Clinical Trial Protocol

	Document Number:	**c14109663-03**
EudraCT No.:	2017-001653-14	
BI Trial No.:	1407-0002	
BI Investigational Product(s):	BI 730357	
Title:	Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers.	
Lay Title:	This study tests how healthy men tolerate different doses of BI 730357 and how the metabolism of midazolam is affected by BI 730357.	
Clinical Phase:	Ib	
Trial Clinical Monitor:	Phone: , Fax:	
Principal Investigator :		
Status:	Final Protocol (Revised Protocol based on Global Amendment 2)	
Version and Date:	**Version:**	**Date:**
	3.0	12 January 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	N/A
Active ingredient name:	BI 730357
Protocol date	19 June 2017
Revision date	12 January 2018
Trial number	1407-0002
Title of trial:	Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers
Principal Investigator:	
Trial site(s):	
Clinical phase:	Ib
Objective(s):	To evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic properties of multiple rising doses of BI 730357 when administered to healthy volunteers.
Methodology:	Double-blind, randomised, placebo-controlled, MRD trial
Number of patients entered:	up to 84 healthy volunteers
Number of patients on each treatment:	12 per dose level; 9 on BI 730357, 3 on Placebo
Diagnosis:	Healthy volunteers

Main in- and exclusion criteria	Inclusion criteria: • Healthy male volunteers • Age ≥18 to 45 years at screening • BMI of 18.5 to 29.9 kg/m^2 Exclusion criteria: • Currently enrolled in another investigational device or drug trial, or less than 30 days (from randomisation) since ending another investigational device or drug trial(s), or receiving other investigational treatment(s) • Live vaccination ≤ 12 weeks prior to randomisation (visit 2), or any plan to receive a live vaccination during the conduct of this study • Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2.3
Test product(s):	BI 730357 Midazolam
dose:	25 mg, 50 mg, 100 mg, 200 mg, 400 mg BI 730357 75 µg midazolam
mode of administration:	Oral
Comparator products:	Placebo to BI 730357
dose:	N/A
mode of administration:	Oral
Duration of treatment:	14 to 28 days
Endpoints	Primary • Safety: Number of subjects with drug-related AEs Secondary After the first dose: • $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)

	• C_{max} (maximum measured concentration of the analyte in plasma) After the last dose: • $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ) • $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)
Safety criteria:	Number of subjects with drug-related AEs
Statistical methods:	Descriptive statistics will be applied for all endpoints Dose proportionality of BI 730357 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed. Linearity index may be estimated using a linear model providing a two-sided 95% CI. Attainment of steady state will be analysed by a repeated measures linear model for trough concentrations of BI 730357 with dose as an additional covariate if permissible.

FLOW CHARTS

FLOW CHART 1: PROCEDURES, DOSE GROUPS WITH 14 DAYS TREATMENT

Trial periods		**Randomisation and Treatment Period**										**Follow up**			
Visit	**1**	**2**	**3**	**4**	**5 to 7**	**8**	**9**	**10**	**11**	**12 to 14**	**15 (EOT)**	**16**	**17**	**18**	**19**
Study Day	**-28 to -1**	**1**	**2**	**3**	**4 to 6**	**7**	**8**	**9**	**10**	**11 to 13**	**14**	**15**	**16**	**17**	**21**
Informed consent	x														
Demographics, medical history, baseline conditions	x														
Randomisation		x													
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Check of in-/exclusion criteria	x	x													
Body height/Body weight	x														
Vital signs (blood pressure, pulse rate)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x					x					x				x
12-lead resting ECG[3]	x	x	x			x			x		x				x
Safety laboratory blood tests	x	x				x			x		x				x
PK blood sampling		x	x	x		x			x	x	x	x	x	x	x
PK urine sampling		x	x								x	x			
Biomarkers (Whole Blood)		x	x			x	x				x	x			x
Administration of BI 730357/Pbo[5]		x	x	x	x	x	x	x	x	x	x				
Termination of study medication											x				
Trial completion															x

FLOW CHART 2: DRUG ADMINISTRATION AND ASSESSMENTS, DOSE GROUPS WITH 14 DAYS TREATMENT

Visit	Day	Planned Time [h:min]	Clock time For actual day [h:min]	Event and comment	ECG[3]	Safety lab	BI 730357 PK_{blood}	PK_{urine}	Biomarker sample
1	-28 to -1			Screening and informed consent	x	x			
2	1	- 0:30	7:30	Randomisation & pre-dose sampling		x	x[4]	x	x
		0:00	8:00	BI 730357 admin[5]	x			x	
		0:15	8:15				x	↓	
		0:30	8:30				x		
		1:00	9:00				x		
		1:30	9:30				x		
		2:00	10:00				x		
		2:30	10:30				x		
		3:00	11:00				x		
		3:30	11:30				x		
		4:00	12:00				x		
		6:00	14:00				x		x
		8:00	16:00				x		
		12:00	20:00				x	↓	
3	2	23:30	7:30				x	x[1,2]	x
		24:00	8:00	BI 730357 admin[5]	x				
4	3	47:30	7:30				x[2]		
		48:00	8:00	BI 730357 admin[5]					
5 to 7	4 to 6		8:00	BI 730357 admin[5]					
8	7	143:30	7:30			x	x[2]		x
		144:00	8:00	BI 730357 admin[5]	x				
9	8	167:30	7:30						x
		168:00	8:00	BI 730357 admin[5]					
10	9		8:00	BI 730357 admin[5]					
11	10	215:30	7:30			x	x[2]		
		216:00	8:00	BI 730357 admin[5]	x				
12	11	239:30	7:30				x[2]		
		248:00	8:00	BI 730357 admin[5]					
13	12	263:30	7:30				x[2]		
		264:00	8:00	BI 730357 admin[5]					
14	13	287:30	7:30				x[2]		
		288:00	8:00	BI 730357 admin[5]					
15	14	311:30	7:30			x	x[4]	x	x
		312:00	8:00	BI 730357 admin[5]	x			x	
		312:15	8:15				x[4]	↓	
		312:30	8:30				x[4]		
		313:00	9:00				x[4]		
		313:30	9:30				x[4]		
		314:00	10:00				x[4]		
		314:30	10:30				x[4]		
		315:00	11:00				x[4]		
		315:30	11:30				x[4]		
		316:00	12:00				x[4]		
		318:00	14:00				x[4]		x
		320:00	16:00				x[4]		
		324:00	20:00				x[4]	↓	

Visit	Day	Planned Time [h:min]	Clock time For actual day [h:min]	Event and comment	ECG[3]	Safety lab	BI 730357 PK_{blood}	PK_{urine}	Biomarker sample
16	15	335:30	7:30				x[4]	x[1,2]	x
17	16	359:30	7:30				x		
18	17	383:30	7:30				x		
EOO	21			End of observation	x	x	x		x

FLOW CHART 3: PROCEDURES, DOSE GROUPS WITH 28 DAYS TREATMENT

Trial periods	**screening**		**Treatment**																		**Follow-up**	
Visit	**1**	**1.1**	**2**	**3**	**4**	**5 to 7**	**8**	**9**	**10**	**11**	**12 to 14**	**15**	**16**	**17 to 18**	**19 to 21**	**22**	**23 to 24**	**25**	**26 to 28**	**29 (EOT)**	**30**	**31**
Study Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4 to 6**	**7**	**8**	**9**	**10**	**11 to 13**	**14**	**15**	**16 to 17**	**18 to 20**	**21**	**22 to 23**	**24**	**25 to 27**	**28**	**29**	**35**
Informed consent	x																					
Demographics, medical history, baseline conditions	x																					
Randomisation			x																			
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Check of in-/exclusion criteria	x	x	x																			
Body height/Body weight	x																					
Vital signs (blood pressure, pulse rate)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x						x													x		x
12-lead resting ECG[3]	x		x	x			x					x								x		x
Safety laboratory blood tests	x		x				x					x								x		x
Midazolam PK blood sampling		x			x							x										
BI 730357 PK blood sampling			x	x	x		x	x			x	x	x	x		x		x		x	x	x
PK urine sampling			x	x								x	x									
Biomarkers (whole blood)			x	x			x	x				x	x			x				x	x	x
Administration of Midazolam[6]		x			x							x										
Administration of BI 730357/Pbo[5]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Termination of trial medication																				x		
Trial completion																						x

FLOW CHART 4: DRUG ADMINISTRATION AND ASSESSMENTS, DOSE GROUPS WITH 28 DAYS TREATMENT

Visit	Day	Planned Time [h:min]	Clock time for actual day [h:min]	Event and comment	ECG[3]	Safety lab	BI 730357 PK_{blood}	Midazolam PK_{blood}	PK_{urine}	Biomarker sample
1	-28 to -2			Screening and informed consent	x	x				
1.1	-1	-24:30	7:30					x		
		-24:00	8:00	Administration of Midazolam[6]						
		-23:45	8:15					x		
		-23:30	8:30					x		
		-23:00	9:00					x		
		-22:00	10:00					x		
		-21:30	10:30					x		
		-21:00	11:00					x		
		-20:00	12:00					x		
		-18:00	14:00					x		
		-16:00	16:00					x		
2	1	- 0:30	7:30[5]	Randomisation & pre-dose sampling		x	x		x	x
		0:00	8:00	Administration of BI 730357[5]	x				x ↓	
		0:15	8:15				x			
		0:30	8:30				x			
		1:00	9:00				x			
		1:30	9:30				x			
		2:00	10:00				x			
		2:30	10:30				x			
		3:00	11:00				x			
		3:30	11:30				x			
		4:00	12:00				x			
		6:00	14:00				x			x
		8:00	16:00				x			
		12:00	20:00				x			
3	2	23:30	7:30		x		x		↓ $x^{1,2}$	x
		24:00	8:00	BI 730357 admin[5]						
4	3	47:30	7:30				x^2	x		
		48:00	8:00	Administration of Midazolam and BI 730357[5]						
		48:15	8:15					x		
		48:30	8:30					x		
		49:00	9:00					x		
		50:00	10:00					x		
		50:30	10:30					x		
		51:00	11:00					x		
		52:00	12:00					x		
		54:00	14:00					x		
		56:00	16:00					x		
5 to 7	4 to 6		8:00	BI 730357 admin[5]						
8	7	143:30	7:30			x	x^2			x
		144:00	8:00	BI 730357 admin[5]	x					
9	8	167:30	7:30				x^2			x

Visit	Day	Planned Time [h:min]	Clock time for actual day [h:min]	Event and comment	ECG[3]	Safety lab	BI 730357 PK_{blood}	Midazolam PK_{blood}	PK_{urine}	Biomarker sample
		168:00	8:00	BI 730357 admin[5]						
10 to 11	9 to 10	215:30	7:30							
12	11	239:30	7:30				x[2]			
		240:00	8:00	BI 730357 admin[5]						
13	12	263:30	7:30				x[2]			
		264:00	8:00	BI 730357 admin[5]						
14	13	287:30	7:30				x[2]			
		288:00	8:00	BI 730357 admin[5]						
15	14	311:30	7:30			x	x	x	x	x
		312:00	8:00	Administration of Midazolam[6] and BI 730357[5]	x				x ↓	
		312:15	8:15				x	x		
		312:30	8:30				x	x		
		313:00	9:00				x	x	↓	
		313:30	9:30				x			
		314:00	10:00				x	x		
		314:30	10:30				x	x		
		315:00	11:00				x	x		
		315:30	11:30				x			
		316:00	12:00				x	x		
		318:00	14:00				x	x		x
		320:00	16:00				x	x		
		324:00	20:00				x			
16	15	335:30	7:30				x		↓	x
		336:00	8:00	BI 730357 admin[5]						
17	16	359:30	7:30				x[2]			
		360:00	8:00	BI 730357 admin[5]						
18	17	383:30	7:30				x[2]			
		384:00	8:00	BI 730357 admin[5]						
19 to 21	18 to 20		8:00	BI 730357 admin[5]						
22	21	479:30	7:30				x[2]			x
		480:00	8:00	BI 730357 admin[5]						
23 to 24	22 to 23		8:00	BI 730357 admin[5]						
25	24	551:30	7:30				x[2]			
		552:00	8:00	BI 730357 admin[5]						
26 to 28	25 to 27		8:00	BI 730357 admin[5]						
29	28	647:30	7:30			x	x			x
		648:00	8:00	BI 730357 admin[5]	x					
		649:00	9:00				x			
		650:00	10:00				x			
		651:00	11:00				x			
		652:00	12:00				x			
		654:00	14:00							x
30	29	672:00	8:00				x			x
31	35	816:00	8:00	End of observation	x	x	x			x

Footnotes to flow charts 1 - 4

[1] Last urine sampling belonging to the previous day 1 (24 hours). The following collection intervals should be used for urine collection: Pre-dose, 0-4, 4-8, 8-12, 12-24

[2] Pre-dose samples

[3] ECG should be recorded after drug administration

[4] Plasma samples for metabolite analysis will be taken in parallel to PK samples only for the 100 mg fasted dose group.
[5] In the fasted dose groups, on all visit days, breakfast should only be taken at least 30 min after the administration of study drug. In the fed dose groups, on all visit days, a standard continental breakfast should be taken after the first blood draw and **before** the intake of study drug.
[6] Midazolam microdose will only be administered in the two highest dose groups

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the Curve
CI	Confidence Interval
Cmax	Maximum measured concentration of BI 730357 in plasma
CML	Clinical Monitor Local
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DC	Dendritic cell
DG	Dose Group
DILI	Drug Induced Liver Injury
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
GCP	Good Clinical Practice
IB	Investigator’s Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IV	intravenous
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose
MST	Medical Sub Team
NOAEL	No-observed-adverse-effect level
OPU	Operative Unit
PD	Pharmacodynamics
PK	Pharmacokinetics
p.o.	per os (oral)
PPASI	Palmoplantar Psoriasis Severity Index
PsA	Psoriatic Arthritis
PsO	Psoriasis
q.d.	quaque die (once a day)
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
SRD	Single Rising Dose
TMF	Trial Master File
TSAP	Trial Statistical Analysis Plan

WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Plaque psoriasis (PsO) is a chronic skin disease characterized by raised, well-demarcated, oval erythematous plaques covered in adherent silvery scale (R11-1257). Lesions are typically painful and/or itchy, and can be associated with a high degree of morbidity. PsO can affect extensive areas of skin; disease severity is in fact defined by body surface area (BSA) as mild (<5%), moderate (5-10%), and severe (>10%) (R11-1259). Approximately 25% of patients are classified as having moderate-to-severe disease. Disease severity correlates inversely with quality of life, as reported by patients with regard to symptom severity and disease impact on functionality and socialization (R16-4115, R11-1260, R03-1208, R16-3072). Plaques on visible skin (e.g., scalp, face, hands) have particular impact on physical, sexual, psychosocial, and even economic status; disease severity is associated with reduced levels of employment and income (R16-3072). PsO is more than a superficial disease, with 30% of patients having joint involvement, and a high correlation between PsO and obesity, diabetes, depression, metabolic syndrome, and cardiovascular risk (R16-4115).

Affecting approximately 2% of the global population, including 25 million North American and European patients, PsO is the most prevalent immune-mediated skin disease (R08-1089). Direct and indirect annual costs attributed to PsO in the US are estimated to be US $6,422 per patient on average, resulting in a total burden of US $35.2 billion. This cost is distributed, roughly in equal thirds, to medical costs, reduced quality of life, and productivity loss (R17-1990). Across Germany, Italy, Spain, UK, and France the per-patient cost of PsO has been estimated to range from US $2,077 to $13,132 annually (R17-1989).

Mainstays of therapy for the treatment of PsO include topical agents, ultraviolet light-based therapies, traditional systemic agents (methotrexate, acitretin, cyclosporine), and more recently, targeted biologic and small-molecule therapies. Steroidal and non-steroidal (e.g., vitamin D analogues, retinoids, tar, anthralin, salicylic acid, tacrolimus) topical agents are efficacious, particularly for mild-to-moderate disease, but typically require long-term

administration, and often provide only incomplete clearance. Long-term adherence to topically-prescribed therapies is often poor, and systemic absorption limits long-term usage of topical corticosteroids, particularly for large surface areas and for facial and genital lesions. Ultraviolet light-based therapies, often combined with the photosensitizing agent psoralen, may be used to treat extensive areas of involved skin, but generally require long-term therapy, and are associated with non-melanoma skin cancer (NMSC). Conventional systemic agents provide relatively inexpensive options to treat more severe or refractory disease, but long-term usage may be substantially limited by the risks of hepatotoxicity, bone marrow suppression, and pulmonary toxicity (methotrexate), teratogenicity (acetretin), and nephrotoxicity and hypertension (cyclosporine). During the past 15 years, antibodies targeting TNFα, and subsequently IL-12/23 and IL-17, have demonstrated substantial efficacy and indeed complete remission rates, with safety and tolerability superior to conventional therapies.

1.2 DRUG PROFILE

1.2.1 Non-Clinical Studies

Relevant non-clinical pharmacology, PK, and toxicology study results are summarized below. Further details are provided in the BI 730357 Investigator Brochure (IB).

The disposition of BI 730357 is characterized in rat, dog and minipig by low clearance and moderate Vd. Moderate to high oral bioavailability was observed across species, which suggests that following oral administration, the bioavailability of BI 730357 in humans is likely to be moderate to high. The plasma protein binding of BI 730357 was high in all tested species (mouse, rat, dog, and human) and there was no preferential partitioning into red blood cells observed. In a quantitative whole body autoradiography study in male Long Evans (pigmented) rats, [^{14}C]-BI 730357-derived radioactivity was readily absorbed and distributed to tissues. There was evidence of CNS exposure to drug-related material. Deposition of radioactivity into MCT of the ocular bulb was moderate to high and long lived.

When incubated with human hepatocytes, BI 730357 undergoes metabolism predominately via CYP3A4 to an oxidative metabolite. This metabolite was also observed following incubations with rat, dog, and minipig suspended hepatocytes. When BI 730357 was incubated with a selective inhibitor of CYP3A4 in a long-term human hepatocyte culture model, the overall metabolism was inhibited by ~90%, confirming that BI 730357 is mainly metabolized by CYP3A4. Therefore, if BI 730357 is primarily metabolically cleared, there is a high risk that coadministration with CYP3A inhibitors will significantly increase BI 730357 exposure and CYP3A inducers could decrease its exposure.

The propensities of BI 730357 to inhibit, inactivate, and/or induce CYP isoforms were evaluated *in vitro*. BI 730357 was determined to be a potentially clinically-relevant CYP3A inactivator and an inducer of CYP1A2, CYP2B6, and CYP3A. The net effect of BI 730357 on a sensitive CYP3A substrate (midazolam) is an anticipated increase of the AUC by 1.8-fold. Induction of CYP1A2 and CYP2B6 by BI 730357 at the projected dose and C_{max} is also predicted to be potentially clinically relevant.

The toxicity profile of BI 730357 has been assessed in safety pharmacology, genetic toxicity, and repeat-dose toxicity studies in rat and dog. In general BI 730357 appears to be well tolerated at clinically-relevant plasma exposure in toxicity studies. BI 730357 is considered non-genotoxic. Based on long half-lives of radioactivity in dermal tissues and results from an *in vitro* phototoxicity assay, BI 730357 has phototoxicity potential.

In summary, the non-clinical data of BI 730357 support clinical trials in male subjects with daily oral administration for up to 28 days. Human exposure up to those achieved at the no

observed adverse effect level (NOAEL) of 5 mg/kg/day in the 4 week dog study (C_{max} 6,660 nM, and AUC_{0-24} 127,400 nM•h in males and females combined) is considered safe.

1.2.2 Clinical Experience in Humans

At the time of the submission of this Trial 1407-0002, preliminary results are available from the Phase Ia first-in-human Trial 1407.1, conducted in Germany and comprising two parts. Part 1 was a randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of single rising doses (SRD) of BI 730357 administered as oral solution (2 mg and 8 mg) and film-coated tablets (25 mg to 400 mg) to 56 healthy male adult subjects in the fasted state. Part 2 was a randomised, open label, single-dose, three-way crossover bioavailability comparison of 25 mg of BI 730357 administered as oral solution, and tablet with or without food to 12 healthy male adult subjects.

The protocol was also amended to evaluate safety and drug exposure of single-dose administration up to 800 mg BI 730357, and to further evaluate food effect at 400 mg and 800 mg doses. Three additional dose cohorts in the fed state were administered with BI 730357. A 400 mg dose cohort with standard diet and 400 and 800 mg cohorts with high-fat diet were evaluated.

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 discernable trend among recipients of placebo and rising dose levels of BI 730357, whether administered under fasted or fed conditions. No serious AEs (SAEs) were reported.

Preliminary PK data were obtained with planned drug administration and sampling times instead of actual times; therefore, final data may deviate from the preliminary data. A summary of the PK parameters of BI 730357 derived in this trial is given in Table 1.2.2:1 for oral solution and tablet.

Following administration of the tablet, BI 730357 was absorbed with a t_{max} between approximately 2 to 3 hours. Thereafter, plasma concentrations decreased rapidly in a mono- or biphasic manner with an estimated terminal half-life ($t_{1/2}$) ranging from approximately 20 to 28 hours.

Table 1.2.2:1 Preliminary geometric mean (geometric CV%) PK parameters of BI 730357 (SRD Part)

	Fasted, Solution		Fasted, Tablet					Fed, Tablet		
Dose	2 mg Solution N=6	8 mg Solution N=6	25 mg Tablet N=6	50 mg Tablet N=6	100 mg Tablet N=6	200 mg Tablet N=6	400 mg Tablet N=6	400 mg Std. diet N=6	400 mg High Fat N=5	800 mg High Fat N=6
AUC_{0-24} [nM*hr]	224 (19.9)	928 (23.6)	1431 (26.5)	2623 (42.3)	4142 (37.5)	6346 (16.0)	9453 (26.0)	17864 (21.6)	22520 (35.6)	33849 (27.2)
AUC_{0-24}/D [nM*hr/mg]	112 (19.9)	116 (23.6)	57.2 (26.5)	52.5 (42.3)	41.4 (37.5)	31.7 (16.0)	23.6 (26.0)	44.7 (26.0)	56.3 (35.6)	42.3 (27.2)
C_{max} [nM]	32.9 (39.4)	154 (28.9)	103 (31.7)	173 (41.9)	284 (30.7)	433 (27.6)	755 (37.4)	1268 (17.5)	1898 (30.2)	2466 (15.7)
C_{max}/D [nM/mg]	16.5 (39.4)	19.2 (28.9)	4.12 (31.7)	3.47 (41.9)	2.84 (30.7)	2.17 (27.6)	1.89 (37.4)	3.17 (17.5)	4.75 (30.2)	3.08 (15.7)
C_{24} [nM]	4.83 (31.7)	18.6 (35.0)	50.5 (26.4)	104 (49.9)	160 (44.3)	289 (21.2)	360 (32.6)	618 (32.4)	649 (55.7)	1060 (31.2)
$t_{1/2}$ [hr]	24.3 (29.1)	24.0 (33.9)	26.6 (29.3)	25.6 (37.0)	23.8 (34.9)	20.0 (29.4)	28.1 (26.8)	29.1 (36.9)	25.8 (50.1)	25.9 (32.3)
t_{max} [hr}	0.95 (36.7)	0.85 (46.1)	2.96 (17.4)	2.90 (41.3)	2.42 (41.8)	2.02 (55.4)	2.77 (38.0)	4.80 (27.5)	3.00 (55.4)	4.40 (38.5)

These preliminary trial data suggest that the exposure (AUC_{0-24}) to BI 730357 increased in a dose-proportional manner for solution between 2 and 8 mg and for tablet up to 50 mg, and thereafter increased in a less-than-dose-proportional manner, with approximately 1.5-fold increase in exposure with each 2-fold increase in dose up to 400 mg. The highest exposures observed in the fasted state (C_{max} of 755 nM and AUC_{0-24} of 9453 nM*hr) at the 400 mg dose level were substantially below (approximately 9- and 13-fold lower, respectively) the NOAEL exposures in the 4-week dog study (C_{max} of 6,660 nM, and AUC_{0-24} of 127,400 nM*hr). A comparison of exposures (for the tablets in the fasted state) showed that with an 8-fold and 16-fold increase in dose from 25 to 200 and 400 mg, the AUCs increased by 4.4 fold and 6.6 fold, respectively.

Comparing 400 mg dose cohorts in the fasted and fed state, the exposures with standard and high-fat diets were approximately 90% and 140% higher, respectively, than the exposure in the fasted state, confirming a positive food effect. Thus, the exposure of BI 730357 when taken with food (standard breakfast) approximately doubled (AUC_{0-24} of 9453 vs 17864 nM*hr) when compared to fasted state at the 400 mg dose level.

The highest exposure in the SRD study was observed at the 800 mg dose cohort when administered with a high-fat diet. This exposure (AUC_{0-24} of 33849 nM*hr) was approximately 1.5-fold higher than the exposure at the 400 mg dose with high-fat diet (AUC_{0-24} of 22520 nM*hr) in comparison to a 2-fold increase in dose. However, this highest exposure was still approximately 4-fold lower when compared to the NOAEL exposures in the 4-week dog study.

1.3 RATIONALE FOR PERFORMING THE TRIAL

As described in section 1.1, the treatment of patients with moderate-to-severe plaque PsO has been greatly enhanced by the introduction of biologic agents, and more options may be added to the armamentarium in the near future. However, these antibody drugs must be administered by subcutaneous injections, and long-term therapeutic effect may be limited by the formation of antidrug antibodies. There remains a medical need for the introduction of new, efficacious oral treatment options.

The aim of Phase Ib Trial 1407-0002 is to investigate the safety, tolerability, and PK of BI 730357 in healthy male volunteers.

As BI 730357 was determined to be a substrate, an inactivator, and an inducer of CYP3A4, which could potentially result in clinically-relevant drug-drug interactions (DDI), a DDI assessment is being conducted in this trial, whereby a microdose of midazolam will be administered to volunteers at two of the highest dose groups of BI 730357. A microdose results in a low enough concentration of midazolam as to not be pharmacologically active and, thus, will not interfere with examination of BI 730357. Furthermore, this assessment will inform us regarding potential DDIs with medications that are CYP3A4 substrates and allow us to determine whether or not to exclude such drugs from subsequent trials.

1.4 BENEFIT - RISK ASSESSMENT

Study participants are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

Blood sampling by venipuncture 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 paresthesia, 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.

Drug-related risks and safety measures

.

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 SRD administration of BI 730357 up to 400 mg in healthy volunteers.
- Progression from one dose group to the next would only be allowed after a safety interim analysis of the results from the precedent dose group. This safety analysis will be performed by a Safety Monitoring Committee (SMC). Further details about the composition of the SMC are provided in section 8.7.
- If 2/3 of subjects in a dose group (6 of 9 subjects) experience an AE assessed as ≥Grade 2 according to Rheumatology Common Toxicity Criteria (RCTC v 2), dose escalation will be suspended until SMC review and agreement to proceed.
- Extensive safety laboratory monitoring will be performed.
- Each dose group of 12 subjects will be divided into 3 cohorts of 4 subjects each. Start of dosing for 1st patient of each cohort will be separated by at least 24 hours. Subjects will stay at the trial site for at least 24 hours after their first study drug administration.
- Start of dosing for the 1st patient of each dose group will be separated by at least 1 week from completion of dosing the previous dose group.
- All subjects will be closely monitored by physical examinations, and safety laboratory and ECG evaluations.
- Individual stopping rules as described in section 3.3.4.1 will be applied.
- UV-light protection measures as described in section 4.2.2.3 will be required until the end of the follow-up period.
- The potential risks which are described above will be minimized by close monitoring and the involvement of a SMC

Based upon preclinical data for BI 730357 and clinical data from SRD Trial 1407.1, as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this clinical trial. Considering the medical need of the development of a better tolerated and more effective oral treatment for patients with PsO, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Phase Ib evaluation of the safety, tolerability, PK, and PD properties of MRD administration of BI 730357 to healthy volunteers for up to 28 days.

2.1.2 Primary endpoint(s)

- Safety: Number of subjects with drug-related AEs, measured by the percentage of patients with drug related AEs within 7 days of treatment, which covers more than the residual effect period defined by 5 half-lifes of the study drug.

2.1.3 Secondary endpoint(s)

After the first dose:

- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose:

- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This Phase Ib (MRD) study 1407-0002 will evaluate 5 dose levels of BI 730357 administered to healthy volunteers for 14 days or 28 days, in fasted or fed state.

Approximately 84 subjects are to be entered into the study and allocated to one out of up to 7 dose groups; each dose group of 12 subjects is to be randomised (9 active:3 placebo) in 3 sequential cohorts, each composed of 3 subjects receiving active study drug and one subject receiving placebo. Subjects are to be evaluated for safety (physical examination, ECG and laboratory studies, AEs, and SAEs) and PK during once-daily study drug treatment for 14 days or 28 days, and for approximately one week after completion of treatment (Figure 3.1.1:2). Twenty-eight day evaluation of the higher dose groups is intended to more thoroughly evaluate BI 730357 safety and tolerability prior to longer term administration to patients with moderate-to-severe plaque PsO in future clinical trials. Dose cohorts are planned in both the fasted and fed states to confirm and further evaluate, after multiple dose administration, the positive food effect that was observed in the SRD trial. Moreover, the fed cohorts will also provide safety data at higher exposures in the fed state, in the event subjects take BI 730357 with food.

Additionally, the potential for DDI with a CYP3A substrate will be assessed in the 2 highest dose groups. This will be conducted in parallel to the multiple dose assessments, using a microdose of midazolam (a sensitive CYP3A substrate) administered at 3 different time points (baseline, Day 3 and Day 14) to examine potential CYP3A inactivation and induction effects of BI 730357.

Decision on dose groups and dose escalation

The dose groups will be investigated consecutively in ascending order of doses or expected exposures, maintaining a time interval of at least 7 days between the last drug administration in the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next dose group will be based upon evaluation of the safety, tolerability and all available PK data of the preceding dose groups. The next dose will only be given if, in the opinion of the Investigator and SMC, no safety concerns arose in the preceding dose group (i.e., no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to section 3.3.4.2).

A dose-escalation decision tree for the trial is shown below in Figure 3.1.1:1.

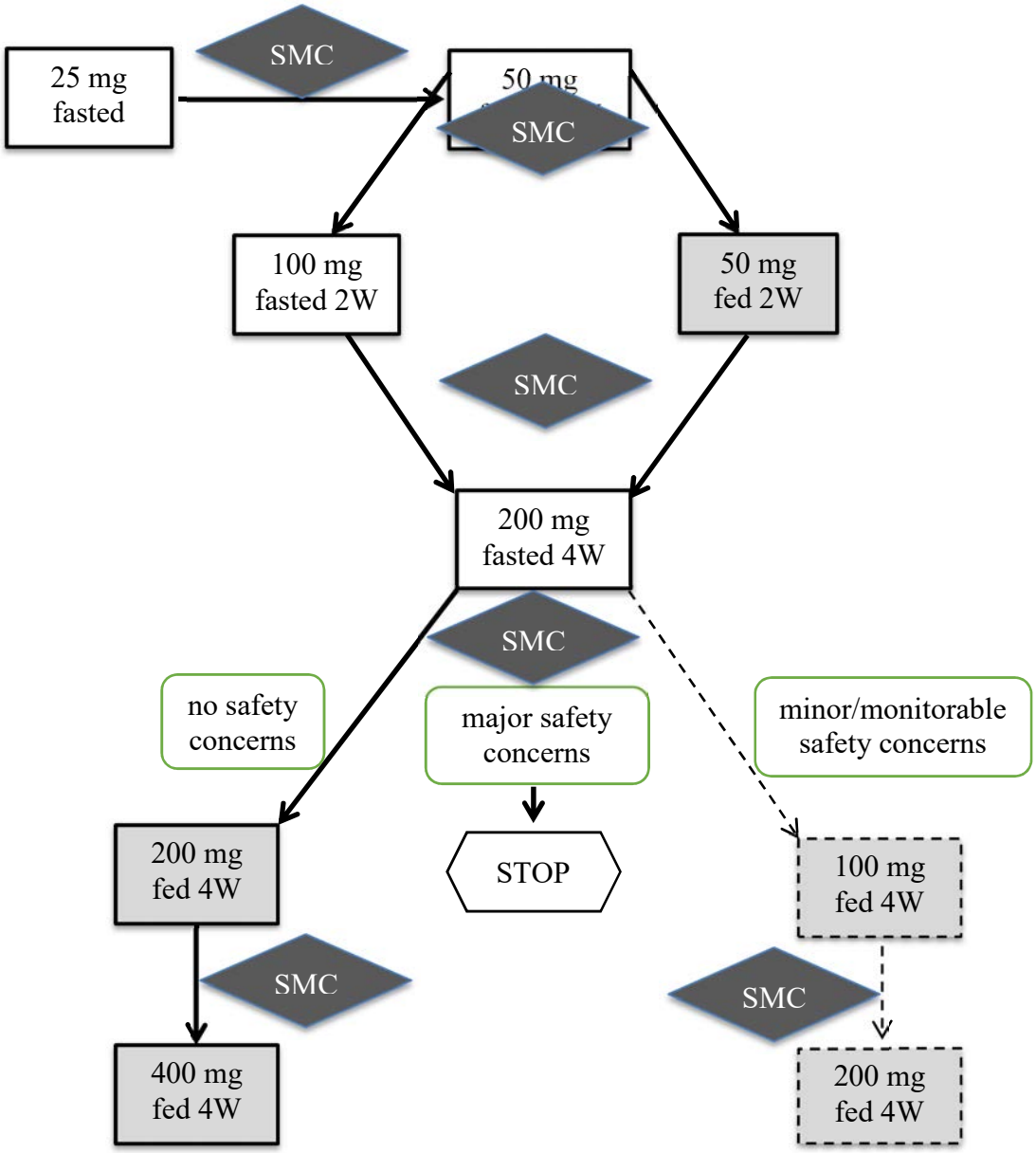

Figure 3.1.1:1 Dose-escalation decision tree
Bolded arrows and boxes = preferred pathway. Dotted lines = alternative pathway.

A SMC will be held after 14 days of dosing of DG 4 (200 mg fasted) to evaluate safety and PK data and decide if either the 200 mg fed cohort (if no safety concerns observed) or the 100 mg fed cohort (e.g., if minor and monitorable safety concerns observed) will be conducted.

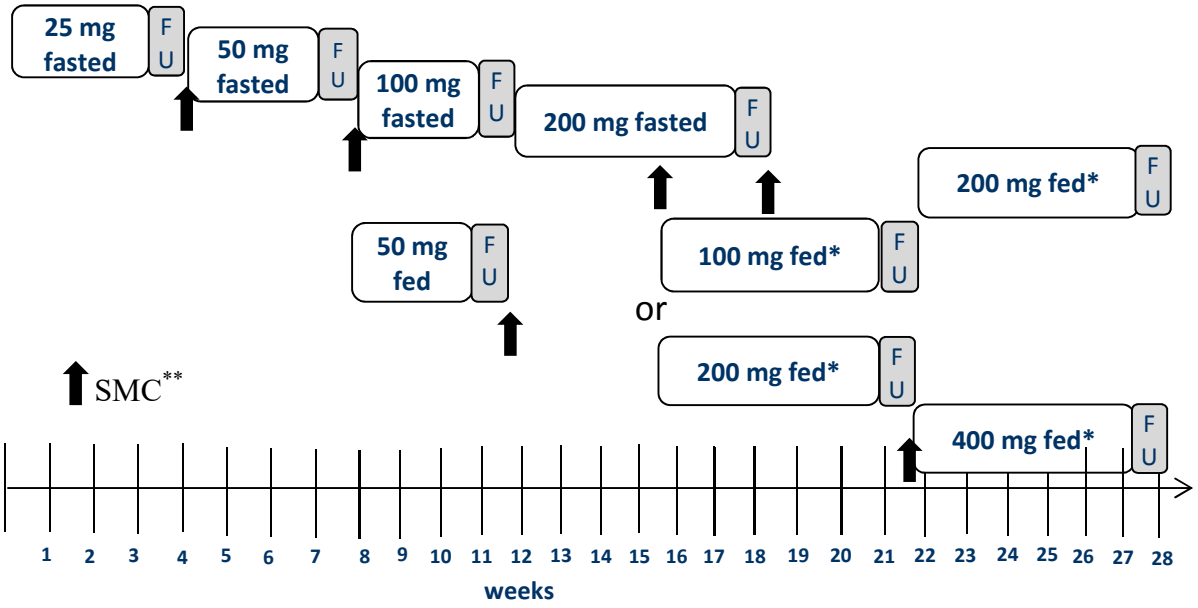

Figure 3.1.1: 2 Trial Design
*Subjects in the two highest dose groups will receive a microdose of midazolam prior to the initiation of study drug and at pre-specified time points during the treatment period.
** SMCs will be held after each dose group and after 14 days of the 200 mg fasted dose group to decide on the treatment of the next dose groups.

The various planned dose groups are listed in Table 3.1.1:1. However, of the 8 listed dose groups, a maximum of 7 dose cohorts will be evaluated. The Sponsor may also decide to conclude this trial without testing a 400 mg dose group upon evaluation of PK and safety data from prior dose groups, thus limiting dosing in subsequent trials to ≤200 mg.

Table 3.1.1:1 Planned dose groups

Dose Group	1	2	3	4	5	6*	7	8*
Daily dose (mg)	25	50	100	200	50	100	200	400
Status	fasted	fasted	fasted	fasted	fed	fed	fed	fed
Treatment duration (days)	14	14	14	28	14	28	28	28
Number of subjects	12	12	12	12	12	12	12	12
Subjects receiving placebo	3	3	3	3	3	3	3	3
Subjects receiving active drug	9	9	9	9	9	9	9	9

*In total, 7 dose groups will be evaluated. Testing of either DG 6 or DG 8 will be decided by the SMC.

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

This trial employs MRD design with a double-blind, placebo control and a 3:1 active: placebo randomisation. Additionally, a DDI assessment will be conducted in the 2 highest dose groups using a fixed-sequence design (midazolam administered alone, followed by midazolam administered with BI 730357 on two separate occasions)
For MRD trials, the design described in section 3.1 is viewed favourably under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 730357.

With the rising dose design, double-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. Each dose group consists of 12 subjects, with 9 on active treatment and 3 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 9 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of PK.
A SMC together with the Principal Investigator will review the emerging safety data after completion of each dose group and decide on whether to proceed to the next higher dose.

A CYP3A DDI evaluation using a microdose of midazolam is considered acceptable, as a microdose of midazolam is not expected to have any pharmacological or PD effects, thus, subjects are not exposed to undue risks and the evaluation of the investigational drug should not be influenced. This assessment will allow for better judgement regarding acceptable co-medications in Phase III development.

3.3 SELECTION OF TRIAL POPULATION

This trial will be conducted in healthy male volunteers.
As the treatment duration in this study is limited to 14 to 28 days, the potential benefit for patients with PsO is considered very low. The potential indirect benefit is limited to the development of an efficacious drug for patients with PsO.

3.3.1 Main diagnosis for trial entry

Healthy male volunteers

3.3.2 Inclusion criteria

1. Healthy male subjects according to the assessment of the Investigator, based on a complete medical history, physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, and clinical laboratory tests
2. Subjects with a partner who is a woman of childbearing potential (WOCBP[1]) must be willing to use male contraception (condom or sexual abstinence) from the first administration of trial medication until 30 days after last administration of trial medication
3. Age of 18 to 45 years (incl.) at screening
4. BMI of 18.5 to 29.9 kg/m^2 (incl.) at screening
5. Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation

3.3.3 Exclusion criteria

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

1. Any finding in the medical examination (including blood pressure, pulse rate or ECG) deviating from normal and judged as clinically relevant by the Investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the Investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the Investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy and/or surgery of the gastrointestinal tract (except appendectomy and simple hernia repair) that could interfere with the PK of the trial medication
7. Diseases of the CNS (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or acute infections which are of relevance in the opinion of the Investigator
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)

[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.

11. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
12. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug
13. Tobacco usage (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Alcohol abuse (consumption of more than 30 g per day)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
18. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
19. Subject is assessed as unsuitable for inclusion by the Investigator; for instance, is considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study
20. Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2.3.

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

3.3.4 Withdrawal of subjects from therapy or assessments

Subjects may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent"), as described in sections 3.3.4.1 and 3.3.4.2 below. Every effort should be made to keep the randomised subjects in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful participant selection, appropriate explanation of the trial requirements and procedures prior to randomisation, as well as the explanation of the consequences of withdrawal. The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF.

3.3.4.1 Withdrawal from trial treatment

An individual subject is to be permanently withdrawn from trial treatment if:

- the subject wants to withdraw from trial treatment, without the need to justify the decision.
- the subject needs to take concomitant drugs that interfere with the investigational product.
- the subject can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy).

- 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 for the remainder of the study.
- !"#$%& '() *+"#,) +- '#).'/)%' '() ,"01)*')23)#$)%*), *.#!$+4.,*"5.# +# ()/.'+5+&$* .!4)#,))4)%' 6$%*5"!$%&&+#.'+#7.0%+#/.5$'$),89:$'(Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 Grade 2 +#($&()#;In addition to these criteria, the physician may discontinue subjects at any time based on his or her clinical judgment.

Given the subject's agreement, the subject will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Charts (FC) 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 trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced. A replacement subject will be assigned a unique study subject number, and will be assigned to the same treatment as the subject he/she replaces.

3.3.4.2 Withdrawal of consent for trial participation

Subjects may withdraw their consent for trial participation at any time without the need to justify the decision. This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore, it may mean that further follow up on safety cannot occur.
If a subject wants to withdraw consent, the Investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the Sponsor

BI, the Sponsor, reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. New toxicological findings or SAEs invalidate the earlier positive benefit-risk-assessment.
2. More specifically, a dose group will be stopped if more than 50% of the subjects in this dose group show drug-related and clinically relevant AEs of moderate or severe intensity, or if at least one drug-related SAE is reported in this dose group that is considered to be unacceptable.
3. Also the trial will be terminated if more than 50% of the subjects in the trial show drug-related and clinically relevant AEs of moderate or severe intensity, or if more than one drug-related SAE is reported that is considered to be unacceptable.
4. The expected enrolment goals overall or at a particular trial site are not met

5. Violation of GCP, or the CTP or the contract with BI by a trial site or Investigator, disturbing the appropriate conduct of the trial
6. The Sponsor decides to discontinue the further development of the investigational product.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Multiple doses of BI 730357, and Placebo to match BI 730357.
Microdoses of Midazolam in Dose Groups 4 and 5.

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:	25 mg, 50 mg
Posology	QD
Route of administration:	Per os

Substance:	Placebo to match BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	--
Posology	QD
Route of administration:	Per os

Table 4.1.1: 2 Probe drug:

Substance:	Midazolam (Midazolam-ratiopharm®)
Pharmaceutical formulation:	Solution for injection
Source:	Ratiopharm GmbH, Germany
Unit strength:	5 mg/ 5 mL diluted to 50 µg/mL*1.5 mL (75 µg)
Posology	QD on Days -1, 3, and 14
Route of administration:	Per os

4.1.2 Selection of doses in the trial

The primary objective of this trial is to investigate the safety, tolerability, and PK of BI 730357 in healthy male subjects following fasting oral MRD administration of 25 mg, 50 mg, and 100 mg q.d. over 14 days, and doses between 100mg and 400 mg q.d. over 28 days. Study medication will be taken either after a fasting period of at least 6 hours or after the intake of a standard continental breakfast, to investigate food effect on BI 730357 exposure. A relatively broad dose range is selected in order to evaluate likely subtherapeutic, therapeutic and supratherapeutic dose levels, without jeopardizing the subjects' safety, and determine whether there is a meaningful safety threshold for this new drug.

The dose range for this trial was selected on the basis of the data obtained in the first-in-human SRD Trial 1407.1. In this study, dose levels up to 800 mg were well tolerated.

As described in section 1.2.1, an anticipated human therapeutic exposure was predicted based on a $C_{min,ss}$ of 140 nM. In Trial 1407.1 this projected trough level at 24 h (C_{24h}) was exceeded for subjects in dose group ≥ 100 mg after SRD BI 730357 administration. Therefore, evaluation of a dose range spanning above and below 100 mg in this trial is appropriate. Evaluation of higher dose levels is further justified for this novel mechanism since it is possible that a $C_{min,ss}$ more than the 140 nM may be necessary (i.e., > IC_{50}) to reach the optimal efficacy.

SRD Trial 1407.1 demonstrated that BI 730357 was safe and well tolerated up to the 800 mg dose. Given that BI 730357 had a half-life of approximately 20 to 28 hours, higher exposures will be expected following MRD administration of comparable doses. Assuming the PK properties remain consistent with single rising dose data after once daily dosing, accumulation of BI 730357 in plasma upon multiple dosing is expected to be 3.0 fold and 2.7 fold compared to simulated single dose AUC and C_{max}, respectively. These accumulation factors are based on the population pharmacokinetic model developed using the interim Trial 1407.1 data (2-compartment PK model with first order absorption and elimination, to and from central compartment) which was used to simulate typical profiles at Day 1 and Day 14.

These simulated steady-state exposures assume linear PK and can be considered as the upper bound for exposures, given that exposures were less than linear at higher single doses in the SRD study. This would also allow a safety comparison to the NOAEL exposures.

Table 4.1.2: 1 Plasma exposures of BI 730357 in SRD Trial 1407.1 (preliminary G.Mean) and expected exposures (fasted state) following MRD administration (expected maximum G.Mean, steady-state exposure based on simulations assuming dose-proportional and linear kinetics)

Dose (fasted)	Observed exposures in Trial 1407.1 (see Table 1.2.2:1)		Expected maximum steady state exposures in 1407.2 following MRD administration in fasted state		
	C_{max} (nM)	AUC_{0-24} (nM*hr)	$C_{trough,ss}$ (nM)	$C_{max,ss}$ (nM)	AUC_{ss} (nM*hr)
25 mg	103	1413	102	235	3376
50 mg	173	2623	233	488	7296
100 mg	284	4142	462	968	14509
200 mg	433	6346	938	1958	29513
400 mg	755	9453	1940	4016	59931

The starting dose of 25 mg q.d. was well tolerated in SRD Trial 1407.1, and considered to be safe. The predicted $C_{trough,ss}$ level at this dose is expected to be below the projected IC_{50} required for efficacy (sub-therapeutic dose). The subsequent doses of 50,100, 200 and 400 mg are expected to achieve steady state trough levels greater than the IC_{50} value. The highest dose level of 400 mg was set to provide a sufficient safety margin for patients in subsequent clinical trials. An additional 14 days of administration at the two highest doses (i.e., 200 mg and 400 mg) will allow assessment of safety for the longer duration in subsequent trials.

Figure 4.1.2:1 and Figure 4.1.2:2 show that with the selected doses, BI 730357 administered under multiple dose conditions (G.Mean) will not exceed the NOAEL exposures.
The C_{max} at the NOAEL in dogs is depicted in the figure below, and is 6660 nM which would be ~ 1.7-fold the human estimated G.Mean $C_{max, ss}$ at 400 mg, the maximum dose used in this trial.

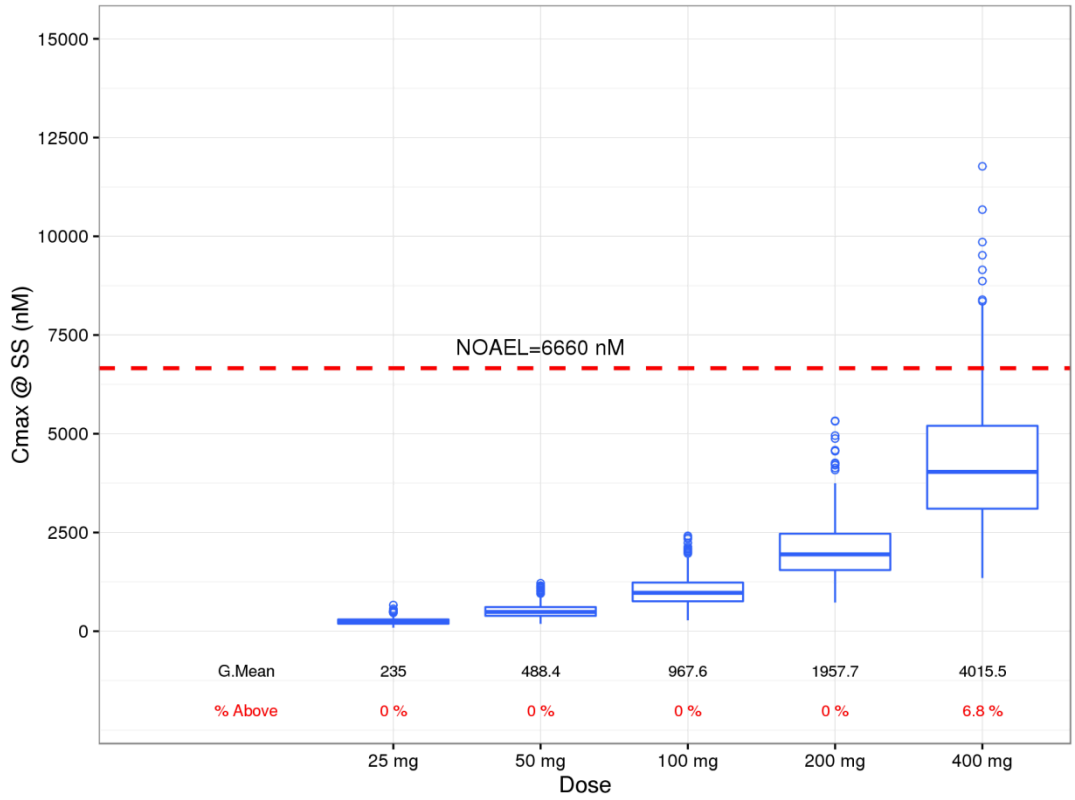

Figure 4.1.2: 1 Predictions of $C_{max,SS}$ based on exposure with BI 730357 in the SRD trial and comparison to NOAEL exposures

Footnote: The boxplots show the predicted distribution of $C_{max,SS}$ of 500 simulated subjects. The predictions are based upon a linear population pharmacokinetic model that was developed using interim PK data of the SRD portion of the 1407.1 study. The bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median) and outliers are represented by open circles. The whiskers are the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The dotted red line represents the mean C_{max} at the NOAEL in dogs of 6660 nM. G.Mean values denotes geometric mean of the predicted $C_{max,SS}$ at each dose level and % Above denotes the percent of individuals above the NOAEL levels.

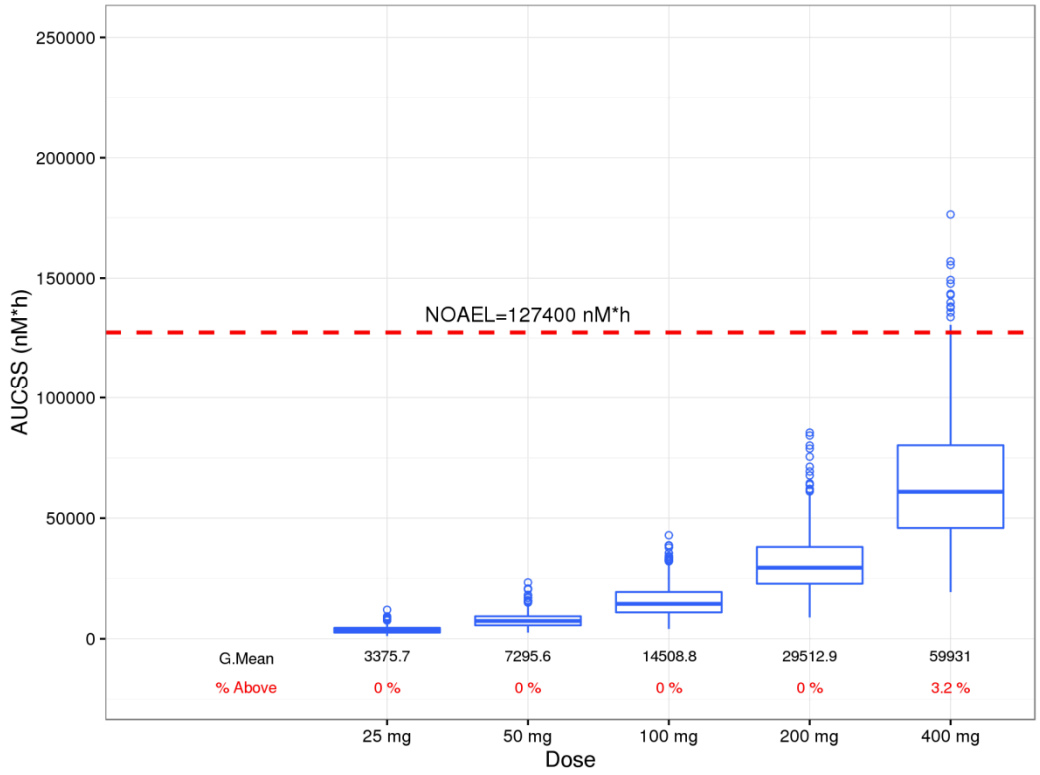

Figure 4.1.2: 2 Predictions of AUC_{SS} based on exposure with BI 730357 in the SRD trial and comparison to NOAEL exposures

Footnote: The boxplots show the predicted distribution of AUC_{SS} of 500 simulated subjects. The predictions are based upon a linear population pharmacokinetic model that was developed using interim PK data of the SRD portion of the 1407.1 study. The bottom and top of the box are the first and third quartiles, and the band inside the box is the second quartile (the median) and outliers are represented by open circles. The whiskers are the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The dotted red line represents the mean AUC at the NOAEL in dogs of 127400 nM*h. G.Mean values denotes geometric mean of the predicted AUC_{SS} at each dose level and % Above denotes the percent of individuals above the NOAEL levels.

Based on non-clinical data, it is predicted that BI 730357 can be safely administered to humans at dose levels achieving exposures of approximately 6660 nM (C_{max}) and 127,400 nM·h (AUC_{0-24}). At the highest dose of 400 mg to be used in this trial, there remains a multiple of exposure (MoE) of 1.7- and 2.1-fold to the estimated $C_{max, ss}$ and AUC_{ss}, respectively.

The dose rationale for the proposed fed cohorts of 50, 100, 200 and 400 mg is to provide safety and PK data at the expected higher exposures in the fed state based on the positive food effect observed in the SRD study (1407.1). This will provide safety coverage in the event that subjects inadvertently take BI 730357 with food in subsequent clinical trials with a fasted-state dose administration schedule. The proposed fed cohorts will also provide the necessary data if BI 730357 needs to be administered with food in future clinical trials.

In order to estimate the exposures of the fed cohorts in 1407.2, an exposure multiple of 2-fold (realistic) to 5-fold (maximum-case scenario) was applied to the SRD exposure (see Table

1.2.2:1) at the 400 mg fed (standard-diet) cohort. The exposures at the lower fed doses (which were not tested in 1407.1) were calculated assuming dose-proportional kinetics. The projected exposures are shown in Table 4.1.2:2, below.

Table 4.1.2: 2 Expected plasma exposures of BI 730357 following MRD administration in fed state (expected G.Mean, steady-state exposure assuming dose-proportional kinetics to 400 mg fed exposure from 1407.1 and a 2-fold to 5-fold exposure multiple)

Dose (fed state std. diet)	Observed exposures in Trial 1407.1 (see Table 1.2.2:1)		Expected steady state exposures in 1407.2 following MRD administration in fed state			
			2-fold accumulation		5-fold accumulation	
	C_{max} (nM)	AUC_{0-24} (nM*hr)	$C_{max,ss}$ (nM)	AUC_{ss} (nM*hr)	$C_{max,ss}$ (nM)	AUC_{ss} (nM*hr)
400 mg	1268	17864	2536	35728	6340	89320
200 mg	Not tested		1268	17864	3170	44660
100 mg			634	8932	1585	22330
50 mg			317	4466	793	11165

Based on the projected exposures listed above, even with a 5-fold accumulation ratio (highly unlikely, but assuming a maximum scenario), the highest $C_{max,ss}$ and AUC_{ss} are still below the NOAEL exposures of 6660 nM (C_{max}) and 127,400 nM·h (AUC_{0-24}). However, it is more likely that the accumulation ratio would be in the 2-3 fold range and, thus, lower exposures are expected.

The dose of midazolam used for the DDI evaluation at two of the highest BI 730357 doses was chosen to be 75 µg, which is within the definition of a microdose ($1/100^{th}$ of the therapeutic dose or 100 µg, whichever is smaller). Since midazolam PK is dose proportional over the microdose to therapeutic dose range, the microdose should still be able to accurately predict CYP3A DDI liability, while remaining below a pharmacologically active concentration. An IV solution has been chosen for administration as an oral solution, as an IV solution is meant to be diluted and, thus, there is data available regarding the stability and compatibility of a diluted solution. Furthermore, the IV solution contains midazolam in isotonic saline solution, while the oral solution has added excipients, making it a less than ideal for such a dilution. Additionally, there is the aspect of feasibility, whereby the oral solution would need to be diluted 1:400, which may not be possible to accurately achieve, while the IV solution would only require a dilution of 1:200. The IV solution has been successfully diluted and administered orally as a microdose in previous clinical studies without any reports of AEs.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be assigned sequentially to dose

groups, and likewise to cohorts within each dose group. Allocation of subjects will thereby not be influenced by trial personnel, rather will be determined only by the subjects' temporal availability.

The list of subject and medication numbers will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each subject

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. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication, if correct dosage cannot be ensured otherwise. On study days one and 14, visit procedures including blood draws will be performed following an overnight fast, which is to start no later than 8 hours before the scheduled dosing. On other days, in the fasted dose groups, the fasting period prior to the withdrawal of blood samples should be at least 6 hours. To ensure a dosing interval of 24 hours, the administration of trial medication should take place at the same time every day. In the fed dose groups, a standard continental breakfast (see table 4.1.4:1) should be taken after blood sampling and before the study drug administration. In the fasted dose groups, the intake of food should not occur earlier than 30 minutes after the drug administration.

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

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: 88 kcal as protein, 133 kcal as carbohydrate, and 237 kcal as fat.

Components may be substituted to accommodate for dietary requirements (i.e. vegetarian, gluten intolerance, etc.). The composition regarding calories, fat, protein and carbohydrates should, however, remain similar.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial is 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 subject's treatment (active or placebo). According to the rising dose design, the current dose level will be known to subjects and investigators.

At the trial site, access to the randomisation schedule is restricted to unblinded pharmacists and pharmacy staff members. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF. Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to 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 randomisation at Day 1 until database lock. See also section 3.1 for information on study design and blinding.
Regarding the Sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist, as well as dedicated contract research organisation (CRO) personnel). The objective of the trial is not expected to be affected.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator by an emergency code break envelope. Unblinding information will also be centrally available at ESMS Global Ltd (Emergency Scientific and Medical Services), London, United Kingdom. ESMS can be reached by telephone at any time and is able to provide information on the assigned treatment by the subject ID number.

Unblinding must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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 and not be shared further.

4.1.6 Packaging, labelling, and re-supply

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

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 (labelled) storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

The Investigator will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

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

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. The Investigator or pharmacist must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial participants. The Investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor< and/or >appointed CRO, the Investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant treatments are allowed.

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.

4.2.2.2 Restrictions on diet and life style

On Days 1 and 14 with intensive PK sampling, participants should be fasted for at least 8 hours prior to administration of study medication.

In the fasted dose groups, at all other visits, the participants should take the medication after at least 6 hours fasting and at least 30 minutes before taking food.

In the fed dose groups, a standard continental breakfast (see table 4.1.4:1) should be taken after the first blood draw and before the administration of medication.

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.

4.2.2.3 Restriction of UV-light exposure

Throughout their participation in the study, participants should avoid sunbathing. 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.
These protection measures must be applied until the end of the follow-up period.

4.2.2.4 Restrictions regarding WOCBP and men able to father a child

Participants able to father a child must use the contraception methods described in section 3.3.3 and in the subject 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 and/or urinary excretion will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see section 3.3.4).

5. ASSESSMENTS

5.1 ASSESSMENT OF SAFETY

5.1.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Charts. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the Flow Chart.
The results must be included in the source documents available at the site.

5.1.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Charts, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

5.1.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.1.3:1. For the sampling time points please see the Flow Charts.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
The central laboratory will send reports to the Investigator. It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically-relevant abnormal findings as judged by the Investigator will be reported as AEs.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see the DILI Checklist provided in the ISF. The amount of blood taken from the subject concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.1.3:1 Safety laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c)[1] Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leucocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Amylase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (reflex in case of elevated CK) Albumin Cholesterol, total[1] Triglycerides[1] LDL-Cholesterol /HDL-Cholesterol[1]

[1] only at screening and EOO-visit

Table 5.1.3:1 Safety laboratory tests cont.

Category	Test name
Hormones (only at screening)	TSH, (free T3 and T4 in case of abnormal TSH)
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leucocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine	Albumin (quantitative) Creatinine
Infections screening (only at the screening visit)	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB

[1] only at screening and EOO-visit

5.1.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the Flow Charts. The Investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the 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.

5.1.5 Other safety parameters

N/A

5.1.6 Assessment of adverse events

5.1.6.1 Definitions of AEs

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.

Serious adverse event

A 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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as "AE Collection" and **AE reporting to Sponsor and timelines"**

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

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
The term 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 above.

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

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

Intensity (severity) of AEs
The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT (R13-3515). Refer to ISF for intensity/severity classification. Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life –threatening

Causal relationship of AEs
Medical judgement should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications).

- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is diminished).

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.

5.1.6.2 Adverse event collection and reporting

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:
  -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 AEs but should only report related SAEs and related AESIs of which the Investigator may become aware of by any means of communication, e.g., phone call. Those AEs should however, not be reported in the CRF.

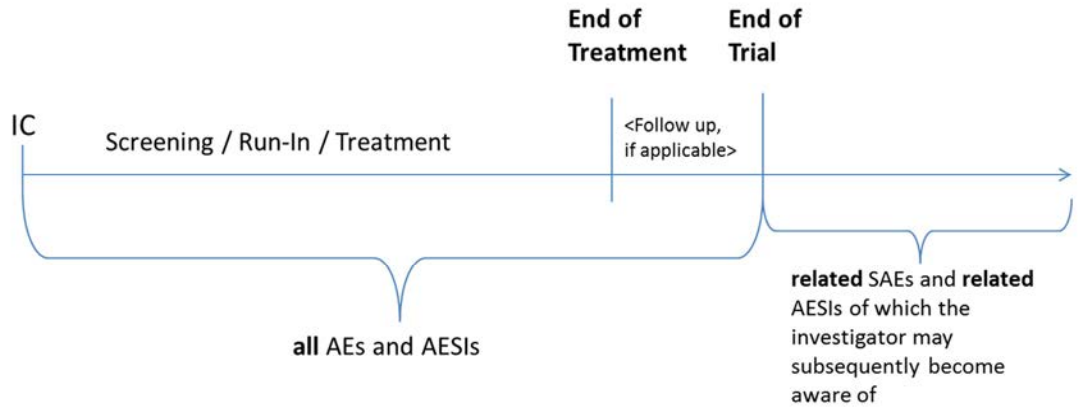

Figure 5.1.6.2: 1 Trial periods for collection of AEs

Participants, who discontinue trial medication prematurely and agree to be contacted further, should be followed up as described in section 3.3.4.1, withdrawal from trial treatment. From then on until the individual subject's end of the trial the Investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs of which the Investigator becomes aware.

AE reporting to 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.

Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the trial medication and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

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

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual subject'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.

Pregnancy

.

Potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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

The pregnancy is not to be reported as an AE.

5.2 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.2.1 Assessment of pharmacokinetics

PK parameters for exposure and disposition will be calculated as stated in sections 2.1.3 and 2.2.2. Other standard single and multiple dose PK parameters will be calculated and further specified in the TSAP.

5.2.2 Methods of sample collection

5.2.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 730357 and CD 6975 (Metabolite) plasma concentrations, 2.7 mL of blood will be taken from an antecubital or forearm vein into a K-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

The EDTA-anticoagulated blood samples will be centrifuged for about 10 minutes at about 2000 g to 4000 g and at 4 to 8 °C or at room temperature. 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.

For quantification of midazolam plasma concentrations, 4 mL of blood will be taken from an antecubital or forearm vein into a K2-EDTA-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. The EDTA-anticoagulated blood samples will be centrifuged for about 10 minutes at about 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 1.0 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 on crushed ice or in an ice-water bath. 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.

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) including anti-drug antibodies (if applicable) 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.

5.2.2.2 Urine sampling for pharmacokinetic analysis

A blank urine sample will be collected before administration of trial medication (within the 3 hours before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Chart will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Subjects are told to empty their bladders at the end of each sampling interval.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e., 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurement. In case more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 minute (manually or using a stir bar or

other stirring device out of PE, PP, Teflon or glass). If required further details on urine sampling will be described in a study-specific lab manual.

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

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

After completion of the trial the urine 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.

5.2.2.3 Plasma sampling for metabolism analysis

Additional K_3-EDTA plasma samples for the identification of drug metabolites will be investigated in the 100 mg fasted dose group. Based on the knowledge gained during the trial conduct, e.g., from preliminary PK results, the dose group may be changed to a different one. The change will be implemented via a non-substantial CTP Amendment.

The blood samples will be drawn in parallel to PK samples on Day 14 at the time points indicated in the Flow Chart (time points for metabolism analysis are the same as for PK). At each of these time points, 2.7 ml blood will be needed for metabolite analysis. Details of sample processing will be described in a study-specific laboratory manual, see ISF. Data from MIST samples will not be transferred into the database.

Only data related to the parent compound and its metabolites will be acquired. Evaluation of the drug metabolism will be reported separately but not included in the CTR of this trial. The study samples will be discarded after completion of the experiments, but not later than 5 years after the final study report has been signed.

5.2.3 Analytical determinations

BI 730357 and CD 6975 concentrations in plasma and BI 730357 concentration in urine will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. Midazolam concentrations in plasma will be determined by a validated LC-MS/MS assay. All details of the analytical methods will be available prior to the start of sample analysis.

5.3.1.1 Methods of sample collection

For the assessment of mRNA expression from whole blood, 4.3 mL blood will be collected from an antecubital or forearm vein into a sodium citrate blood drawing tube at the times indicated in the Flow Chart and treated within 60 minutes with stimulation conditions described in 5.4.1.

For the assessment of IL-17A protein in plasma, 4.5 mL blood will be collected from an antecubital or forearm vein in a lithium heparin-anticoagulant blood drawing tube at the times indicated in the Flow Chart and treated within 60 minutes with stimulation conditions described in 5.4.1.

Sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g., preliminary PK data), including addition of samples and visits, as long as the total blood volume taken from each subject does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

Detailed instructions for sampling, handling and shipment of samples are provided in the ISF / Lab Manual.

After completion of the study the samples may be used for further biomarker investigations. The study samples will be discarded after completion of any additional investigations but not later than 3 years after the end of the trial.

5.4 OTHER ASSESSMENTS

5.5 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial except from the skin biopsies are standard measurements in multiple rising dose trials and will be performed in order to monitor safety aspects in an appropriate way.

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

Information about race should be obtained from all study participants as allowed by local regulations. This is because the prevalence and characteristics of psoriasis differ widely between subjects of different racial origin. It will thus be worthwhile to assess if patients of different race will respond differently to the study treatment.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All subjects are to adhere to the visit schedule as specified in the Flow Charts. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. 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 and be assessed pre-dose at all dosing visits. All blood samplings on all visits which are not intensive PK-days should occur prior to the intake of medication.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

No trial procedures should be done unless the subject has consented to taking part in the trial. Once consented, the subject is considered to be enrolled in the trial and have started screening. The subject should be recorded on the enrolment log. Screening procedures may be extended to more than one physical visit, if needed.

Re-screening will not be permitted. Subjects who fail screening following Visit 1 assessments should be registered as a screen failure.

After the informed consent process is complete and written informed consent is obtained, the subjects will be assessed for study eligibility including laboratory assessments.
All other assessments will also be performed as summarized in the study Flow Charts.
All subsequent visits should be scheduled.

6.2.2 Treatment period(s)

Please refer to Flow Charts 1 to 4.

6.2.3 Follow up period and trial completion

For all randomised subjects termination of trial medication and trial completion must be recorded on the corresponding eCRFs.

6.2.3.1 Early treatment and trial termination:

If a subject cannot or will not continue in the trial, he should complete EOT visit procedures instead of the planned treatment period visit and return to the clinic for FU/EOO Visit 1 week after last dose of study medication.

6.2.3.2 Trial completion

Participants who finish the treatment period will return to the clinic for Follow-up Visits. Trial completion is defined as subjects having reached the FU visit within the specified window per the Flow Chart.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The primary objective of this trial is to investigate the safety and tolerability of BI 730357 by using descriptive statistics for all endpoints comparing active dose groups to placebo. The primary endpoint is defined in section 2.1.2. Inferential statistics is not planned (as explained in section 7.2).

The secondary objective is the exploration of the PK and PD of BI 730357. Endpoints as specified in section 2.1.3 and section 2.2.2 will be analysed by descriptive statistics. Secondary endpoints as defined in section 2.1.3 will be subjected to analysis of dose proportionality by use of the power model. Trough concentration values will be analysed regarding attainment of steady state as a pre-requisite for calculation of steady state parameters. Additionally, the linearity index will be estimated. Furthermore, the relative bioavailability of midazolam in the presence and absence of BI 730357 at the highest dose(s) will be evaluated and the relationship between trough exposure and IL-17 inhibition will be explored. Refer to section 7.3 further details.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of up to 7 different dose groups of BI 730357 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods.

The analysis of PK and PD data will also be descriptive. Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e., confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

All individual data will be listed.

All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the treated set.

The primary endpoint will be analysed only descriptively on the treated set. For more details see section 7.3.4. Safety analyses will be based on the actual treatment received at randomisation.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important

protocol violations (IPVs) will be identified no later than in the Blinded Report Planning Meeting and provided in the TSAP.

Specifications of important protocol violations will be provided in the TSAP.

7.3.1 Primary endpoint analyses

Analysis of safety and tolerability is described in section 7.3.4.

7.3.2 Secondary endpoint analyses

The secondary parameters (refer to section 2.1.3) will be calculated according to the BIStandard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472, current version).

Reasons for exclusion of single PK parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be determined for the test product excluding the subjects experiencing emesis
- The subject experiences emesis at any time during the labelled dosing interval
- Time deviations
- Use of restricted medications

The subject set for the evaluation of PK endpoints (PKS) will include all treated subjects that provide at least one observation for at least one secondary endpoint without important protocol violations relevant for the evaluation of PK endpoints. Whether a protocol violation is relevant will be decided no later than in the Blinded Report Planning Meeting.

Excluded subjects will be listed with their individual plasma concentrations and individual PK parameters, however, they will not be included in descriptive statistics for plasma concentrations, PK parameters or other statistical assessment.

Only the fasted dose groups will be used for the assessments of dose proportionality, lineartity index, and the attainment of steady state.

Assessment of dose proportionality

Dose proportionality will be assessed using the PK endpoints as specified in section 2.1.3.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

Where

Y_{ij}	logarithm of the PK endpoint for subject j at dose level i; where i = 1, 2, …, 4-5, j = 1, 2, …, 9;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed PK endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Linearity index

Linearity with respect to multiple administration will be explored using the linearity index (LI) that will be computed as follows:

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

In order to construct a confidence interval for LI, a statistical model using $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ will be set up: A linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random and 'AUC type' a fixed effect.

[1] $Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, where

Y_{ij} logarithm of the response (AUC after first dose, AUC after last dose) for subject j and AUC type i; where i = 1 (after first dose) or 2 (after last dose) and j=1, 2,…, n

μ the overall mean

τ_i the AUC type i

s_j the effect associated with subject j (random effect)

e_{ij} random error associated with subject j at AUC type i (assumed to be independent and identically normally distributed).

A pairwise comparison of both areas via the log transformed difference

$\log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = \log(AUC_{\tau,ss}) - \log(AUC_{0-\infty})$

will then be performed including calculation of a 2-sided 95% CI. The back transformed point estimate then represents the estimate of LI. Perfect linearity with respect to multiple administrations holds true if this index equals unity.

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable across dose levels, they can be analysed simultaneously. The corresponding model will then include the log transformed dose as (additional) covariate.

Attainment of steady state

Attainment of steady state will be explored by using the trough concentrations of BI 730357 between days 2 and 14 or 28 respectively and the concentrations taken directly at the end of the first and the last dosing interval ($C_{\tau,1}$, $C_{\tau,14/28}$) for each dose level. Pairwise comparisons of concentrations are performed using 2-sided 95% CIs based on the t-distribution. The calculation is based on a repeated measures linear model on the logarithmic scale.

$Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, where

Y_{ij} logarithm of the concentrations for subject j at time i, i = 1, 2, … and j=1, 2,…, n

μ the overall mean,

τ_i the effect associated with time point i (repeated effect),

s_j (random) effect of subject j, j=1, 2, ..., n

e_{ij} random error associated with subject j at time i (assumed to be independent and identically normally distributed).

Dose can be included as an additional covariate if there is evidence that the trough concentration profiles are comparable across dose levels.

The model will be used to explore the time to steady state by pairwise comparing concentrations from different time points: log-transformed differences between all subsequent time points ($\log(C_{pre,i}/C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$, where j>i) will be compared and adjusted means (Least Squares Means) as well as 2-sided 95% CIs will be calculated.

Thereafter, these quantities will be back-transformed by exponentiation to give the corresponding (adjusted) ratio and CI.

Comparisons which reveal CIs (for the adjusted ratio) not including 100% will be inspected to determine if the differences between time points are resulting from not yet attaining steady-state.

For further details refer to the TSAP (such as selection of covariance structure and comparison of time points).

Graphical displays

To support the analyses of dose proportionality, linearity and attainment of steady state, graphical representations of the data might be created. These might include (but are not limited to) individual time-courses of trough plasma concentrations and the (geometric) mean plasma concentration time profiles.

Further details will be given in the TSAP if needed.

7.3.4 Safety analyses

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

All treated 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 AEs will concentrate on treatment-emergent AEs, i.e., all AEs occurring between start of treatment and end of the residual effect period. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs 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 the database lock.

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The PK parameters listed in sections 2.1.3, 2.2.1 and 2.2.2 will be calculated according to the relevant BI internal procedures.

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

The following descriptive statistics will be calculated for plasma concentrations and PK parameters: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The exception to this is t_{max}, where only median, minimum and maximum will be calculated. The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with three significant digits in the clinical trial report.

For handling of missing data, please refer to section 7.5.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software, Version 9.4 (or later).

7.4 INTERIM ANALYSES

No inferential statistical interim analysis is planned. However, after each dose group the Investigator (or deputy) is allowed to postpone further dose progression until a preliminary analysis of the data already obtained has been performed. Refer to section 8.7 for more information.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect complete data at all visits.
With respect to safety evaluations, it is not planned to impute missing values.

Missing PK data will be handled as follows:

Plasma concentration - time profiles
Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analysed), and BLQ (below the limit of quantification) will be ignored and not replaced by zero at any time point (applies also to the lag phase). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the "2/3 rule" is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e., BLQ, NOR, NOS, NOA are included).

Pharmacokinetic parameters
In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored.

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

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g., descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in Section 15 of the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

More details will be included in the TSAP, if needed.

7.6 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.
The Sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.
More details can be found in section 4.1.5.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of up to 84 subjects in this trial depending on the number of dose groups as described in section 3.1. The planned sample size is not based on a power calculation. The size of 12 subjects per dose group (9 on active treatment, and 3 on placebo) is commonly used in multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of additional intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g., preliminary PK data), i.e., the actual number of subjects entered may exceed 84.

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 Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

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

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

The certificate of insurance cover is made available to the Investigator and the subjects, and is stored in the ISF.

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to subject participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional subject-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative."

The subject must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

The subject must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

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 subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

8.3.2 Direct access to source data and documents

The Sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY

Individual subject data obtained as a result of this trial is considered confidential, and disclosure to third parties is prohibited with the exceptions noted below. Subject privacy will be ensured by using subject identification code numbers.

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

Treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated 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.

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ("Last Subject Out").

The "**Last Subject Drug Discontinuation"** (LPDD) date is defined as the date on which the last subject at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

This trial is sponsored by BI.

A SMC composed of Principal Investigator, members of the BI Trial Team and a trial independent member will be established, to review individual and aggregated safety data at the conclusion of dosing for each dose group, to determine the acceptability of safety and tolerability, and recommend next dose level/does escalation. Details of the SMC responsibilities and procedures are described in the SMC Charter.

Relevant documentation on the participating (Principal) Investigators (e.g., their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
  .

Data Management and Statistical Evaluation will be conducted done by BI according to BI SOPs.

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

A central laboratory service vendor will be used in this trial. Details will be provided in the Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R03-1208 NPF psoriasis score. Psoriasis Forum. 8:2. 2002

R05-2548 Finlay AQ, Khan GK. Dermatology Life Quality Index (DLQI) – a simple practical measure for routine clinical use. Joint Ann Mtg of the British Association of Dermatologists and the Canadian Dermatology Association , Oxford, 6-10 July 1993. Clin Exp Dermatol. 19. 210-216. 1994.

R08-1089 Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. Nature. 445:7130. 866-873. 2007.

R10-1424 Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat.16:5. 639-656. 2006.

R11-1257 Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: psoriasis. N Engl J Med. 361:5. 496-509. 2009.

R11-1259 Menter A, Griffiths CEM. Psoriasis 2: current and future management of psoriasis. Lancet. 370. 272-284. 2007.

R11-1260 Griffiths CEM, Baker JNWN. Psoriasis 1: pathogenesis and clinical features of psoriasis. Lancet. 370. 263-271. 2007.

R13-2643 Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PDR, et.al. Secukinumab in Crohn´s Disease Study Group. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn´s disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 61:12. 1693-1700. 2012.

R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol 34:6. 1401-1414. 2007.

R15-1961 European Medicines Agency. Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. 23 January 2014.

R15-2001 Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding' (February 19, 2015). Cran rproject org web packages DoseFinding DoseFinding pdf. Comprehensive R Archive Network. 2015.

R15-3845 Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 159. 997-1035. 2008.

R15-5200 Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatol Treat. 26:1. 23-31. 2015.

R16-3072 Horn EJ, Fox KM, Patel V, Chiou CF, Dann F, Lebwohl M. Association of patient-reported psoriasis severity with income and employment. J Am Acad Dermatol. 57:6. 963-971. 2007.

R16-3073 Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: toward a new understanding of psoriasis pathogenesis. J Am Acad Dermatol. 71:1. 141-150. 2014.

R16-3149 Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology. 129. 311-321. 2010.

R16-4115 Mattei PL, Corey KC, Kimball AB. Cumulative life course impairment: evidence for psoriasis. Curr Probl Dermatol. 44. 82-90. 2013.

R17-1989 Burgos-Pol R, Martinez-Sesmero JM, Ventura-Cerda JM, Elias I, Caloto MT, Casado MA. The cost of psoriasis and psoriatic arthritis in 5 European countries: a systematic review. Actas Dermos Sifiliogr. Engl. Ed. 107:7. 577-590. 2016.

R17-1990 Vanderpuye-Orgle J, Zhao Y, Lu J, et al. Evaluating the economic burden of psoriasis in the United States. J Am Acad Dermatol. 72:6. 961-967. 2015.

R95-0013 Broom C. Design of first-admistration studies in healthy man. In: O´Grady J, Linet Ol, editors. Early Phase Drug Evaluation in Man. London. Macmillan Press. 206-213. 1190.

R96-3541 Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. Dermatologica. 157. 237-244. 1978.

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 Prediction of BI 730357 Pharmacokinetics and Therapeutic Dose in Human. Current version.

10. APPENDICES

No appendices included in this protocol.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		06 October 2017
EudraCT number		2017-001653-14
BI Trial number		1407-0002
BI Investigational Product(s)		BI 730357
Title of protocol		Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
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		
Change #1:		
Section to be changed		All sections of the protocol
Description of change		Removal of all sections and text referring to Part 2 (Phase II, proof of concept in patients with plaque psoriasis) of the previous protocol version.
Rationale for change		Separate the two parts of the protocol and make the Phase I multiple rising dose in healthy volunteers a self-contained trial.
Change #2:		
Section to be changed	3.3.2	Inclusion criterion #3
Description of change		"Age of 18 to 50 years (incl.) at screening" changed to "Age of 18 to 45 years (incl.) at screening"
Rationale for change		Adapt age range to Phase I standard as requested by health authority (BfArM)
Change #3		
Section to be changed	3.3.4.1	Withdrawal from trial treatment
Description of change		Addtion of individual stopping rule: An individual subject is to be permanently withdrawn from trial treatment if "during the course of treatment the subject experiences cardiovascular or hematologic adverse event (including laboratory abnormalities), with Rheumatology Common Toxicity Criteria

		(RCTC) Version 2.0 Grade 2 or higher."
Rationale for change		Adhere to respective EMA guideline and FDA request.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		12 January 2018
EudraCT number		2017-001653-14
BI Trial number		1407-0002
BI Investigational Product(s)		BI 730357
Title of protocol		Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers
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		
Change #1:		
Section to be changed	1.2	Drug profile
Description of change		
Rationale for change		Clarification
Change #2:		
Section to be changed	1.2.2	Clinical Experience in Humans
Description of change		Include updated results from SRD trial
Rationale for change		Update and provide justification for change #3.
Change #3:		
Section to be changed	 3.1 4.1.2 4.1.4 4.2.2 7.3.2	Flow charts #2 and #4 Overall trial design Selection of doses Drug assignment Restrictions Secondary endpoint analyses
Description of change		Addition of fed dose groups 50 mg, 200 mg and either 100 or 400 mg. Removal of 400 mg fasted dose group. Number of subjects increased from 60 to up to 84. Decision tree added.
Rationale for change		To assess the effect of food on drug exposure
Change #4		

Section to be changed	4.1.4	Drug assignment
Description of change		Contents of continental breakfast added
Rationale for change		
Change #5:		
Section to be changed	4.1.1	Identity of the investigational medicinal products Table 4.1.1:2.
Description of change		5 mg/ 5 mL diluted to 5 µg/mL*15 mL (75 µg) Changed to: 5 mg/ 5 mL diluted to 50 µg/mL*1.5 mL (75 µg)
Rationale for change		Correction of editorial error
Change #6:		
Section to be changed	5.2.2 5.2.3	Methods of sample collection Analytical determinations
Description of change		Addition of drug metabolites to be tested for
Rationale for change		New metabolites identified
Change #7:		
Section to be changed	5.3.1.3 5.3.1.4	Methods of sample collection Analytical determinations
Description of change		Sections were removed
Rationale for change		Editorial change: Sections were duplicates of sections 5.3.1.1 and 5.3.1.2

APPROVAL / SIGNATURE PAGE

Document Number: c14109663 **Technical Version Number:3.0**

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

Title: Phase Ib evaluation of the safety and tolerability and effect on midazolam metabolism of the administration of multiple rising doses of BI 730357 to healthy volunteers

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician		12 Jan 2018 14:01 CET
Author-Clinical Monitor		12 Jan 2018 15:03 CET
Approval-Team Member Medicine		14 Jan 2018 21:56 CET
Author-Trial Clinical Pharmacokineticist		15 Jan 2018 10:54 CET
Approval-Therapeutic Area		16 Jan 2018 11:22 CET
Verification-Paper Signature Completion		16 Jan 2018 13:28 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed