Clinical Trial Protocol

	Document Number:	**c22181693-04**
EudraCT No. **EU Trial No.**	2018-003487-31	
BI Trial No.	1407-0005	
BI Investigational Medicinal Product(s)	BI 730357	
Title	Phase II long-term extension study to assess the safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis	
Lay Title	A study to test how well patients with plaque psoriasis tolerate BI 730357 over a longer period and how effective it is	
Clinical Phase	Phase II	
Clinical Trial Monitor	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Status	Final Protocol (Revised Protocol based on Global Amendment 3.0)	
Version and Date	**Version: 4.0**	**Date: 06 Oct 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	05 Dec 2018
Revision date	06 Oct 2020
BI trial number	1407-0005
Title of trial	Phase II long-term extension study to assess the safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
Coordinating Investigator	[redacted]
Trial sites	Multi-centre trial
Clinical phase	II
Trial rationale	To provide patients with extended access to a potentially beneficial oral psoriasis intervention and gain long-term safety information.
Trial objectives	To assess long-term safety, tolerability, and efficacy of BI 730357 in patients with moderate to severe chronic plaque psoriasis.
Trial endpoints	Primary endpoint: • The occurance of treatment emergent adverse events (TEAEs) up to Week 288. Secondary endpoints: • Achievement of Psoriasis Area and Severity Index (PASI)50/ PASI75/PASI90/ PASI100 at Week 24 • Achievement of Static Physician's Global Assessment (sPGA) clear or almost clear at Week 24 • Achievement of sPGA clear at Week 24 • Time to loss of PASI50/PASI75/PASI90/PASI100 for patients who achieve the response up to Week 288 • Time to loss of sPGA clear or almost clear for patients who achieve the response up to Week 288 • Time to loss of sPGA clear for patients who achieve the response up to Week 288
Trial design	Double blind (double dummy), placebo-controlled, parallel design comparison of 5 treatment groups for 12 weeks, followed by open label treatment of 2 treatment groups
Total number of patients entered	Up to approximately 270 patients
Number of patients on each treatment	To be determined by response in the preceding study and the number of patients that participate in the extension study. Approximate possible ranges provided.

	Patients entering extension trial from Part 1 of trial 1407-0030 (Fasted) double blind treatment period until Week 12: • 25 mg (0 to 40 patients) • 50 mg (0 to 80 patients) • 100 mg (0 to 80 patients) • 200 mg (40 to 100 patients) • placebo (0 to 20 patients) (Fasted) open label treatment period: • 100 mg (80 to 140 patients) • 200 mg (60 to 100 patients) Patients entering extension trial from Part 2 of trial 1407-0030 (Fed) open label treatment period: • 400 mg (0 to 90 patients)
Diagnosis	Patients with moderate-to-severe plaque psoriasis who have completed treatment in the preceding trial
Main in- and exclusion criteria	• Have completed treatment in the preceding trial without early discontinuation, agree to continue treatment in 1407-0005, and o for patients entering from Part 1 of trial 1407-0030 ▪ ≥PASI50 response upon completing the trial 1407-0030 Week 24 end-of-treatment visit o for patients entering from Part 2 of trial 1407-0030 ▪ ≥PASI50 response upon completing the trial 1407-0030 Week 12 end-of-treatment visit or perceived patient improvement, at the discretion of the Investigator. • Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control • Have not developed any of the exclusion criteria of the preceding trial, including relevant chronic or acute infections • Must agree to continue to avoid intake of any restricted medication • No plan to receive a live vaccination during trial conduct • Must agree to continue to adhere to the rules of UV-light protection • No ongoing AEs related to trial medication (including gastric intolerance) from 1407-0030
Test product(s)	BI 730357
dose	25 mg, 50 mg, 100 mg, 200 mg, 400 mg BI 730357 per day
method and route of administration	Oral (p.o.)

Comparator product(s)	Placebo to BI 730357 (for patients entering from Part 1 of trial 1407-0030, 12 week double blind period only)
dose	Not applicable
method and route of administration	p.o.
Duration of treatment	Approximately 6 years
Statistical methods	Descriptive statistics include exposure adjusted rate of patients reporting a TEAE, responder analysis, and time to loss of response.

FLOW CHART

Trial Periods	**Screening/ Double Blind Treatment**	**Open Label Treatment**																
Visit	**1**[1, 2]	**1.1**[3]	**1.2**[3]	**1.3**[3]	**2**	**2.1**[3]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**(Day 1)**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156**
Visit window (days)		±7	±7	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	x																	
Demographics	x																	
Medical history	x																	
Smoking/alcohol history	x																	
Baseline conditions	x																	
In-, ex-criteria	x																	
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Body weight	x[1]								x				x				x	
Vital signs	x[1]	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Physical examination	x[1]	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Resting 12 lead ECG	x[1]								x				x				x	
Pregnancy testing[4]	x[1]	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Contact IRT	x				x		x	x	x	x	x	x	x	x	x	x	x	x
Dispense study medication	x				x		x	x	x	x	x	x	x	x	x	x	x	x
Collect study medication					x		x	x	x	x	x	x	x	x	x	x	x	x
PASI, sPGA	x[1]				x		x	x	x	x	x	x	x	x	x	x	x	x
[redacted]	[redacted]																	
[redacted]	[redacted]																	
[redacted]	[redacted]																	
[redacted]	[redacted]																	

Trial Periods	**Screening/ Double Blind Treatment**	**Open Label Treatment**																
Visit	**1**[1, 2]	**1.1**[3]	**1.2**[3]	**1.3**[3]	**2**	**2.1**[3]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Week	**(Day 1)**	**2**	**4**	**8**	**12**	**14**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156**
Visit window (days)		±7	±7	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Columbia-Suicide Severity Rating Scale (C-SSRS)[7]	x[1]				x		x	x	x	x	x	x	x	x	x	x	x	x
Safety laboratory samples	x[2]	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x
Biomarker samples (serum)	x[1]								x				x					
Whole blood (PBMC) for flow cytometry (pre-dose)[8]	x[1]								x				x					
[redacted]	[redacted]																	
Termination of trial medication																		
Trial completion[10, 11]																		
Vital status collection[13]																		

Trial Periods	**Open Label Treatment**											**Follow-Up**
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**EOT**[12]	**EOO**[11]
Week	**168**	**180**	**192**	**204**	**216**	**228**	**240**	**252**	**264**	**276**	**288**	**292**
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent												
Demographics												
Medical history												
Smoking/alcohol history												
Baseline conditions												
In-, ex-criteria												
Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x	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	x	x	x	x	x	
Resting 12 lead ECG			x				x				x	
Pregnancy testing[4]	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x
Contact IRT	x	x	x	x	x	x	x	x	x	x	x	
Dispense study medication	x	x	x	x	x	x	x	x	x	x		
Collect study medication	x	x	x	x	x	x	x	x	x	x	x	
PASI, sPGA	x	x	x	x	x	x	x	x	x	x	x	
[redacted]												
Columbia-Suicide Severity Rating Scale (C-SSRS)[7]	x	x	x	x	x	x	x	x	x	x	x	x
Safety laboratory samples	x	x	x	x	x	x	x	x	x	x	x	
Biomarker samples (serum)											x	
Whole blood (PBMC) for flow cytometry (pre-dose) [8]											x	
[redacted]												

Trial Periods	**Open Label Treatment**											**Follow-Up**
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**EOT**[12]	**EOO**[11]
Week	**168**	**180**	**192**	**204**	**216**	**228**	**240**	**252**	**264**	**276**	**288**	**292**
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Termination of trial medication											x	
Trial completion[10, 11]												x
Vital status collection[13]												x

Flow Chart Footnotes:

[1] Visit 1 will occur on the same day as End of Treatment (EOT) Visit in 1407-0030. Weight, vital signs, physical exam, ECG, pregnancy test, PASI, sPGA, [redacted], C-SSRS, biomarker samples, whole blood (PBMC) for flow cytometry and [redacted] are performed only once on that day as part of the EOT Visit in 1407-0030. Visit 1 may be delayed up to 16 weeks if necessary for administrative reasons. If Visit 1 is delayed, these procedures will be done at Visit 1, except for PK, Biomarker and flow cytometry samples.

[2] Safety laboratory samples will be taken twice in the same day as part of both the EOT Visit in 1407-0030 and for Visit 1 in 1407-0005. Visit 1 collection is only for the following laboratory tests that are not assessed at EOT in study 1407-0030: infection testing, glycosylated Hbc, LDL-cholesterol/HDL-cholesterol, cholesterol total, and triglycerides. If Visit 1 is delayed, then a sample will be taken at Visit 1 to include all tests included in the two samples and only one sample will be taken at EOT for 1407-0030.

[3] For patients entering from Part 1 of trial 1407-0030, Visit 2.1 is a phone visit, with only adverse events and concomitant medication collected. Visits 1.1, 1.2 and 1.3 do not apply.
For patients entering from Part 2 of trial 1407-0030, Visits 1.1, 1.2 and 1.3 to be performed at the clinic with all procedures indicated, Visit 2.1 does not apply.

[4] Only applicable for women of childbearing potential. Urine pregnancy tests will be performed at all visits prior to administration of study drug. In case of a positive urine pregnancy test, a serum pregnancy test will be done. More frequent testing should be done if required by the local regulation or per investigator judgment.

[redacted]

[7] C-SSRS 'since last visit' version used at all visits.

[8] Whole blood Peripheral Blood Mononuclear Cell (PBMC) sampling should be taken approximately within 1 hour prior to administration of study drug.

[redacted]

[10] Patients who discontinue trial treatment prematurely should undergo the EOT visit as soon as possible and the End of Observation (EOO) Visit 4 weeks thereafter.

[11] Patients switching to licensed BI 730357 upon completion of active treatment in this study should not complete a washout period. Instead, their last trial visit will be EOT and trial completion will occur at that visit. These patients will not return for EOO Visit.

[12] Timing of the EOT visit is variable depending on when BI 730357 is approved and available on the market in the patient's country. Study visits (performing Visit 24 assessments and procedures) may continue every 12 weeks until licensed BI 730357 becomes available or the trial is terminated.

[13] For patients who discontinue trial treatment prematurely, vital status will be collected once a year by telephone call starting from the last trial visit performed until the end of the originally planned observation period.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the Curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
CI	Confidence Interval
C_{max}	Maximum Concentration
CML	Clinical Monitor Local
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
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450
DC	Dendritic Cell
DILI	Drug Induced Liver Injury
[redacted]	[redacted]
DMC	Data Monitoring Committee
ECG	ElectroCardioGraphy
EDC	Electronic Data Capture
EOO	End Of Observation
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
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
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
MRD	Multiple Rising Dose
MST	Medical Sub Team
[redacted]	[redacted]
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
PD	Pharmacodynamics
PG	PharmacoGenetic
P-gp	P-glycoprotein
PK	Pharmacokinetics
p.o.	Oral
PoCC	Proof of Clinical Concept
[redacted]	[redacted]
PRO	Patient Reported Outcomes
[redacted]	[redacted]
PsA	Psoriatic Arthritis
PsO	(Plaque) Psoriasis
[redacted]	[redacted]
PXR	Pregnane X Receptor
q.d.	quaque die (once a day)
[redacted]	[redacted]
REP	Residual Effect Period
[redacted]	[redacted]
SAE	Serious Adverse Event
SIB	Suicidal Ideation and Behaviour
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
sPGA	Static Physician's Global Assessment
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TEAE	Treatment Emergent Adverse Event
TDMAP	Trial Data Management and Analysis Plan
TMF	Trial Master File
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
[redacted]	[redacted]
VEGF	Vascular Endothelial Growth Factor
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).

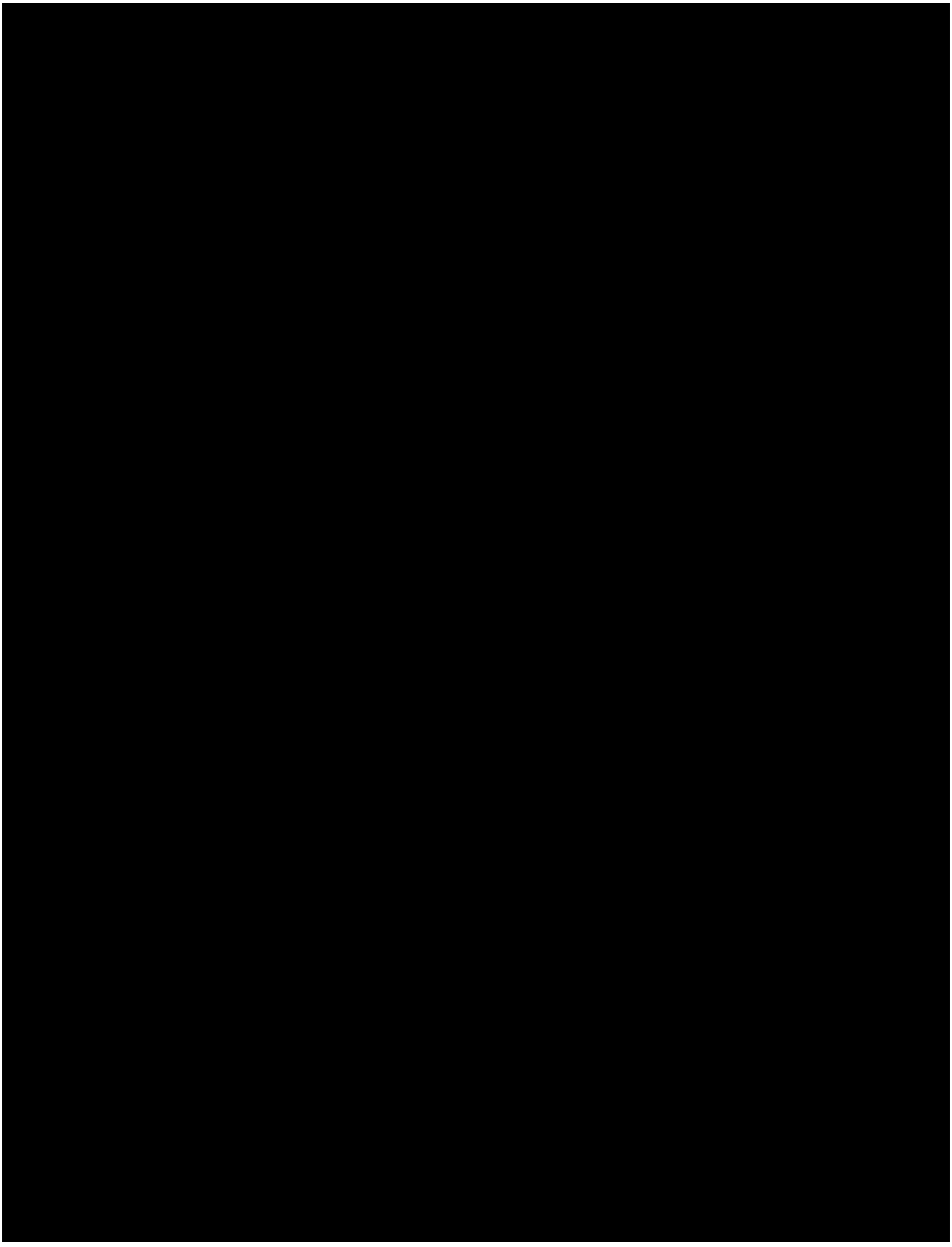
Mainstays of therapy for the treatment of PsO include topical agents, ultraviolet light-based therapies, traditional systemic agents (methotrexate, acitretin, cyclosporine), and more recently, targeted biologic and small-molecule therapies. Steroidal and non-steroidal topical agents (e.g., vitamin D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

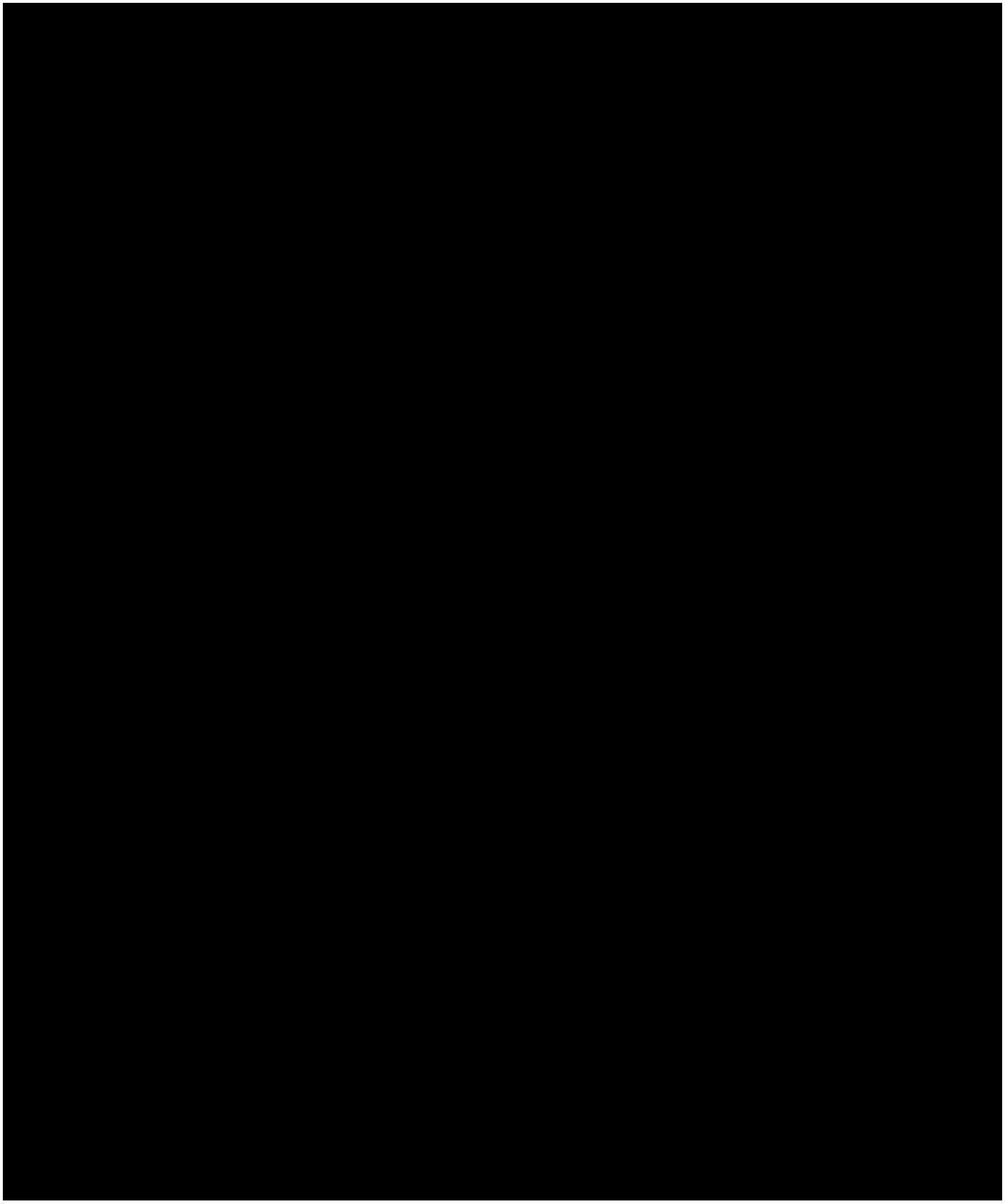
1.2 DRUG PROFILE

Residual Effect Period

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



[redacted]



1.3 RATIONALE FOR PERFORMING THE TRIAL

As described in Section 1.1, the treatment of patients with moderate-to-severe plaque psoriasis 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.

[redacted].

The preceding Phase II Trial 1407-0030 will allow for the investigation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis. Favorable results of 1407-0030 will serve as a PoCC in the treatment of psoriasis, for refinement of Phase III dose selection, and to support further development in other disease indications.

The aim of this extension Trial 1407-0005 is to provide additional safety and efficacy data of up to approximately six years treatment in up to approximately 270 patients treated with BI 730357. The trial is designed to gain long-term safety information to support registration submissions. Furthermore, the study will provide patients with extended access to a potentially beneficial intervention.

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.

No health-related risk is expected from the total planned blood withdrawal over approximately 6 years.

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. Evaluation of BI 730357 dose levels selected for administration in this trial is supported by pre-clinical, as well as clinical safety data from Trial 1407.1 and 1407-0002 (see Section 1.2).

Dose reassignments planned in this trial (refer to Section 3.1) will be contingent on an independent external Data Monitoring Committee (DMC) evaluation of all available data from Phase II Trial 1407-0030 regarding the safety of the dose levels proposed (refer to Section 8.7).

Since preclinical data indicate that BI 730357 has phototoxicity potential, patients in this trial will be advised to apply protection measures as described in Section 4.2.2.2. Solarium radiation, or treatment with ultraviolet light (e.g., PUVA) or use of medication with known phototoxicity potential (e.g., doxycycline) is 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. [redacted] 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 dogs 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.

While there is no precedent clinical data implicating association between [redacted] and important AEs such as Major Adverse Cardiovascular Events (MACE) and Suicidal Ideation and Behaviour (SIB), these AEshave been associated with biological entities targeting PsO and other T[redacted] disease indications. In the interest of ensuring subject safety, these important AEs are to be evaluated throughout the BI 730357 clinical development program, and trial subjects will be proactively screened for SIB in accordance with available regulatory guidance. Thus far no AEs consistent with MACE or SIB have been identified in the clinical program.

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 effects in this study (see Section 5.2.6.1).

Patients with PsO receiving BI 730357 may experience improvement in disease severity. However, this is a newly-developed drug at an early stage of testing, therefore an individual benefit for patients cannot be guaranteed. 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 a DMC evaluation. These risks are considered manageable and outweighed by the potential benefits of the study drug.

As with other immunomodulatory treatments, BI 730357 may potentially increase the risk of infections in patients participating in clinical trials. Therefore, risk mitigation measures (e.g., exclusion of patients with increased risk of infections, close monitoring of adverse events, provision of guidance pertaining to treatment and management of acute infections occurring during the trial) have been included. Any patient with suspected or diagnosed COVID-19 infection should be treated according to standard of care, and interruption of trial medication should be considered.

Patients with the targeted BI 730357 indications may be at greater risk of cardiovascular disease and associated risk factors, comorbidities in which the likelihood of severe illness from COVID-19 may be increased. Patients with evidence of a current or previous disease or medical condition (other than the target indication) that is clinically significant in the opinion of the investigator are excluded from participation in all trials with BI 730357. To prioritize the safety of patients, in areas with significant COVID-19 morbidity, remote visits will be permitted as needed to replace onsite patient visits in these trials. To ensure that patients may safely continue to participate in the clinical trial, remote visits will require, at a minimum, investigator assessment of new and ongoing adverse events, concomitant therapies, and patient compliance with the trial protocol and

study drug. The BI trial team will remain in close contact with the investigator during the execution of a remote visit.

Trial conduct and protocol-defined procedures do not impose additional risk to trial participants. To address potential risks associated with operational aspects related to the participation in clinical trials in the context of the COVID-19 pandemic, different risk mitigation measures are considered, based on local requirements and development of the pandemic.

Recruitment of clinical trials will proceed when it is considered safe to do so in accordance with local public health guidance.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The overall purpose of this extension trial is to assess long-term safety, tolerability, and efficacy of BI 730357 in patients with moderate to severe chronic plaque psoriasis.

2.1.2 Primary endpoint

- The occurance of treatment emergent adverse events (TEAEs)
- up to Week 288.

2.1.3 Secondary endpoints

- Achievement of Psoriasis Area and Severity Index (PASI)50/PASI75/PASI90/ PASI100 at Week 24
- Achievement of Static Physician's Global Assessment (sPGA) clear or almost clear at Week 24
- Achievement of sPGA clear at Week 24
- Time to loss of PASI50/PASI75/PASI90/PASI100 for patients who achieve the response up to Week 288
- Time to loss of sPGA clear or almost clear for patients who achieve the response up to Week 288
- Time to loss of sPGA clear for patients who achieve the response up to Week 288

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

Trial 1407-0005 is a multicentre, long-term extension trial in patients who have completed Phase II PoC/dose-ranging trial 1407-0030 with demonstrated improvement in disease severity and acceptable safety and tolerability of trial drug, as described below. The trial is designed to evaluate long-term safety and efficacy of BI 730357 in patients with moderate-to-severe plaque PsO.

Two groups of patients are to be entered into this trial, including up to (approximately) 180 patients entered in the original trial 1407-0030 protocol (now Part 1) and up to (approximately) 90 patients entered in an extended dose-ranging segment, now Part 2 of the amended trial 1407-0030 protocol. Actual numbers of subjects entering the extension trial are to be determined by response in the preceding study and the number of patients that participate in the extension study.

In the first group (Part 1), patients will be considered eligible to participate in this long-term extension trial upon completing the trial 1407-0030 Week 24 end-of-treatment visit with a ≥PASI50 response. BI 730357 dose levels of up to 200 mg *q.d.*are to be administered under fasting conditions to patients in this group, reflecting the dose levels evaluated during Part 1 of trial 1407-0030.

- Patients entering the extension trial will remain on their blinded BI 730357 dose treatment from the preceding trial until the open label period of 1407-0005 begins at Visit 2/Week 12.
- At Visit 2/Week 12, patients presently assigned to double blind treatment of placebo, 25 mg, 50 mg, and 100 mg will be reassigned to the 100 mg open label dose, and patients presently assigned to the double blind treatment of 200 mg will be reassigned to 200 mg open label dose. Refer to Figure 3.1: 1.

In the second patient group (Part 2), patients will be considered eligible to participate in this trial upon completing the trial 1407-0030 Week 12 end-of-treatment visit with a ≥PASI50 response or perceived patient improvement, at the discretion of the Investigator. Patients are to be considered eligible only if also without ongoing AEs consistent with intolerance of trial medication (including gastric intolerance) that in the opinion of the investigator would compromise the safety of the patient.

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- All patients entering the extension trial are to be assigned at Visit 1 to receive open-label treatment with 400 mg *q.d.* (fed), the anticipated therapeutic BI 730357 dose. Refer to Figure 3.1: 2.

It is expected that Visit 1 of trial 1407-0005 will be performed on the same day of the EOT Visit of trial 1407-0030 in both patient groups. In the event that patients completing Part 2 of trial 1407-0030 are not able to be entered immediately into the extension trial due to administrative reasons (e.g., pending protocol approval, availability of trial medication), Visit 1 of the extension trial may be delayed for no more than 16 weeks.In the event of a delay, the CTM should be consulted and refer to the Flow Chart for procedures to be conducted.

The treatment period is this trial will be approximately 6 years.

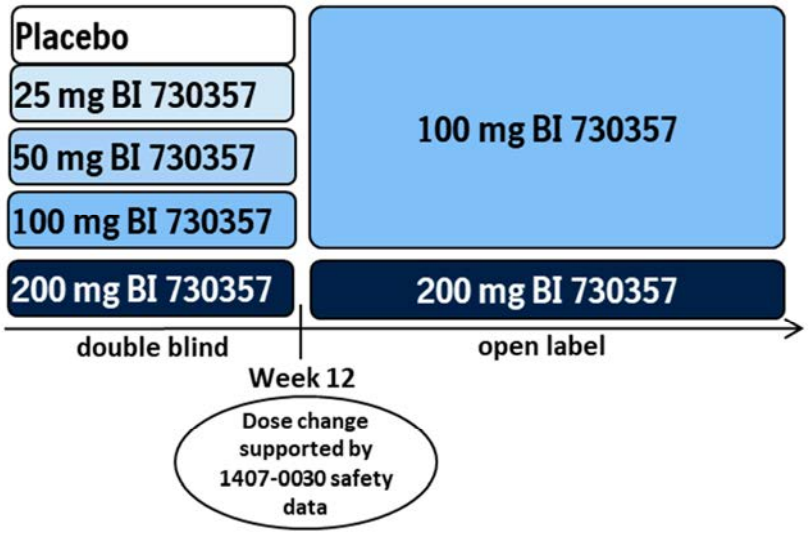

Figure 3.1: 1 Trial 1407-0005 dose assignment/reassignment for patients entering from Part 1 of trial 1407-0030

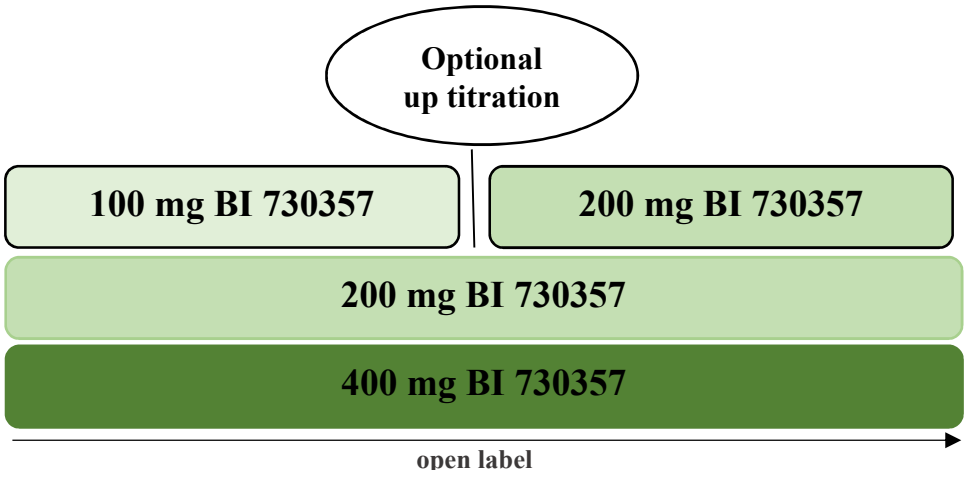

Figure 3.1: 2 Trial 1407-0005 dose assignment for patients entering from Part 2 and continuing from Part 1 of trial 1407-0030

Dose selection at Week 12 is based on the safety and tolerability data from the SRD Trial 1407.1 and the MRD Trial 1407-0002, and will be contingent on DMC evaluation of all available data from Phase II trial 1407-0030. For patients entering from Part 1 of trial 1407-0030, if an unacceptable risk regarding the safety of the 200 mg dose level is reported by the DMC, the open label BI 730357 dose assignments beginning at Week 12, as shown in Figure 3.1: 1, is to be altered to assign all patients to the 100 mg *q.d.* dose group. For additional details and logistics, refer to Section 8.7. Refer to Section 4.1.2 for dose selection rationale.

All patients entering from Part 2 of trial 1407-0030 are to receive the 400 mg *q.d.* dose, as long as no unacceptable risks are identified during Part 2 of trial 1407-0030. Once Part 2 patients begin enrolling in this trial, existing patients receiving 100 mg *q.d.* in this trial will be given the option to titrate up to the 200 mg *q.d.* dose, if the investigator determines that the patients may benefit from the higher dose.

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

Trial 1407-0005 is designed as a long-term extension clinical trial, and is expected to generate additional safety information to support registration submissions. Therefore, the primary endpoint is focused on safety. All patients who complete treatment with BI 730357 or placebo in the preceding Trial 1407-0030 and achieve a PASI50 response at Week 24 of that trial will be invited to participate to receive long-term treatment. Our goal in this study is to obtain additional safety, tolerability and efficacy data following long-term drug administration

For patients entering the extension trial from Part 1 of trial 1407-0030, the 12-week double blind treatment period (refer to Section 3.1) is intended to maintain the blind of the preceding trial while collecting additional data for the doses allocated at EOT in the preceding trial. After DMC review of all available safety data from 1407-0030 (refer to Section 8.7), the dose levels selected for the open label period of the extension trial will be confirmed and the long-term assessment of the 100 mg *q.d.* and 200 mg *q.d.* dose groups will begin at Visit 2/Week 12 (refer to Section 3.1). Visit 2.1 will be conducted by telephone 2 weeks after this transition as a precaution to monitor patient safety. Trial 1407-0005 may include placebo patients who have achieved a PASI 75 at Week 12 of 1407-0030 and a PASI50 at Week 24 of 1407-0030. Patients in this category that have meet these efficacy criteria would also need to be satisfied with their blinded treatment allocation at Week 24 of trial 1407-0030 and therefore selected to continue treatment by participating in the extension study. These patients will begin active treatment of 100 mg BI 730357 at Visit2/Week 12 of the extension study.

Based on safety and efficacy data from Part 1, Part 2 of trial 1407-0030 extends dose ranging of BI 730357 to 400 mg *q.d.* and 200 mg *b.i.d.*, to be administered under fed conditions. Given that PoC efficacy has been demonstrated in Part 1 of trial 1407-0030, in the second patient group, patients are to be considered eligible to participate in 1407-0005 upon completing the trial 1407-0030 Week 12 end-of-treatment visit with ≥50% improvement in PASI50 or perceived patient improvement, at the discretion of the Investigator. Furthermore, given that patients in this group are to receive long-term BI 730357 at a substantially higher dose than in those in the first group, in the interest of safety, patients are to be considered

eligible only if also without ongoing AEs consistent with intolerance of trial medication (including gastric intolerance), that in the opinion of the investigator would compromise the safety of the patient.
. Visits 1.1, 1.2 and 1.3 will be conducted in person for these patients to monitor patient safety, particularly as placebo patients may continue into this trial and receive active drug.

As a trial with an open label period, we realize that no powered or controlled analysis can be done. However, we will be able to evaluate initial tendencies and at the same time permit our early study participants an opportunity to maintain access to a therapy that has the potential to have clinical benefit.

3.3 SELECTION OF TRIAL POPULATION

The trial is intended to provide extended access of BI 730357 to up to approximately 180 male and female patients in Part 1 and approximately 90 patients in Part 2 that complete Trial 1407-0030 at approximately 30 study sites.

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

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

3.3.1 Main diagnosis for trial entry

Patients with moderate-to-severe plaque psoriasis who have completed treatment in the preceding trial.

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

3.3.2 Inclusion criteria

1. 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. Patients with moderate-to-severe plaque PsO who have completed treatment in the preceding trial without early discontinuation, agree to continue treatment in 1407-0005, and

- for patients entering from Part 1 of trial 1407-0030

- achieve a ≥PASI50 response upon completing the trial 1407-0030 Week 24 end-of-treatment visit

- for patients entering from Part 2 of trial 1407-0030
  - achieve a ≥PASI50 response upon completing the trial 1407-0030 Week 12 end-of-treatment visit or perceived patient improvement, at the discretion of the Investigator

3. 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

Having developed any of the following exclusion criteria from the preceding study:

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.
3. Currently enrolled in another investigational device or drug trial or is receiving other investigational treatment(s) (with the exception of 1407-0030).
4. Intake of any restricted medication as specified in Section 4.2.2.1 or any drug considered likely to interfere with the safe conduct of the trial.
5. Any plan to receive a live vaccination during the conduct of the trial.
6. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled.
7. 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.
8. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
9. Any documented active or suspected malignancy, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix.
10. Relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis, and tuberculosis.
11. Evidence of a disease (including known or suspected IBD, 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.
12. 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.

13. Unwillingness to adhere to the rules of UV-light protection as described in Section 4.2.2.2.
14. Ongoing AEs consistent with intolerance of trial medication (including gastric intolerance) from 1407-0030, that in the opinion of the investigator would compromise the safety of the patient.

3.3.4 Withdrawal of patients from treatment or assessments

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

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to undergo the procedures for early treatment discontinuation, follow up, and vital status collection.

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

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and case report form (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 experiences an intolerable increase of PsO, the trial medication will be discontinued and anti-psoriatic agents may be used as rescue medications (refer to Section 4.2.1).
- 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 referred 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, follow up, and vital status collection as outlined in the Flow Chart and Section 6.2.3.

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

If a patient becomes pregnant during a trial, the study medication needs to be discontinued. The patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report (CTR) until last patient visit and any events thereafter will be reported in the BI Pharmacovigilance database.

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial (refer to Section 8.7 for DMC role in this process).
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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. The placebo will only be given until the open label period of the extension trial begins.

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.
Route of administration:	Per os

Substance:	Placebo to match BI 730357 (until open label drug supply is dispensed)
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Not applicable
Posology	q.d.
Route of administration:	Per os

4.1.2 Selection of doses in the trial and dose modifications

The dose range for Part 1 of the preceding trial 1407-0030 was selected on the basis of the preclinical data, and on safety data obtained in first-in-human SRD trial 1407.1 and MRD trial 1407-0002, which respectively demonstrated that single BI 730357 dose levels of up to 800 mg q.d. and multiple dose levels of up to 200 mg q.d. were well tolerated.

For patients entering from Part 1 of trial 1407-0030, BI 730357 doses of 25, 50, 100, and 200 mg q.d. or placebo as assigned in the preceding Trial 1407-0030, will be continued for patients in the extension trial 1407-0005 for the initial 12 week double-blind treatment period. At Visit 2/Week 12 patients will be assigned to either the 100 mg or 200 mg BI 730357 (refer to Section 3.1). This change in treatment assignment will be supported by a DMC review of all available safety data from trial 1407-0030; if an unacceptable risk regarding the safety of the 200 mg dose level is reported by the DMC, a plan has been provided within the protocol for an alternative dosing scheme with all patients assigned to the 100 mg BI 730357 open label treatment dose (refer to Section 8.7). Patients currently enrolled at the 100 mg *q.d.* dose at the time Part 2 begins will have the option of increasing to the 200 mg dose based upon investigator assessment that the increased dose could benefit the patient.

Based on PK-PD modeling developed to describe the concentration and PASI data obtained in Part 1 of trial 1407-0030, Part 2 of 1407-0030 extends dose ranging of BI 730357 to 400 mg *q.d.* and 200 mg *b.i.d.*, to be administered under fed conditions. The target human therapeutic efficacy exposures are currently based on 400 mg administered *q.d.* under fed conditions to patients with moderate-to-severe plaque PsO (P20-07441). Therefore, for patients entering from Part 2 of trial 1407-0030, BI 730357 400 mg *q.d.* is to be administered to all eligible patients.

4.1.3 Method of assigning patients to treatment groups

For patients entering from Part 1 of trial 1407-0030, during visit 1, eligible patients will continue to receive their treatment allocation of BI 730357 received in the preceding study, in a blinded fashion, via Interactive Response Technology (IRT). Upon completion of Visit 2/Week 12 the patients in this extension study will be assigned to an open label BI 730357 dose, via IRT (refer to Section 3.1).

Patients entering from Part 2 of trial 1407-0030 will all be assigned to open label BI 730357 400 mg *q.d.*

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. 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.

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.

Patients will receive four tablets per day from Visit 1 until Visit 2. In Table 4.1.4: 1, the medication schedule for each treatment group is listed for continuation of the double-blind 1407-0030 dose regimen until Visit 2/Week 12.

Upon the start of the open label treatment at Visit 2/Week 12, patients will be reassigned (see Section 3.1) via IRT to either the 100 mg treatment group or the 200 mg treatment group until

the End of Trial Visit. If a safety signal is identified by the DMC, an alternative dosing plan will be followed and all patients will be assigned via IRT to the 100 mg treatment group until the End of Trial Visit (see Section 3.1 and Section 8.7).

Placebo tablets will no longer be administered during the open label period.

Table 4.1.4: 1 Study medication dosing guide

	25 mg/placebo tablet	50 mg/placebo tablet	100 mg/placebo tablet
25 mg treatment group	1 active	1 placebo	2 placebo
50 mg treatment group	1 placebo	1 active	2 placebo
100 mg treatment group	1 placebo	1 placebo	1 active 1 placebo
200 mg treatment group	1 placebo	1 placebo	2 active
400 mg treatment group	0 placebo	0 placebo	4 active
Placebo group	1 placebo	1 placebo	2 placebo

To ensure a dose interval of about 24 hours, the medication should be taken in the morning at approximately the same time every day. 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.

Patients should be instructed not to take their medication on the morning of trial visits as they will be dosed in the clinic.

During the COVID-19 pandemic or other unforeseen situations, physical visits to the sites may need to be restricted to ensure patient's safety. Based on a thorough assessment of the benefits and risks, and consultation with the CTM, the investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Double blind treatment period – Part 1 only

Patients, investigators and everyone involved in trial conduct or analysis will remain blinded with regard to the randomised treatment assignments during the double blind treatment period until Week 12 for each patient. The randomisation code for this trial period will be kept secret by Clinical Trial Support up to database lock of the preceding trial.

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.

Open label period – Part 1 and Part 2
Please refer to Section 3.1 for open label treatment assignment beginning at Week 12 for Part 1 and Day 1 for Part 2 and 3.2 for rationale. In the open label period of this trial, treatment allocation will not be concealed.

4.1.5.2 Unblinding and breaking the code

For the blinded period of this trial, 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 BI's Pharmacovigilance group 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 clinical research organisation (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 storage conditions on the medication label. Where necessary, a temperature log must be maintained for documentation
If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

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 protocol 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 Clinical Monitor Local (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. Refer to Section 6.2.3 for early treatment and trial termination instructions.

In case of any 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 electronic case report form (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 CML. 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 a mental health professional for further 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 and the patient is undergoing early treatment and trial termination. 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 antipsoriatic medications, concomitant treatments 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 in preceding study until EOO in this study
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 CYP2B6, or CYP2C8 , CYP2C9, or CYP2C19.	One week prior to randomisation in preceding study until EOO in this study
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 in preceding study through EOO in this study
Investigational device or product (other than antipsoriatic drugs)	30 days prior to randomisationin preceding study through EOO in this study
Any drug known to interfere with or to aggravate PsO including but not limited to lithium and interferons	4 weeks prior to randomisation in preceding study through EOO in this study
BCG (Bacillus Calmette-Guérin) vaccine	1 year prior to randomisation in preceding study through 1 year after last administration of study drug in this study
Investigational antipsoriatic drugs	12 weeks prior to randomisation in preceding study through EOO in this study
[redacted]	[redacted]
[redacted]	[redacted]
Systemic anti-psoriatic medications or phototherapy	12 weeks prior to randomisation in preceding through EOO in this study
Other systemic immunomodulating treatments (e.g. methotrexate, cyclosporine A, corticosteroids[1]), apremilast (Otezla®1,cyclophosphamide, tofacitinib (Xeljanz)) [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).	30 days prior to randomisation in preceding through EOO in this study
Other systemic psoriasis treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis)	30 days prior to randomisation in preceding through EOO in this study
Photochemotherapy (e.g., PUVA)	30 days prior to randomisation in preceding through EOO in this study
Phototherapy (e.g., UVA, UVB)	2 weeks prior to randomisation in preceding through EOO in this study

Table 4.2.2.1: 1 (cont.) Restricted antipsoriatic medications, concomitant treatments and food cont'd

Medication or class of medications	Specified restriction time
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) [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 where PASI is assessed	2 weeks prior to randomisation in preceding through EOO in this study

4.2.2.2 Restrictions on diet and life style

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

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.

Throughout their participation in the study, patients should avoid prolonged exposure to sunlight and 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 sunglasses 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.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.2) must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 28 days after the last dose of study drug.

Highly effective methods include:

- 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 WOCBP 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 Clinical Research Associate (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. [redacted]

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of body weight will be performed at the time points specified in the Flow Chart.

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, 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. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling time points please see the Flow Chart.

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

Blood samples for safety will be drawn prior to drug administration, under fasted conditions.

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 adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF or

Electronic Data Capture (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
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

[1] Only at Visit 1, Visit 5, Visit 9, Visit 13, Visit 17, Visit 21 and EOT Visit

Table 5.2.3: 1 Safety laboratory tests Cont'd

Category	Test name
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)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis with microscopic examination if urine analysis abnormal	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine Blood Urine Leukocyte Esterase Urine pH
Urine	Albumin (quantitative) Creatinine
Infection testing	Hepatitis B Surface Antigen (qualitative)[1] Hepatitis C Antibodies (qualitative)[1] HIV-1 and HIV-2 Antibody (qualitative)[1] QuantiFERON®-TB[1]

[1] Only at Visit 1, Visit 5, Visit 9, Visit 13, Visit 17, Visit 21 and EOT Visit

5.2.4 Electrocardiogram

ECGs will be read and evaluated centrally. The 12-lead ECGs will be recorded as scheduled in the Flow Chart. 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 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 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 was administered at Visit 1 of 1407-0030 (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 of that trial. The lifetime and past year history of suicidal ideation and behavior was also recorded in 1407-0030.

After the screening visit, the assessment 'since last visit' version was performed at each visit of 1407-0030 and will be administered at each visit of this extension trial. 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 Adverse Event (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 Cardiovascular 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 MACE. See Section 8.7.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation,
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based 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.

5.2.6.1.3 AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the 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, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

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

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

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

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

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 AESI to ensure timely characterization, monitoring and reporting of any such events in this study.

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

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by [redacted] (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

5.2.6.1.6 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 reduced).

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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

- From signing the informed consent onwards until the individual 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 new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.

Vital Status Collection

Patients who discontinue trial medication prematurely, who agree to be contacted further but do not agree to physical visits, 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 the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions,

the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

5.2.6.2.3 Information required

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.4 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.

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]

5.5 BIOBANKING

Section not applicable.

5.6 OTHER ASSESSMENTS

Section not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial 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.

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 patients are to adhere to the visit schedule as specified in the Flow Chart. 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 and the respective protocol sections. Additional details on procedures at selected visits are provided below.

During COVID-19 or other exceptional circumstances, when it is impossible to conduct study visits at the study site, the study visit may be performed at the patient's home or remotely (via telephone and/or internet based means of communication or by use of a home health nurse). The visit may also be performed as a hybrid of home and remote visit. All home/remote visits need to be discussed with and approved by the CTM. Local regulatory and legal requirements of the participating country still apply.

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents a clinically relevant safety issue as an adverse event. Use of a local lab must first be approved by the CTM.

All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data

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:

(1) PSS
[redacted]

The C-SSRS will be administered for eligibility confirmation and at all visits for assessment of suicidality (cf. Section 5.2.5.1).

6.2.1 Screening period

No trial procedures should be done unless the patient has consented to taking part in the trial. Once consented, the patient 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.

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 patients 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.

6.2.2 Treatment period

The treatment period starts with Visit 1 and ends with the EOT visit. The patients will be fasted for each visit.

The patients will return to the clinic for regularly scheduled visits as specified in the Flow Chart. 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, vital signs, and ECG
- Laboratory samples

All assessments must be performed before the medication is taken.

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.

Early treatment and trial termination

If study medication is discontinued prior to the planned Flow Chart End of Treatment (EOT) Visit, the patient should undergo the EOT Visit as soon as possible and the End of Observation (EOO) Visit 4 weeks after last dose of study medication.

Vital status should be collected once a year by telephone call starting from the last trial visit performed until the end of the originally planned observation period.

Trial completion

Patients who finish the treatment period will return to the clinic for EOT Visit. Trial completion is defined as patients having reached the EOT visit within the specified window per the Flow Chart.

Patients switching to licensed BI 730357 upon completion of active treatment in this study should not complete a washout period. Instead, their last trial visit will be EOT and trial completion will occur at that visit. These patients will not return for EOO Visit.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an extension trial of patients with moderate to severe chronic plaque psoriasis treated with BI 730357 after participation in preceding Trial 1407-0030. Descriptive statistics include exposure adjusted rate of patients reporting a TEAE, responder analysis (e.g., achievement of PASI75, sPGA of clear or almost clear, etc.), and time to loss of response (e.g. achievement of PASI75, sPGA of clear or almost clear, etc.).

This trial is designed to gain as much exposure as possible with adequate documentation of safety, efficacy, and tolerability.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no formal statistical hypothesis testing in this trial.

7.3 PLANNED ANALYSES

The descriptive analyses will be based on cumulative event incidence rates at critical timepoint, proportions of patients achieving a response (e.g., achieving PASI75, sPGA of clear or almost clear, etc.), and Kaplan Meier empirical survival curves to describe patterns of event incidence.

The treated set (TS) in this trial for analyses is defined as:

- All patients who received at least one dose of treatment in the extension trial. It will be the main analysis set for presentation of safety and efficacy of the extension trial.

Further analysis sets will be defined in the TSAP if necessary.

For all analyses, baseline refers to the baseline value in the 1407-0030 study.

7.3.1 Primary endpoint analyses

Refer to Section 7.3.4 for the description of safety analyses including that for the primary endpoint.

7.3.2 Secondary endpoint analyses

The rate of achievement of PASI50/PASI75/PASI90/PASI100 at Week 24 in the extended dosing period will be calculated. The same methods will be used to analyse other binary secondary endpoints, including achievement of sPGA clear or almost clear, sPGA clear. Time to loss of response (e.g. PASI75, sPGA of clear or almost clear, etc.) will be analysed descriptively by Kaplan Meier curves.

Additional information on these analyses will be provided in the TSAP.

[redacted]

7.3.4 Safety analyses

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

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

Exposure-adjusted adverse event incidence rates (per the primary endpoint) will be calculated using the following approach:

- The incidence rate (per 100 subject years) of a selected adverse event (also known as the incidence density rate or person-time incidence rate) is defined as the number of subjects experiencing the adverse event per treatment group during the time at risk divided by the total time of subjects at risk in that treatment group to contribute an event to the analysis multiplied by 100 (per 100 subject years), where:

  Time at risk [subject years] = (date of onset of AE – study drug start date + 1) / 365.25

  If, for a subject, no treatment emergent adverse event occurred, then the time at risk will be censored at the minimum of (date of death; drug stop date + 28 days; last contact date).
  For each AE, the incidence rate will therefore be calculated as:

  Incidence rate [per 100 subject years (pt-yrs)] = 100 * number of subjects with TEAE / Total TEAE-specific time at risk [subject years].

Exact 95% confidence intervals (CI) around the observed AE incidence rate will also be provided.

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

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

No interim analysis is planned. DMC will be in place with tasks as described in Section 8.7. Additionally, the efficacy analysis may be conducted by visit while the data collection for selected other analyses is still ongoing.

7.5 HANDLING OF MISSING DATA

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

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

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

7.6 RANDOMISATION

There is no randomisation for this trial. The participants in this extension trial will be assigned with pre-specified treatment regimen and doses of BI 730357 as specified in Section 3.1.

7.7 DETERMINATION OF SAMPLE SIZE

The sample size will be up to approximately 270 patients. It will be determined by patients who have completed the randomized treatment period without early treatment discontinuation in 1407-0030 and are willing and able to continue treatment in this extension trial. Patients in the subsequent Psoriasis trials are expected to enroll in this extension trial, if applicable.

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

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

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the 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 the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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.

Copies of source documents necessary for adjudication assessment will be provided to the vendor upon request. Before sending or uploading those copies, 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.

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 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.

Remote source data verification is acceptable in rare cases where onsite monitoring visits cannot take place due to the COVID-19 pandemic or other unforeseen circumstances. Remote source data verification must first be approved by the CTM and must be aligned with local laws and regulations.

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 in Section 8.7.

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

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

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

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

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external 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

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 Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **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. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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 and efficacy data of the trial. 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.

Part 1

Prior to the first patient advancing to the open label phase of 1407-0005, the DMC will review all available 1407-0030 safety data. The review will include data from a large fraction of patients that have completed Week 4, as well as, any patient safety data available beyond Week 4. The DMC will evaluate the safety of the 100 mg and 200 mg dose levels proposed for the open label period and provide a recommendation regarding the acceptability of proceeding with these doses. After this review, the DMC will continue to review the accumulating safety data on an ongoing basis. Details are specified in a charter.

If an unacceptable risk regarding the safety of the 200 mg dose level is reported by the DMC, the 100 mg and 200 mg BI 730357 dose groups planned for the open label treatment period will be changed to have all patients receive the 100 mg dose (Refer to Section 3.1). If this alternative dosing scheme is required to be implemented due to identification of a safety signal, investigators will be informed by written communication from the Team Member Medicine and Clinical Trial Leader prior to the first patient reaching Week 12 in 1407-0005. IRT will be used to directly implement the changed dosing assignment and will require no additional actions by investigators or site staff.

Part 2

If an unacceptable risk regarding the safety of the 400 mg dose level is reported by the DMC prior to or during the implementation of Part 2, then Part 2 dosing may be amended as required. If any changes to Part 2 are required due to identification of a safety signal, investigators will be informed by written communication from the Team Member Medicine and Clinical Trial Leader.

During the conduct of the trial, the DMC will continue to review the accumulating safety data on an ongoing basis. Details 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 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) (R15-5200). 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:

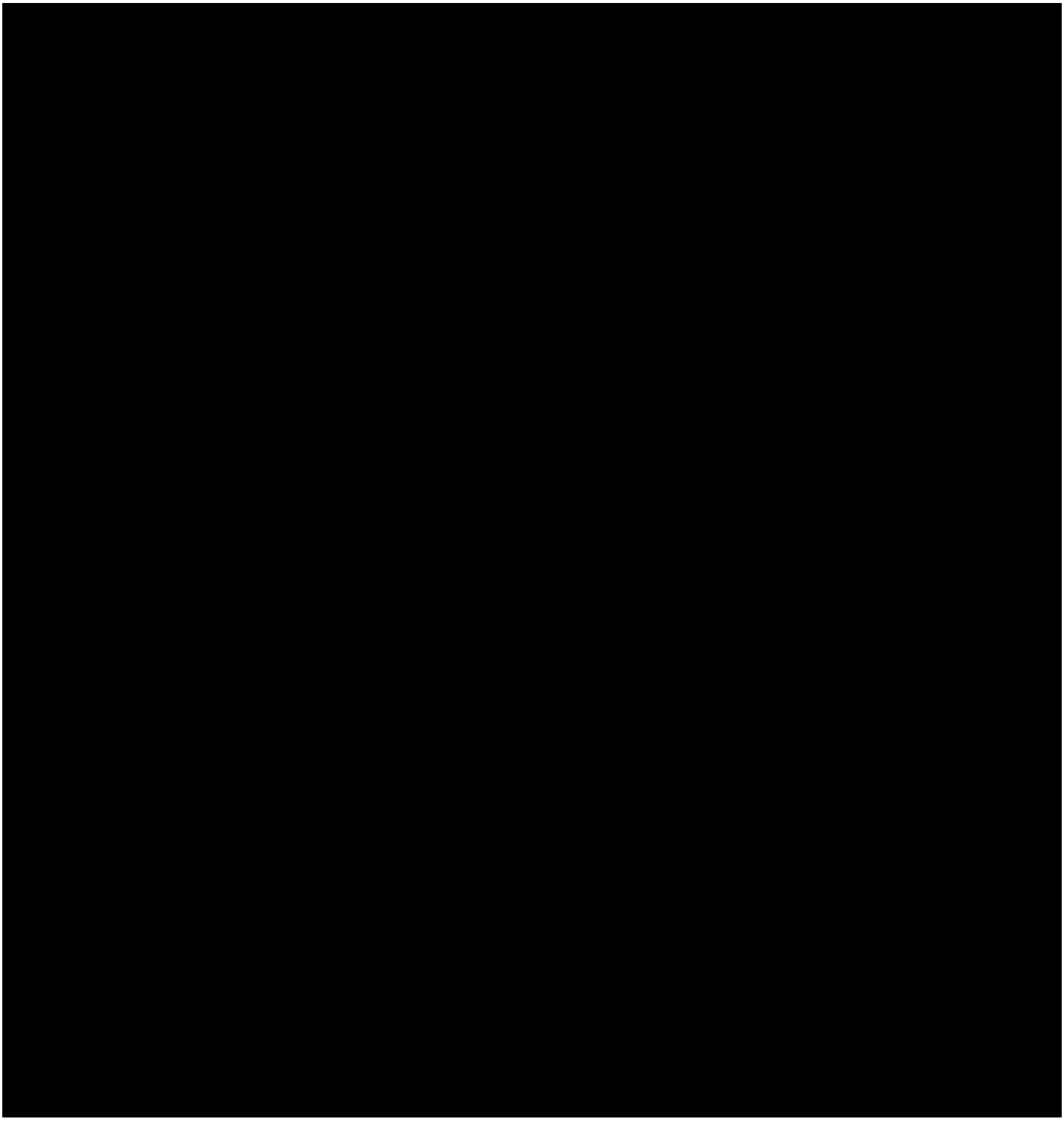
Clear	0 = 0 for all three
Almost clear	1 = mean >0, <1.5
Mild	2 = mean >= 1.5, <2.5
Moderate	3 = mean >= 2.5, <3.5
Severe	4 = mean >= 3.5

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
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

[redacted]

[redacted]



11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		21 May 2019
EudraCT number **EU number**		2018-003487-31
BI Trial number		1407-0005
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II long-term extension study to assess the 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	Title page Synopsis	Coordinating Investigator Coordinating Investigator
Description of change		Updated address.
Rationale for change		Correction.
Section to be changed	Synopsis 3.3.2 4.2.2.3 5.2.6.2.4	Main in- and exclusion criteria Inclusion criteria Contraception requirements Pregnancy
Description of change		Removed the requirement for contraception in male study participants and use of a barrier method. Aligned impacted sections.
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	1.2 1.4	Drug profile 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	4.2.1 5.2.6.1.4	Other treatments and emergency procedures Adverse events of special interest
Description of change		"Mycobacterium tuberculosis" replaced by "all mycobacterial infections".
Rationale for change		To include and cover a more complete picture of opportunistic infections in the definition.
Section to be changed	4.2.2.1	Restrictions regarding concomitant treatment
Description of change		Revisions to table 4.2.2.1:1. CYP3A4 substrates deleted from the list of restricted medications. Additional details and examples added.
Rationale for change		No drug-drug interactions of CYP3A4 substrates are to be expected and text added for clarification.
Section to be changed	4.2.2.2	Restrictions on diet and life style
Description of change		Rephrased fasting instructions.
Rationale for change		For clarification.
Section to be changed	5.2.1	Physical examination
Description of change		Removed height.
Rationale for change		Height is not measured per trial flow chart.
Section to be changed	6.2.2	Treatment period
Description of change		Removed unnecessary ordering of assessments.
Rationale for change		ECG may be performed in any order with the other assessments it is grouped with.
Section to be changed	1.2 7.3.4	Drug profile 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.
Section to be changed	1.4 3.1 3.1: 1 3.2 4.1.2 8.7	Benefit-risk assessment Overall trial design and plan Dose assignment in extension Trial 1407-0005 Discussion of trial design Selection of doses in the trial Administrative structure of the trial

Description of change		Details added and refined regarding the timing and process for DMC review of 1407-0030 data prior to the start of open label dosing in 1407-0005.
Rationale for change		DMC oversight wording revised to align with the charter.
Section to be changed	1.2 1.4 4.2.2.2 5.2.3 5.2.5.1 5.2.5.2 5.3.4 8.7	Drug profile Benefit – risk assessment Restrictions on diet and life style Safety laboratory parameters Suicidality Major adverse cardiovascular event (MACE) Pharmacokinetic – pharmacodynamic relationship Administrative structure of the trial
Description of change		Linguistic and stylistic errors corrected.
Rationale for change		Improved readability.

11.2 GLOBAL AMENDMENT 2

Date of amendment		04 Jun 2019
EudraCT number **EU number**		2018-003487-31
BI Trial number		1407-0005
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II long-term extension study to assess the 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	Title page	Version and date
Description of change		No changes to the content of the protocol have been made between Version 2.0 and 3.0.
Rationale for change		Technical update due to errors in the signature process for Version 2.0.

11.3 GLOBAL AMENDMENT 3

Date of amendment		06 Oct 2020
EudraCT number **EU number**		2018-003487-31
BI Trial number		1407-0005
BI Investigational Product(s)		BI 730357
Title of protocol		Phase II long-term extension study to assess the 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	Title Page and synopsis	Title Page and synopsis
Description of change		Change title from Clinical Trial Monitor to Trial Clinical Monitor and change name
Rationale for change		New standard title and new monitor assigned.
Section to be changed	Synopsis	Synopsis
Description of change		Add description of Part 1 and 2. Add information describing Part 2 throughout synopsis. Updated number of patients to add Part 2. Changed wording for primary endpoint. Added exclusion criterion for ongoing drug related adverse events from 1407-0030.
Rationale for change		Adding Part 2 to align with the addition of Part 2 to trial 1407-0030 and allow those patients to roll over to this trial.

Section to be changed	Flow Chart	Flow Chart
Description of change		Add Visits 1.1, 1.2 and 1.3 for Part 2 patients and clarification that Visit 2.1 is unchanged for Part 1 patients and not applicable for Part 2 patients. Add an allowable administrative delay for Part 2 patients at Visit 1.
Rationale for change		Additional safety information to be collected during first 12 weeks for patients in Part 2 to ensure safety of placebo patients from 1407-0030 rolling over and starting at the 400 mg q.d. dose.

Section to be changed	1.1	Medical Background
Description of change		Add updated psoriasis background information and new reference, remove old reference.
Rationale for change		To provide most recent available information.
Section to be changed	1.2	Drug Profile
Description of change		Data from non-clinical and toxicology studies has been updated, including the addition of gastritis finding in dogs. Data from clinical studies has been updated to replace interim results from Phase 1 trials with final results and add interim results from ongoing Trial 1407-0030.
Rationale for change		To provide most recent available information and align with current IB.
Section to be changed	1.3	Rationale for performing the trial
Description of change		Update the rationale to include information regarding Part 2.
Rationale for change		Provide information on the rationale for Part 2 dosing and design.
Section to be changed	1.4	Benefit-Risk Assessment
Description of change		Added text on AESI of gastric intolerance or gastritis. Information on DDI potential and malignancy has been updated. Information regarding potential Cyp3A interactions has been updated.
Rationale for change		To provide background on why gastric AEs are added to AESIs. To reflect the latest results from DDI and toxicology trials.
Section to be changed	2.1.2	Primary Endpoint
Description of change		Changed wording for primary endpoint.
Rationale for change		The definition of ‘an endpoint’ should be at individual level at one particular time point, and to make the wording consistent across protocols in the project.
Section to be changed	3.1 3.2 3.3	Overall trial design and plan Discussion of trial design, including the choice of control groups Selection of trial population
Description of change		Updated to describe original patient population

		as Part 1 and add new patient population as Part 2. Describe the design and dosing paradigm for Part 2.
Rationale for change		Adding Part 2 to align with the addition of Part 2 to trial 1407-0030 and allow those patients to roll over to this trial.
Section to be changed	3.3.2	Inclusion criteria
Description of change		Add criteria for Part 2 patients to roll over from 1407-0030 trial to this trial.
Rationale for change		Adding Part 2 to align with the addition of Part 2 to trial 1407-0030 and allow those patients to roll over to this trial.
Section to be changed	3.3.3	Exclusion criteria
Description of change		Remove candidiasis as an exclusion and add exclusion for ongoing drug related AEs.
Rationale for change		Candidiases is no longer considered an exclusion for BI 730357 and safety concern with drug related AEs over long term treatment. Added exclusion criterion for ongoing drug related adverse events from 1407-0030.
Section to be changed	4.1.2 4.1.3 4.1.4 4.1.5	Selection of doses in the trial and dose modifications Method of assigning patients to treatment groups Drug assignment and administration of doses Blinding
Description of change		Updated to describe original patient population as Part 1 and add new patient population as Part 2. Describe the design and dosing paradigm for Part 2. Add option to allow patients from Part 1 on 100 mg dose to up-titrate to 200 mg dose.
Rationale for change		Adding Part 2 to align with the addition of Part 2 to trial 1407-0030 and allow those patients to roll over to this trial. Data from 1407-0030 trial indicates 100 mg dose is sub-optimal.
Section to be changed	4.1.4	Drug assignment and administration of doses
Description of change		Added language to 4.1.4 regarding options for limiting physical visits if needed due to Covid 19.

Rationale for change		Provide guidance to investigators to manage visit disruptions due to Covid 19.
Section to be changed	4.2.2.1	Restrictions regarding concomitant treatment
Description of change		Updated text to align with new DDI data..
Rationale for change		To ensure restrictions are current.
Section to be changed	5.2.3	Safety laboratory parameters
Description of change		Removed urine sediment as separate section, add to description of urinalysis. Update Urine RBC and WBC description
Rationale for change		Updated to correspond to current central laboratory standard tests and reporting.
Section to be changed	5.2.6.1:4	Adverse events of special interest.
Description of change		AE consistent with gastric intolerance or gastritis are designated as AESI.
Rationale for change		To ensure timely characterisation, monitoring and reporting of such effects.
Section to be changed	6.1	Visit schedule
Description of change		Add language to allow modifications to visits in response to Covid-19.
Rationale for change		Allow flexibility to monitor patient status during Covid 19 if in person visits are not possible.
Section to be changed	8.3.2	Direct access to source data and documents
Description of change		Add language regarding remote source data verification.
Rationale for change		Remote source data verification now permitted in certain circumstances.
Section to be changed	8.7	Administrative structure of the trial
Description of change		Add information regarding DMC review of Part 2.
Rationale for change		Adding Part 2 to align with the addition of Part 2 to trial 1407-0030 and allow those patients to roll over to this trial.
Section to be changed	9.1	Published references
Description of change		Add reference P20-07441 and delete reference R11-1259.
Rationale for change		To add new reference used in text and remove reference it replaced.
Section to be changed	9.2	Unpublished References

Description of change		Reference DSUR s00083382-01 added.
Rationale for change		To add new reference used in added text.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	07 Oct 2020 18:18 CEST
Author-Clinical Pharmacokineticist		08 Oct 2020 15:31 CEST
Approval-Biostatistics		08 Oct 2020 23:52 CEST
Approval-Therapeutic Area [redacted]		09 Oct 2020 15:48 CEST
Approval-Team Member Medicine		09 Oct 2020 23:03 CEST
Verification-Paper Signature Completion		12 Oct 2020 14:34 CEST

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