximately 20g)	33
1 cup of decaffeinated coffee or tea (without sugar)	2
Sum[1]	458

[1] The total caloric content is supplied approximately as following: approx. 88 kcal as protein, approx. 133 kcal as carbohydrate, and approx. 237 kcal as fat.

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Table 4.1.4: 2 BI 730357, placebo and ciprofloxacin treatments

Treatment group	Fasting condition predose	Substance	Pharmaceutical form	Unit strength	Number of units /dose volume per administration	Total dose
A	Fed[1]	BI 730357	Film-coated tablet	100 mg	4 tablets QD	400 mg
A	Fed[1]	Placebo	Film-coated tablet	--	4 tablets QD	--
B	Fed[1]	Ciprofloxacin	Film-coated tablet	500 mg	1 tablet BID	1000mg
A	Fed[2]	BI 730357	Film-coated tablet	100 mg	3 tablets BID	600 mg
A	Fed[1]	Placebo	Film-coated tablet	--	3 tablets BID	--

1 Drug administration after a standard continental breakfast
2 Drug administration after a standard continental breakfast and evening snack

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

At the trial site, access to the randomization schedule to treatment A or B will be restricted to pharmacists and dedicated staff members.

The Treatment A parts (BI 400 mg QD/placebo and BI 300 mg BID/placebo) of this study are designed double-blind with regard to the subjects and the Investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subj

A	Fed[1]	Placebo	Film-coated tablet	--	4 tablets QD	--

ect's treatment (active or placebo).

Subjects, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind part of the trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The subjects, Investigators and study site staff will not be aware of the treatment allocation (i.e., active vs placebo) from the time of randomization at Day 1 until database lock.

The access to the randomisation code will be kept restricted until its release for analysis.

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The randomisation codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo subjects. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

In addition, the trial pharmacokineticist may receive the blinded (dummy subject numbers will be used) results of the measurements to perform the preliminary PK analysis.

Treatment B of this study will be conducted according to an open-label design however, the sub-investigator conducting photosensitivity assessments will be blinded. This means that the photosensitivity assessments will be evaluated by persons who are independent of the other clinical trial procedures and not involved in other aspects of the trial. Treatment B will be administered on the same days as Treatment A.

4.1.5.2 Unblinding and breaking the code

An emergency code break (envelope) for treatment A will be available to the investigator. This code break may only be opened in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately about the unblinding. The treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. The reason for opening the code break must be documented on the envelope and/or appropriate CRF page.

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

4.1.6 Packaging, labelling, and re-supply

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

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA), as provided in the list of contacts, must be contacted immediately.

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4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethicsAvailability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

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 return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant treatments are allowed.

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In case of AEs in need of treatment, symptomatic therapy according to investigator judgment will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

In addition, a list of medications with potential drug-drug interactions, transport and phototoxic interactions and/or references can be found in the Appendix 10.1. For further guidance investigators are referred to the actual Investigator´s Brochure or may contact the sponsor.

4.2.2.2 Restrictions on diet and life style

Subjects must be fasted for at least 6 hours prior to collection of the safety laboratory samples.

Foods which are known strong or moderate inhibitors of CYP 3A (e.g., fruit juices from star fruit, paw paw, grapefruit) should be avoided during the study participation.

The use of tanning beds is not allowed during the study.

Throughout their participation in the study, participants should avoid direct sunlight. When exposed to sunlight study participants should protect skin areas not covered by clothes by using sun-protection creams and lip balms with sun protection factor 30 or higher with protection against UV-A and UV-B. Additionally, subjects should wear sunglasses when exposed to direct sun or other sources of UV-light.

These protection measures must be applied until the EOT visit.

4.2.2.3 Contraception requirements

Women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

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 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

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5. ASSESSMENTS

5.1 ASSESSMENT OF PHOTOSENSITIVITY

Two Multiport Solar Simulator models 601 ([redacted] will be used for irradiation (150 W or 300 W xenon arc lamp, dichroic mirror, and equipped with filters to produce UVA or UVA+B (290-400nm) outputs). This light source is equipped with 6 liquid light wave guides extending out of the case and an automated shutter device allowing for precise delivery of UV light doses per individual wave guide. Actual irradiation values delivered by the individual light guides will be recorded throughout the study using a PMA2100 Radiometer ([redacted]) equipped with a PMA2113 UVA sensor (physical irradiation in the range of 320 to 400 nm) and with a PMA2103 UVB sensor (biologically weighted, erythemal effective irradiation).

A series of unprotected naive skin test sites on the back will be irradiated with the following three different conditions, meant to simulate three different environmental sunlight exposure scenarios/conditions:

1. Condition 1: Full range solar UVB/UVA (290 to 400 nm, UBV content ~10%), simulating midday summer outdoor sun exposure (assessed in $\mu w/cm^2$).

2. Condition 2: UVA only (320 to 400 nm, UVB content <0.03%), simulating indoor exposure behind window glass with a secondary assessment of erythema and local skin reactions at 25 J cm^{-2}(assessed in mw/cm^2).

[redacted]

Subjects will be exposed to a series of 6 graded full range solar UVB/UVA exposures (Condition 1) and UVA only exposures (Condition 2), each 25% greater than the previous dose. Following irradiation, skin sites will be evaluated for erythema or skin darkening (for UVA-only exposure in the absence of additional, drug-induced phototoxicity).

The MED will be defined as the lowest dose that produced uniform redness (condition 1) or darkening (condition 2) (assessed in joules (J) for UVA and millijoules (mJ) for UVB/UVA).

An approximate $MED_{preliminary}$ will be irradiated on day -3 and will be evaluated 10 min, 1 h and 24 h post irradiation. The initial $MED_{preliminary}$ will be used to fine-tune the irradiation range for the determination of a precise $MED_{baseline}$ on day -2. The $MED_{baseline}$ irradiation will occur on day-2 and will be evaluated 10 min, 1 h and 24 h post irradiation. [redacted]

Outpatient pre-treatment photosensitivity testing will occur prior to the dose administration on day 1 as follows:

Day -3

- Irradiate Preliminary MEDs (Condition 1 and Condition 2) followed by MED assessments at 10 ±2 minutes, 1 hour ±5 minutes

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Day -2

- Assessment of Preliminary MEDs at at 24 hours ±10 minutes post irradiation.
- Irradiate Baseline MEDs (Condition 1 and Condition 2, +/- 30 min to planned time) followed by MED assessments at 10 ±2 minutes, 1 hour ±5 minutes

Day -1

- Assessment of Baseline MEDs (Condition 1 and Condition 2) at 24 hour±10 minutes post irradiation.
- Irradiate Baseline Condition 3 (+/- 30 min to planned time) followed by assessments at 10 ±2 minutes and 1-hour ±5 minutes.

Day 1

[redacted]

Post-treatment photosensitivity testing will occur 2 hours (±10 minutes) after final dose administration on day 8, with the same irradiation conditions as on day -1 as follows:

Day 8

- Irradiate MEDs (Condition 1 and Condition 2) followed by MED assessments at 10 ±2 minutes, 1 hour ±5 minutes
- Irradiate Condition 3 followed by assessments at 10 ±2 minutes, 1 hour ±5 minutes

Day 9

- Assessment of MEDs (Condition 1 and Condition 2) at 24 hour±10 minutes post irradiation.
- Assessment of Condition 3 at 24 hours post hours ±10 minutes post irradiation.

[redacted]

The photosensitivity index (PI) will be calculated as the ratio of the $MED_{baseline}$ versus $MED_{on\ drug}$ for irradiation Conditions 1 and Conditions 2.

Additionally, inflammatory responses (erythema and local skin reactions) and superficial skin effects will be scored (see scales in Table below) under all conditions at baseline (10 min, 1 h and 24 h post-irradiation), and post-treatment day 8 (10 min, 1 h, 24 h, 48 h and 72 h post-irradiation).

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Inflammatory skin reactions will be scored according to:

Skin Reaction Grading Scales

Erythema Grading Scale	Local Skin Reaction	Superficial Effects Grading
0 No evidence of erythema	**E** Edema-swelling, spongy feeling when palpated	**g** Glazing
1 Very slight erythema (barely perceptible)	**P** Papule-red, solid, elevation	**y** Peeling
2 Well defined erythema	**V** Vesicle-small elevation containing fluid	**c** Scab, dried film of serous exudate of vesicular or bullous reaction
3 Moderate to severe erythema	**B** Bullous reaction-fluid filled lesion (blister)	**d** Hyperpigmentation (reddish-brown discoloration of test-site)
4 Severe erythema (beet redness)	**S** Spreading-evidence of the reaction beyond the irradiated area	**h** Hypopigmentation (loss of visible pigmentation at test site)
	W Weeping-result of a Vesicular or bullous reaction serious exudate	**f** Fissuring-grooves in the superficial layers of the skin
	I Induration-solid, elevated, hardened, thickened skin	
	- Response occurs ≤25% of test site	

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, skin, head, neck, throat, lymph nodes, lungs, cardiovascular and neurological systems, abdomen, and extremities.

Measurements of height and body weight will be performed at screening only.

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.

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This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a supine position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1 below. For the sampling time points please see the flowchart. Additional testing for infectious deseases can be added at any timepont during the study, as requested by the authority, or judged by the investigator.

All analyses will be performed by a site local laboratory, the respective reference ranges will be provided in the ISF.
Subjects have to be fasted for at least 6 hours prior to the blood sampling for the safety laboratory.

The laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.6.1 and the DILI Checklist provided in the ISF. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The clinical local laboratory will transfer the results of the analysis to the sponsor/ sponsor representative.

Table 5.2.3: 1 Safety laboratory

Functional lab group	**Test name**	A[1]	B[2]	C[3]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red blood cells (RBC)	X	X	X
	White blood cells (WBC)	X	X	X
	Platelet count	X	X	X
	MCV	X	X	X
	MCH	X	X	X
	MCHC	X	X	X
	RDW	X	X	X
Automatic WBC differential (relative and absolute)	Neutrophiles total	X	X	X
	Lymphocytes total	X	X	X
	Eosinophiles	X	X	X
	Basophiles	X	X	X
	Monocytes	X	X	X

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	Lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) INR	X X X		
Functional lab group	**Test name**			
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (AP) Gammaglutamyl transferase (GGT) Creatine kinase (CK) Lipase Amylase	X X X X X X X	X X X X	X X X X X X
Substrates	Glucose Creatinine Urea Nitrogen Uric Acid Total bilirubin Direct bilirubin Total protein Albumin Globulin Albumin/Globulin ratio C-Reactive Protein (CRP) Total cholesterol	X X X X X X X X X X X X	X X X X X X	X X X X X X
Electrolytes	Calcium Sodium Potassium Chloride Phosphate	X X X X X		X X X X X
Serum Pregnancy test (only for female subjects of childbearing potential) at screening, day -1 and if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin	X	X[4]	
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urine bilirubin Urine Blood Urine leukocyte esterase Urine pH Specific gravity	X X X X X X X X X		X X X X X X X X X

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Urine sediment (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			
Urine Pregnancy test (only for female subjects of childbearing potential) at EoT	Human Chorionic Gonadotropin in the urine			X

[1] A: parameters to be determined at screening examination

[2] B: parameters to be determined on Days 1 and 8

[3] C: parameters to be determined at end of trial examination

[4] Day -1 only

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.

The tests listed in Table 5.2.3: 1 and Table 5.2.3: 2 may be repeated as required. The results of the Exclusionary laboratory tests listed below will not be entered in the CRF/database and will not be reported in the CTR. Except for drug screening, it is planned to perform these tests during screening only. Drug screening will be performed at screening and prior to administration of trial medication on Day -1 (for time points refer to Flow Chart).

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Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine Barbiturates Buprenorphine Benzodiazepine Cocaine Methadone methabolite Methadone Methamphetamine Ecstasy Morphine Opiates Oxycodone Phencyclidine Tricyclic antidepressants Marijuana
Infectious serology (blood)[1]	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) IGRA-T (e.g. QuantiFERON®-TB Gold IT Test)

[1] Additional testing for infectious deseases can be added as requared

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed prior to admission on Day -1, 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.

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

5.2.4 Electrocardiogram

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

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

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

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5.2.5 Other safety parameters

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

The following should also be recorded as an AE in the 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 exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF.

5.2.6.1.2 Serious adverse event

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

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

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room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered "Always Serious"

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

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

Hepatic injury

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

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

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

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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Severe infections (according to RCTC grading)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression.

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.

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- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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

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

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5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a 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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

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

5.2.6.2.4 Exemptions to SAE reporting

Not applicable

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

PK parameters for exposure and disposition will be calculated. Standard multiple dose PK parameters will be calculated and further specified in the TSAP.

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The relationship between BI 730357 plasma concentrations, photosensitivity endpoints, and AEs may be assessed.

5.3.2 Methods of sample collection

For quantification of BI 730357) plasma concentrations, 4 mL of blood will be taken from an antecubital or forearm vein into a K-3EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart and in Appendix 10.2. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

After blood draw all samples have to be protected against direct sunlight to avoid conversion of present metabolite into parent drug BI 730357. The EDTA-anticoagulated blood samples will be centrifuged for about 10 minutes at app. 1000 to 2000 g at about 2 to 4°C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL plasma the second aliquot should contain the remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 120 minutes, with interim storage at room temperature. For each aliquot the time when the sample was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory the plasma samples will be stored at about -20°C or below until analysis.

Quantification of ciprofloxacin plasma concentrations will not be performed.

At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, and planned sampling time. Further information, such as matrix and analyte, may also be provided.

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

The results of any further investigations are not planned to be part of the CTR but can be included into the CTR if necessary.

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[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial, except from the skin type and photosensitivity assessments, are standard measurements in clinical trials and will be performed in order to monitor safety aspects in an appropriate way.

UV photo safety testing (conduct and interpretation of ultraviolet (UV) irradiation) is well established at the clinical site and will be performed by clinical, medical and technical staff which is appropriately trained and familiar with the methods and assessments required in this trail.

The number of investigator designees performing skin evaluations is kept as small as possible to ensure consistency. All dermatological assessments will be performed in a room with standardized environmental conditions (e.g., light conditions, temperature).

Therefore, the appropriateness of all measurements applied in this trial is given.

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6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All subjects have to adhere to the visit schedule as specified in the Flow charts. Each visit date is to be counted from Day 1.

Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Study procedures to be performed at each visit are listed in the Flow Charts and the respective protocol sections. Additional details on procedures at selected visits are provided below.

Measurement of vital signs should precede blood sampling. All blood samplings on all visits which are not intensive PK-days should occur prior to the intake of medication.

For detailed description of the trial procedures, please refer to the Flow Charts.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period

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

The screening should take place no more than 28 days before Day 1.

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, and temperature), 12-lead ECG, laboratory tests, and a physical examination. Subjects who have laboratory test value (e.g., platelet count) clinically outside acceptable ranges, may have the test repeated once to determine eligibility; however, the result of re-assessment must be available prior to randomisation (Day 1).

After all general screening clinical assessments were performed, only subjects who meet eligibility criteria will undergo UV irradiation and preliminary photosafety testing will be performed.

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The preliminary photosensitivity examination will be performed no later than Day -3, followed by the base line irradiation and photosensitivity assesments stariting on day -2.

Baseline Conditions

Subjects eligible for the study participation will be admitted to the clinical site on day -1, and check of In/Exclusion criteria as well as Base-line photosensitivity assessment will be performed.

If possible, spare subjects will be provided for each group to guarantee the start of a complete group. The spare subjects will participate in all trial activities up to Day 1, i.e. on Day -1 they will be admitted to the clinic and all examinations, which have been scheduled up to drug administration on Day 1 will be performed. The spare subjects from one group will be given the option to participate in the next planned group.

6.2.2 Treatment period(s)

Treatment A

Subjects will be randomized in the morning on Day 1 and receive 400mg of BI 730357 or placebo once daily over 8 days, or 300mg of BI 730357 or placebo twice daily 12 hours apart over 8 days with the single dose on day 8, in order to reach pharmacokinetic steady state;

UVB/UVA irradiation will occur 2 hours after the last dose of either IP or placebo, and photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) will be performed at 10 (+/- 2) minutes, and 1 (+/- 5 min), 24(+/- 10 min) [redacted]

Treatment B

Subjects will receive their first dose of 500 mg ciprofloxacin on the morning of Day 3. Twelve (12) hours later, subjects received their second dose of 500 mg ciprofloxacin. Subjects continued a twice-daily dosing regimen through to the morning of Day 8 to ensure they have reached pharmacokinetic steady state

UVB/UVA irradiation will occur 2 hours after the last dose of Ciprofloxacin, and photosensitivity assessments (determination of $MED_{On\ drug}$ and evaluation of erythema/local skin reactions) were performed at 10 (+/- 2) minutes, and 1(+/- 5 min), 24(+/- 10 min), [redacted]

For details on time points for 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.

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6.2.3 Follow-up period and trial completion

End of Trial

Subjects who completed the treatment according to the protocol, as well as subjects who discontinued treatment before the end of the planned treatment period should undergo the end of trial visit 7 days after last intake of the study medication.

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial refer to the Flow charts.

All abnormal values (including laboratory parameters) that are judged 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 subject's end of trial must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' 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.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objective of this trial is to investigate the photosensitivity under three distict exposure conditions of BI 730357 following 8 days of administration (i.e. steady state) on the basis of the primary and secondary endpoints. The trial is designed to allow comparisons between BI 730357 and placebo as well as BI 730357 and a positive control (ciprofloxacin). These comparisons will be evaluated statistically by use of a mixed model for repeated measures.

Each double blind randomization group (Part A: BI 730357 400 QD/placebo and BI 730357 300 BID/placebo) will be analysed separately for the assessment of photosensitivity.

7.1 NULL AND ALTERNATIVE HYPOTHESES

BI 730357 vs placebo

The assessment for absence of photosensitivity will be based upon the differences in mean photosensitivity index (PI) between BI 730357 and placebo two-sided 90% confidence intervals (CIs) for the differences in the photosensitivity index (Section 7.2.2) between BI 730357 and placebo using an acceptance range of -0.4 to 0.4. This method is equivalent to the two-sided t-test procedure, each at the 5% significance level.

The following comparisons will be performed:

- BI 730357 400 mg QD vs placebo 400 mg QD
- BI 730357 300 mg BID vs placebo 300 mg BID

The following hypotheses are tested:

Null hypothesis H_0 (Photosensitive): $\mu_{BI} - \mu_{pbo} \leq -\delta$ *or* $\mu_{BI} - \mu_{pbo} \geq \delta$

Where μ_{BI} and μ_{pbo} are the means of the endpoint for BI 730357 and placebo, respectively, and δ is the limit that defines the acceptance range for photosensitivity equivalence.

Alternative hypothesis H_a (Absence of photsensitivity): $-\delta < \mu_{BI} - \mu_{pbo} < \delta$

In this trial, the equivalence limit δ is 0.4 which is consistent with historical criteria used for positive photosensitivity for a drug (R19-3037).

The rejection of the null hypothesis at the $\alpha = 0.05$ level is equivalent to the inclusion of the 90% confidence interval for $\mu_{BI} - \mu_{pbo}$ in the acceptance range $(-\delta, \delta)$.

Although there are multiple endpoints where the photosensitivity index will be statistically compared, an alpha adjustment is not needed because it is required that all endpoints meet the equivalence criterion as described above simultaneously.

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BI 730357 vs ciprofloxacin, Placebo vs ciprofloxacin

Comparisons between the mean PI between BI 730357 and ciprofloxacin as well as between placebo and ciprofloxacin at the different timepoints under conditions 1 and 2 will be performed.

The planned comparisons are:

- BI 730357 400 mg QD vs ciprofloxicin
- BI 730357 300 mg BID vs ciprofloxicin
- Placebo for 400 mg QD vs ciprofloxicin
- Placebo for 300 mg BID vs ciprofloxicin

At each timepoint the null hypothesis will be that there is no difference in the mean PI of BI 730357 compared to ciprofloxacin:

Null hypothesis H_0: $\mu_{BI/pbo} - \mu_{cipro} = 0$

Where $\mu_{BI/pbo}$ and μ_{cipro} are the means of the endpoint for BI 730357 or placebo and ciprofloxicin, respectively

The alternative hypothesis will be that the means are not equal:

Alternative hypothesis H_a: $\mu_{BI/pbo} - \mu_{cipro} \neq 0$

A significant finding of increased photosensitivity of ciprofloxacin compared to BI 730357 and to placebo at the $p<0.05$ level will be supportive in concluding that the trial was appropriately designed to test the photosensitivity of BI 730357.

7.2 PLANNED ANALYSES

7.2.1 General considerations

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.
- Full analysis set (FAS): This set includes all subjects in the treated set (TS) who provide at least one photosensitivity endpoint that was defined as primary or secondary and was not excluded due to a protocol deviation relevant to the evaluation

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of photosensitivity. Descriptive and model based analyses of photosensitivity endpoints will be based on the FAS.

Additional analysis sets, refinements of the above definitions, or other relevant details may be specified in the TSAP. The implications that patients with important protocol deviations (including receiving incorrect medication) might have on the analysis will be discussed at the report planning meeting(s) and decisions will be documented in the decision log.

7.2.2 Primary endpoint analyses

Photosensitivity index (PI)

The photosensitivity index (PI) under conditions 1 and 2 is the measurement used for the primary endpoints. It is defined as the ratio of the precise $MED_{baseline}$ to the $MED_{on\text{-}drug}$ (see Section 5.1) at each respective post-irradiation timepoint. Therefore, there will be $MED_{baseline}$ at 10 min, 1h, and 24h that will be used for the respective PI calculations, PI_{10min}, PI_{1h}, and PI_{24h}. For example, the PI_{1h} will be the precise $MED_{baseline}/MED_{on\text{-}drug}$ where each MED was measured at the 1 hour post-irradiation time point. The two primary endpoints are PI at 24 hours under conditions 1 and 2.

A mixed model for repeated measures on PI values will be utilized for the analysis. The model will include treatment (BI 730357, Placebo, ciprofloxacin), time (10min, 1h, 24h, 48h, and 72h), and treatment-time interaction as fixed effects and subject as a random effect. Adjusted means and differences in PI and 90% CIs for the 2 contrasts of interest (i.e. BI 703357 – placebo at 24h) will be calculated from the model.

The analysis will be carried out separately for condition 1 and condition 2.

Additional details, including the full specification of the FAS (if needed) and the handling of patients who may not have post-baseline data, will be included in the TSAP.

7.2.3 Secondary endpoint analyses

The secondary endpoints for differences in PI at 10min and 1h under conditions 1 and 2 will be calculated from the same model as described for the primary analyses.

Additionally percent change from baseline in MED at 10min, 1h, and 24h will be calculated as $((MED_{on\text{-}drug}-MED_{baseline})/ MED_{baseline})*100$ at each timepoint and the same model using described in the primary analysis will be used in the analyses of these endpoints.

[redacted]

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7.2.5 Safety analyses

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

The safety analysis will be done by 'randomised treatment'.

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

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

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

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Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.2.6 Other Analyses

Details of other analyses, if needed, will be included in the TSAP.

7.2.7 Interim Analyses

No statistical interim analysis is planned. However, after completion of the 400mg dose group the independent Investigator and BI medical representatives will review blinded photosafety data of treatment A group to determine the acceptability of photosafety. After the team review of these data, it may be recommended, or in case of unfavourable results - to test the higher dose of 300mg BID for treatment A. In addition, a preliminary blinded PK analysis will be performed to estimate the PK exposure.

7.3 HANDLING OF MISSING DATA

No imputation is planned for missing MED, PI, or assessments of skin reaction data.

7.4 RANDOMISATION

The first set of subjects will be first randomised to the Treatment A (BI 400 mg QD/placebo) or Treatment B group in a 3:1 ratio. The random list will be provided by BI to the dedicated study staff.

Subjects allocated to the treatment group A will be randomised in a 3:1 ratio in a double blind manner, which reflects the ratio of subjects receiving active drug to placebo.

Subjects allocated to treatment B group will receive ciprofloxacin.

In order to investigate a second BI730357 dose of 300 mg BID, a second set of subjects be randomised in a 3:1 ratio in the same double blind manner described for Treatment A above, which reflects the ratio of subjects receiving active drug to placebo.

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

More details can be found in section 4.1.5.

7.5 DETERMINATION OF SAMPLE SIZE

It is planned to include initially a total of 84 healthy male and female subjects (36 subjects for Treatment A 400 mg QD, 36 subject for Tretment A 300 mg BID; 12 subjects for Treatment B) in this trial.

The planned numbers of subjects should be sufficient for the exploratory evaluation of photo-safety of each of the BI 730357 dose groups. Based on a similarly designed study for evaluation of pradigastat the observed mean (standard deviation) over all PI measurements for 9 patients who received placebo and 12 subjects who received ciprofloxacin was 1.08 (0.12) and 1.61 (0.55), respectively (R19-3037).

Assuming a common standard deviation of 0.15 and an expected difference in mean PI of 0 between BI 730357 and placebo, each of the two group 0.05 one-sided t-tests will have 99% power to reject the null hypothesis that BI 730357 and placebo are not equivalent (the difference in means, $\mu_{BI} - \mu_{pbo}$, is ≥ 0.4 and $\mu_{BI} - \mu_{pbo} \leq -0.4$) in favor of the alternative hypothesis that the means of the two groups are equivalent (nQuery Advisor, version 7).

Additionally, for the planned comparison of mean PIs for BI 730357 and ciprofloicin, a two group Satterthwaite t-test with a 0.05 two-sided significance level will have 87% power to detect a difference in means of 0.6 (the difference between μ_{cipro} of 1.60 and a μ_{BI} of 1.0) assuming standard deviation of ciprofloxacin is 0.600 and standard deviation for BI 730357 is 0.15 when the sample sizes in the two groups are 12 and 27, respectively (nQuery Advisor, version 7). Using the same assumptions and calculation for 12 ciprofloxacin and 9 placebo instead of 27 BI 370357 subjects the power is 86%. Based on the similar study of pradigastat, the drop-out rate will be minimal. Further details will be discussed in the TSAP.

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

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

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.”

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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. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the 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 patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the subjects' source documents.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)

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- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Subject's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- 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.

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

Exemptions from expedited reporting are described in section 5.2.6.2.4, if applicable.

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8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

A final report of the clinical trial data will be written only after all subjects have completed the trial to incorporate and consider all data in the report.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at one clinical site. A Principal Investigator is responsible to coordinate co-investigators at the site participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating 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 activities, in order to

- manage the trial in accordance with applicable regulations and SOPs applicable in a FOT setting,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and oversight of the vendors.

The organisation of the trial will be performed by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

CRO will perform Project Management, Clinical Field Monitoring, Medical Monitoring,

Data Management, Statistical Evaluation and Reporting.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI and CRO SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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9. REFERENCES

9.1 PUBLISHED REFERENCES

R19-2246 Highlights of prescribing information, CIPRO (ciprofloxacin hydrochloride) tablet, for oral use.

R19-3127 Ciprofloxacin [redacted] US PI 03-2019

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TheDGAT 1inhibitor pradigastat does not induce photosensitivity in healthy human subjects: a randomized controlled trial using three defined sunlight exposure conditions. Photochem Photobiol Sci 15 (9), 1155 - 1162 (2016)

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version.

c09228382 Investigators´s Brochure. BI 730357. Psoriasis (ankylosing spondylitis, psoriatic arthritis, asthma, inflammatory bowel disease). Current version.

n00250111 [redacted]
Prediction of BI 730357 Pharmacokinetics and Therapeutic Dose in Human. Current version.

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10. APPENDICES

10.1 RESTRICTED MEDICATION AND FOOD

Other investigational products	• 30 days or 5 half-lives, whatever is longer, prior to randomization through EOT
Disease, surgery	• Major surgery performed within 8 weeks prior to screening visit or planned within 8 weeks after screening visit (e.g. hip replacement)
-Drugs or foods (e.g., seville oranges, grapefruit, paw paw and their products) which are strong or moderate inhibitors or inducers of CYP3A4 (e.g, rifampicin, phenytoin), or -Sensitive substrates of CYP1A2 (e.g., alosetron, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine, and caffeine when used as a medication), or -Sensitive substrates of CYP 2B6 (e.g., bupropion).	• One week prior to randomisation until EOT (Sensitive substrates of CYP3A4 are not excluded from the trial).
Drugs which are substrates of P-gp (e.g. dabigatran, digoxin and fexofenadine etc.)	• One week prior to randomisation until EOT
Drugs with known phototoxic or photoallergic potential (e.g., tetracyclines, fluoroquinolones)	• One week prior to randomisation until EOT
BCG (Bacillus Calmette-Guérin) vaccine	• 1 year prior to randomisation through 1 year after last administration of study drug

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10.2 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.2: 1 Time schedule for PK blood sampling during treatment course A 400 mg QD

Day	Time Point [hh:min][1]	CRF Time /PTM	Event	Sample No.
1	Just before drug administration	-1:00	PK Blood	1
	0:00	0:00	1st Drug administr.	---
	4:00	4:00	PK Blood	2
2	8:00/Predose	24:00	PK Blood	3
3	8:00/Predose	48:00	PK Blood	4
4	8:00/Predose	72:00	PK Blood	5
5	8:00/Predose	96:00	PK Blood	6
6	8:00/Predose	120:00	PK Blood	7
7	8:00/Predose	144:00	PK Blood	8
8	8:00/Predose	168:00	PK Blood	9
	9:00	169:00	PK Blood	10
	10:00	170:00	PK Blood	11
	11:00	171:00	PK Blood	12
	12:00	172:00	PK Blood.	13
	14:00	174:00	PK Blood	14
	20:00	180:00	PK Blood	15
9	8:00	192:00	PK Blood	16
10	8:00	216:00	PK Blood	17
11	8:00	240:00	PK Blood	18

[1] Time windows allowed for PK sampling:

Within 1 h pre-dose and 4 h post dose on day 1; -10 min pre-dose samples on days 2 to 8; +/- 5 min 1/2/3/4/6/12 h on day 8; +/- 15 min on days 9/10/11.

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Table 10.2: 2 Time schedule for PK blood sampling during treatment course A 300 mg BID

Day	Time Point [hh:min][1,2]	CRF Time /PTM	Event	Sample No.
1	Just before drug administration	-1:00	PK Blood	1
	8:00	0:00	1st Drug administr.	---
	9:00	1:00	PK Blood	2
	10:00	2:00	PK Blood	3
	11:00	3:00	PK Blood	4
	12:00	4:00	PK Blood	5
	14:00	6:00	PK Blood	6
	16:00	8:00	PK Blood	7
	18:00	10:00	PK Blood	8
	20:00	12:00	PK Blood	9
5	8:00/Predose	96:00	PK Blood	10
6	8:00/Predose	120:00	PK Blood	11
7	8:00/Predose	144:00	PK Blood	12
8	8:00/Predose	168:00	PK Blood	13
	9:00	169:00	PK Blood	14
	10:00	170:00	PK Blood	15
	11:00	171:00	PK Blood	16
	12:00	172:00	PK Blood.	17
	14:00	174:00	PK Blood	18
	20:00	180:00	PK Blood	19
9	8:00	192:00	PK Blood	20
10	8:00	216:00	PK Blood	21
11	8:00	240:00	PK Blood	22

[1] Time windows allowed for PK sampling:

Within 1 h pre-dose and 4 h post dose on day 1; -10 min pre-dose samples on days 5 to 8; +/- 5 min 1/2/3/4/12 h on day 8; +/- 15 min on days 9/10/11.

[2] All timepoints are relative to the drug administration time.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 Mar 2020
BI Trial number		1407-0037
BI Investigational Medicinal Product		BI 730357
Title of protocol		Partially-blind, randomized, parallel group, placebo and active comparator-controlled Phase I clinical trial to evaluate the photosensitivity potential of BI 730357
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		4.1.5.1 Blinding; 7.2.7 Interim analysis;
Description of change		The following sentence was added on page 38: In addition, the trial pharmacokineticist may receive the blinded (dummy subject numbers will be used) results of the measurements to perform the preliminary PK analysis. The following sentence was added on page 62: In addition, a preliminary blinded PK analysis will be performed to estimate the PK exposure.
Rationale for change		The administrative amendment is incorporated to allow preliminary analysis of blinded PK data. The results from the blinded PK analysis will be compared with the historical data upon which the study was designed. This blinded evaluation possibility was overseen in the original protocol, and is now added per this non-substantial amendment

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11.2 GLOBAL AMENDMENT 2

Date of amendment		01 Apr 2020
BI Trial number		1407-0037
BI Investigational Medicinal Product		BI 730357
Title of protocol		Partially-blind, randomized, parallel group, placebo and active comparator-controlled Phase I clinical trial to evaluate the photosensitivity potential of BI 730357
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		Synopsis; Flow chart 300 mg BID; 1.4.2 Risks; 3.1 Overall Trial Design; 3.2 Discussion of Trial Design; 4.1.1 Investigational Treatments; 4.1.2 Selection of doses in the trial and dose modifications 7.5 Determination of Sample size analysis;
Description of change		Additional dose group 300 mg of BI 730357 or Placebo BID has been added.
Rationale for change		Results of the Week 12 primary analysis for trial 1407-0030 demonstrated proof-of-concept, as well as acceptable safety and tolerability in the treatment of patients with moderate-to-severe plaque PsO for BI 730357 at the 200 mg dose; Modelling of primary analysis data indicates that the efficacy plateau of BI 730357 may not have been reached with 200 mg dose q.d., and that higher exposures may provide better efficacy. Therefore efficacy, safety, tolerability, and pharmacokinetics of BI 730357 400 mg q.d. and 200 mg b.i.d. will be

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		evaluated as possible therapeutic doses in patients. Psoriasis patients have shown higher exposures than those of healthy volunteers; therefore in order to investigate possible phototoxic effects in exposures which approximate those of patients treated with 200 mg b.i.d., healthy volunteers will be treated with 300 mg b.i.d. under fed conditions in this trial.

APPROVAL / SIGNATURE PAGE

Document Number: c27983101 **Technical Version Number:3.0**

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

Title: Partially-blind, randomized, parallel group, placebo and active comparator-controlled Phase I clinical trial to evaluate the photosensitivity potential of BI 730357

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	01 Apr 2020 14:53 CEST
Author-Trial Statistician		01 Apr 2020 15:02 CEST
Author-Trial Clinical Pharmacokineticist		01 Apr 2020 16:00 CEST
Approval-Therapeutic Area [redacted]		01 Apr 2020 16:19 CEST
Approval-Team Member Medicine		01 Apr 2020 18:37 CEST
Verification-Paper Signature Completion		01 Apr 2020 18:38 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed