TRIAL STATISTICAL ANALYSIS PLAN

c35126725-01

BI Trial No.:	1407-0005
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
Investigational Product(s):	BI 730357
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	03 MAR 2021 SIGNED
Version:	1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
CTC	Common Terminology Criteria
CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management And Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
EDC	Electronic Data Capture
EMEA	European Agency For The Evaluation Of Medicinal Products
FAS	Full Analysis Set
ICH	International Conference On Harmonisation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
PK	Pharmacokinetics
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
PV	Protocol Violation
RPM	Report Planning Meeting
Q1	Lower Quartile
Q3	Upper Quartile
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
TESS	Treatment Emergent Signs And Symptoms
ToC	Table of Contents
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There were no changes to the statistical analyses proposed in the study protocol.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to Week 288.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol

5.2.2 Secondary endpoint(s)

- 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

Details for scoring Psoriasis Area and Severity Index (PASI) and static physician global assessment are described in Section 10.1 and 10.2 of the CTP. The percent reduction from baseline is calculated by % PASI reduction from baseline = ((PASI at baseline - PASI at Visit X) / PASI at baseline) * 100, at all follow up visits. Achieving an X% or larger reduction from baseline PASI score is denoted as PASIX.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

All patients need to complete the preceding Phase II psoriasis Trial 1407-0030 and meet entry criteria for this study.

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 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.

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.

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.

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.

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

Figure 6.1: 1 Trial 1407-0005 dose assignment/reassignment for patients entering from Part 1 of trial 1407-0030

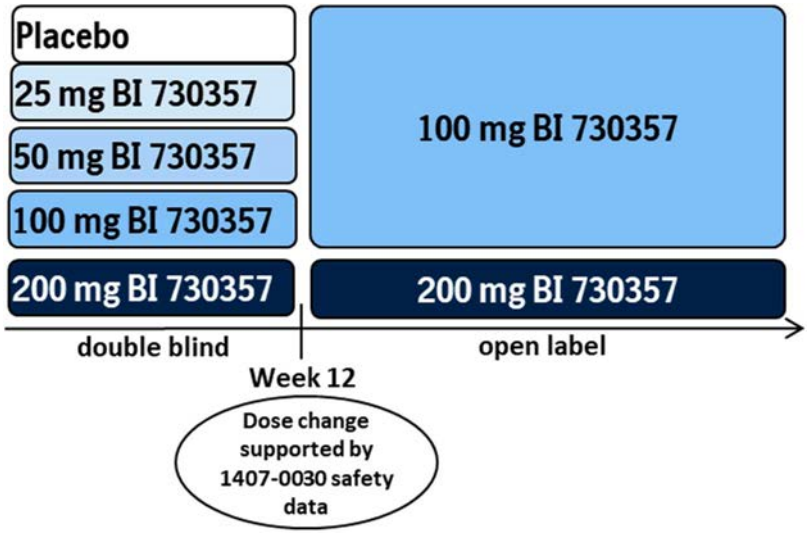
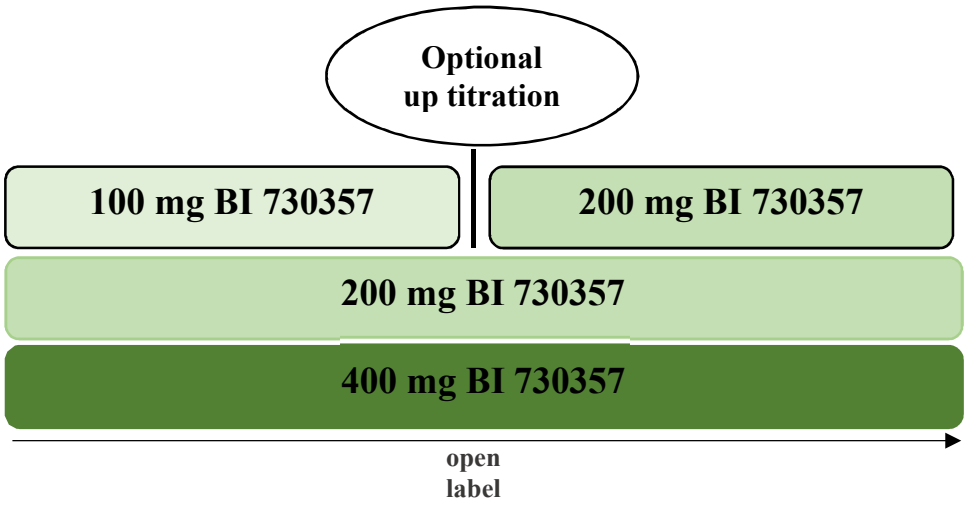


Figure 6.1: 2 Trial 1407-0005 dose assignment for patients entering from Part 2 and continuing from Part 1 of trial 1407-0030



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, is to be altered to assign all patients to the 100 mg *q.d.* dose group.

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 g *q.d.* dose, if the investigator determines that the Patients may benefit from the higher dose.

The first Part 2 patients enrolled in this study on December 10, 2020 and at that time all Part 1 patients had been in the study more than 12 weeks and had titrated to 100 mg q.d.

Subjects will be analyzed according to the treatment to which they were treated. The following study periods based on actual start and stop dates of study treatment administration are defined as follow.

Table 6.1: 1 Definition of Treatment Periods

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening[#]	NA	NA
On-treatment*	Date/Time of the first administration of trial treatment	Date of the last administration of trial treatment + REP
Follow-up	Date of the last administration of trial treatment + REP+1 day	Date of the last per protocol visit

Patients in the 1407-0030 trial that fulfil the criteria for rollover will be asked to participate in this extension trial. Upon their agreement, they will immediately enter the treatment phase. Therefore, no screening period is defined in this trial.
* Within the On-treatment period, it can be divided into Period 1 (first 12 weeks) and Period 2 (after 12 weeks) for patients from part 1 of the 1407-0030 trial.

For the main safety analyses, Adverse Events (AEs) for patients who rolled over from Part 1 of trial 1407-0030 will be classified to one of the following time periods: “first 12 weeks of treatment”, “second treatment period”, or “follow up”. Section 7.3.4 of the protocol specifies that, all AEs and laboratory assessments with an onset between start of treatment and end of the residual effect period (REP), a period of 7 days after the last dose of trial medication for this trial, will be assigned to the “on-treatment” period for evaluation.

Detailed rules for assigning AEs to these time periods based on the onset dates of the AEs for patients who rolled over from Part 1 of the 1407-0030 trial are listed below (such AEs will be classified as new-onset TEAEs):

- If date of Start of Treatment visit in trial (1407-0005) ≤ AE onset date < date of first intake after week 12 re-assignment, then the AE is assigned to “first 12 weeks of treatment”.
  If an AE occurs on the day of week 12 visit, actual time between AE onset and study medication taken will be compared to determine AE time period (first 12 weeks, second treatment period).

If the subject discontinues before the day of week 12 visit, date of first intake after week 12 re-assignment will be missing, the AE will still be assigned to "first 12 weeks of treatment".

- If date of first intake after week 12 re-assignment ≤ AE onset date ≤ date of last intake + 7 days, then the AE is assigned to "second treatment period".

Section 7.3.4 of the protocol specifies that adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment emergent'. Worsening will be determined by a more severe grade according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 Detailed rules for assigning such AEs of patients from Part 1 of the 1407-0030 trial to these time periods based on the onset dates and worsening dates of the AEs are listed below (such AEs such be classified as worsening-severity TEAEs):

- If AE onset date ≤ date of End of Treatment visit in the preceding trial (1407-0030) < AE worsening date < date of first intake after week 12 re-assignment, then the AE is assigned to "first 12 weeks of treatment".
  If an AE worsening occurs on the day of week 12 visit, actual time between AE onset and study medication taken will be compared to determine AE time period (first 12 weeks, second treatment period).

  If the subject discontinues before the day of week 12 visit, date of first intake after week 12 re-assignment will be missing, the AE worsening will still be assigned to "first 12 weeks of treatment".
- If date of first intake after week 12 re-assignment ≤ AE worsening date ≤ date of last intake + 7 days, then the AE is assigned to "second treatment period".

For patients who rolled over from Part 1 of the 1407-0030 trial if the onset date of an AE occurs prior to Week 12 and continues beyond Week 12 with a worsening RCTC grade after Week 12 then the AE will be captured as a TEAE both during the firsr12-week period of 1407-0005 (as a new-onset TEAE) and during the second treatment period (beyond Week 12, as a worsening-TEAE).

Because there is no scheduled titration for patients who rolled over from Part 2 of trial 1407-0030 adverse events will only be summarized for the entire treatment period and will not be summarized for the first 12 weeks and after 12 weeks for these patients.

Due to differing doses, differing titration schedules and different timeframe for entering this study between patients from part 1 and part 2 of trial 1407_00030, several sets of adverse event analyses, each consisting of 11 summaries, will be presented:

- Events up to 12 weeks for patients who rolled over from Part 1 of trial 1407_00030 with treatment columns BI 25 mg, BI 50 mg, BI 100 mg and BI 200 mg
- Events after 12 weeks for patients who rolled over from Part 1 of trial 1407_00030

with treatment columns BI 25 mg/BI 100 mg, BI 50 mg/BI 100 mg, BI 100 mg/BI 100 mg and BI 200 mg/ BI 200mg.

- All events for patients who rolled over from Part 2 of trial 1407-0030 with treatment column BI 400 mg
- All events from all patients who rolled over from trial 1407-0030 (part 1 and part 2 combined) where events are classified under the treatment at onset in 1407-0005 with treatment columns BI 25 mg, BI 50 mg, BI 100 mg, BI 200 mg and BI 400 mg

Patients from part 1 of trial 1407_00030 who discontinue study treatment prior to Week 12 will be excluded from the second and fourth sets of analyses above. Due to varying length of exposure to the various doses, exposure adjusted incidence rates will be presented in addition to number and percentage of patients with events in the fifth set above (classification by dose at onset).

For the analysis of other safety data (laboratory data, vital signs ,suicidal ideation) summaries will be presented for the entire study, for the first 12 weeks of the study and after 12 weeks on study. For these outputs data from patients who rolled over from Part 1 and Part 2 of study 1407-0030 will be combined. In some of these data displays each treatment appears on a separate page. If deemed appropriate, additional displays showing descriptive statistics with figures for selected outcomes will be presented.

For efficacy summaries of response at Week 24 all patients from Part 1 of trial 1407-0030 will have data will be grouped as follows:

- 100 mg patients from part 1 of trial 1407-0030
  - 25 mg/100mg
  - 50 mg/100 mg
  - 100 mg/100mg
- 200 mg patients from part 1 of trial 1407-0030
- All patients from part 1 of trial 1407-0030
- 400 mg patients from part 2 of trial 1407-0030
- All patients from part 1 and part 2 of trial 1407-0030 combined

For efficacy summaries of time to loss of response data will be grouped as follows:

- 100 mg patients from part 1 of trial 1407-0030 (combing 25 mg/100mg, 50 mg/100 mg and 100 mg/100mg)
- 200 mg patients from part 1 of trial 1407-0030
- 400 mg patients from part 2 of trial 1407-0030

Efficacy response at Week 12 and 36 for patients from Part 2 of trial 1407-0030 will be summarized.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

A protocol deviation (PD) is important if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. Refer to Identify and Manage Important Protocol Deviations (iPD) (7).

The documentation of the iPD categories and how to handle iPDs in the analysis are done in the DV domain.

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYSED

There are two patient sets defined in this trial:

- Enrolled Set (ES)
  This patient set includes all patients who signed the informed consent form and were also enrolled, regardless whether the patient was treated with trial medication or not.

- Treated Set (TS)
  The TS includes all patients in the ES who received at least 1 dose of trial medication and is based on the actual treatment received at enrollment visit

The ES will be used for patient disposition.

The TS will be used for demographics, baseline characteristics, treatment exposure, analyses of all efficacy endpoints and safety analyses (including adverse events, laboratory measurements, vital signs, and ECG).

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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.

6.6.1 Efficacy data

An observed case analysis will be performed for the primary analysis of the secondary outcomes PASI 50, PASI 75, PASI 90, PASI100, and sPGA clear or almost clear endpoints at week 24.

For the secondary outcome time to loss of PASI50/PASI75/PASI90/PASI100 for patients who achieve the response up to Week 288, patients who do not have the PASI assessment performed at a visit and maintained the PASI response at all scheduled visits prior to the missing visit will be treated as censored at the day after the last visit where the PASI response was attained.

For the secondary outcome time to loss of sPGA clear or almost clear for patients who achieve the response up to Week 288, patients who do not have the sPGA assessment performed at a visit and maintained the sPGA response at all scheduled visits prior to the missing visit will be treated as censored at the day after the last visit where the sPGA response was attained.

For the secondary outcome time to loss of sPGA clear for patients who achieve the response up to Week 288, patients who do not have the sPGA assessment performed at a visit and maintained the sPGA response at all scheduled visits prior to the missing visit will be treated as censored at the day after the last visit where the sPGA response was attained.

[redacted]

[redacted]

If at any time a patient uses an inappropriate concomitant medication, then all future data will be excluded for binary variables and for continuous variables and will not be implemented beyond the date of the prohibited medication..

6.6.2 Safety data and other data

In general, missing data will not be imputed and only observed values will be analyzed.

6.6.3 AE dates and times

Missing or incomplete AE dates will be imputed according to "Handling of missing and incomplete AE dates" (3).

[redacted]

6.6.5 Blood serum and plasma biomarker data

Missing blood serum and plasma biomarker data will not be imputed. Values below the limit of quantification (BLQ) of the assay will be imputed to BLQ/2. Values above the limit of quantification (ALQ) will be imputed to the ALQ.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

For laboratory safety measurements, the last measurements taken prior to the intake of BI 730357 or placebo will be considered as baseline.

In general, measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment will also be considered pre-treatment values.

The visit schedule with accompanying details can be found in Flow Chart in the CTP. Measurements taken after start of treatment will be considered either on- or off-treatment values based on definition in Table 6.1: 1.

On-treatment measurements for EOT and EOS visit for early discontinued patients will be allocated to visits by means of time windows with the limit between adjacent windows half-way between the planned dates for the visits; the middle day is counted to the window of the later visit. Mutually exclusive relative day windows are defined below to provide derived visits that correspond to the post-baseline time points. For example, Visit 2 is planned on Day 84 and Visit 3 is planned on Day 168. Therefore, the window of Visit 2 reaches until Day 125 while the window of Visit 3 starts on Day 126. The visit schedule with corresponding windows is given in the following table.

Table 6.7: 1 Time windows for patient visits

Window No.	Window label	Nominal visit	Nominal day	Interval
1	Day 1	Visit 1	1	N/A
2	Week 12	Visit 2	84	[2, 125]
3	Week 24	Visit 3	168	[126, 209]
4	Week 36	Visit 4	252	[210, 293]
5	Week 48	Visit 5	336	[294, 377]
6	Week 60	Visit 6	420	[378, 461]
7	Week 72	Visit 7	504	[462, 545]
8	Week 84	Visit 8	588	[546, 629]
9	Week 96	Visit 9	672	[630, 713]
10	Week 108	Visit 10	756	[714, 797]
11	Week 120	Visit 11	840	[798, 881]
12	Week 132	Visit 12	924	[882, 965]
13	Week 144	Visit 13	1008	[966, 1049]
14	Week 156	Visit 14	1092	[1050, 1133]
15	Week 168	Visit 15	1176	[1134, 1217]
16	Week 180	Visit 16	1260	[1218, 1301]
17	Week 192	Visit 17	1344	[1302, 1385]
18	Week 204	Visit 18	1428	[1386, 1469]
19	Week 216	Visit 19	1512	[1470, 1553]
20	Week 228	Visit 20	1596	[1554, 1637]
21	Week 240	Visit 21	1680	[1638, 1721]
23	Week 252	Visit 22	1764	[1722, 1805]
24	Week 264	Visit 23	1848	[1806, 1889]
25	Week 276	Visit 24	1932	[1890, 1973]
26	Week 288	EOT	2016	[1974, 2029]
27	Week 292	EOS	2044	[2030, ∞]

If there are multiple values for an efficacy endpoint in one window (visit), use the one from scheduled visit. If value from scheduled visit is not present, the visit closest to the nominal day will be selected for assessing endpoints at a particular visit and for by-visit displays. If the visits are equidistant from the nominal day, then the earlier visit will be selected. All measured values will be stored in analysis datasets.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Reporting of clinical trials and project summaries” .

The individual values of all patients will be listed, sorted by treatment, patient number and visit. The listings will be included in Appendix 16.2 of the CTR.

For EoT tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For appendix tables, the set of summary statistics is: N / Mean / SD / Min / Q1 (lower quartile) / Median / Q3 (upper quartile) / Max.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category “missing” will be displayed only if there are actually missing values. Percentages will be based on all patients in the respective patient set no matter whether they have non-missing values or not.

No interim analysis is planned for this trial.

For patients from Part 1 of the 1407-0030 trial planned treatment for first 12 weeks of treatment is defined as treatment patient received at the end of 1407-0030. Planned treatment for after 12 weeks (Period 2) is defined as the treatment patient assigned from IVRS at week 12 visit (V2). For patients who titrate according to the protocol from 100 g *q.d.* dose to 200 g *q.d.* dose,if the investigator determines that the patient may benefit from the higher dose, 200 g *q.d.* dose will be the planned dose after the titration.

Subject data listings of data used in the analyses (i.e. demographic and baseline characteristics and key efficacy endpoints) will also be provided and included in Appendix 16.2 of the CTR.

Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients screened, entered, screened but not entered, treated, entered but not treated. Within treated patients, data for patients rolled over from Part 1 of trial 1407-00030 will be summarized by treatment periods (period 1 - first 12 weeks of treatment and period 2 – open label treatment after week 12) for treatment ongoing patients, patients complete planned treatment period and patients who are prematurely discontinued, by reason.

Because there is no scheduled titration for patients from Part 2 of trial 1407-0030 disposition will be summarized without distinguishing the first 12 weeks from after 12 weeks for these patients.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic parameters collected and to be presented include, but are not limited to, the following:

- Gender (Male, Female)
- Race and ethnicity (as defined in the eCRF)
- Age [years]
- Height [cm]
- Weight [kg]
- Body mass index [kg/m2] (defined as weight [kg]/(height [cm]/100)2)
- Smoking history (Never-smoked, Ex-smoker, Currently smokes)
- Alcohol History (Non-drinker, drinks – no interference, drinks – possible interference)
- Region
- PsA history (diagnosed, suspected, no PsA)
- Prior biologic use for psoriasis (Yes/No)

Baseline disease characteristic to be presented include, but are not limited to, the following:

- PASI score
- Body surface area (affected by plaque psoriasis)
- sPGA

[redacted]

Number (%) of patients with psoriasis therapy history will be summarized, including both non-topical drug therapy and non-drug therapy.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

A table of the number (%) of patients with concomitant diagnoses from baseline condition by system organ class (SOC) and preferred term (PT) will be included along with a supporting listing. Concomitant diagnoses will be coded with the most recent version of MedDRA in effect at database lock.

Concomitant medication will be described as a table of number (%) of patients with on-treatment medication use. On-treatment is defined as medication with a stop date after or on the day of first trial drug intake and before last trial drug intake + 7 days.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be reported based on calculation as described in CTP section 4.3. Only descriptive statistics are planned for this section of the report. Treatment non-compliance is defined as any enrolled patients having taken at least one dose of study medication with an overall compliance rate not between 80% and 120% inclusive. Overall compliance is calculated based on unweighted average of study drug compliance rate at each visit during the treatment period. For the patients who discontinued the study treatment prematurely only the visits on or before premature discontinuation will be used for the calculation of overall compliance.

Summary statistics of overall compliance in the treated set will be given for the number of subjects as well as the corresponding percentage with compliance in the categories <80%, 80% - 120%, >120%, missing.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to Week 288. The primary analysis will be based on the exposure adjusted rate of patients reporting a treatment emergent adverse event (TEAE) up to Week 288.

Exposure-adjusted adverse event incidence rates 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 for each subject and each TEAE preferred term:

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

  If, for a subject, no treatment emergent adverse event occurred for the preferred term, then the time at risk will be censored at the minimum of (date of death; drug stop date + 7 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 using exact Poisson regression.

[redacted]

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

For the convenience of writing and reviewing, all PASI and sPGA endpoints at different time points (secondary and further clinical endpoints) are first described generally in this section prior to addressing each secondary objective specifically.

Psoriasis Area and Severity Index (PASI)
Details for scoring Psoriasis Area and Severity Index (PASI) and its components are described in Section 10.1 of the CTP. The percent reduction from baseline is calculated by % PASI reduction from baseline = ((PASI at baseline - PASI at Visit X) / PASI at baseline) * 100, at all visits with PASI collected. Achieving an X% or larger reduction from baseline PASI score is denoted as PASI X.

Static Physician's Global Assessment (sPGA)
The sPGA is scored using the following levels of assessment:
0 - clear 1 - almost clear 2 - mild 3 - moderate 4 - severe

Secondary Outcome Achievement of PASI50/PASI75/PASI90/PASI100 at Week 24

Descriptive statistics of the percentage of patients who achieve a PASI score of at least 50% (PASI 50), 75% (PASI 75), 90% (PASI90) and 100% (PASI100) reductions from baseline at Week 24 will be tabulated for each treatment group. The number of patients, number of patients attaining the PASI response, percentage of patients attaining the PASI response at Week 24 with corresponding exact 95% confidence interval will be presented based on the Clopper Pearson method.

The primary analysis of these secondary outcomes will be based on an observed case analysis.

Secondary Outcome Achievement of sPGA clear or almost clear at Week 24

Descriptive statistics of the percentage of patients who achieve sPGA of clear or almost clear (sPGA score of 0 or 1 ("clear or almost clear")) at Week 24 will be tabulated for each treatment group. The number of patients, number of patients attaining the sPGA response, percentage of patients attaining the sPGA response at Week 24 with corresponding exact 95% confidence interval will be presented based on the Clopper Pearson method.

The primary analysis of these secondary outcomes will be based on an observed case analysis.

Secondary Outcome Achievement of sPGA clear at Week 24

Descriptive statistics of the percentage of patients who achieve sPGA of clear (sPGA score of 0 ("clear ")) at Week 24 will be tabulated for each treatment group. The number of patients, number of patients attaining the sPGA response, percentage of patients attaining the sPGA response at Week 24 with corresponding exact 95% confidence interval will be presented based on the Clopper Pearson method.

The primary analysis of these secondary outcomes will be based on an observed case analysis.

Secondary Outcome Time to Loss of PASI50/PASI75/PASI90/PASI100 for patients who achieve the response up to Week 288

For the time to loss of response (PASI 50/ PASI 75/ PASI 90/ PASI 100) the time to event will be calculated as

- Time to first loss (with observed event) = [date of first loss] – [date of first visit with qualifying response] + 1
- Time to first loss (censored) = [date of last visit with qualifying response] – [date of first visit with qualifying response] + 1
- If a patient never attains PASI 50/ PASI 75/PASI 90/PASI 100 then the patient will not contribute to the analysis of this outcome.

Time to loss of response will be analysed descriptively by Kaplan Meier curves. If at least 50% of patients lose response, the median time to loss of response will be estimated median of time to loss with 95% confidence interval will be presented.

Secondary Outcome Time to Loss of sPGA clear or almost clear at Week 24 for patients who achieve the response up to Week 288

For the time to loss of response (sPGA clear or almost clear), the time to event will be calculated as:

- Time to first loss (with observed event) = [date of first loss] – [date of first visit with qualifying response] + 1
- Time to first loss (censored) = [date of last visit with qualifying response] – [date of first visit with qualifying response] + 1
- If a patient never attains sPGA clear or almost clear then the patient will not contribute to the analysis of this outcome.

Time to loss of response will be analysed descriptively by Kaplan Meier curves. If at least 50% of patients lose response, the median time to loss of response will be estimated median of time to loss with 95% confidence interval will be presented.

Secondary Outcome Time to Loss of sPGA clear at Week 24 for patients who achieve the response up to Week 288

For the time to loss of response (sPGA clear), the time to event will be calculated as:

- Time to first loss (with observed event) = [date of first loss] – [date of first visit with qualifying response] + 1
- Time to first loss (censored) = [date of last visit with qualifying response] – [date of first visit with qualifying response] + 1
- If a patient never attains sPGA clear then the patient will not contribute to the analysis of this outcome.

Time to loss of response will be analysed descriptively by Kaplan Meier curves. If at least 50% of patients lose response the median time to loss of response will be estimated median of time to loss with 95% confidence interval will be presented.

7.7 EXTENT OF EXPOSURE

Exposure will be presented as total days on treatment and total study medication intake assessed by actual treatment received. For example, a Placebo patient that switches to BI 730357 100 mg at Week 12 should have 12 weeks of exposure under the Placebo column and their number of days on BI 730357 100 mg under BI 730357 100 mg column.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). Analysis will be performed as defined in Section 7.3.4 of the CTP.

7.8.1 Adverse Events

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs (not the number of AEs).

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 7 days after last drug intake will be assigned to the received treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + 7 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

According to ICH E3 (5), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and PT using the version of MedDRA at the database lock. Separate tables will be provided for subjects with SAEs, AEs leading to treatment discontinuation and related AEs.

The system organ classes will be sorted by default by decreasing frequency and PTs will be sorted by decreasing frequency within SOC.

For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (4).

The severity of AEs will be summarised by the maximum intensity of the events each patient had (as indicated by the recorded RCTC version 2 grade). This will show the number and percent of patients who had at most mild, moderate, severe, and life threatening events. Severe adverse event is defined as an AE with RCTC grade equals to 3 (severe) or 4 (life threatening).

Groupings of adverse events and adverse events of special interest (AESI)
The AESI have been defined in the protocol.

Other user-defined special adverse event grouped term for BI 730357 specified in the following Table 7.8.1:1.

Table 7.8.1: 1 User Defined Adverse Event Group Terms

N	Term	Definition #
1	SMQ Drug Related Hepatic Disorders	SMQ Drug related hepatic disorders – comprehensive search (20000006)
2	SMQ Opportunistic infections	MedDRA SMQ Opportunistic Infections (narrow)
3	Tuberculosis related terms	BIcMQ "Tuberculosis related terms" BIcMQ (30000107)(broad)
4	Severe infections	SOC "Infections and infestations" with eCRF severity grade >= Rheumatology Common Toxicity Criteria (RCTC) Grade 3
5	Gastritis related terms	• BIcMQ Gastritis (broad) [32008061]

This column indicates whether the Term(s) provided in the second column are MedDRA preferred terms (PT), Standardised MedDRA Queries (SMQ) or BI customised MedDRA Queries (BIcMQ).

In addition, adjudicated MACE (provided by [redacted] will be summarized by indication, treatment, primary system organ class and preferred term.

The user defined AE categories will be updated accordingly with Safety SAP updates.

The following periods will be defined for assessing adverse events for patients from Part 1 of the 1407-0030 trial.:

- First 12 weeks of treatment
- Second treatment period

For patients from Part 1 of the 1407-0030 trial, AEs with onset date on day of week 12 visit, the AE onset time will be compared with first drug administration time of the dose dispensed at the Week 12 visit to determine AE period. The treatment label for second period will be a combination of actual treatment in first 12 weeks of treatment and second period treatment.

Additionally an analysis including patients from both parts of the 1407-0030 trial will be performed in which adverse events are classified under the dose the patient was receiving at the onset of the TEAE.

AE summaries

An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarized by treatment, primary system organ class and preferred term according to MedDRA. Separate tables will be provided for patients with:

- Drug-related AEs
- AESIs

- AEs leading to discontinuation
- Serious AEs
- Other significant AEs
- AE by worst RCTC intensity
- Investigator defined drug-related serious AEs
- User defined AE categories

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). The number and percent of patients with possibly clinically significant on treatment abnormalities as identified by use of clinically significant ranges for each laboratory parameter collected will be presented. The patients from both parts of 1407-0030 with possibly clinically significant abnormalities will be identified by actual treatment received at study entry.

Each laboratory value will be graded using the RCTC (version 2.0) grading of laboratory abnormalities. A summary table of the baseline grade compared with the last available on treatment grade will display the number and percent of each type of transition in grade by laboratory parameter within each treatment period and treatment group. A second table will show the number and percent of patients with each type of transition from baseline to their worst on-treatment grade.

A graphical summary highlighting potential cases of Hy's Law by actual treatment received at study entry will be presented. The maximum on-treatment values of total bilirubin and ALT will be plotted each on a scale as multiples of the upper limit of normal. The figure will show areas that meet the criteria of cholestasis (total bilirubin > 2x ULN), Temple's corollary (ALT > 3 x ULN) and Hy's Law as the combination of these two factors. A similar figure using maximum AST values in place of ALT will be constructed. An accompanying listing will show by sample date and study day the full course of the total bilirubin, ALT, AST and alkaline phosphatase values for patients whose total bilirubin are > 2xULN or AST or ALT values > 3 x ULN at any time during the study (all treatment periods). The listing will indicate where the value meets the criteria, either falling in the cholestasis range, that for Temple's corollary or where the combination meets that for Hy's Law itself.

Laboratory measurements taken up to the residual effect period of 7 days after the last administration of study drug will be considered as on-treatment.

Study visits will be presented by the Visit labels in Table 6.7:1.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

Abnormal ECG recordings will be noted, and clinically relevant abnormal findings will be reported as AEs by the investigator.

7.8.5 Others

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

For patients rolled over from Part 1 of trial 1407-0030 the unblinded treatment information will be loaded into the trial database only after all patients have completed the blinded 12-week treatment period.

For patients rolled over from Part 2 of trial 1407-0030 the treatment information will be loaded into the trial database upon entry into study 1407-0005.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
5.	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
[redacted]	[redacted]

11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**03-MAR-2021**	[redacted]	None	This is the final TSAP