Clinical Trial Protocol

	Document Number:	**c20414608-08**
EudraCT No.:	2017-004659-21	
BI Trial No.:	1407-0030	
BI Investigational Product(s):	BI 730357	
Title:	Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis	
Lay Title:	This study is done in patients with plaque psoriasis and tests how well they tolerate BI 730357 and how effective it is.	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted] Phone: [redacted], Fax: [redacted]	
Coordinating Investigator:	[redacted]	
Status:	Final Protocol (Revised Protocol (based on Global Amendment 7)	
Version and Date:	**Version:**	**Date:**
	8.0	24 August 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	N/A
Active ingredient name:	BI 730357
Protocol date	26 March 2018
Revision date	24 August 2020
Trial number	1407-0030
Title of trial:	Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Coordinating Investigator:	[redacted]
Trial site(s):	Multi-centre trial conducted in approximately three countries
Clinical phase:	II
Trial rationale:	Favorable results of this trial will serve as a Proof of Clinical Concept in the treatment of PsO and for the refinement of Phase III dose selection.
Trial objective(s):	The primary objective is based on Week 12 co-primary endpoints of PASI 75 and sPGA 0/1, and overall safety. Secondary objectives of Part 1 are to evaluate the safety of BI 730357 through 24 weeks of treatment, and the effects of dose escalation and longer treatment duration on efficacy.
Trial endpoints	Co-primary endpoints: • ≥ 75% reduction from baseline PASI score (PASI 75) at Week 12 • sPGA score of clear or almost clear at Week 12 Secondary endpoints (endpoints beyond Week 12 apply only to Part 1): • ≥50% reduction from baseline PASI score (PASI 50) at Week 12 • ≥90% reduction from baseline PASI score (PASI 90) at Week 12 • 100% reduction from baseline PASI score (PASI 100) at Week 12 • sPGA score of clear at Week 12 • ≥75% reduction from baseline in PASI score (PASI 75) at Week 16, 20, 24

	• sPGA score of clear or almost clear at Week 16, 20, 24 • Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale at week 12 • Achievement of a Dermatology Life Quality Index score of 0 or 1 at Week 12
Trial design:	Two Part design (Part 1 and Part 2) double-blind, randomised, placebo-controlled, parallel
Total number of patients randomized:	Part 1: 180 Part 2: 90
Number of patients on each treatment:	Part 1: 20 on Placebo, 40 on each of the 4 active treatment arms Part 2: 10 on Placebo, 40 on each of 2 active treatment arms
Diagnosis :	Patients with moderate-to-severe plaque psoriasis
Main in- and exclusion criteria	Inclusion criteria: • Male or female patients. Women of childbearing potential[1] must be ready and able to use a highly effective method of birth control. • Age 18 to 75 (both inclusive) years at screening • BMI < 35 • Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. • Patients must be candidates for systemic psoriasis therapy • Moderate-to-severe plaque psoriasis: a. BSA ≥10%, and b. PASI ≥12, and c. sPGA moderate or severe Exclusion criteria: • Nonplaque forms of psoriasis, current drug-induced psoriasis, active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations • Current enrolment in another investigational device or drug trial, or less than 30 days (from randomisation) since ending another

[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.
[2]Defined as a Child-Pugh Score of B or C.

	investigational device or drug trial(s), or receiving other investigational treatment(s) • Use of a. any biologic agent within 12 weeks, or b. any anti-IL-23 biologic agent within 24 weeks prior to randomisation, or c. systemic anti-psoriatic medications or phototherapy within 4 weeks prior to randomisation, or d. topical anti-psoriasis medications within 2 weeks prior to randomisation • Live vaccination ≤ 12 weeks prior to randomisation (visit 2), or any plan to receive a live vaccination during the conduct of this study • Relevant chronic or acute infections, including human immunodeficiency virus, viral hepatitis, candidiasis and tuberculosis. • Evidence of a current or previous disease (including known or suspected inflammatory bowel disease and cardiovascular disease) or medical finding that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data • Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial • Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2.3 • Patients in Part 2: Moderate-to-severe hepatic impairment[2]
Test product(s):	BI 730357
dose:	Part 1: 25 mg, 50 mg, 100 mg, 200 mg BI 730357 once daily Part 2: 400 mg BI 730357 once daily, 200 mg BI 730357 twice daily
mode of administration:	p.o. Part 1: fasted Part 2: fed
Comparator products:	Placebo to BI 730357
dose:	N.A.
mode of administration:	p.o.
Duration of treatment:	Part 1: 24 weeks

	Part 2: 12 weeks
[redacted]	
Statistical methods:	Part 1: The primary objective includes demonstration of proof of clinical concept with respect to a non-flat dose response curve, characterization of the dose-response relationship within the therapeutic range, and selection of the dose range for phase III development. For this purpose, the primary analysis uses methodology for dose finding, employing both multiple comparison procedures and modelling techniques (MCPMod). Part 2: A Bayesian borrowing approach will be implemented to estimate treatment effect; no hypothesis testing will be performed in the confirmatory sense. The primary endpoint is defined in section 2.1.2

FLOW CHART, PART 1

Trial Periods	**Screening**	**Treatment**										**Follow- up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**EOT**	**FU 1 (EOO)**
Week	**-4 to -1**	**1**	**1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Day	**-28 to -7**	**1**	**4**	**8**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**
Visit window (days)				±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed consents[1]	x											
Demographics	x											
Randomisation		x										
Medical history	x											
Smoking/alcohol history	x											
Psoriasis therapy history	x											
Psoriasis arthritis history	x											
Baseline conditions	x											
In-, ex-criteria, incl. infections	x	x										
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x
Body height	x											
Body weight	x							x			x	
Vital signs	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x			x		x			x	
Resting 12 lead ECG	x	x	x	x		x		x			x	x
Pregnancy testing[2]	x	x				x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x
IRT call	x	x				x	x	x	x	x	x	
Dispense study medication		x				x	x	x	x	x		
Collect study medication						x	x	x	x	x	x	
BSA[3]	x											
PASI, sPGA assessment	x	x		x	x	x	x	x	x	x	x	x
NAPSI, PPASI, PSSI[4]		x				x		x			x	
Pain VAS[5]		x				x		x			x	
PSS [6]		x	x	x	x	x	x	x	x	x	x	x
DLQI[7]		x				x		x			x	
C-SSRS[8]	x	x	x	x	x	x	x	x	x	x	x	x
Safety lab samples	x	x	x	x	x	x	x	x	x	x	x	x
PG samples for Biobanking		x										
Biomarker samples (serum)		x	x	x	x	x	x	x	x	x	x	
Whole blood (PBMC for flow cytometry), pre-dose		x				x					x	
PK samples [9]		x[9]	x	x	x	x[9]	x	x[9]	x	x	x	x
Optional skin Photographs[10]		x				x		x				
Optional skin biopsies [11]		x				x		x			x	
Termination of trial medication[12]											x	
Screening for LTE [13]											x	
Trial completion												x

Footnotes:

[1] Trial informed consent and informed consent about pharmacogenetics, skin photography and skin biopsies if applicable.
[2] Serum pregnancy test at screening and if urine pregnancy test is positive.
[3] Assessment of Body Surface Area affected by plaques psoriasis
[4]Nail Psoriasis Severity Index, Palmoplantar Psoriasis Severity Index, Psoriasis Scalp Severity Index will be done if applicable
[5] Only for patients with psoriatic arthritis
[6] The Psoriasis Symptom Scale (PSS) will be completed by the patients during all clinic visits except V1.
[7] Dermatology Life Quality Index
[8] C-SSRS, Columbia-Suicide Severity Rating Scale: Screening/Baseline version at Screening, Follow-up version at all other visits.
[9] PK-blood samples: Days 1, 29, and 85, full PK profiles (pre-dose, 0:15, 0:30, 1, 2, 3 post-dose) will be sampled; All other days should be pre-dose plasma samples only.
[10] Optional psoriasis skin lesions photographs. Only at sites in the US. Refer to the procedure in the ISF.
[11] Optional skin biopsies will be taken from a subset of study participants. At baseline, two sets of lesional + non-lesional biopsies will be collected- one set for RNAseq and one set for IHC (immunohistochemistry) – in total four punches of four mm each. At the other timepoints two sets of lesional biopsies (2 punches) will be taken - one set for RNAseq and one set for IHC – in total two punches of four mm each. All biopsies should be completed pre-dose at each time point. Patients will be separately asked to consent for this procedure.
[12] No administration of study medication at the EOT visit.
[13] Patients who are completing Part 1 of this trial according to protocol will be offered to roll over into a long term extension trial (LTE).

FLOW CHART, PART 2

Trial Periods	**Screening**	**Treatment**							**Follow- up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**EOT**	**FU 1 (EOO)**
Week	**-4 to -1**	**1**	**1**	**1**	**2**	**4**	**8**	**12**	**16**
Day	**-28 to -7**	**1**	**4**	**8**	**15**	**29**	**57**	**84**	**113**
Visit window (days)			±1	±3	±3	±3	±3	±3	±7
Informed consents[1]	x								
Demographics	x								
Randomisation		x							
Medical history	x								
Smoking/alcohol history	x								
Psoriasis therapy history	x								
Psoriasis arthritis history	x								
Baseline conditions	x								
In-, ex-criteria, incl. infections	x	x							
Concomitant therapy	x	x	x	x	x	x	x	x	x
Body height	x								
Body weight	x							x	
Vital signs	x	x	x	x	x	x	x	x	x
Physical examination	x	x	x			x		x	
Resting 12 lead ECG	x	x	x	x		x		x	x
Pregnancy testing[2]	x	x				x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x
IRT call	x	x				x	x	x	
Dispense study medication		x				x	x		
Collect study medication						x	x	x	
BSA[3]	x								
PASI, sPGA assessment	x	x		x	x	x	x	x	x
NAPSI, PPASI, PSSI[4]		x				x		x	
Pain VAS[5]		x				x		x	
PSS [6]		x	x	x	x	x	x	x	x
DLQI[7]		x				x		x	
C-SSRS[8]	x	x	x	x	x	x	x	x	x
Safety lab samples	x	x	x	x	x	x	x	x	x
PG samples for Biobanking		x							
Biomarker samples (serum)		x	x	x	x	x	x	x	
Whole blood (PBMC for flow cytometry), pre-dose		x				x		x	
PK samples [9]		x	x	x	x	x	x	x	
Optional skin biopsies [10]		x				x		x	
Termination of trial medication[11]								x	
Screening for LTE[12]								x	
Trial completion									x

Footnotes:
[1] Trial informed consent and informed consent about pharmacogenetics, skin photography and skin biopsies if applicable.
[2] Serum pregnancy test at screening and if urine pregnancy test is positive.
[3] Assessment of Body Surface Area affected by plaques psoriasis

[4]Nail Psoriasis Severity Index, Palmoplantar Psoriasis Severity Index, Psoriasis Scalp Severity Index will be done if applicable

[5] Only for patients with psoriatic arthritis

[6] The Psoriasis Symptom Scale (PSS) will be completed by the patients during all clinic visits except V1.

[7] Dermatology Life Quality Index

[8] C-SSRS, Columbia-Suicide Severity Rating Scale: Screening/Baseline version at Screening, Follow-up version at all other visits.

[9] Trough PK-samples will be drawn at all visits from V2 through EOT. Details about PK-blood samples collection are provided in the PK blood sampling flow chart.

[10] Optional skin biopsies will be taken from a subset of study participants. At baseline, two sets of lesional + non-lesional biopsies will be collected- one set for RNAseq and one set for IHC (immunohistochemistry) – in total four punches of four mm each. At the other timepoints two sets of lesional biopsies (2 punches) will be taken - one set for RNAseq and one set for IHC – in total two punches of four mm each. All biopsies should be completed pre-dose at each time point. Patients will be separately asked to consent for this procedure.

[11] Last administration of study medication at the EOT visit.

[12] Patients completing the treatment period of this trial will be offered to roll over into a long term extension trial (LTE).

PK BLOOD SAMPLING FLOW CHART FOR TROUGH SAMPLES AND POPULATION PK, SAMPLES COLLECTED FROM ALL PATIENTS IN PART 2

Visits	Week	Day	Time Relative to morning BI 730357 Dosing	Blood sampling for PK
2, 3, 4, 5, 6, 7, EoT	1, 2, 4, 8, 12	1, 4, 8, 15, 29, 57, 84	- 90 to - 5 minutes before start of morning dosing	X
2, 5, EoT	1, 2, 12	1, 15, 84	15 minutes to 1 hour after morning dose	X
2, 5, EoT	1, 2, 12	1, 15, 84	1:30 to 2:15 after morning dose	X
2, 5, EoT	1, 2, 12	1, 15, 84	2:45 – 3:30 after morning dose	X

PK BLOOD SAMPLING FLOW CHART FOR INTENSIVE PK SUBSTUDY, PART 2

(Participation will be optional and require a separate informed consent.)

Visits	Week	Day	Time to/after morning BI 730357 Dosing	Blood sampling for PK
2, EoT	1, 12	1, 84	- 90 to - 5 minutes before start of dosing	X
2, EoT	1, 12	1, 84	30 minutes ± 5 minutes	X
2, EoT	1, 12	1, 84	1:00 h ± 10 minutes	X
2, EoT	1, 12	1, 84	2:00 h ± 10 minutes	X
2, EoT	1, 12	1, 84	3:00 h ± 10 minutes	X
2, EoT	1, 12	1, 84	5:00 h ± 20 minutes	X
2, EoT	1, 12	1, 84	8:00 h ± 30 minutes	X
2, EoT	1, 12	2, 85	24:00 h*	X
EoT	12	86	48:00 h ± 2 hours**	X
EoT	12	87	72:00 h ± 2 hours**	X

*Day 2 sample must be taken within 30 min before next BI 730357 dosing.
** For patients continuing in the LTE the 48 hours and the 72 hours sampling will be omitted.

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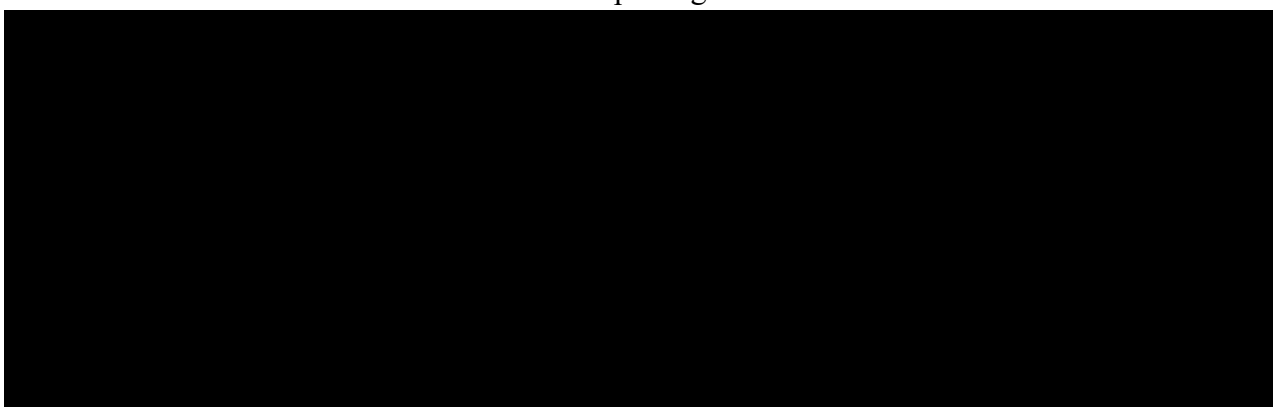


ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the Curve
BI	Boehringer Ingelheim
b.i.d.	bis in die (twice daily dosing)
BMI	Body Mass Index
BSA	Body Surface Area
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Clinical Monitor Local
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Clinical Research Organisation
CRP	C-Reactive Protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DC	Dentritic Cell
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	ElectroCardioGraphy
EDC	Electronic Data Capture
ePRO	Electronic Patient Reported Outcome
EOO	End Of Observation
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
[redacted]	
IB	Investigator’s Brochure
IBD	Inflammatory Bowel Disease
IC	Inhibitory Concentration
ICH	International Conference on Harmonisation
IHC	ImmunoHistoChemistry
ILC	Innate Lymphoid Cell
IL	InterLeukin
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
iSTAT	independent Statistician

i.v.	intravenous
LBD	Ligand Binding Domain
LoEE	List of Essential Elements
LPLT	Last Patient Last Treatment
LTE	Long Term Extension trial
LXR	Liver X Receptor
MACE	Major Adverse Cardiovascular Event
MCT	Melanin Containing Tissue
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Sub Team
NMSC	Non-Melanoma Skin Cancer
NOAEL	No Observed Adverse Effect Level
OPU	Operative Unit
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral Blood Mononuclear Cell
Pbo	Placebo
PD	Pharmacodynamics
PG	PharmacoGenetic
PK	Pharmacokinetics
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PPASI	Palmoplantar Psoriasis Severity Index
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
PsO	(Plaque) Psoriasis
PSS	Psoriasis Symptom Scale
PXR	Pregnane X Receptor
q.d.	quaque die (once a day)
RAR	Retinoic Acid Receptor
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
ROR	RAR related Orphan Receptor
SAE	Serious Adverse Event
s.c.	subcutaneous
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
sPGA	Static Physician's Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
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 (<3%), moderate (3-10%), and severe (>10%) (P20-07441). 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).

The immunologic mechanism of PsO involves initial dendritic cell (DC) activation by cutaneous pathogens, leading to IL-23 secretion, promoting Th17 differentiation and stabilization. Keratinocytes are the principal target, in addition to DCs, dermal fibroblasts, and endothelial cells, for IL-17, resulting in the expression of numerous chemokines which direct chemotaxis and inflammation, and of defensin and S100A family peptides which alter expression of multiple genes involved in cell adhesion. The critical role of IL-17 in PsO pathogenesis has been extensively evaluated in IL-17-knockout animal models and confirmed in humans. Th17 cells, the majority of which are of memory phenotype, are enriched in the papillary dermis of psoriatic plaques. Disease severity has been shown to correlate directly with IL-17A level (R16-3073). The central role of IL-23 and IL-17 activity in the pathogenesis of disease has been proven unequivocally by the substantial clinical efficacy of biologic agents targeting these cytokines in the treatment of patients with moderate-to-severe plaque PsO.

Mainstays of therapy for the treatment of PsO include topical agents, ultraviolet light-based therapies, traditional systemic agents (e.g., methotrexate, acitretin, cyclosporine), and more recently, targeted biologic and small-molecule therapies. Steroidal and non-steroidal topical agents (e.g., vitamin D analogues, retinoids, tar, anthralin, salicylic acid, tacrolimus) 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

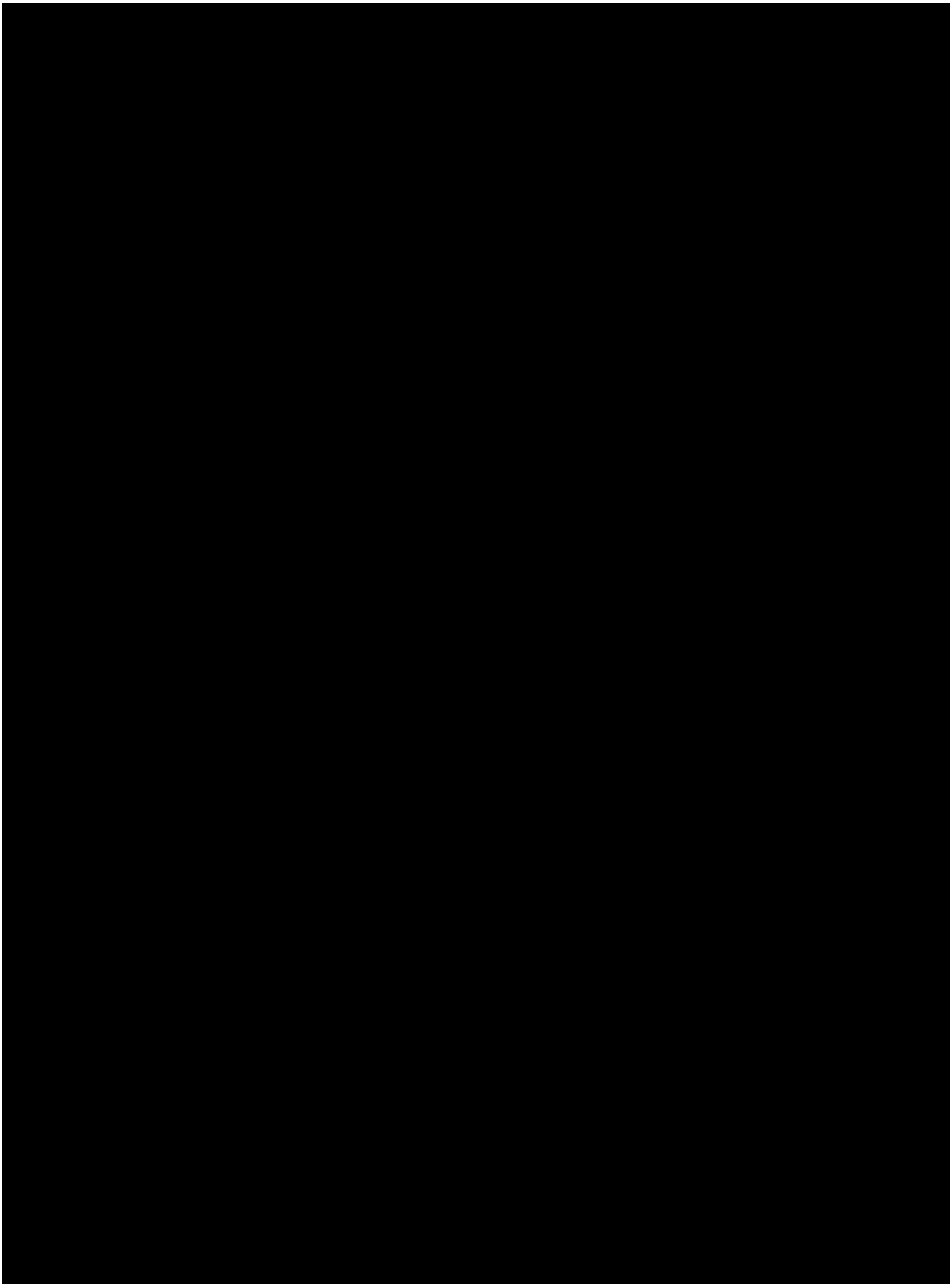
of topical corticosteroids, particularly for large surface areas and for facial and genital lesions. Ultraviolet light-based therapies, often combined with the photosensitizing agent psoralen, may be used to treat extensive areas of involved skin, but generally require long-term therapy, and are associated 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.

Retinoic acid-related orphan receptor (ROR) γt is a nuclear hormone receptor/transcription factor expressed in Th17 cells and in distinct subsets of lymphoid cells, including NK cells, innate lymphoid cells (ILC), and γδ T-cells. RORγt sits at a key focal point, integrating multiple signals, including T cell receptor engagement and cytokines (e.g., IL-1, IL-6, IL-23), and driving the expression of multiple genes (e.g., IL-17A, IL-17F, IL-22, IL-23R). Via sitting at this focal node integrating multiple signals and effecting multiple outputs, RORγt has the potential to have a broader effect in Th17-mediated diseased than individual cytokine blockades alone (e.g., IL-23 or IL-17).

1.2 DRUG PROFILE

Boehringer Ingelheim (BI) is developing the new chemical entity (NCE), RORγt antagonist BI 730357, for the treatment of patients with plaque PsO and other Th17-mediated diseases. BI 730357 binds in the ligand-binding domain (LBD) of RORγt and inhibits co-activator peptide recruitment, thereby blocking the RORγt-mediated transcription of pro-inflammatory cytokines, and of IL-23R.

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



1.2.2 Clinical Experience in Humans

BI 730357 is currently in Phase II clinical development, targeting the treatment of adults with plaque PsO, [redacted] Seven Phase I trials have been completed, and 3 Phase I or Phase II trials are currently ongoing, including this trial. The Investigator's Brochure (c09228382) provides the most current and complete detail of BI 730357 clinical experience. The most relevant details of Phase I clinical development to date are provided below.

Phase Ia first-in-human trial 1407.1 evaluated single-rising dose administration of BI 730357 ranging from 2 mg through 800 mg, given as oral solution (2 mg and 8 mg) and film-coated tablets (25 mg to 800 mg) to healthy male adult subjects aged 18 to 45 years. Approximately 84 subjects were to be entered into the trial; each group of 8 subjects was randomized (6 active:2 placebo) into sequential dose groups under fasting (2 mg, 8 mg, 25 mg, 50 mg, 100 mg, 200 mg, and 400 mg), and fed conditions (400 mg, 800 mg). An additional 12 subjects were recruited into a 3-way crossover substudy, and administered 25 mg BI 730357 as oral solution, tablet fasting, and tablet fed. In total, 66 male adult subjects received BI 730357.

Safety evaluations included physical examination, vital signs, ECG, laboratory tests, and adverse events (AEs). AEs, which generally reflected commonly-occuring 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. No serious AEs (SAEs) were reported. Overall, single-dose administration of BI 730357 was well tolerated by healthy male subjects in this clinical trial.

Phase Ib trial 1407-0002 evaluated MRD administration of BI 730357 ranging from 25 mg to 400 mg, given as film-coated tablets to healthy male adult subjects aged 18 to 45 years. Approximately 84 subjects were to be entered into the trial; each group of 12 subjects was randomized (9 active:3 placebo) into one of 4 sequential dose groups under fasting conditions (25 mg, 50 mg, 100 mg, 200 mg), and 3 sequential dose groups under fed conditions (50 mg, 200 mg, and 400 mg). Subjects were dosed for 14 days (dose groups up to 100 mg) or 28 days (200 mg and 400 mg dose groups).

Safety evaluations included physical examination, vital signs, ECG, laboratory tests, and AEs. No deaths, SAEs, or severe AEs were reported during the trial. Overall, administration of BI 730357 to healthy male subjects at doses up to 400 mg for up to 28 days was well tolerated.

The highest exposures observed in this study were substantially below the NOAEL exposures observed in the 4-week dog study.

In fasted individuals, exposure (C_{max} and AUC) increased in a less than dose-proportional manner over the entire dosing range, both for single and multiple dosing. Steady state was attained by 7 days of multiple dosing, with an accumulation of approximately 2-fold for both C_{max} and AUC. Under fed conditions, BI 730357 plasma exposures (AUC and C_{max}) were observed to be higher compared with the same dose level under fasted conditions.

[redacted]

Part 1 of this **current and ongoing trial 1407-0030** was clinically completed Jan 2020. Primary analysis of data through Week 12 show that the overall frequency of patients with at least 1 treatment-emergent AE was 50.6% for patients receiving BI 730357 (range 47.5% to 53.8%), vs. 55.0% of placebo recipients. No drug-related SAEs were reported. One severe AE, "psoriasis," was reported; all other reported AEs were mild to moderate in severity. This was also the only reported an AE leading to discontinuation of trial drug.

Overall, administration of BI 730357 to patients with moderate-to-severe plaque PsO at doses up to 200 mg for at least 12 weeks, under fasted conditions, has been well tolerated.

Results of the Week 12 primary analysis for trial 1407-0030 also demonstrate proof of concept in the treatment of patients with moderate-to-severe plaque PsO for BI 730357 at the 200 mg dose. PASI 75 was achieved by 12 (30.0%) of patients receiving 200 mg BI 730357, and sPGA of clear or almost clear was achieved by 11 (27.5%) of 200 mg recipients at Week 12.

Preliminary data on predose trough exposures in Part 1 of this trial show that exposure was higher in the patient population than healthy volunteers in previous studies.

[redacted]

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.

RORγt has the potential to demonstrate substantial efficacy in the treatment of PsO, via a broader effect in Th17-mediated disease than provided by individual cytokine blockade alone (e.g., IL-23 or IL-17). The favorable preclinical data and acceptable safety, tolerability and PK demonstrated after single dose administration to healthy male volunteers in first-in-human trial 1407.1 and in MRD trial 1407-0002 position BI 730357 favorably for advancement into a PoCC evaluation in adult patients with moderate-to-severe plaque PsO.

The aim of this Phase II trial is to investigate safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque PsO. Favorable results of this trial will serve as a PoCC in the treatment of PsO, for refinement of Phase III dose selection, and to support further development in other disease indications.

[redacted]

Rationale for performing Part 2:

Modelling of data from Part 1 of this trial indicates that the efficacy plateau of BI 730357 may not have been reached with 200 mg dosed q.d. under fasted conditions, and that exposures resulting from posologies dosing BI 730357 higher, under fed conditions, and/or twice daily may provide better efficacy. Part 2 of this trial therefore plans to evaluate the efficacy, safety, tolerability, and PK of 400 mg q.d. and 200 mg b.i.d. administration of BI 730357, under fed conditions, to patients with moderate-to-severe plaque PsO.

It is anticipated that higher median BI 730357 exposures, as expected with 400 mg dosed q.d., and 200 mg dosed b.i.d. under fed conditions for 12 weeks will not exceed the NOAEL thresholds observed in 13 week general toxicity studies (see section 1.2.1). Treatment with doses of up to 400 mg q.d.under fed conditions to healthy volunteers for up to 28 days in Phase Ib MRD trial 1407-0002, and with doses of up to 200 mg q.d. under fasting conditions for more than 12 weeks thus far in Part 1 of this trial did not identify any safety signals (see section 1.2.2).

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 the trial will amount to approximately 350 mL (over 24 weeks in Part 1) and 250 mL (over 12 weeks in Part 2). In the optional intensive PK substudy, approxamitely an additional 60 mLwill be withdrawn. No health-related risk is expected from this blood withdrawal.

Drug-related risks and safety measures

As the nature of the target and the mechanism of action of BI 730357 are well understood, comparable compounds have been tested by other companies before, and the animal models

are believed to be predictive for the effects in humans, BI 730357 is not seen as a high risk compound.

The pharmacological effects of BI 730357 are dose dependent, and no evidence for prolonged or irreversible effects has been observed. Multiple dose administration of up to 200 mg BI 730357 q.d. fasted (over 24 weeks in Part 1) and of up to 400 mg q.d. fed (over 12 weeks in Part 2) is supported by pre-clinical, as well as clinical safety data from trial 1407.1 and trial 1407-0002 (see section 1.2.2).

Since preclinical data indicate that BI 730357 has phototoxicity potential, subjects in this trial will be advised to apply protection measures as described in section 4.2.2.3. Solarium radiation, treatment with ultraviolet light (e.g., PUVA), and use of medication with known phototoxicity potential (e.g., doxycycline) are prohibited during this clinical trial until the end of the follow-up period.

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

As with other immune-targeted therapies, impaired host defense is a theoretical target-related toxicity, potentially resulting in increased risk of infection and/or malignancy. Th17 cells play an important role in defense against extracellular bacteria and fungi at mucosal surfaces (R16-3166), (R16-3149). In some studies, IL-17-antagonists were associated with increased infections (R13-2643). Homozygous, but not heterozygous RORC knockout mice have a high incidence of T cell lymphoma, thought to originate in the thymus (R16-2630). While the translatability of the knockout phenotype to pharmacological RORγ antagonism and to humans is unknown, this raises the hypothetical concern for clinical T cell lymphoma risk. The exact cause of T-cell lymphomas in RORC knockout mice is not fully understood, but changes in homeostasis in the thymus, such as thymocyte apoptosis and proliferation, are thought to play a role. No evidence of an increased risk of lymphoma development or changes preceding lymphoma development has arisen based on the BI 730357 toxicology studies in rat and dog of up to 26- and 39-week duration, respectively. AEs and SAEs consistent with malignancy, and specifically those representing lymphoma, are to be evaluated throughout the BI 730357 clinical development program. Thus far, no clinical signal regarding malignancy has been identified in BI 730357 clinical trials.

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when BI 730357 is administered.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also section 5.2.6, adverse events of special interest.

Even though gastritis development is not expected in humans, AE consistent with gastric intolerance or gastritis are designated as AEs of special interest (AESI) to ensure timely characterization, monitoring, and reporting of any such effects in this study (see sections 1.2.1 and 5.2.6.1).

Results of the Week 12 primary analysis from Part 1 of this trial demonstrate proof-of-concept in the treatment of patients with moderate-to-severe plaque PsO for BI 730357 at the 200 mg dose. Patients with plaque PsO receiving BI 730357 may therefore experience improvement in disease severity. Considering the data and modelling from the Part 1 Week 12 primary analysis of this trial, higher efficacy may be observed in Part 2 of this trial with the expected higher BI 730357 exposures resulting from dosing posologies to be evaluated. However, this is a newly-developed drug at an early stage of testing, therefore an individual benefit for patients cannot be guaranteed. In addition, patients may be randomized to placebo treatment and not see any potential benefit. Nonetheless, the results from toxicity and safety pharmacology studies demonstrated an acceptable profile for clinical trials with daily oral administration. The potential risks which are described above will be minimized by close monitoring and the involvement of an independent external DMC. These risks are considered manageable and outweighed by the potential benefits of the study drug.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This is a Phase II evaluation of PoCC, based on the safety, tolerability, and efficacy of multiple doses of BI 730357 administered to patients with moderate-to-severe plaque PsO. This study will also serve the selection of doses for the further development of BI 730357.

- The primary objective is based on Week 12 co-primary endpoints of PASI 75 and sPGA 0/1, and overall safety.
- Secondary objectives of Part 1 are to evaluate the efficacy and safety of BI 730357 through 24 weeks of treatment.

2.1.2 Primary endpoint(s)

The co-primary endpoints are:

- Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 12
- Achievement of an sPGA score of clear or almost clear at Week 12

At the trial level, the co-primary endpoints will be the proportion of patients achieving PASI 75 and a sPGA score of clear or almost clear at Week 12 in each of the treatment groups.

For descriptions and definitions of PASI and sPGA used in this trial, please refer to appendices 10.1 and 10.2 respectively.

2.1.3 Secondary endpoint(s)

Secondary endpoints beyond Week 12 apply only to Part 1.

- Achievement of ≥50% reduction from baseline in PASI score (PASI 50) at Week 12
- Achievement of ≥90% reduction from baseline in PASI score (PASI 90) at Week 12
- Achievement of 100% reduction from baseline in PASI score (PASI 100) at Week 12
- Achievement of sPGA score of clear at Week 12
- Achievement of ≥75% reduction from baseline in PASI score (PASI 75) at Week 16, 20, 24
- Achievement of an sPGA score of clear or almost clear at Week 16, 20, 24
- Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale (PSS) at Week 12
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 12

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a Phase II trial consisting of two parts.

Part 1:

Part 1 is a randomised, placebo-controlled, parallel-group, double-blind evaluation of approximately 180 male and female patients with moderate-to-severe plaque PsO.

Patients will be randomised 2:2:2:2:1 to one of 4 BI 730357 treatment groups A to D, of which A will receive the lowest and D the highest dose of BI 730357; treatment group E will receive placebo.

At the Week 12 primary efficacy endpoint, non-responders will be reassigned to the next higher dose level or to the highest dose level, if they have been in the placebo arm (see Figure 3.1: 1). Placebo recipients who achieve a PASI 75 response will remain on placebo through Week 24.

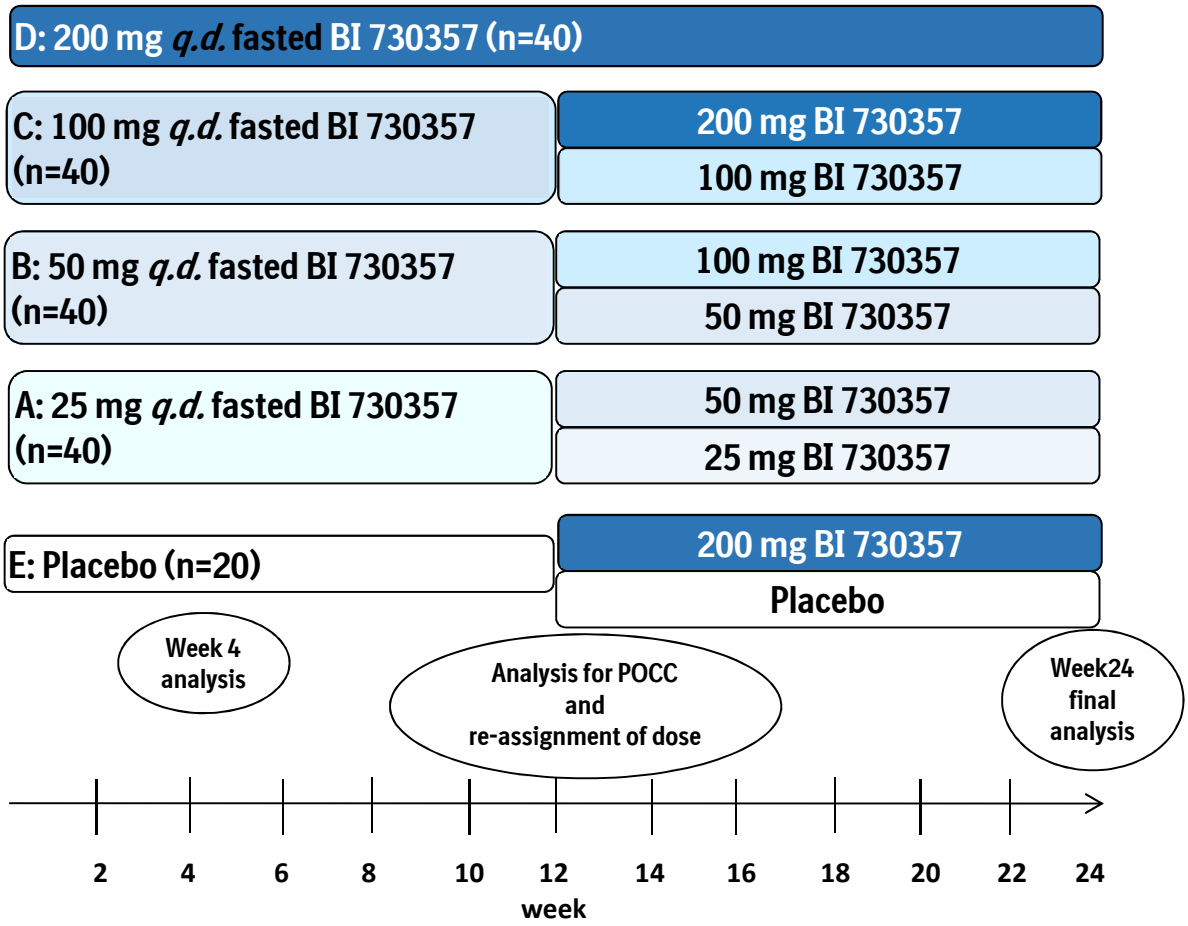


Figure 3.1: 1 Trial Design, part 1

Patients from dose groups A to C who fail to achieve a PASI 50 response at Week 12 will be switched to the next higher respective dose. Patients who have achieved a PASI 50 response will continue on their initial dose of BI 730357, in order to evaluate whether a greater response can be achieved with continued treatment. This design is intended to permit placebo recipients the opportunity to receive active study drug after Week 12 if they continue to experience substantial disease. Likewise, recipients of BI 730357 at lower dose levels (A through C) will be provided the opportunity to receive a higher dose of study drug. However, in order to fully evaluate the time-to-response curve in patients who demonstrate a partial response to BI 730357 at Week 12, the response threshold for BI 730357 recipients (PASI 50) is set lower than for placebo recipients (PASI 75). Moreover, this reassignment will allow dose selection for Phase III based on efficacy evaluation over the full 24 weeks of treatment and obtain maximum safety information regarding the safety of high-dose exposure. It is anticipated that the best timing and the best cut-off for co-primary efficacy endpoint evaluation in Phase III studies will be refined based upon the results of this trial. Safety (physical examination, ECG, laboratory, AEs, and SAEs), efficacy, PK and target engagement are to be evaluated through Week 24.

Part 2:

Part 2 is a randomised, placebo-controlled, parallel-group, double-blind evaluation of approximately 90 male and female patients with moderate-to-severe plaque PsO.

Patients will be randomised 4:4:1 to one of two BI 730357 treatment groups V (200 mg b.i.d.) or U (400 mg q.d.); treatment group W will receive placebo. In Part 2, the trial medication should be taken with a meal. The treatment will last for 12 weeks when the primary efficacy endpoint will be assessed (see Figure 3.1: 2).

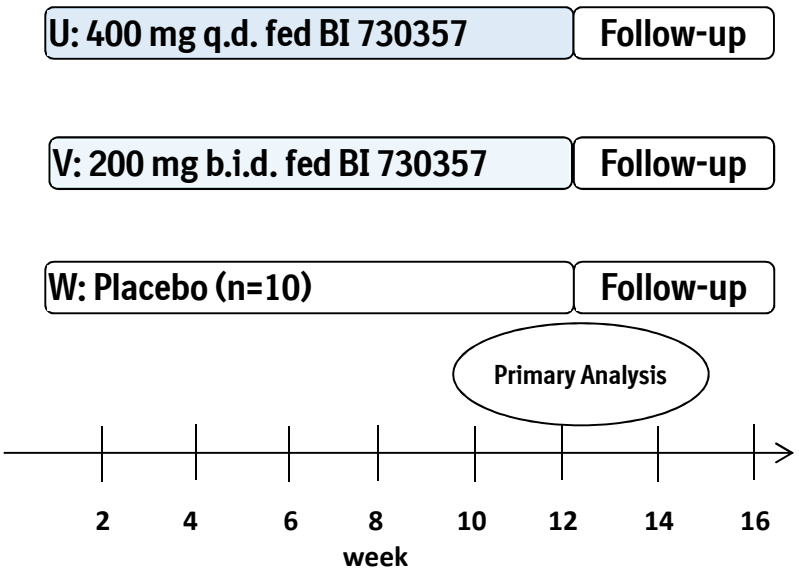


Figure 3.1: 2 Trial Design, part 2

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

A randomised, double blind, placebo-controlled, parallel design has been chosen in order to evaluate safety, efficacy, PK, and PD of BI 730357 in patients with moderate-to-severe plaque PsO. A placebo control arm has been chosen to be included in order to evaluate the absolute effects of BI 730357 on safety and tolerability. This is acceptable, as the duration of the placebo treatment, if no spontaneous improvement of the disease occurs, will be limited to 12 weeks, and no intolerable disease progression is to be expected during this period.

Patients completing the treatment priod of the trial will be offered to roll over into an extension trial, in which they will continue receiving study medication.

[redacted]

3.3 SELECTION OF TRIAL POPULATION

The trial is intended to provide PoCC of BI 730357 in the treatment of moderate-to-severe plaque PsO. Therefore, in Part 1 approximately 180 male and female patients suffering from this condition will be included at about 32 study sites. In Part 2, approximately 90 male and female patients will be included.

Screening of patients will be competitive, i.e., screening will stop at all sites once a sufficient number of patients have been screened. Investigators will be notified about screening completion, and will then not be allowed to screen additional patients for this trial.

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

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

3.3.1 Main diagnosis for trial entry

Male or female patients with moderate-to-severe plaque PsO.

3.3.2 Inclusion criteria

1. Male or female patients. WoCBP[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly from date of screening until 4 weeks after last treatment in this trial. A list of contraception methods meeting these criteria is provided in the patient information.

([1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.)

2. Age 18 to 75 years (both inclusive) at screening
3. BMI < 35 kg/m^2 at screening
4. Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.
5. Patients must be candidates for systemic PsO therapy. Moderate-to-severe plaque psoriasis:
   a. BSA ≥10%
      and
   b. PASI ≥12
      and
   c. sPGA moderate or severe
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3.3.3 Exclusion criteria

1. Nonplaque forms of PsO (including guttate, erythrodermic, or pustular), current drug-induced PsO (including a new onset or exacerbation of PsO from, e.g., beta blockers, calcium channel blockers, lithium), active ongoing inflammatory diseases (including but not limited to inflammatory bowel disease (IBD)) other than PsO that might confound trial evaluations.
2. Previous enrolment in this trial or previous exposure to BI 730357.
3. Current enrollment in another investigational device or drug trial, less than 30 days (from randomisation) since ending another investigational device or drug trial(s), or receipt of other investigational treatment(s). For antipsoriatic treatments, wash-out periods are provided in exclusion criterion 4 and in section 4.2.2.1.
4. Use of
   a. any biologic agent within 12 weeks, or
   b. any anti IL-23 biologic agent within 24 weeks prior to randomisation, or

c. systemic anti-psoriatic medications or phototherapy within 4 weeks prior to randomisation, or

d. topical anti-psoriasis medications within 2 weeks prior to randomisation (c.f. section 4.2.2.1)
(Exception: Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits where PASI is assessed)

5. Receipt of a live vaccination within 12 weeks prior to randomisation (visit 2), or any plan to receive a live vaccination during the conduct of this trial
6. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
7. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
8. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable trial participant or unlikely to complete the trial.
9. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within 12 months after screening, e.g., hip replacement
10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
11. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately-treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix
12. Relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis, candidiasis and tuberculosis.
13. Evidence of a current or previous disease (including known or suspected IBD and cardiovascular disease), or medical finding that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.
14. Any suicidal ideation, including grade 4 or 5 in the Columbia Suicide Severity Rating Scale (C-SSRS) in the past 12 months (i.e., active suicidal thought with intent but without specific plan), or active suicidal thought with plan and intent in the past.
15. Unwillingness to adhere to the rules of UV-light protection as described in section 4.2.2.3.
16. Any kind of photodermatosis.
17. Patients in Part 2: Moderate to severe hepatic impairment[2].

([2] Defined as a Child-Pugh Score of B or C)

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

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withraw consent to trial participation as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below. Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, 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. If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient may be withdrawn from trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.
- The patient needs to take concomitant drugs that interfere with the investigational product as listed in Table 4.2.2.1: 1.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thought with intent but without specific plan, or active suicidal thought with plan and intent). The patient should immediately be refered to a mental health professional for further work-up.
- In addition to these criteria, the physician may discontinue subjects at any time based on his or her clinical judgment.

In case of a temporary reason, trial treatment should be restarted as early as possible if medically justified. Even if the trial treatment is permanently discontinued, the patient remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the FLOW CHART, Part 1 and FLOW CHART, Part 2 and section 6.2.3. For all patients, 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.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time, without the need to justify the decision. If a patient 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

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

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 730357 and Placebo to match BI 730357.

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, 100 mg
Posology	q.d. or b.i.d.
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	q.d. or b.i.d.
Route of administration:	Per os

4.1.2 Selection of doses in the trial

The dose range for this trial is selected on the basis of the data obtained in first-in-human SRD trial 1407.1 and in MRD trial 1407-0002. In addition, for Part 2 dose selection, Week 12 primary analysis data and modelling from Part 1 were considered.

In the SRD trial, single dose levels of up to 800 mg, and in the MRD trial, multiple dose levels of up to 400 mg administered q.d. under fed conditions were well tolerated.

Part 1:

The doses of 25, 50, 100, and 200 mg q.d., administered fasted, are selected for Part 1 of this trial. The dose range for this trial was selected on the basis of the PK and safety data obtained in the SRD and MRD trials (1407.1 and 1407-0002, respectively) combined with the preclinical efficacy data.

The proposed BI 730357 dose selection strategy for PoCC evaluation in PsO patients was predicated upon the estimated whole blood BI 730357 IL-17 IC_{50} concentration in murine models, from which an anticipated human therapeutic trough exposure of 140 nM at steady state ($C_{min,ss}$) was predicted (with a corresponding $AUC_{0-24,ss}$ of 5200 nM•h). The target $C_{min,ss}$ in human was determined based on the effective plasma concentration required to reduce the tissue level of IL-17 by 80% in an IL-23 induced minicircle mouse model [c09228382].

Part 2:

Modelling of data from Part 1 of this trial indicates that the efficacy plateau of BI 730357 may not have been reached with 200 mg dosed q.d. under fasted conditions, and that exposures resulting from posologies dosing BI 730357 higher, under fed conditions, and/or twice daily may provide a better efficacy. Doses of 200 mg b.i.d. and 400 mg q.d. administered under fed conditions are therefore selected for Part 2 of this trial (see section 1.3). The higher BI 730357 exposures achieved with 200 mg b.i.d. and 400 mg q.d. administered under fed conditions for 12 weeks are expected to be safe with regard to the NOAEL levels observed in 13 week general toxicity studies (see section 1.2.1). In addition, treatment of patients with BI 730357 doses of up to 200 mg q.d. under fasted conditions for up to 24 weeks in part 1 of this trial, and administration of BI 730357 to healthy volunteers at doses of up to 400 mg *q.d.*under both fasted and fed conditions for up to 28 days in MRD trial 1407-0002 did not identify any safety signals (see section 1.2.2).

In summary, the data generated in Part 2 of this trial will extend characterization of the dose-response relationship within a wider therapeutic range, and enable selection of the dose range for Phase III development.

4.1.3 Method of assigning patients to treatment groups

In Part 1, during visit 2, eligible patients will be randomised in a 2:2:2:2:1 ratio to one of 4 BI 730357 dose groups A to D, or placebo, in a blinded fashion via Interactive Response Technology (IRT). At the Week 12 primary efficacy endpoint, non-responders will be reassigned to the next higher dose level or to the highest dose level, if they have been in the placebo arm (see Figure 3.1: 1). Placebo recipients who achieve a PASI 75 response will remain on placebo through Week 24.

In Part 2, eligible patients will be randomised in a 4:4:1 ratio to one of 2 BI 730357 dose groups, or placebo, in a blinded fashion via Interactive Response Technology (IRT). Treatment will be completed at Week 12.

4.1.4 Drug assignment and administration of doses for each patient

Study medication will be dispensed at the investigational sites according to the FLOW CHART, Part 1 and FLOW CHART, Part 2. On days of scheduled patient visits, the study medication will be administered at the study site after the other visit procedures have been performed. On days with no scheduled study visit, the patient will take their medication at home.

In Part 1, patients will receive four tablets once per day. In Table 4.1.4: 1, the medication for the first twelve weeks of treatment is listed. Part 1 treatment period is 24 weeks in total.

Table 4.1.4: 1 Trial medication during first twelve weeks of Part 1

	25 mg/pbo tbl	50 mg/pbo tbl	100 mg/pbo tbl
A: 25 mg treatment group	1 active	1 pbo	2 pbo
B: 50 mg treatment group	1 pbo	1 active	2 pbo
C: 100 mg treatment group	1 pbo	1 pbo	1 active 1 pbo
D: 200 mg treatment group	1 pbo	1 pbo	2 active
E: Placebo (pbo) group	1 pbo	1 pbo	2 pbo

In Part 1, after twelve weeks treatment, patients may be assigned to a higher dose group, depending on their response as assessed by PASI.

In Part 1, from the start of the treatment period, patients will be instructed to take the trial medication once daily with a glass of water. Patients must take the study medication after at least 6 hours fasting and should not eat for 30 minutes after drug administration. The medication should be taken in the morning at approximately the same time every day, to ensure a dose interval of about 24 hours. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken.

In Part 2, patients will receive 6 tablets per day: 4 tablets in the morning and 2 tablets in the evening. See Table 4.1.4: 2.

Table 4.1.4: 2 Trial medication in Part 2

	Morning	Evening
U: 400 mg q.d.fed treatment group	4 active 100 mg	2 pbo
V: 200 mg b.i.d. fed treatment group	2 pbo 2 active 100 mg	2 active 100 mg
W: Placebo fed treatment group	4 pbo	2 pbo

In Part 2, treatment will be completed at Week 12.

In Part 2, patients must take the trial medication with a meal. Patients should be instructed not to take their medication on the morning of trial visits, as they will be dosed in the clinic. On days of trial visits, all visit procedures should be completed first before the patient has their meal and takes their morning dose.

In Part 2, the dosing interval should be approximately 12 hours. If a dose is missed by more than 6 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, and everyone involved in trial conduct or analysis will remain blinded with regard to the randomised treatment assignments until after database lock.

The randomisation code will be kept secret by Clinical Trial Support up to database lock.

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

A trial-independent statistician (iSTAT) will be assigned to prepare the summary reports for the DMC based on the agreed upon format and layout. All information, including adverse events, mortality, and laboratory parameters, will be provided in unblinded fashion. This will be accomplished by using coded labels and providing the DMC members with the decoding information separately.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate 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 [redacted] to access the randomisation code for individual patients 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). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (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 or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

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

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics, if not site-to-site shipments are formally organized by the sponsor. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. 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

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (cf. section 3.3) may be permissible. All concomitant medications should be carefully evaluated by the Investigator, and the CML should be contacted when there are questions regarding concomitant medications.

In the event that a patient experiences an intolerable increase of PsO during the course of the trial, the trial medication will be discontinued and anti-psoriatic agents may be used as rescue medications.

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.

Severe infections according to RCTC grading, serious infections, and opportunistic or mycobacterial infections:
Treatment of the infection should be initiated promptly according to local standard of care. Treatment with trial medication should be discontinued.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with the trial medication, and notify the CTM. Diagnostics and treatment should be initiated according to local standard of care.

Suicidality
In case of signals of suicidal ideation the patient should be referred to psychiatric work up.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications, classes of medications, and foods listed in Table 4.2.2.1: 1 must not be taken for the time periods as specified. Classes of antipsoriatic medications listed in Table 4.2.2.1: 1 are likewise restricted, however may be permitted as rescue treatment, at the investigator's discretion, if a patient experiences an intolerable increase of PsO during the course of the trial. In such cases, the investigator must notify the BI CML and document the details of the drug used and reason in the eCRF.

A comprehensive list of restricted medications can be found in the ISF.

Table 4.2.2.1: 1 Restricted medications and food

Medication or class of medications	Specified restriction time
Drugs with known phototoxic or photoallergic potential (e.g., tetracyclines, fluorchinolones)	One week prior to randomisation until EOO
Drugs or foods (e.g., seville oranges, grapefruit, paw paw and their products) which are known inhibitors or moderate or strong inducers of CYP3A, or are sensitive substrates of CYP1A2, or CYP2B6, or CYP2C8 , CYP2C9, or CYP2C19.	One week prior to randomisation until EOO
Drugs with narrow therapeutic windows which are substrates of P-gp, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1, and MATE2-K.	One week prior to randomisation until EOO
Investigational products (other than antipsoriatic drugs)	30 days prior to randomisation through EOO (end of observation visit)
Any drug known to interfere with or to aggravate PsO including but not limited to lithium and interferons	4 weeks prior to randomisation through EOO
BCG (Bacillus Calmette-Guérin) vaccine	1 year prior to randomisation through 1 year after last administration of study drug
Investigational antipsoriatic drugs	12 weeks prior to randomisation through EOO
Biologic agents (other than IL-23 antibodies) within 12 weeks	12 weeks prior to randomisation through EOO
IL-23 antibody drugs (e.g., ustekinumab, guselkumab, tildrakizumab, risankizumab)	24 weeks prior to randomisation through EOO

Table 4.2.2.1: 1 Restricted medications and food cont.

Investigational device or product (excludes psoriasis products)	30 days prior to randomisation
Other systemic immunomodulating treatments (e.g., methotrexate, cyclosporine A, corticosteroids[1]), apremilast (Otezla®1,cyclophosphamide, tofacitinib (Xeljanz))	
Other systemic psoriasis treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis)	
Photochemotherapy (e.g., PUVA)	
Phototherapy (e.g., UVA, UVB)	14 days prior to randomisation
Topical treatment for psoriasis or any other skin condition (e.g. corticosteroids[2], vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy, fruit acids)	

[1] No restriction on corticosteroids with only a topical effect (e.g. inhalant corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

[2] Exception: Topical steroids of US class 6 (mild, such as Desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits when PASI is assessed.

4.2.2.2 Restrictions on diet and lifestyle

In Part 1, the participants should take the medication after at least 6 hours fasting and should not eat for 30 minutes after drug administration.

In Part 2, the medication should be taken with a meal.

Foods which are known strong or moderate inhibitors of CYP 3A (e.g., seville oranges, grapefruit, paw paw and their products) should be avoided during the study participation. Moisturizers/emollients containing retinoids and the use of tanning beds are not allowed during the study.

4.2.2.3 Restriction of UV-light exposure

Throughout their participation in the study, patients should avoid prolonged exposure to sunlight an artificial UV light. When exposed to direct 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. Patients should wear sun glasses when exposed to direct sun or other sources of UV-light. These protection measures must be applied until the end of the follow-up periods.

4.2.2.4 Contraception requirements

Female patients:
WoCBP (for the definition please refer to section 3.3.2) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 28 days after the last dose of study drug.
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm.

Or

- Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g., calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

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

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

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actually taken} \times 100}{\text{Number of which should have been taken}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The skin condition will be assessed by using the PASI and sPGA as described in Appendix 10.1 and 10.2 and the ISF. Further assessments will include NAPSI, PPASI and PSSI.

Symptoms and quality of life will be assessed by PSS and DLQI. Pain symptoms in patients with PsA will be assessed by the Pain VAS.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the FLOW CHART, Part 1 and FLOW CHART, Part 2. 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, Part 1 and FLOW CHART, Part 2.

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the FLOW CHART, Part 1 and FLOW CHART, Part 2, 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.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1.

Blood samples for safety will be drawn prior to drug administration. In Part 2, patients do not have to be fasted for the blood sampling.

For the sampling time points please see FLOW CHART, Part 1 and FLOW CHART, Part 2.

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 (please refer to section 5.2.6).

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

The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests

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 Immunophenotyping of T cell subsets[1]
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

Table 5.2.3: 1 Safety laboratory tests cont.

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 C-Reactive Protein (CRP, High sensitivity) Cholesterol, total[1] Triglycerides[1] LDL-Cholesterol /HDL-Cholesterol[1]
Urine Pregnancy test (only for female patients of childbearing potential - test done in clinic)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential) at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH, (free T3 and T4 in case of abnormal TSH)
Autoantibodies (only at screening)	Rheumatoid Factor
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)[2] HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB

[1] only at screening and EOO-visit; [2]A positive hep C antibody result should be confirmed by hep C-RNA PCR, before a patient is excluded.

5.2.4 Electrocardiogram

ECGs will be read and evaluated centrally. The 12-lead ECGs will be recorded as scheduled in the FLOW CHART, Part 1 and FLOW CHART, Part 2. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

If necessary, additional ECGs may be recorded for safety reasons.

The digital ECG recordings will be transmitted to a vendor for central evaluation and the results will be reported to the site.

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

5.2.5 Other safety parameters

5.2.5.1 Suicidality

Suicidal thoughts and behavior will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, R08-1147).

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report. In this trial, paper forms will be used for the assessment of the C-SSRS®, and results will be transcribed into the e-CRF.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the Screening Visit/Visit 1 (using the ‘baseline/ screening’ version) with the aim to exclude patients with active moderate or severe symptomatology within a specified time prior to the screening or screening visit. The lifetime and the past year history of suicidal ideation and behavior will also be recorded.

After the screening visit, the assessment ‘since last visit’ version will be performed at each visit. The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting psychiatrist or other mental health professional expert. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient, and/or is to consult a mental health professional. If the positive report is confirmed, appropriate actions for the patient’s safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.

For ‘Self-injurious behavior, without suicidal intent’, standard AE / SAE reporting rules are to be applied.

For each negative report (suicidal ideation type 1, 2 or 3) after the start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.5.2 Major Adverse Cardovascular Event (MACE)

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular and thrombotic events reported during the conduct of the study, to assure consistent assessment of major adverse cardiovascular events (MACE). See section 8.7.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

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

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

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

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

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

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

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

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 described in section 5.2.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

In accordance with the European Medicines Agency initiative on Important Medical Events, 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. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described 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 (e.g., icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain) without lab results (e.g., 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.

Severe infections (according to RCTC grading)

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

Gastric intolerance and gastritis:
Even though gastritis development is not expected in humans, AE consistent with gastric intolerance or gastritis are designated as AE of special interest (AESI), to ensure timely characterization, monitoring and reporting of any such events in this study (for details, please refer to section 1.2.1).
Not all gastrointestinal events will be considered AESI. Only events that are consistent with the following definitions are considered AESI and will need to be reported accordingly:

- Any AE of "nausea" or "vomiting" of moderate or worse severity (according to RCTC, OR of prolonged duration (≥ 7 days), OR
- Any AE of "gastritis" (regardless of duration or severity)

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.

5.2.6.2 Adverse event collection and reporting

AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for 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 eCRF.

Patients 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 patient'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 conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions, and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

Pregnancy
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

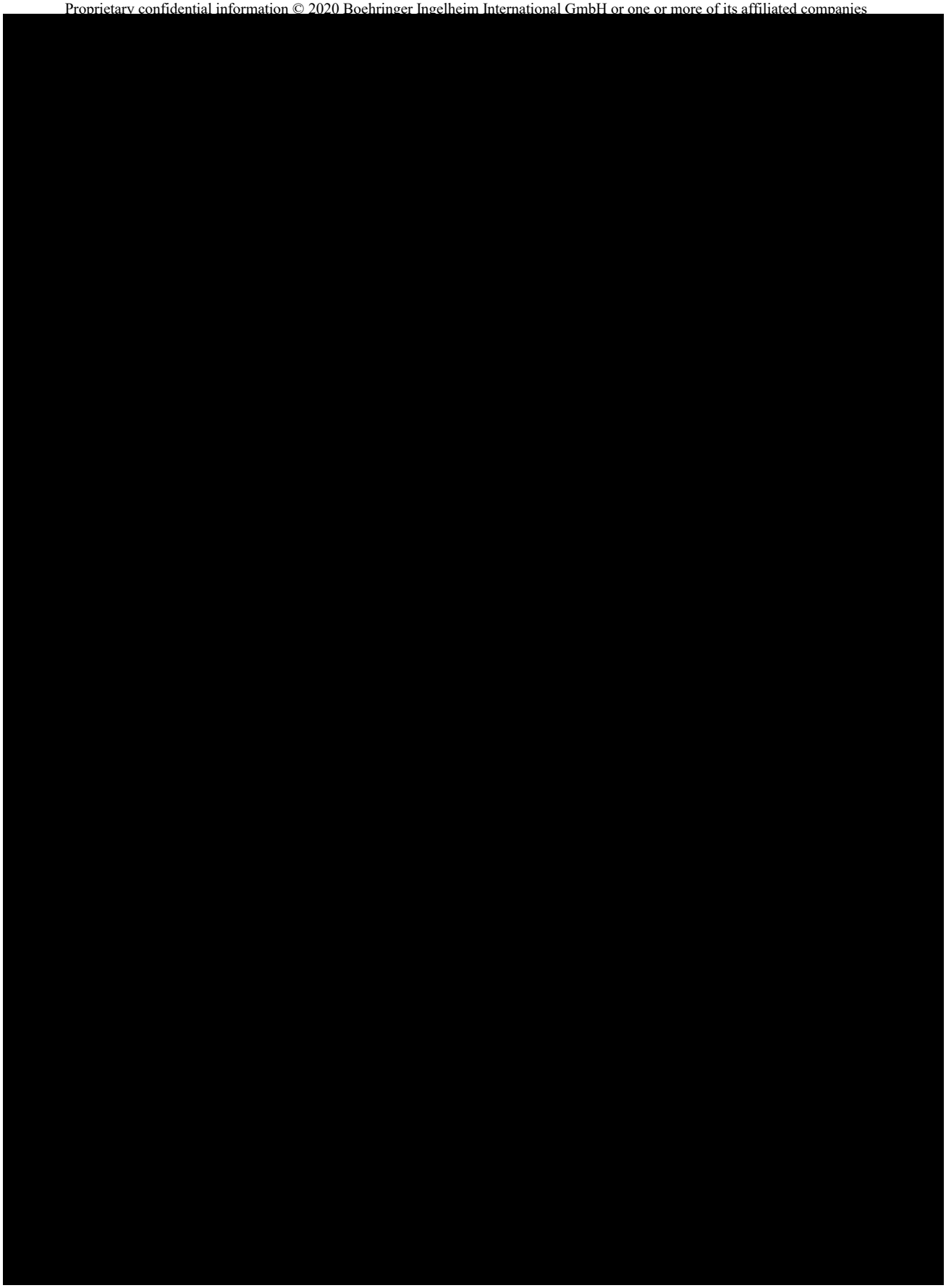
Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

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).

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

[redacted]

[redacted]



[redacted]

5.6 OTHER ASSESSMENTS

5.6.1 Photography of skin lesions

In part 1 and at selected sites, participation is voluntary and not a prerequisite for participation in the trial. Photography of skin lesions will be performed optionally for additional documentation. Front and back trunk as well as target lesions photographs will be taken preferably as the time-points specified in the FLOW CHART, Part 1 per instructions in the ISF.

The patient's consent must be obtained prior to take the photographs. Patients must be unrecognizable on the photos (refer to the procedure in the ISF).

In Part 2, no skin photos will be taken.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial except from the skin biopsies and photos are standard measurements in PsO treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way.

Skin biopsies, although not standard, are also widely used in PsO trials and indispensable for the understanding of the disease pathophysiology and effects of the treatments which are investigated. Only a subset of patients will be asked for skin biopsies. A separated informed consent will be obtained from these patients.

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 patients 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 CHART, Part 1 and FLOW CHART, Part 2. 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 CHART, Part 1 and FLOW CHART, Part 2 and the respective protocol sections. Additional details on procedures at selected visits are provided below.

Assessments – as applicable to the respective visit - should be performed in the following order:

- Informed consent
- Demographics, medical history and baseline conditions
- Concomitant therapies or changes in concomitant therapies
- Height
- Weight
- Vital signs
- Physical examination
- 12-Lead ECG, local assessment
- Pregnancy test (in females of childbearing potential)
- Safety laboratory (blood samples)
- Biomarkers (blood samples)
- PK sampling (for intensive PK sampling, please refer to flowchart)
- Assessment of eligibility criteria
- Breakfast or light dinner (for patients in the pk sub-study who take their evening dose at the site)
- Dispensation/administration of study medication
  (In Part 1, no study medication should be dispensed/administered at the EOT visit. In Part 2, last drug administration is at EOT)

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

PROs should be completed by the patient on his/her own in the pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team.

The PSS will be completed by the patient at all visits, except V1, on a paper form.

The order of completion for PROs is as follows, as applicable for each PRO at relevant visits according to the FLOW CHART, Part 1 and FLOW CHART, Part 2:

(1) PSS
(2) DLQI
(3) Pain VAS (for patients with concomitant PsA)

The Baseline/screening scale of the C-SSRS will be administered for eligibility confirmation and the follow-up scale at all visits for assessement of suicidality.

6.2.1 Screening period

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 patient should be recorded on the enrolment log. The patient should be registered in IRT as a screened patient.Screening procedures may be extended to more than one physical visit, if needed.

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

Re-testing for certain eligibility criteria can be performed once for abnormal laboratory, results.

After the informed consent process is complete and written informed consent is obtained, the subjects will be assessed for study eligibility including laboratory assessments as indicated in section 5.2.6.

All other assessments will also be performed as summarized in the study FLOW CHART, Part 1 and FLOW CHART, Part 2. Patients will be asked to continue their background medication without changes and to adhere to their administration algorithm.

All subsequent visits should be scheduled.

6.2.2 Treatment period

The treatment period starts with Visit 2 and ends with the EOT visit. Randomisation will occur at Visit 2 using IRT.

The patients will return to the clinic for regularly scheduled visits as specified in the FLOW CHART, Part 1 and FLOW CHART, Part 2. At these visits, the occurrence of safety and efficacy endpoints, trial medication compliance, concomitant therapy or intervention will be assessed.

At all treatment visits, the order of assessments (as applicable) should be followed:

- Completion of the questionnaires
- Physical examination, urine pregnancy and vital signs
- ECG
- Laboratory samples

All assessments must be performed before the medication is taken. Patients in Part 2 should have a meal within 30 minutes prior to taking their medication.

6.2.3 Follow up period and trial completion

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

6.2.3.1 Early treatment and trial termination:

If study medication is discontinued prior to the planned FLOW CHART, Part 1 and FLOW CHART, Part 2 EOT visit, every effort should be made to have the patient continue in the trial and complete all of the remaining Treatment Period Visits and FU Visit. Trial termination should be completed at the FU Visit. If a patient cannot or will not continue in the trial, the patient should complete EOT visit procedures instead of the planned treatment period visit and return to the clinic for FU/EOO Visit 4 weeks after last dose of study medication.

6.2.3.2 Trial completion

Patients who finish the randomised treatment period will return to the clinic for Follow-up Visit. Trial completion is defined as patients having reached the FU visit within the specified window per the FLOW CHART, Part 1 and FLOW CHART, Part 2. Patients who complete the randomised treatment period without early treatment discontinuation will have the option to participate in a long term extension (LTE) trial, if their psoriasis has improved and if they have well tolerated the study treatment. In Part 2, patients may also be offered participation in the LTE, if they feel that they have benefited from the trial treatment.
After the EOT Visit, the visit schedule is dependent on LTE participation:

- Patient who will not participate in the LTE study will return to the clinic for FU/EOO Visit. Trial termination will be completed at FU/EOO. The decision not to enter the LTE will be registered in IRT at the EOT Visit.
- Patients who participate in the LTE will complete the EOT visit as the final 1407-0030 study visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Part 1:
The primary trial objective includes demonstration of PoCC with respect to a non-flat dose response curve, characterization of the dose-response relationship within the therapeutic range, and selection of the dose range for phase III development. See section 2.1.1 for details on the objective of this trial. For this purpose, the primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod). The co-primary endpoints are defined in section 2.1.2.

Part 2:
A Bayesian borrowing approach will be implemented to estimate treatment effect by PASI 75 and sPGA. No hypothesis testing will be performed. The primary endpoint is defined in section 2.1.2

Baseline refers to the measurement recorded at randomisation (Visit 2); if data at Visit 2 is missing, then data from Visit 1 will be considered baseline. The percent reduction from baseline is calculated by % PASI reduction from baseline = ((PASI at baseline - PASI at Visit X) / PASI at baseline) * 100, at all follow up visits. Achieving an x% or larger reduction from baseline PASI score is denoted as PASI X.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Part 1:
The co-primary endpoints are based on Week 12 PASI 75 and sPGA 0/1 response. The null hypothesis is that there is a flat dose response curve comparing the placebo and the BI 730357 dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 730357 over placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided α of 5%). The pre-specified models and their parameters used for this test are outlined in section 7.3.1.

Part 2:
The co-primary endpoints are based on Week 12 PASI 75 response and sPGA 0/1. PASI 75 at week 12 will be analysed based on a Bayesian borrowing approach.

7.3 PLANNED ANALYSES

The following patient analysis sets are defined:

- The efficacy analyses will be based on the intent-to-treat principle, comprising all participants who were randomised and received at least one dose during the trial. The

efficacy analyses will be based on the planned treatment; this set of patients is called the Full Analysis Set (FAS).

- Safety analyses will be based on the actual treatment received; this set of patients is called the Treated Set (TS).

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

7.3.1 Primary endpoint analyses

Part 1:
The achievement of PASI 75 at Week 12 is the first co-primary endpoint, and is a binary variable with values of 0 or 1. The achievement of a sPGA score of clear or almost clear at Week 12 is the second co-primary endpoint and is a binary variable with values of 0 or 1.

After the last patient reaches Week 12, the analyses for PoCC and dose-finding will be performed on each co-primary endpoint using multiple comparison and modelling techniques (MCPMod) [R10-1424, R15-1961] for binary data whereby several possible dose response models (patterns) will be evaluated, while keeping full control of the type I error at 5%, one-sided, to identify the best-fitting model or subset of models.

A non-flat dose-response relationship is established if for each co-primary endpoint, the null hypothesis of no dose effect (i.e., a flat dose response curve) is rejected for at least one of the pre-specified models with respect to the alpha chosen.

For the sample size calculation, the maximum effect size is assumed to be 50%, with the placebo effect size assumed to be 10% for PASI 75 at Week 12. The maximum effect size is assumed to be 50% with the placebo effect size assumed to be 10% for sPGA (0/1) at Week 12. Further details are given in section 7.7.

The following models shapes have been selected as the candidate set of possible dose response patterns (Figure 7.3.1:1) based on current expectation. Assuming the following dose groups will be tested: placebo, active BI 730357 25 mg, 50 mg, 100 mg, and 200 mg.

- Linear: no assumptions needed
- Emax 1: 30% of the maximum effect is achieved at 50 mg
- Emax 2: 80% of the maximum effect is achieved at 50 mg
- Exponential: 5% of the maximum effect is achieved at 25 mg
- Logistic: 10% of the maximum effect is achieved at 25 mg
  80% of the maximum effect is achieved at 100 mg

Note that the actual shapes and assumptions on proportion of maximum effect are applied on the logit scale for binary data, e.g. linear model. For interpretation convenience, dose response curves in Figure 7.3.1: 1 are converted to original scale of PASI 75 and sPGA 0/1 probability.

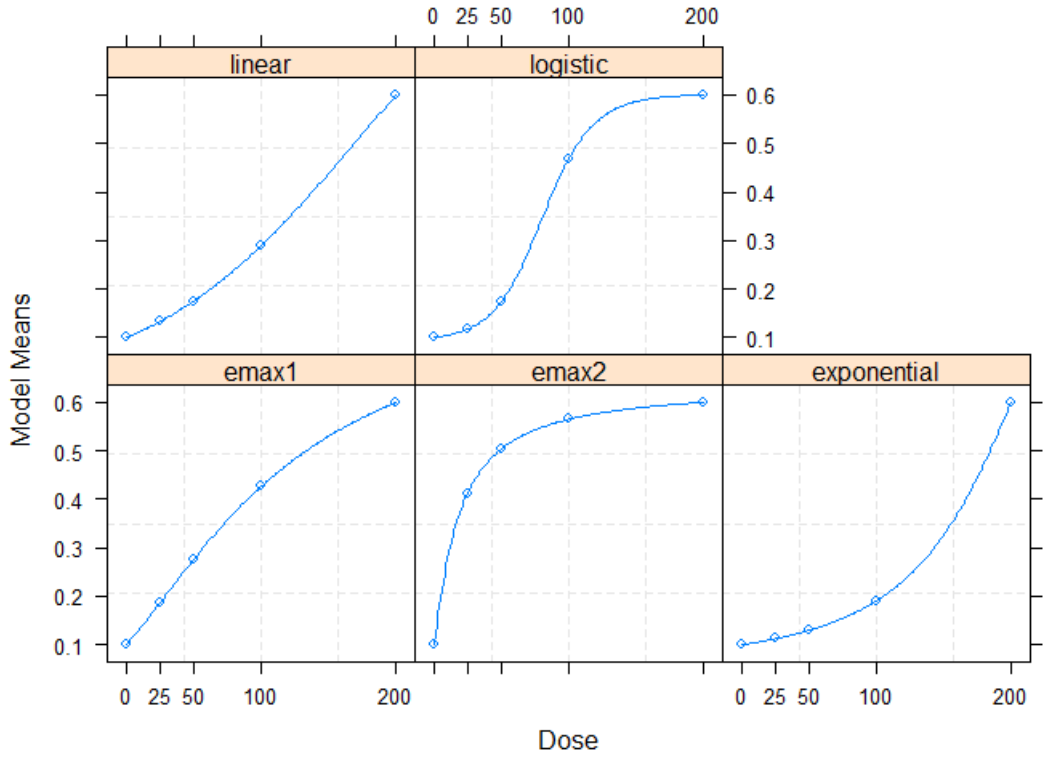


Figure 7.3.1: 1 Shape of the models within the candidate set

PoCC is established if for each co-primary endpoint, at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship for each of the candidate dose response models with a contrast test controlled for the family–wise type I error rate at one sided $\alpha = 5\%$.

If PoCC is established, the statistically significant (best fitting) model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters from the data. The final model will be obtained via model averaging across the significant models based on Akaike Information Criterion (AIC). The target dose(s) can be estimated from that model by incorporating information on the minimum clinically relevant effect and accounting for safety. Only doses within the dose range investigated (0 to 200 mg) will be considered although the actual modelling will be performed on a broader range of doses including extrapolation.

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates.

Comparisons between treatment groups will be exploratory in nature. Comparisons between treatment groups regarding the co-primary endpoints will also be performed using the Chi-square test for each of the four active treatments versus placebo. In addition, unadjusted absolute risk differences of the response rates at Week 12 between BI 730357 arms and the placebo group will be analysed. The proportion of responders in each arm, the risk difference

between each BI 730357 arm and placebo with 95% exact confidence intervals will be displayed. This is considered the secondary analysis for the primary endpoint(s). More details on the above analyses as well as additional sensitivity analyses will be given in the TSAP.

For the PoCC analysis, the analyses will be performed by BI personnel independent of the trial team in order to prevent potential introduction of operational bias. A logistics plan prepared and approved in accordance with Sponsor's specific procedures will detail procedures used to ensure that all members of the trial team remain blinded. The logistics plan will also contain a detailed list of functions that need to be unblinded to perform this analysis.

Part 2:
The achievement of PASI 75 at Week 12 will be summarized in the form of proportion of patients achieving PASI 75 at Week 12 as an outcome measure so as to perform the primary analysis.

The primary analysis on PASI 75 at week 12 will be based on a Bayesian borrowing approach. For the placebo control group, an informative prior is based on historical data whereas the prior for the BI 730357 group is non-informative. The derivation of the informative prior is based on a meta-analytic predictive (MAP) prior approach which is additionally robustified against prior-data conflicts by adding a vaguely informative component to the prior.

A Bayesian approach with an informative mixture beta prior for the placebo group will be used. The prior is a combination of a mixture of informative beta priors derived from historical trials and a vaguely informative beta prior. The weight on the vaguely informative beta prior is 50%. The prior considered is: 0.388 * Beta (8.269, 132.315) + 0.112 * Beta (2.546, 27.521) + 0.5 * Beta (0.07, 0.93). Non-informative beta prior Beta(1, 1) is used for BI active treatment arms.The actual prior may be updated based on additional historical information being available, including result from part I. The final prior will be documented in the TSAP.

The primary analysis for sPGA clear or almost clear at week 12 will be analysed by summarizing the proportion of responders in each arm with 95% exact confidence intervals. If considered necessary, same approach as PASI 75 based on Bayesian borrowing approach.

The proportions of 200 mg b.i.d. and 400 mg q.d. recipients who achieve PASI 75 improvement criteria at Week 12., will be respectively compared with that of placebo recipients. For that purpose, the posterior probability distribution for the risk difference will be evaluated and compared to specific boundary values. The dual criteria will be assessed to evaluate the effect of BI 730357: (1) significance: a posterior probability of at least 90% that the PASI 75 response rate for patients on BI 730357 is higher than that for patients on placebo; and (2) relevance: a posterior probability of at least 50% that the PASI 75 response rate for patients on BI 730357 is higher than that for patients on placebo by various boundary values. If at least one dose satisfy both criteria, it is considered as "pass". If neither doses have significance or relevance criteria been met, it is considered as "not pass". Otherwise it is in the "consider" zone, where sPGA 0/1 at week 12 will be jointly evaluated.

7.3.2 Secondary endpoint analyses

Part 1:
If considered necessary, a MCPMod approach will also be applied to selected secondary endpoints.

The same methods as discussed for the secondary analysis for the primary endpoints will be used to analyse clinical binary secondary endpoints, if applicable.

For binary endpoints after Week 12, two analysis strategies will be considered as following:

- The analysis will be done based on the original treatment assignment at randomisation. Non-responders at Week 12 will be imputed as failure for binary endpoints after Week 12.
- For non-responders at Week 12, analysis based on the escalated treatment they received at Week 12 will also be considered.

For PSS total score at Week 12, point estimates and two-sided 95% confidence intervals for mean reduction from baseline and difference between each BI 730357 arm and placebo will be provided.

Part 2:
For PSS total score at Week 12, point estimates and two-sided 95% confidence intervals for mean reduction from baseline in each arm will be provided.

For other binary secondary endpoints, the proportion of responders in each arm with 95% exact confidence intervals will be displayed.

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

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e., all adverse events 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 patients with abnormal values or clinically relevant abnormal values.

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

[redacted]

7.4 INTERIM ANALYSES

Part 1:
When the last patient completes the 4 Week visit, there will be an administrative interim analysis for the purpose of internal planning other indications of BI 730357. An independent team will be formed to perform this analysis. Details will be specified in an interim analysis logistic plan. As the trial will continue unchanged irrespective of the results, no statistical adjustment for the primary endpoint is required.

When the last patient completes the Week 12 visit (timepoint of primary endpoint), the primary analysis will be performed. In order to support the further double-blinded conduct of the trial until the Week 24 visit, the Trial Team will be kept blinded on the individual patients' treatment group assignment. A separate team will be formed to perform this analysis. Details will be specified in the logistic plan.

In summary, Part 1 of this trial will be double-blinded until the final analysis when the last patient completes Week 24. More details about the analyses will be specified in the TSAP.

Part 2:
No interim analysis is planned for the Part 2 of this trial.

For both trial parts, an independent DMC will follow the DMC charter and be responsible for reviewing safety data periodically to ensure patient safety and to monitor the conduct of the trial and the integrity of the data. Refer to section 8.7 for more information for DMC.

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.

The following rules will be used to impute for missing data:
- For all non-binary endpoints, LOCF (Last Observation Carried Forward) will be used to impute missing values
- For all binary endpoints (i.e., endpoints that are either 1 (patient responded) or 0 (patient did not respond)):
    - If no data after that visit*, then impute as failure (NRI [No Response Imputation])

- If data at visits* before and after, only impute as success if both visits are successes; else impute as failure.

* Patients that take prohibited medications to treat PsO will be treated the same as those that discontinued from the trial, i.e., subsequent visits following start of prohibited medication will be considered as failure for binary endpoints.

Missing items from the Quality of Life questionnaires will be handled according to the measure instructions (cf. Appendix 10.6). If there is no data for a particular visit, then it will be imputed following the same rules as described above.

[redacted]

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

7.6 RANDOMISATION

An IRT will be used for the assignment of subjects to treatment groups.

Part 1:
Patients will be randomised in blocks to double-blind treatment. Patients will be randomised to one of 4 BI 730357 dose groups and placebo in a 2:2:2:2:1 ratio. In total, approximately 40 patients will be allocated to each BI 730357 active dose group, and approximately 20 patients to placebo. Refer to section 3.1 for the details.

Part 2:
Patients will be randomised to the 200 mg b.i.d., 400 mg q.d. BI 730357 dose group or placebo in a 4:4:1 ratio. In total, approximately 40 patients will be allocated to BI 730357 200 mg b.i.d. dose group, 40 patients will be allocated to BI 730357 400 mg q.d. dose group and approximately 10 patients to placebo. Refer to section 3.1 for the details.

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

7.7 DETERMINATION OF SAMPLE SIZE

Part 1:
Sample size calculation is mainly driven by safety considerations.

Based on an assumed maximum treatment effect size of BI 730357 vs. placebo for the PASI 75 endpoint, as well as on the pre-specified models listed in section 7.3.1, the power is provided in the Table 7.7: 1 for different scenarios for one of the co-primary endpoint PASI 75. The maximum treatment benefit is assumed to be 50% compared to placebo (60% vs 10%) for PASI 75 at Week 12.

The maximum treatment benefit is assumed to be 50% compared to placebo (60% vs 10%) for sPGA 0/1 at Week 12. The same dose- response assumptions are made for the sPGA (0/1). As PASI 75 and sPGA (0/1) are highly correlated, a sample size of about 180 (=40:40:40:40:20 to 4 BI 730357 active dose groups and placebo, refer to section 3.1) evaluable patients will have an overall power > 90% to show a significant non-flat dose-response curves across the different doses and placebo using MCPMod approach with parameters as listed in section 7.3.1.

Table 7.7: 1 Power of MCPMod for each candidate set model and min, max, average power for PASI 75

Model	**Assumption A (e.g., maximum treatment effect=0.5, allocation 40:40:40:40:20)**	**Assumption B (e.g., maximum treatment effect=0.4, allocation 40:40:40:40:20)**	**Assumption C (e.g., maximum treatment effect=0.01, allocation 40:40:40:40:20)**	**Assumption D (e.g., maximum treatment effect=0.3, allocation 40:40:40:40:20)**
Linear	99.9%	99.4%	6.6%	95%
Emax 1	99.7%	98.0%	6.5%	90.2%
Emax 2	94.5%	85.9%	6.1%	70.5%
Logistic	99.7%	99.7%	6.8%	96.9%
Exponential	99.9%	99.8%	6.6%	97.1%
Min	94.5%	85.9%	6.1%	70.5%
Max	99.9%	99.9%	6.8%	97.1%
Average	98.8%	96.6%	6.6%	90.0%

Assumptions considered:

- A: Main scenario reflecting assumption listed in section 7.3.1. Assuming PASI 75 response rate is 10% (placebo), 60% for the 200 mg dose group. Sample size considered is 180 patients with 2:2:2:2:1 allocation ratio.
- B: Similar scenario as A, but response rate at 200 mg dose group is lower at 50%.
- C: Scenario reflection almost no treatment benefit.
- D: Same scenario as A and B, but with a lower maximum treatment benefit.

The calculations for the PoCC step have been performed using DoseFinding R-package [R15-2001]. Calculations were performed using R version 3.4.2. The R codes for the sample size calculations as well as the analyses using the MCPMod approach will be provided in the TSAP.

Part 2:
Posterior probabilities are evaluated based on assumed response rates of 7% on placebo and 52% on BI 730357 200 mg b.i.d. and 400mg q.d., respectively, when assuming sample sizes for BI 730357 200 mg b.i.d., 400 mg q.d. and placebo group are 40, 40 and 10, respectively, and the prior specified in Section 7.3.1. Dual criteria for establishing an overall “pass” are

used. For example, under the dual criterion 1) significance P(BI – PBO > 0 | Data) > 0.95; and 2) relevance P(BI – PBO > 0.40 | Data) > 0.5, if there is a truly treatment difference of 40% in response rates, the given sample size provides a chance of >90% to detect the treatment benefit in at least one active dose group. A "passed" indicates at least one dose satisfies both significance and relevance criteria; A "not passed" indicates neither dose satisfies either of these two criteria. Table 7.7: 2 presents the probabilities of decisions under different cases.

Table 7.7: 2 Posterior probabilities for each scenario under different significance and relevance criteria settings

Significance criterion	Relevance criterion	Assumed PASI 75 response rate 200 b.i.d., 400 q.d., PBO	P(Passed[#])	P(Not passed[#])	P(Consider[#])
P(BI – PBO > 0 | Data) > 0.9	P(BI- PBO > 0.35 | Data) > 0.5	7% , 7% vs. 7%	0	66%	34%
		52%, 52% vs. 7%	99%	0	1%
		52%, 52% vs 15%	92%	3%	5%
P(BI – PBO > 0 | Data) > 0.9	P(BI- PBO > 0.4 | Data) > 0.5	7% , 7% vs. 7%	0	66%	34%
		52%, 52% vs. 7%	94%	0	6%
		52%,52% vs 15%	82%	3%	15%
P(BI – PBO > 0 | Data) > 0.9	P(BI- PBO > 0.45 | Data) > 0.5	7% , 7% vs. 7%	0	66%	34%
		52%, 52% vs. 7%	82%	0	18%
		52%, 52% vs 15%	66%	3%	31%
P(BI – PBO > 0 | Data) > 0.95	P(BI- PBO > 0.35 | Data) > 0.5	7% , 7% vs. 7%	0	84%	16%
		52%, 52% vs. 7%	99%	0	1%
		52%,52% vs 15%	92%	5%	3%
P(BI – PBO > 0 | Data) > 0.95	P(BI- PBO > 0.4 | Data) > 0.5	7% , 7% vs. 7%	0	84%	16%
		52%, 52% vs. 7%	94%	0	6%
		52%,52% vs 15%	82%	5%	12%
P(BI – PBO > 0 | Data) > 0.95	P(BI- PBO > 0.45 | Data) > 0.5	7% , 7% vs. 7%	0	84%	16%
		52%, 52% vs. 7%	82%	0	18%
		52%, 52% vs 15%	66%	5%	29%

[#] - Passed: At least one dose satisfied both criteria.
- Not passed: neither dose has either relevance or significance criteria satisfied
- Consider: all other scenarios

sPGA 0/1 at week 12 will be supportive if the trial result based on PASI 75 falls into "consider" zone.

The calculations for the Bayesian posterior probability calculation are based on R-package RBesT using R version 3.5.1.

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.

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

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

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow 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.

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

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). The investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

The 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 AND PATIENT PRIVACY

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

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. Two separate reports will be written for Part 1 and Part 2 of this trial.

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Data Monitoring Committee
A Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will evaluate safety data, efficacy data and results of interim analyses. The DMC will receive notification of urgent significant safety concerns including severe infections, suicidality reports, MACE and DILI cases for immediate evaluation. While DMC members

may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate RAs/HAs, IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

MACE adjudication committee
An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular and thrombotic events reported during the conduct of the study to assure consistent assessment of major adverse cardiovascular events (MACE).This review will be blinded to treatment allocation; the events that are to be adjudicated and the adjudication process will be detailed in the MACE Adjudication Committee Charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF. The investigators will have access to the BI clinical trial portal [redacted] 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,
- ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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

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

A central laboratory service, a central ECG service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual, the ECG instructions and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 PASI SCORE DEFINITION AND USE

The PASI score is an established measure of clinical efficacy for psoriasis medications (R96-3541).

The PASI is a tool which provides a numeric scoring for patients overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, infiltration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an X% reduction (or PASI X), where X is 50, 75, 90 and 100.

To calculate the PASI score, the four main body areas are assessed: **head (h), trunk (t), upper extremities (u) and lower extremities (l)**. These correspond to 10, 30, 20 and 40% of the total body area respectively.

The **area of psoriatic involvement** of these four areas (Ah, At, Au, and Al) is given a numerical value: 0 = no involvement, 1 = <10%, 2 = 10 to <30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, and 6 = 90 to 100% involvement.

The **signs of severity, erythema (E), infiltration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = striking erythema, and 4 = exceptionally striking erythema.

The PASI score is calculated according to the following formula:

PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al

10.2 STATIC PHYSICIAN GLOBAL ASSESSMENT (SPGA)

The sPGA used in this trial is a 5 point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions (Table 10.2: 1) (!"# $#%&'&The assessment is considered "static" which refers to the patients disease state at the time of the assessments, without comparison to any of the subject's previous disease states, whether at Baseline or at a previous visit.

A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

The Investigator (or qualified site personnel) scores the erythema, induration and scaling of all psoriatic lesions from 0 - 4 based on the following descriptors:

Erythema

0 Normal (post-inflammatory hyper/hypopigmentation may be present)
1 Faint, diffuse pink or slight red coloration
2 Mild (light red coloration)
3 Definite red coloration (Dull to bright red)
4 Bright to Deep red coloration of lesions

Induration (plaque elevation)

0 None
1 Just detectable (slight elevation above normal skin)
2 Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)
3 Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)
4 Severe thickening with hard edges (marked elevation typically with hard or sharp edges)

Scaling

0 No scaling
1 Minimal focal scaling (surface dryness with some desquamation)
2 Predominately fine scaling (fine scale partially or mostly covering lesions)
3 Moderate scaling (coarser scale covering most or all of the lesions)
4 Severe /coarse scaling covering almost all or all lesions (coarse, non-tenacious scale predominates)

Scoring: a composite score is generated from the above data and the final sPGA is determined from this composite score as follows:

Clear 0 = 0 for all three
Almost clear 1 = mean >0, <1.5
Mild 2 = mean >= 1.5, <2.5
Moderate 3 = mean >= 2.5, <3.5
Severe 4 = mean >= 3.5

Table 10.2: 1 sPGA Rating Scale for Overall Psoriatic Disease

Score	Short description	Detailed description
0	clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	almost clear	Normal to pink coloration Just detectable (possible slight elevation above normal skin) No to minimal focal scaling
2	mild	Pink to light red coloration Mild thickening (slight but definite elevation, typically edges are indistinct or sloped) Predominantly fine scaling

Table 10.2: 1 sPGA Rating Scale for Overall Psoriatic Disease cont.

3	moderate	Dull to bright red coloration Clearly distinguishable to moderate thickening Moderate scaling
4	severe	Bright to deep dark red coloration; Severe thickening with hard edges Severe coarse scaling covering almost all or all lesions

10.3 NAPSI: NAIL PSORIASIS SEVERITY INDEX

The NAPSI assesses how much of the fingernail is affected with psoriasis with scores ranging from 0 to 80.

If a patient has nail psoriasis, the physician will assess the nail psoriasis at each protocol defined time point. Fingers (5) on each hand will be individually examined for two distinct assessments and are graded as follows:

- Nail Matrix Assessment:
  0 = None
  1 = present in 1 quadrant of nail
  2 = present in 2 quadrants of nail
  3 = present in 3 quadrants of nail
  4 = present in 4 quadrants of nail

- Nail Bed Assessment:
  0 = None
  1 = present in 1 quadrant of nail
  2 = present in 2 quadrants of nail
  3 = present in 3 quadrants of nail
  4 = present in 4 quadrants of nail

The sum of the scores will be added resulting a range of 0 to 80. If an individual finger assessment is missing (not done), the average of the remaining measured digits will be imputed and added to the sum. If < 50% of the finger assessments are missing the imputation will be performed. If more than 50% of the assessments are missing then the sum of the scores will be left as missing.

10.4 PPASI: PALMOPLANTAR PSORIASIS SEVERITY INDEX

The PPASI provides a numeric scoring for psoriasis affecting the hands and feet with scores ranging from 0 to 72. It is a linear combination of percent of surface area of hands and feet that are affected and the severity of erythema, induration, and desquamation.

If a patient has palmoplantar psoriasis, the physician will assess the psoriasis at each protocol defined time point. Both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows:

- Erythema, Induration and Desquamation:

0 = None
1 = Slight
2 = Moderate
3 = Severe
4 = Very Severe

- Percent of Palm and Sole Area Covered:

  0 = Clear
  1 = <10%
  2 = 10-29%
  3 = 30-49%
  4 = 50-69%
  5 = 70-89%
  6 = 90-100%

The PPASI is a composite score and will be computed for each palm and sole, left and right and is derived from the sum of the scores for erythema (E), induration (I) and desquamation (D) multiplied by the score recorded for the extent of palm and sole area involved.

PPASI is calculated as follows: (sum of scored for E+I+D)*Area *0.2(location: right palm) + (sum of scored for E+I+D)*Area *0.2(location:left palm) + (sum of scored for E+I+D)*Area*0.3(location: right sole) +(sum of scores for E+I+D)*Area *0.3(location: left sole). The range is 0 to 72.

10.5 PSORIASIS SCALP SEVERITY INDEX (PSSI)

If a patient has scalp psoriasis, the physician will assess the erythema (redness), induration (hardness), desquamation (shedding of skin) and percent of scalp covered at each protocol defined time point.

- Erythema, Induration and Desquamation:

  0 = None
  1 = Slight
  2 = Moderate
  3 = Severe
  4 = Very Severe

- Percent of Scalp Covered:

  1 = <10%
  2 = 10-29%
  3 = 30-49%
  4 = 50-69%
  5 = 70-89%
  6 = 90-100%

The PSSI is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score recorded for the extent of scalp area involved. The range is 0 to 72.

10.6 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The DLQI is a subject-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (R05-2548). The DLQI has a one-week recall period. Item scores range from 0 (not relevant/not at all) to 3 (very much). Question 7 is a "yes"/ "no" question where "yes" is scored as 3.

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on subject's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on subject's life. The higher the score, the more the quality of life is impaired. A 4-point change from baseline is considered a clinically important difference.

10.7 PSORIASIS SYMPTOM SCALE (PSS)

The PSS will be completed by the patients during all clinic visits except V1.

The PSS is a four-item patient-reported outcome (PRO) instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis. The symptoms included are: pain, redness, itching and burning from psoriasis. Current symptom severity is assessed for a 24 hour recall periodusing a 5-point verbal rating scale ranging from 0 (none) to 4 (very severe). The PSS was developed based on published evidence supporting the development of two similar, proprietary patient-reported outcome instruments: the Psoriasis Symptom Inventory and the Psoriasis Symptom Diary. These measures were developed in accordance with FDA PRO Guidance and have published evidence of reliability, validity, and ability to detect change (R14-3562, R14-3559, R15-1219, R15-1410, R15-1411).

Psoriasis Symptom Scale

Listed below are a set of problems that people with psoriasis have said are important. For each question, tick the box that best describes the severity of your symptoms during the past 24 hours. Please answer every question.

1. How severe was your pain from your psoriasis during the past 24 hours?
- None
- Mild
- Moderate
- Severe
- Very severe

2. How severe was the redness from your psoriasis during the past 24 hours?
- None
- Mild
- Moderate
- Severe
- Very severe

3. How severe was your itching from your psoriasis during the past 24 hours?
- None

- Mild
- Moderate
- Severe
- Very severe

4. How severe was your burning from your psoriasis during the past 24 hours?
- None
- Mild
- Moderate
- Severe
- Very severe

10.8 PAIN VAS

The Pain VAS will be self-administered by the patient (for PsA patients) at visits indicated in the FLOW CHART, Part 1 and FLOW CHART, Part 2.

The patient's assessment of pain will be performed using a horizontal 100 mm visual analog scale (VAS), ranging from 0 (no pain) to 100 (severe pain) after the question:

> "How much pain have you had because of your psoriatic arthritis in the past week? Place a vertical (|) mark on the line to indicate the severity of the pain."

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 July 2018
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
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		
COMMENT: The first version of this protocol has never been submitted to any regulatory authority. This revision is the first protocol version which is used outside of BI.		
Section to be changed	1.2.1	Non-clinical studies
Description of change		Inclusion of data from non-clinical safety data.
Rationale for change		Results from additional animal toxicology studies have become available (embryofetal toxicology, 39 week chronic toxicity in beagle dogs
Section to be changed	1.2.2.	Clinical Experience in Humans
Description of change		Final results from the SRD study and interim data from the MRD study were included.
Rationale for change		Final report of the SRD study and interim date from the MRD up to for weeks dosing with 200 mg BI 730357 have become available.
Section to be changed	3.3.2	Inclusion criteria
Description of change		added: # 4: Diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient #5: Patients must be candidates for systemic PsO therapy.
Rationale for change		To further specify the target patient population for this study.

11.2 GLOBAL AMENDMENT 2

Date of amendment		15 Nov 2018
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Flowchart
Description of change		Added: Assessment of body weight at Visit 8.
Rationale for change		To obtain information on possible weight change after 12 weeks of study treatment.
Section to be changed	3.3.2	Inclusion criteria
Description of change		Added: upper age limit of 75 years inclusive.
Rationale for change		To adjust the age range to standards of Phase 2 trials in this indication.
Section to be changed	3.3.3	Exlusion criteria
Description of change		Deleted from ex criterion #3: “or previous enrolment in this trial”
Rationale for change		Avoid duplication as this is already stated in ex-criterion #2.
Section to be changed	3.3.3	Exlusion criteria
		Added: 16. Any kind of photodermatosis.
		For clarification
Section to be changed	Table 4.2.2.1:1	Restricted Medications
Description of change		“or photoallergic” added to “Drugs with known phototoxic potential
Rationale for change		For clarification.
Section to be changed	Table 4.2.2.1:1	Restricted Medications
Description of change		Added: Biologic agents (other than IL-23 antibodies) should not be taken within 12

		weeks prior to randomisation through EOO
Rationale for change		For clarification. Biologics were already excluded by exclusion-criterion #4a.
Section to be changed	6.1	Visit Schedule and Flowchart footnotes
Description of change		Added: no study medication should be dispensed/administered at the EOT visit
Rationale for change		For clarification
Section to be changed	8.1	Trial approval, patient information, informed consent
Description of change		Added to "the investigator": *…or delegate* obtains written consent …". Added to "The investigator": "…*or* [redacted] *delegate* must sign …"
Rationale for change		Administrative change to include delegation of informed consenting in countries where this is allowed by local regulations.

11.3 GLOBAL AMENDMENT 3

Date of amendment		18 February 2019
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Global Amendment due to urgent safety reasons		
Global Amendment		
Section to be changed	1.2.1 1.4	Non-clinical studies benefit-risk assessment
Description of change		Information added that no drug-drug interactions of CYP3A4 substrates and BI 730357 as a perpetrator are to be expected
Rationale for change		To include results from a recently completed clinical multiple rising dose study with a midazolam micro-dose sub study.
Section to be changed	3.3.2 4.2.2.4	Inclusion criteria contraception requirements
Description of change		Deleted from inclusion criterion #1: Requirement for contraception in male study participants.

Rationale for change		Based on nonclinical data (no genotoxicity demonstrated or suspected human teratogenicity/fetotoxicity at therapeutic systemic exposure levels) no measures are needed for contraception in male trial participants with a partner that is a WoCBP.
Section to be changed	3.3.3 4.2.2.1	Exclusion criteria Restricted medications
Description of change		Explanatory corrections to exclusion criterion #3 and to table 4.2.2.1:1. CYP3A4 substrates deleted from the list of restricted medications. Otherwise, more details and examples were added but no basically new information.
Rationale for change		For clarification
Section to be changed	4.2.1 5.2.6.1	Other treatments and emergency procedures Definition of AEs
		"Mycobacterium tuberculosis" replaced by "all mycobacterial infections".
		To include and cover a more complete picture of opportunistic infections in the definition.
Section to be changed	[redacted]	
Description of change		
Rationale for change		
Section to be changed	7.3	Planned analyses
Description of change		- "treated set" will be used instead of "safety set" - Point estimates instead of Wilcoxon rank test for the analysis of Psoriasis Symptom Scale - Wilcoxon rank test will not be used for analysis of Dermatology Life Quality Index
Rationale for change		Statistical considerations
Section to be changed	7.3.4	Safety analysis
Description of change		Residual effect period reduced from 28 days to 7 days.
Rationale for change		Correction.

		The follow-up period after end of treatment will remain at 28 days.

11.4 GLOBAL AMENDMENT 4

Date of amendment		27 March 2020
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Global Amendment due to urgent safety reasons		no
Global Amendment		Yes
COMMENT: The main purpose of this amendment is the addition of two active and one placebo group to the trial. A PK intensive substudy was added to provide understanding of how exposure is impacted by high doses and by food.		
Section to be changed	Synopsis	
Description of change		Information clarified for Part 1 and added Part 2 in the following sections: • Trial objectives • Trial endpoints • Trial design • Total number of patients randomized • Number of patients on each treatment • Test Product – Dose • Mode of administration • Duration of treatment • Statistical methods Criteria for Pharmacokinetics added
Section to be changed	Flow chart	
Description of change		A separate flow chart for Part 2 has been included.
Rationale for change		To reflect the procedures of the second part of this trial.
Section to be changed	Flow chart	
Description of change		Flowcharts for collection of PK samples have been added.

Section to be changed	Table of Contents	
Description of change		Flow Charts added to TOC. Section 11.4 added to reference Global Amendment 4.
Section to be changed	1.2.1.	Non-Clinical Studies
Description of change		Information about preclinical data has been updated.
Rationale for change		To reflect the latest status of information and align with current IB.
Section to be changed	1.2.2.	Clinical Experience in Humans
Description of change		Replace interim results from Phase 1 trials by final results. Addition of information about interim results from ongoing trial 1407-0030.
Rationale for change		Provide most recent available information and align with current IB.
Section to be changed	1.3	Rationale for performing the trial
Description of change		Rationale for extending this trial by Part 2 added.
Rationale for change		To provide justification for performing Part 2.
Section to be changed	1.4	Benefit-Risk Assessment
		Information on blood-volume to be collected during Part 2 added. Information on new dose groups added.
Section to be changed	1.4	Benefit-Risk Assessment
Description of change		Information on DDI potential has been updated.
Rationale for change		To reflect the latest results from DDI trials.
Section to be changed	2.	Trial Objectives and Endpoints
Description of change		Objectives and endpoints for Parts 1 and 2 were specified. Pharmacokinetic endpoints added for intensive PK subset.
Rationale for change		To provide clarification on objectives and endpoints.
Section to be changed	3.1	Overall Trial Design and Plan
Description of change		Information on Part 2 design added.
Rationale for change		

Section to be changed	3.2	Discussion of trial design
[redacted]		
Section to be changed	3.3	Selection of trial population
Description of change		Information on Part 2 added
Rationale for change		To provide total number of new patients included in Part 2.
Section to be changed	3.3.3	Exclusion criteria
Description of change		Added exclusion of hepatic impairment for Part 2.
Rationale for change		To exclude patients with higher grade hepatic impairment.
Section to be changed	4.1.2	Selection of doses in the Trial
Description of change		Justification of doses used in Part 2 added.
Section to be changed	4.1.3	Method of assigning patients to treatment groups
Description of change		Information on randomisation ratio of Part 2 added. In Part 2, patients will have to take their study medication with a meal.
Rationale for change		Food will increase the exposure to the study.drug.
Section to be changed	4.1.4	Drug assignment and administration
Description of change		Details about dose groups and dosing instructions for Part 2 added.
Rationale for change		In Part 2 higher doses will be used. Study drug will be taken either once or twice daily and with a meal.
Section to be changed	4.1.5	Blinding and procedures for unblinding
Description of change		Details added on DMC review of PK summary report for Part 2.
Rationale for change		To provide clarification on how PK information will be reviewed.
Section to be changed	4.2.2.1	Restrictions regarding concomitant treatment
Description of change		Table 4.2.2.1: 1 was updated.
Rationale for change		To reflect latest results from DDI studies and take into account the higher study drug doses

		used in Part 2.
Section to be changed	4.2.2.2	Restrictions on diet and life-style
Description of change		Information added for Part 2.
Rationale for change		To remain consistent with all protocol amendment changes.
Section to be changed	5.2.3	Table 5.2.3: 1 Safety laboratory tests
Description of change		Removed requirement for patients to be fasted for blood sample collections. Footnote added that a positive hep C antibody test should be confirmed by PCR.
Rationale for change		For clarification.
Section to be changed	5.3.1	Assessment of pharmcokinetics
Description of change		Information on pk assessments in Part 2 added.
Section to be changed	5.3.2	Method of pharmacokinetic sample collection
Description of change		Information on pk assessment in Part 2 added
Rationale for change		To clarify procedure requirements for PK assessment.
Section to be changed	5.6.1	Photography of skin lesions
Description of change		In Part 2, no photos will be taken.
Rationale for change		Sufficient number of photos have been collected in Part 1.
Section to be changed	6.1	Visit schedule
Description of change		Information added, that in Part 2 study medication should be taken with a meal.
Rationale for change		To find out about the influence of food on drug exposure.
Section to be changed	6.2.2	Treatment period
Description of change		Information about taking medication in Part 2 added.
Rationale for change		To clarify medication must be taken with a meal.
Section to be changed	6.2.3.2	Trial completion
Description of change		Information added, that patients who complete Part 2 will not be able to roll over into the long term extension trial.
Rationale for change		Currently, the LTE trial does not offer doses above 200 mg per day, so patients would have to reduce doses when rolling over.

Section to be changed	7.	Statistical Methods and Determination of Sample Size
Description of change		Wording about statistical plans for Part 2 added.
Section to be changed	8.6	Trial Milestones
Description of change		Wording added to reference Part 1 and Part 2.
Rationale for change		For clarification.
Section to be changed		Entire document
Description of change		Typos and formatting adapted according BI Style Guide.
Rationale for change		BI Style Guide.
Section to be changed	9.2	Unpublished References
Description of change		Reference DSUR s00083382-01 added
Rationale for change		

11.5 GLOBAL AMENDMENT 5

Date of amendment		12 May 2020
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Global Amendment due to urgent safety reasons		
Global Amendment		Yes
Section to be changed	1.2.1	Non-Clinical Studies
Description of change		Information on gastritis finding in beagle dogs added.
Rationale for change		Include update information
Section to be changed	1.4	Benefit-Risk Assessment
Description of change		Added: “AE consistent with gastric intolerance or gastritis are designated as AE of special interest (AESI).
Rationale for change		To provide background on why gastric AEs are added to AESIs.
Section to be changed	5.2.6.1	Assessment of Adverse Events
Description of change		AE consistent with gastric intolerance or

		gastritis are designated as AE of special interest
Rationale for change		To ensure timely characterisation, monitoring and reporting of such effects.

11.6 GLOBAL AMENDMENT 6

Date of amendment		01 July 2020
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Global Amendment due to urgent safety reasons		
Global Amendment		Yes
Section to be changed	4.1.4	Drug assignment and administration
Description of change		Details on dosage regimen for Part 2 updated.
Rationale for change		To reflect changes to drug packaging for Part 2.

11.7 GLOBAL AMENDMENT 7

Date of amendment		24 August 2020
EudraCT number **EU number**		2017-004659-21
BI Trial number		1407-0030
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Global Amendment due to urgent safety reasons		
Global Amendment		Yes
<u>COMMENT</u>: The main purpose of this amendment is to allow patients completing Part 2 to continue treatment in a long term extension trial.		
Section to be changed	Synopsis	Main in- and exclusion criteria
Description of change		"and men able to father a child" was deleted from contraception requirement.
Rationale for change		To correct the discrepancy to the protocol body.
Section to be changed	FC Part 2	Flow Chart, Part 2
Description of change		An additional row and footnote was included to explain that patients completing the treatment period of this trial will be offered to roll over

		into a long term extension trial (LTE).
Rationale for change		
Section to be changed	PK FC	PK BLOOD SAMPLING FLOW CHART FOR INTENSIVE PK SUBSTUDY, PART 2
Description of change		Footnote added to explain that for patients continuing in the LTE the 48 hours and the 72 hours sampling will be omitted.
Rationale for change		The 48 h and 72 h samples are meant for the assessment of the trial drug wash-out kinetics. They do not make sense, if the patient continues taking study medication.
Section to be changed	1.2.1	Non Clinical Studies
Description of change		Section was updated
Rationale for change		To reflect the current state of knowledge and align with the latest version of the Investigators Brochure.
Section to be changed	1.2.2	Clinical Experience in Humans
Description of change		Section was updated.
Rationale for change		To reflect the current status of clinical trials with BI 730357 and align with the latest version of the Investigators Brochure.
Section to be changed	4.1.2	Selection of Doses in the Trial
Description of change		Section was updated.
Rationale for change		To reflect the current state of knowledge and align with the latest version of the Investigators Brochure.
Section to be changed	6.2.3.2	Trial Completion
Description of change		Added: “In Part 2, patients may also be offered participation in the LTE, if they feel that they have benefited from the trial treatment.“
Rationale for change		In Part 1, both investigators and patients frequently asked if continuation in the LTE was possible, even though the objective threshold of 50% PASI improvement had not been achieved. They stated that symptoms, which are not captured by PASI (e.g. itching) and subjective wellbeing had improved. In addition, Part 1 results indicate that 12 week treatment may not achieve maximal response and further improvement may be seen after extended treatment with the study drug.

Section to be changed	9.1	References
Description of change		Reference R11-1259 was deleted. New reference added. P20-07441.
Rationale for change		To reflect the current state of knowledge and align with the latest version of the Investigators Brochure.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	25 Aug 2020 13:06 CEST
Approval-Clinical Pharmacokinetics		25 Aug 2020 15:22 CEST
Approval-Biostatistics		26 Aug 2020 17:33 CEST
Approval-[redacted] Medicine		28 Aug 2020 10:23 CEST
Approval-Team Member Medicine		03 Sep 2020 16:17 CEST
Verification-Paper Signature Completion		03 Sep 2020 20:14 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed