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

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

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

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

[5] Only for patients with psoriatic arthritis

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

[7] Dermatology Life Quality Index

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

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

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

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

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

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

[redacted]

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

Part 2:

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

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

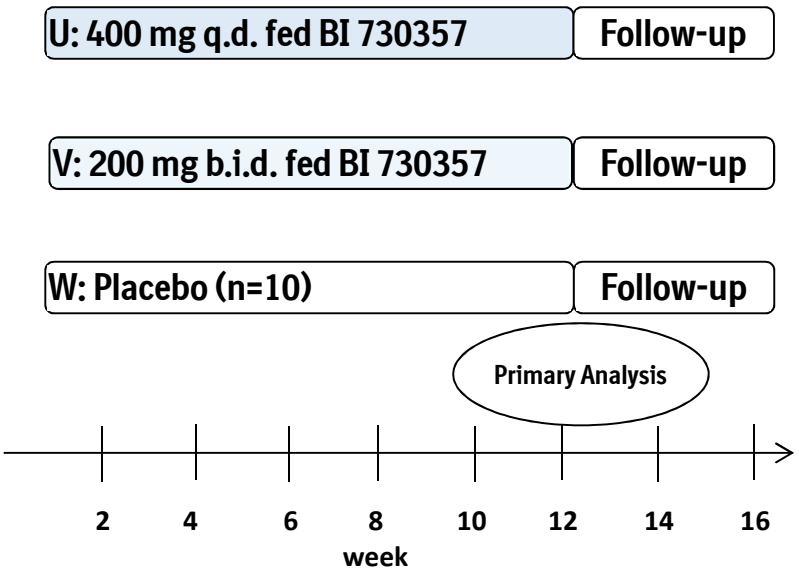


Figure 3.1: 2 Trial Design, part 2

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

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

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

[redacted]

3.3 SELECTION OF TRIAL POPULATION

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

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

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

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

3.3.1 Main diagnosis for trial entry

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

3.3.2 Inclusion criteria

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

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

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

3.3.3 Exclusion criteria

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

and explain the options for continued follow up after withdrawal from trial treatment. Please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

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

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

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

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

Table 5.2.3: 1 Safety laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c)[1] Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leucocytes Platelet Count/ Thrombocytes Immunophenotyping of T cell subsets[1]
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Amylase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate

AEs considered "Always Serious"

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

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

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

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class.

AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs:

Hepatic injury

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

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

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

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

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

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

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

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

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

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

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

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

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

In Part 2, no skin photos will be taken.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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

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

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All subjects are to adhere to the visit schedule as specified in the FLOW CHART, Part 1 and FLOW CHART, Part 2. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Study procedures to be performed at each visit are listed in the FLOW CHART, Part 1 and FLOW CHART, Part 2 and the respective protocol sections. Additional details on procedures at selected visits are provided below.

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

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

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

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

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

6.2.1 Screening period

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

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

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

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

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

All subsequent visits should be scheduled.

6.2.2 Treatment period

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

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

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

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

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

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

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

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

7.3.1 Primary endpoint analyses

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

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

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

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

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

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

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

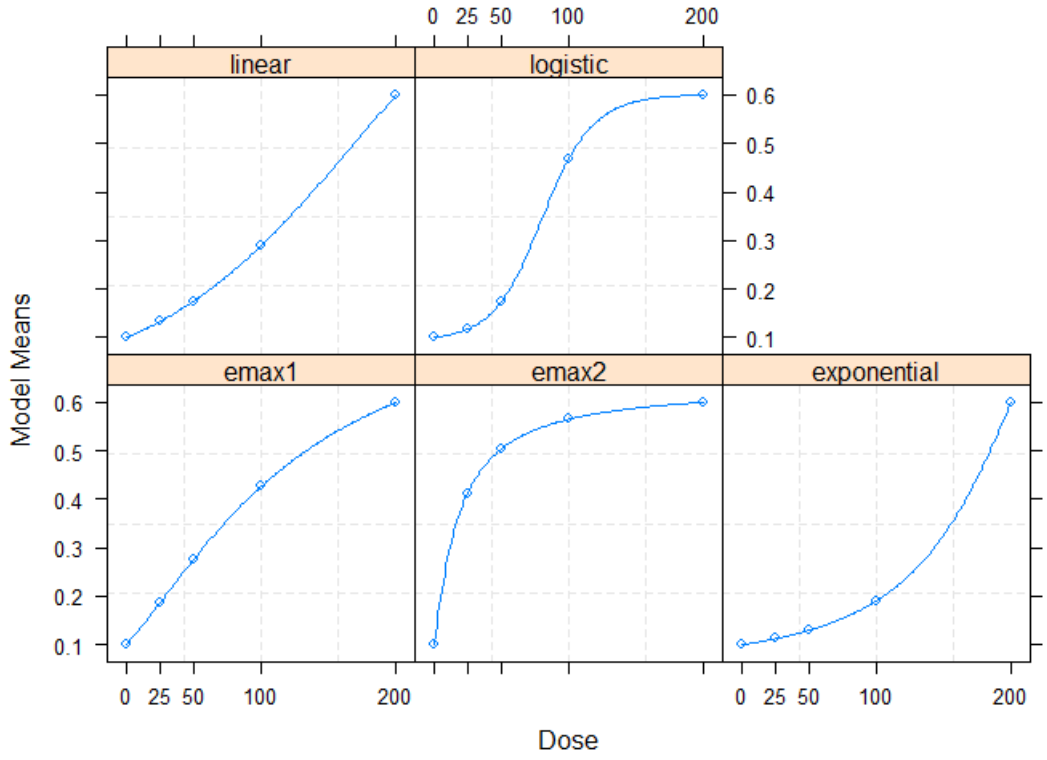


Figure 7.3.1: 1 Shape of the models within the candidate set

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

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

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

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

start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

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

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

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

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

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

FLOW CHART, PART 2

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

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

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

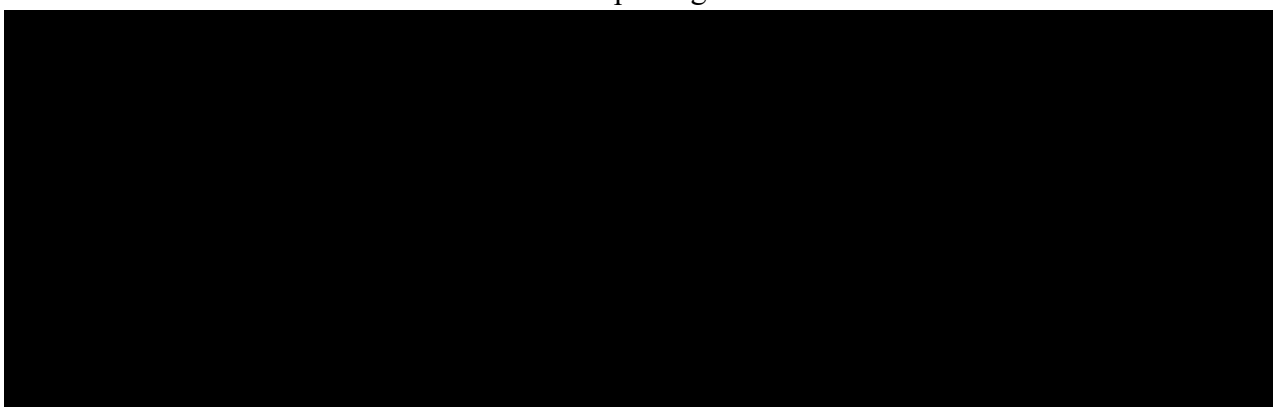
Visits	Week	Day	Time Relative to morning BI 730357 Dosing	Blood sampling for PK
2, 3, 4, 5, 6, 7, EoT	1, 2, 4, 8, 12	1, 4, 8, 15, 29, 57, 84	- 90 to - 5 minutes before start of morning dosing	X
2, 5, EoT	1, 2, 12	1, 15, 84	15 minutes to 1 hour after morning dose	X
2, 5, EoT	1, 2, 12	1, 15, 84	1:30 to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

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

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

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

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



1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Plaque psoriasis (PsO) is a chronic skin disease characterized by raised, well-demarcated, oval erythematous plaques covered in adherent silvery scale (R11-1257). Lesions are typically painful and/or itchy, and can be associated with a high degree of morbidity. PsO can affect extensive areas of skin; disease severity is in fact defined by body surface area (BSA) as mild (<3%), moderate (3-10%), and severe (>10%) (P20-07441). Approximately 25% of patients are classified as having moderate-to-severe disease. Disease severity correlates inversely with quality of life, as reported by patients with regard to symptom severity and disease impact on functionality and socialization (R16-4115, R11-1260, R03-1208, R16-3072). Plaques on visible skin (e.g., scalp, face, hands) have particular impact on physical, sexual, psychosocial, and even economic status; disease severity is associated with reduced levels of employment and income (R16-3072). PsO is more than a superficial disease, with 30% of patients having joint involvement, and a high correlation between PsO and obesity, diabetes, depression, metabolic syndrome, and cardiovascular risk (R16-4115).

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

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

Mainstays of therapy for the treatment of PsO include topical agents, ultraviolet light-based therapies, traditional systemic agents (e.g., methotrexate, acitretin, cyclosporine), and more recently, targeted biologic and small-molecule therapies. Steroidal and non-steroidal topical agents (e.g., vitamin D analogues, retinoids, tar, anthralin, salicylic acid, tacrolimus) are efficacious, particularly for mild-to-moderate disease, but typically require long-term administration, and often provide only incomplete clearance. Long-term adherence to topically-prescribed therapies is often poor, and systemic absorption limits long-term usage

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

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

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

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 730357 and Placebo to match BI 730357.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1:

Substance:	BI 730357
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	25 mg, 50 mg, 100 mg
Posology	q.d. or b.i.d.
Route of administration:	Per os

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

4.1.2 Selection of doses in the trial

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

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

Table 5.2.3: 1 Safety laboratory tests cont.

Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (reflex in case of elevated CK) Albumin C-Reactive Protein (CRP, High sensitivity) Cholesterol, total[1] Triglycerides[1] LDL-Cholesterol /HDL-Cholesterol[1]
Urine Pregnancy test (only for female patients of childbearing potential - test done in clinic)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential) at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH, (free T3 and T4 in case of abnormal TSH)
Autoantibodies (only at screening)	Rheumatoid Factor
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leucocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine	Albumin (quantitative) Creatinine
Infections screening (only at the screening visit)	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative)[2] HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB

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

5.2.4 Electrocardiogram

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

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

Severe infections (according to RCTC grading)

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

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

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

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

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

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

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

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.

[redacted]

6.2.3 Follow up period and trial completion

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

6.2.3.1 Early treatment and trial termination:

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

6.2.3.2 Trial completion

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

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

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

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

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

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

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

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

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

[redacted]

7.4 INTERIM ANALYSES

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

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

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

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

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

7.5 HANDLING OF MISSING DATA

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

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

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

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

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

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

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

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

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

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