TRIAL STATISTICAL ANALYSIS PLAN

c25658163-02

BI Trial No.:	1407-0030
Title:	Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis
BI Investigational Product(s):	BI 730357
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
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[redacted]

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
AE	Adverse Event
BRPM	Blinded Report Planning Meeting
BES	Biopsy Evaluable Set
CTC	Common Terminology Criteria
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
IPD	Important Protocol Deviation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary For Regulatory Activities
MCPMod	Multiple Comparison Procedure and Modelling
MQRM	Medical Quality Review Meeting
MMRM	Mixed Effect Model Repeated Measurement
PASI	Psoriasis Area Severity Index
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
REP	Residual Effect Period

Term	Definition / description
SA	Statistical Analysis
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
sPGA	Static Physician's Global Assessment
TOM	Trial Oversight Meeting
ToC	Table of Contents
TS	Treated Set
TMW	Trial Medical Writer
TSAP	Trial Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9, 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.

The trial data is stored in the BI Rave (BRAVE) database system.

SAS® Version 9.4 will be used for analyses.

R version 3.3.2 or later with “DoseFinding” package (9) will be used for MCPMod analysis.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The co-primary endpoints are:

- Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 12
- Achievement of a sPGA score 0 or 1 at Week 12

The co-primary endpoints are the proportion of patients achieving PASI 75 and sPGA 0/1 at Week 12 by treatment group.

Details for scoring Psoriasis Area and Severity Index (PASI) and static Physician Global Assessment (sPGA) are described in Section 10.1 and 10.2 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Secondary endpoints

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

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

At Week 12, patients will remain in their treatment group or be reassigned depending on the primary efficacy endpoint result:

- Non-responders will be reassigned to the next higher dose level or to the highest dose level based on the original treatment assignment at randomization.
- Placebo recipients (group E) who achieve a PASI 75 response will remain on placebo through Week 24. Otherwise, they will be assigned with the highest dose level starting from Week 12.
- 200 mg recipients will not be titrated at week 12.

For example, patients from dose groups A to C who fail to achieve a PASI 50 response 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. Patients from dose group D will remain on the dose group D through Week 24.

Patients will be analyzed according to the treatment to which they were randomized. The following study periods based on actual start and stop dates of study treatment administration are defined:

Table 6.1: 1 Definition of treatment periods

Analysing Treatment Period	**Start Date (including)**	**Stop Date (excluding)**
Screening	Date of informed consent	• Date of medication randomization -1 day
On-treatment period	Date of medication randomization	• Date of last study medication intake + 7 days
Follow-up	Date of last study medication intake +8 days	• Last contact date

For the main safety analyses, Adverse Events (AEs) will be classified to one of the following time periods: “screening”, “on-treatment”, 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 are listed below:

- If date of informed consent ≤AE onset date and <date of first drug administration, then the AE is assigned to “screening”

- If date of first drug administration ≤AE onset date ≤date of last intake +7 days, then the AE is assigned to "on-treatment"
- If AE onset date > date of last drug administration+7 days, then the AE is assigned to "follow-up"

AE will be reported for first and second 12 weeks separately. If an AE onsets on the day of week 12 visit, actual time of AE and time of drug administration on week 12 visit will be compared to determine under which period such AE will be reported.

6.2 IMPORTANT PROTOCOL DEVIATION

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. Patients with important PDs that could potentially impact the evaluation of the primary endpoint(s) will be excluded from PPS, if applicable).

A list of important PDs (IPDs) is given in Table 6.2: 1. Important PDs will be reviewed at Medical Quality Review Meetings (MQRMs) conducted periodically during the trial. A list of protocol deviation will be discussed at the Blinded Report Planning Meetings (BRPMs).

If the data show other important PDs, this table will be supplemented accordingly at BRPMs or through team review of the manual PD log. The decision whether a subject will be excluded from the analysis will be made at the final BRPM prior to Database Lock (DBL).

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from (if applicable)	Automatic/ Manual
A					
	A1	**Entrance criteria not met**	Inclusion criteria not met as specified in the protocol		
	A1.1	Demographic or pregnancy testing inclusion criterion not met	Inclusion criteria 1,2,3 not met	None	Automatic
	A1.2	Psoriasis inclusion criterion not met	Inclusion criteria 4 not met	PPS	Automatic
	A1.3	Patient does not meet the specified moderate to severe plaque-type psoriasis	Inclusion criteria 5 not met	PPS	Automatic and Manual
	A2	**Exclusion criteria not met**	Exclusion criteria not met as specified in the protocol		
	A 2.1	Patient has active/past clinically important diseases, has significant laboratory values, or pregnancy-related exclusion criteria met	Exclusion criteria 1, 9,10,11,12,13 not met	None	Automatic
	A 2.2	Patient has participated in another clinical trial within 30 days before the randomization or previously enrolled in trial	Exclusion criteria 2,3 not met	PPS	Automatic and Manual

Table 6.2: 1 (Cont'd) Important protocol deviations

Category / Code		Description	Requirements	Excluded from (if applicable)	Automatic/ Manual
	A 2.3	Patient has not sufficient wait time since last intake of restricted medication or must or wish to continue the intake of restricted medications	Exclusion criteria 4,6 not met	PPS	Automatic and Manual
	A 2.4	Patient has received a live vaccine	Exclusion criteria 5 not met	None	Automatic/ Manual
	A 2.5	Patient has chronic alcohol/drug abuse	Exclusion criteria 8 not met	None	Automatic
	A 2.6	Patient has suicidal ideation	Exclusion criteria 14 not met	None	Automatic
B		**Informed consent**			
	B1	Informed consent missing	Informed consent not available/not done	All	
	B2	Date of informed consent was after the date of any study related procedure, or the patient signed the wrong version of ICF	Informed consent late	PPS if ICF after procedure (A). None if wrong version. (M)	Automatic and Manual
C		Trial medication and randomisation			
	C1.1	Incorrect trial medication taken prior to week 12	Medication kit assigned not matching treatment patient was randomised to (cross-treatment1) and/or not matching IVRS assignment	PPS	Automatic and manual
	C1.2	Incorrect trial medication taken after week 12	Medication kit assigned not matching treatment patient was randomised to (cross-treatment1) and/or not matching IVRS assignment	None	Automatic and manual
	C2	Non-compliance	Overall compliance <80% or >120% Non-compliance caused by treatment cessation due to a cardiovascular procedure should not be classified as a protocol violation.	PPS	Automatic
	C3	PASI score entered in IRT entry error at week 12	PASI score entered in IRT not the same as entered in CRF page at randomization and week 12	None	Automatic and Manual

Table 6.2: 1 (Cont'd) Important protocol deviations

Category / Code		Description	Requirements	Excluded from (if applicable)	Automatic/ Manual
	C4	Medication code broken inappropriately	Medication code broken inappropriately - reason for medication code break	None	
D		**Concomitant medication**			
	D 1.1	Prohibited medication use potential impact patient safety[2] in first 12 weeks	Prohibited medication used may impact patient safety profile in first 12 weeks of treatment	None	Manual
	D 1.2	Prohibited medication use potential impact patient safety[2] in second 12 weeks	Prohibited medication used may impact patient safety profile in second 12 weeks of treatment	None	Manual
	D 1.3	Prohibited medication use potential impact patient efficacy[3] in first 12 weeks	Prohibited medication used may impact patient efficacy profile in first 12 weeks of treatment	PPS	Manual
	D 1.4	Prohibited medication use potential impact patient efficacy[3] in second 12 weeks	Prohibited medication used may impact patient efficacy profile in second 12 weeks of treatment	None	Manual
E		**Study Specific**			
	E 1	Dispense expired drug		None	

[1] cross-treatment means actual treatment received is different from randomized or IRT assigned treatment type.
[2] Prohibited medication use potential impact patient safety are manually reviewed in MQRM or TOM. Decision are documented in related meeting minutes and final BRPM minutes.
[3] Prohibited medication use potential impact patient efficacy includes all pre-treatment PsO therapy not meet washout period or concomitant use during study conduct specificied in CTP table 4.2.2.1:1.

6.3 SUBJECT SETS ANALYSED

There are five patient sets defined in this trial:

- Randomised Set (RS)

The RS includes all patients who signed the informed consent form and were also randomised, regardless whether the patient was treated with trial medication or not.

- Treated Set (TS)

The TS includes all patients in the RS who received at least 1 dose of trial medication and is based on the actual treatment received at randomization visit and week 12 visit, if applicable.

- Full Analysis Set (FAS)

The FAS includes all patients in the RS who received at least 1 dose of trial medication and provided baseline and at least 1 post-randomisation measurement of PASI.

- Per Protocol Set (PPS)

The PPS, a subset of FAS, includes all patients who did not have an IPD affecting the primary efficacy endpoint or patients safety (see Table 6.2: 1 for details).

[redacted]

Patient disposition will be based on randomized set.

The FAS will be used for the analyses of demographics, baseline characteristics and all efficacy endpoints. The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e., efficacy analyses will be analysed as randomised using the FAS.

The TS will be used for the analyses of concomitant medication use, medical history, PsO therapy history, treatment exposure, compliance, and safety (including adverse events, laboratory measurements, vital signs, and ECG). Safety analyses will assign patients to the treatment group based on the actual treatment received.

PPS for sensitivity analysis will be considered if necessary. Decision will be documented in BRPM minutes.

If a patient erroneously receives the wrong dose of trial drug, the patient's efficacy data will be analysed in the randomized treatment group and the patient's safety data will be analysed in the actual treatment group. If a patient receives placebo instead of randomized BI730357 study medication, this will be noted as an IPD.

[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

General imputation rules for continuous and binary endpoints are described in protocol section 7.5.

Missing data imputations at the interim analysis at completion of both week 4 and week 12, will be performed using all available on-treatment data observed up to the respective analysis cut-off date.

6.6.1 Efficacy data

If at any time a patient uses an inappropriate concomitant medication, then all future data will be treated as failure for binary variables and LOCF (using the last on-treatment observation prior to inappropriate concomitant medication use) for continuous variables. As part of the LOCF technique, baseline values will be carried forward if no post-baseline value is available.

If a patient is missing items from a questionnaire measured at a visit, these will be handled according to the instructions given in Section 10.11 of the protocol specific to each questionnaire.

For the NAPSI, PSSI, and PPASI assessment, if the CRF is marked as “No” indicating that the patient does not have nail, scalp, palmo-plantar disease, then the total score will be set as zero (0) for that assessment in the analysis dataset.

For efficacy endpoints which are continuous in nature, a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will be used for inferential analysis, if applicable. No imputation will be performed for data used in MMRM.

6.6.2 Safety data and other data

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

Missing or incomplete AE dates will be imputed according to BI standards (see DM&SM) "Handling of missing and incomplete AE dates"). (1)

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For efficacy endpoints, baseline is defined as the pre-treatment observation at Visit 2. If Visit 2 is missing, then Visit 1 will be used for baseline.

For laboratory safety measurements, the last measurements taken prior to the treatment start 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 1. 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 6 is planned on Day 29 and Visit 7 is planned on Day 57. Therefore, the window of Visit 6 reaches until Day 42 while the window of Visit 7 starts on Day 43. The visit schedule with corresponding windows is given in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of on-treatment efficacy, safety lab, vital signs, and biomarker measurements to visits for statistical analysis

Window No.	Window label	Nominal visit	Nominal day	Interval
0	Baseline	VISIT 2	1	N/A
1	Week 1	VISIT 3	4	[2,4]
2	Week 1	VISIT 4	8	[5,11]
3	Week 2	VISIT 5	15	[12,21]
4	Week 4	VISIT 6	29	[22,42]
5	Week 8	VISIT 7	57	[43,70]
6	Week 12	VISIT 8	85	[71,98]
7	Week 16	VISIT 9	113	[99,126]
8	Week 20	VISIT 10	141	[127,154]
9	Week 24	EOT	169	[155,182]
10	Week 28	EOS	197	[183,∞]

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.

The same visit windows will be used for safety laboratory and vital sign assessments. If there are multiple safety or laboratory values in one time window on treatment, the worst value will be selected for the by-visit analyses.

Analysis of AE data, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Frequency tables for these data will be using on-treatment data only. Therefore, no assignment to time windows will be necessary for such data.

While the nominal times listed in this section should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

For visits without an assigned value based on time windows, a value will thereafter be imputed as defined in Section 6.6. LOCF imputation of efficacy endpoints, when applicable, will be performed based on all available observations obtained during the on-treatment period, irrespective of whether the observation was selected in any time window.

7. PLANNED ANALYSIS

According to CTP Section 7.4, there are two interim analyses planned for this study.

1) An administrative interim analysis for the purpose of internal planning other indications of BI 730357 will be performed when the last patient completes the 4 week follow-up visit
    a. Output will comprise only baseline summaries, key efficacy endpoints(i.e. PASI, sPGA) and key adverse events tables
    b. No separate report is planned to be written for this analysis
2) The interim for the primary analysis (at an interim time point) will be performed when the last patient completes the 12 week follow-up visit

For each interim analysis, the trial team will perform a blinded analysis and an independent team will perform unblinded analyses. In order to support the further double-blinded conduct of the trial until the week 24 visit, the trial team are kept blinded on the individual patients' treatment group assignment. Details of each interim analysis are specified in the trial interim analysis logistic and access plan for week 4 and week 12 separately.

The analysis of the entire efficacy, safety, and biomarker data collected through the full 28 weeks of follow-up will be performed once all entered patients have completed the trial (up to EOT/Week 28 Visit); at that time point, a final database lock will be done and all on-treatment data through week 28 will be reported.

General remarks:

The format of the listings and tables will follow the standards defined in the BI corporate guideline "Reporting of clinical trials and project summaries" (6).

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.

Planned treatment for first 12 weeks of treatment is defined as treatment patient assigned from IVRS at randomization visit (visit2). Planned treatment for second 12 weeks of treatment is defined as the treatment patient assigned from IVRS at week 12 visit (V8).

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 will be summarized by treatment periods (period 1 - first 12 weeks of treatment and period 2 – second 12 weeks of treatment) for treatment ongoing patients, patients complete planned treatment period and patients who are prematurely discontinued, by reason. Disposition will be listed by country.

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] (continuous)
- Weight Group (>100kg vs. $\leq$ 100 kg)
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/100)$^{2)}$
- Body mass index [kg/m^2] ($\geq$30 vs. <30)
- 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:

- BSA (Visit 1)
- PASI score
- sPGA
- NAPSI, PPASI, PSSI
- Pain VAS
- PSS total score
- DLQI

For NAPSI, PPASI, PSSI and pain-VAS, report is only based on patients are applicable to the measurement per protocol, e.g. pain VAS only for patients with psoriatic arthritis.

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.

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

7.3 TREATMENT COMPLIANCE

Treatment compliance will be reported from baseline to Week 24 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 randomized 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.

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

7.4.1 Primary Analysis

After the last patient reaches Week 12, the primary analyses of the primary endpoints will be performed in all randomized patients who receive at least one dose of treatment based on randomised treatment (FAS) using the Multiple Comparison Procedures and Modelling (MCP-Mod) approach (7, 8).

First, the response rate for co-primary endpoints at week 12 of each dose group will be estimated using a logistic regression model. The model will include the fixed effect of treatment (categorical dose) and baseline PASI score as covariate. SAS procedure **"proc logistic**" will be used to fit the logistic regression model.

$$\boldsymbol{logit}(\boldsymbol{y_{ij}}) = \boldsymbol{\beta S_i + \tau_j}$$

i ~ subject, j ~ treatment

y_{ij} = the response variable for primary endpoints
S_i = the baseline measurement of subject i (=1,2,…)
β = coefficient of baseline effect
τ_j = the effect of treatment j (= 1, ..,Y)

The adjusted mean estimates of response at logit scale for each dose groups, as well as the estimated variance-covariance matrix will then be analysed using MCPMod for dose-response analysis.

The multiple comparison procedure will be implemented using of optimal contrast tests which control the family-wise type I error rate at one-sided $\alpha = 0.05$. The optimal contrasts corresponding to the candidate models are calculated as in the trial design stage and shown in Table 7.4:1. The actual analysis contrast coefficients will be based on using the estimated variance-covariance matrix from the data.

Table 7.4: 1 MCPMod contrast coefficient (design stage)

	Contract coefficients for dose				
Model	0	25 mg	50 mg	100 mg	200 mg
Linear	-0.179	-0.350	-0.301	-0.037	0.868
Emax1	-0.248	-0.467	-0.272	0.214	0.774
Emax2	-0.553	-0.458	0.048	0.388	0.575
Logistic	-0.210	-0.429	-0.403	0.341	0.702
Exponential model	-0.133	-0.264	-0.261	-0.231	0.889

If at least one dose-response model is statistically significant, rejecting the null hypothesis of a flat dose-response curve indicates a benefit of BI 730357 over placebo. Test statistics and p-values will be displayed for different dose response models.

Once the significance of a dose-response signal is established, the selected dose-response model(s) will be re-fitted to the data without any parameter assumptions to generate a set of new estimates of the model parameters from the data. The final dose-response model will be estimated by averaging significant model(s) based on their Akaike Information Criterion (AIC) (the smaller the AIC value the better model fit). Fitted response rate and difference to placebo for all investigated dose-response models will be tabulated at each dose along with logistic regression estimate and the weighted AIC estimate.

Fitted dose-response curve(s) for significant model(s) will be graphically presented with 95% confidence band across investigated dose range (0 to 200mg).

The adjusted mean estimates from the logistic regression and fitted MCPMod estimates of response rate are both on the logit scale. The absolute and difference in proportions will be calculated by transforming the estimate back to the probability scale. More details please refer to Section 9.4.

7.4.2 Secondary analyses

For both co-primary endpoints, the point estimate and two-sided 90% and 95% exact confidence intervals for proportion of responder will be displayed for each treatment group. The unadjusted absolute difference in proportion between active groups and placebo group regarding the co-primary endpoints will be estimated with 90% and 95% Pearson-Clopper

exact confidence intervals and p-value calculated by Chi-square test. This is considered the secondary analysis for the primary endpoint(s).

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoints

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

- PASI 75 at week 16

The same methods as discussed for the secondary analysis for the primary endpoint will be used to analyse clinical binary secondary and further endpoints for each treatment group as well as treatment comparison.

For the convenience of writing and reviewing, all PASI and sPGA endpoints at different time points (secondary and further clinical endpoints) are described in this section.

For the analysis of binary efficacy endpoints after week 12 based on non-responder imputation, patients switch treatment at week 12 will be imputed as failure for records after week 12, under original randomized treatment arm.

Psoriasis Area and Severity Index (PASI)
Treatment comparison for unadjusted absolute difference in proportion between active groups and placebo group will be performed for achievement of 50% (PASI50), 75% (PASI75), 100% (PASI 100) at week 12 and 75% (PASI 75) at Week 16, 20 and 24.

Descriptive statistics of total PASI score and PASI total score change from baseline, PASI total score percentage change from baseline and 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 will be tabulated by treatment over time. Additionally, these will be graphically represented by line plots over time.

[redacted]

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 - marked 5 - severe
Details for scoring sPGA and its components are described in Section 10.2 of the CTP.

Treatment comparison for unadjusted absolute difference in proportion between active groups and placebo group will be performed for sPGA equals to 0 at week 12 and sPGA clear or almost clear at week 12, 16, 20 and 24.

The number and proportion of patients who achieve a sPGA score of 1 (clear) or 2(almost clear) over time will be tabulated for each treatment group.

Additionally, the proportion of patients shifting from their baseline sPGA values to different values over time will be tabulated for each treatment group.

PSS total score change from baseline at week 12

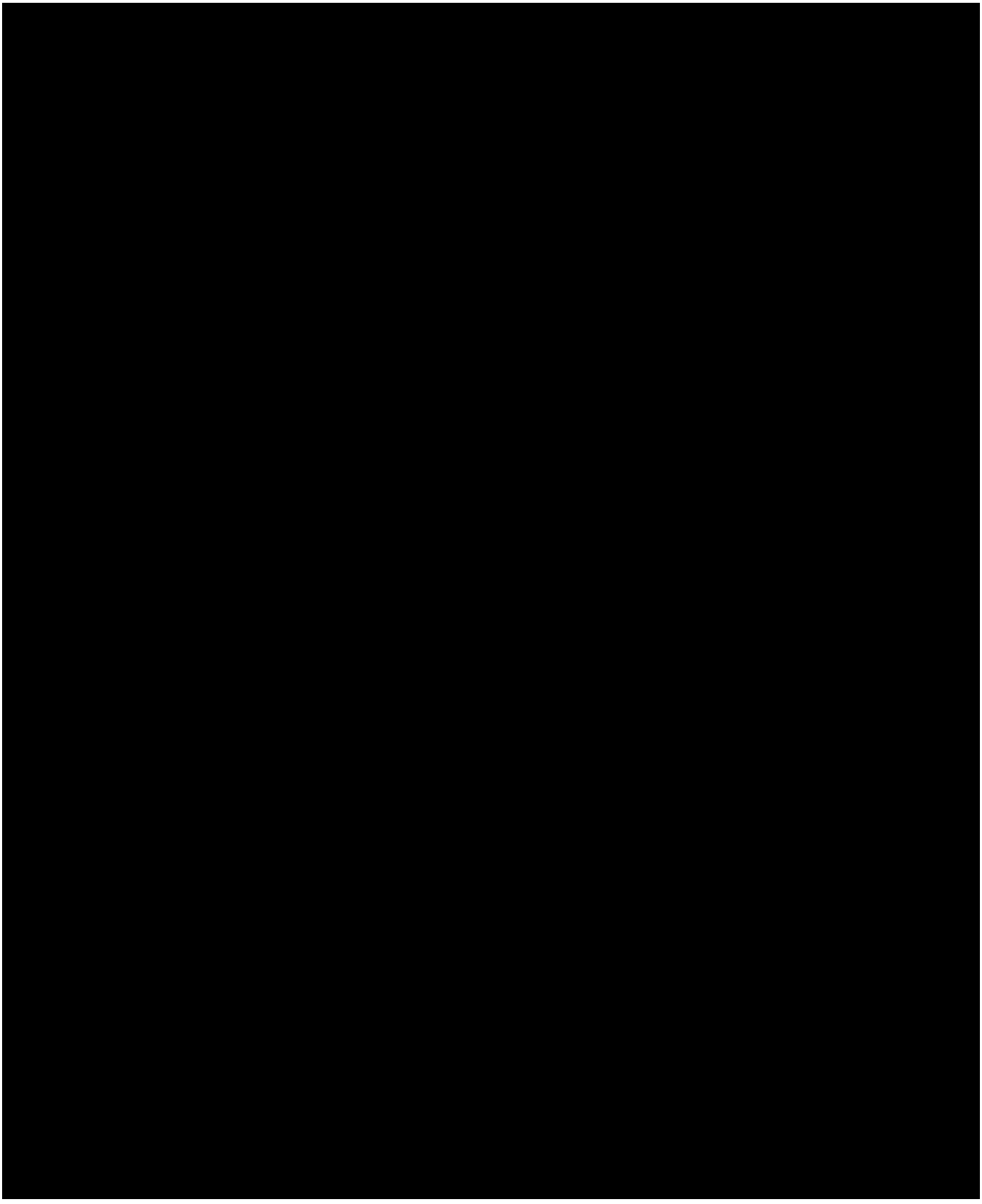
For change from baseline in PSS total score at Week 12 and treatment comparison, a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will be used. The analyses will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline PSS total score and baseline PASI score-by-visit interaction. Patient will be considered as a random effect. An unstructured covariance structure for within subject variation will be used.

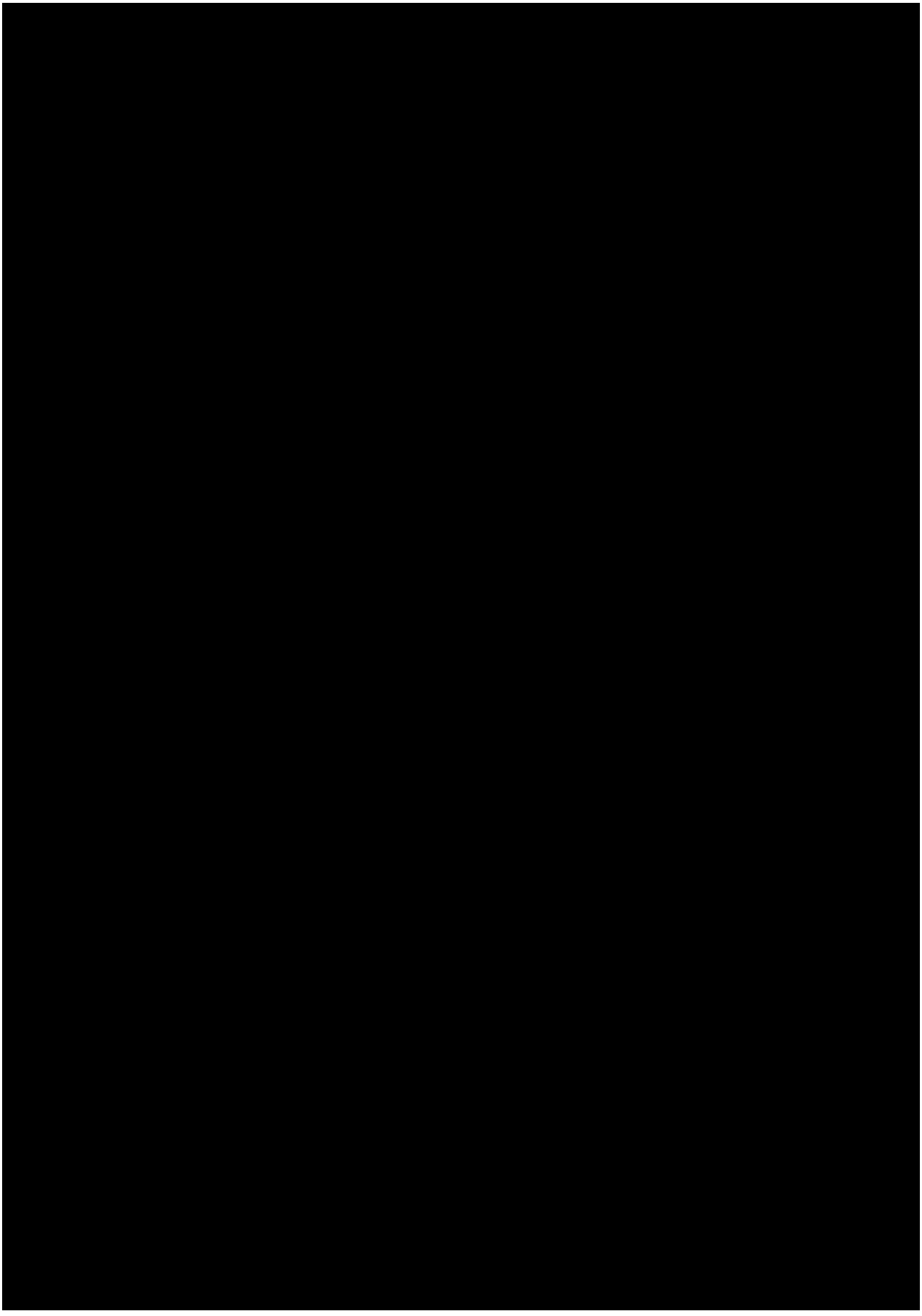
The number and proportion of patients who PSS total score 0 over time will be tabulated for each treatment group.

Additionally, the proportions of patients shifting from their baseline PSS values to different values over time will be tabulated for each treatment group for each individual domain (pain, redness, itching, burning).

DLQI score of 0 or 1 at week 12
Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at week 12 will analysed by treatment comparison of unadjusted absolute difference in proportion between active groups and placebo group with 90% and 95% exact confidence intervals. This is considered the secondary analysis for the primary endpoint(s).

For DLQI, if one question is left unanswered this is scored 0 and the total score is summed and expressed as usual out of a maximum of 30;





7.7 EXTENT OF EXPOSURE

Exposure will be presented as categorized period of "1-28", "29-56", "57-84" and "≥85" days based on dose received for total study medication intake. Exposure will be summarized and presented separately for first 12 weeks and second 12 weeks of treatment.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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).

Multiple overlapping or adjacent recordings (AE occurrences) of the same AE are collapsed into one AE event if all AE attributes are identical as defined in (3, 4).

Two AE occurrences are considered to be time-overlapping if the start date of the second, later occurrence is earlier or equal to the end date of the first occurrence.
Two AE occurrences are considered to be time-adjacent if the start date of the second, later occurrence is one day later than the end date of the first occurrence. The default definition for the gap of one day may be changed on the project level.

If multiple overlapping (AE occurrences) of the same AE have different attributes, the AEs will be queried to confirm whether they are in fact one occurrence or to correct the end date of the first occurrence to match the start date of the second occurrence.

After this process of collapsing the events to remove duplication and clarify any inconsistencies, the resulting data will form the basis for all reporting of AEs in the listings, tables, and figures.

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' (3, 4).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug administration and within 7 days of last drug administration will be assigned to the assigned treatment. All adverse events occurring before first drug intake will be assigned to ‘screening’.

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 protocols as hepatic injury defined by the following alterations of liver parameters:

- For patients with normal liver function at Baseline: 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.

See Section 7.3.2 for a description of the assessment of potential Hy’s Law cases.

Other user-defined special adverse event grouped term for BI 730357 specified in Table 7.8.1:1 will be reported.

Table 7.8.1: 1 Other special groupings of adverse events

N	AESI	Term	Definition#
1	Yes	Drug Induced Liver Injury*	SMQ Drug related hepatic disorders – comprehensive search (20000006)
2	Yes	Opportunistic infections*	BIcMQ “Opportunistic infections” BIcMQ (30000108)
3	Yes	Tuberculosis*	BIcMQ “Tuberculosis” BIcMQ (30000107)
4	Yes	Severe infections*	SOC “Infections and infestations” with CRF grade >=3

Table 7.8.1:1 Other special groupings of adverse events

5	No	Cardiovascular, Cerebrovascular, events (including MACE)	• SOC 'cardiac disorders' (fatal cases only) • SOC 'vascular disorders' (fatal cases only) • SMQ Myocardial Infarction (20000047) • SMQ Haemorrhagic central nervous system vascular conditions (20000064) • SMQ Ischaemic central nervous system vascular conditions (20000063) PTs: cardiac death, sudden cardiac death, sudden death

*: adverse event of special interest (AESI). AESI will be collected according to eCRF

The following periods will be defined for assessing adverse events:

- First 12 weeks of treatment
- Second 12 weeks of treatment

For AE occurs on day of week 12 visit, actual AE onset time will be compared with first drug administration time to determine AE period. The treatment label for second 12 weeks will be a combination of actual treatment in first 12 weeks of treatment and second 12 weeks of treatment.

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
- Severe AEs (RCTC grade 3 or 4)
- Investigator defined drug related SAE
- Other significant AEs
- AE by worst RCTC intensity
- Investigator defined drug-related serious AEs
- Special AE grouped term

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards. For lab descriptive, two separate tables for first 12 weeks of treatment and entire study period will be provided. For the entire period table, a new treatment label for each patient: start with treatment received at randomization and be updated if the patient have switched the treatment during the course of trial (by concatenating the second treatment after the first treatment) will be derived.

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 with possibly clinically significant abnormalities will be identified within the initial on-treatment period by study treatment.

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 parameter within each treatment period, and treatment group. For these shift tables, only the double blind period will be considered. Parameters using categorised values, such as the urinalysis parameters, will show the shift table among those values in a similar manner to the RCTC graded values. Last and worst value will be considered with respect to each period. For example, if patient have entered the second 12 weeks of treatment, then the last value for first 12 weeks table is considered as the last value measured before week 12 reassignment.

A graphical summary highlighting potential cases of Hy's Law within each treatment group 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 randomized 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

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (see DM&SM: Display and Analysis of Laboratory Data) (5).

Listing and descriptive statistics of laboratory values over time as well as median and interquartile range (IQR) of changes between baseline and extreme abnormal value on treatment will be provided. Baseline is understood as the last available measurement before study drug administration. Extreme abnormal value on treatment is understood as the on treatment laboratory value which is most significantly away from the reference range.

Frequency of patients with transitions relative to reference range and listing of patients with significant abnormal laboratory values will be presented as well.

In cases of repeated measurements performed for the same visit the last observation will be used for tabulations.

7.8.4 ECG

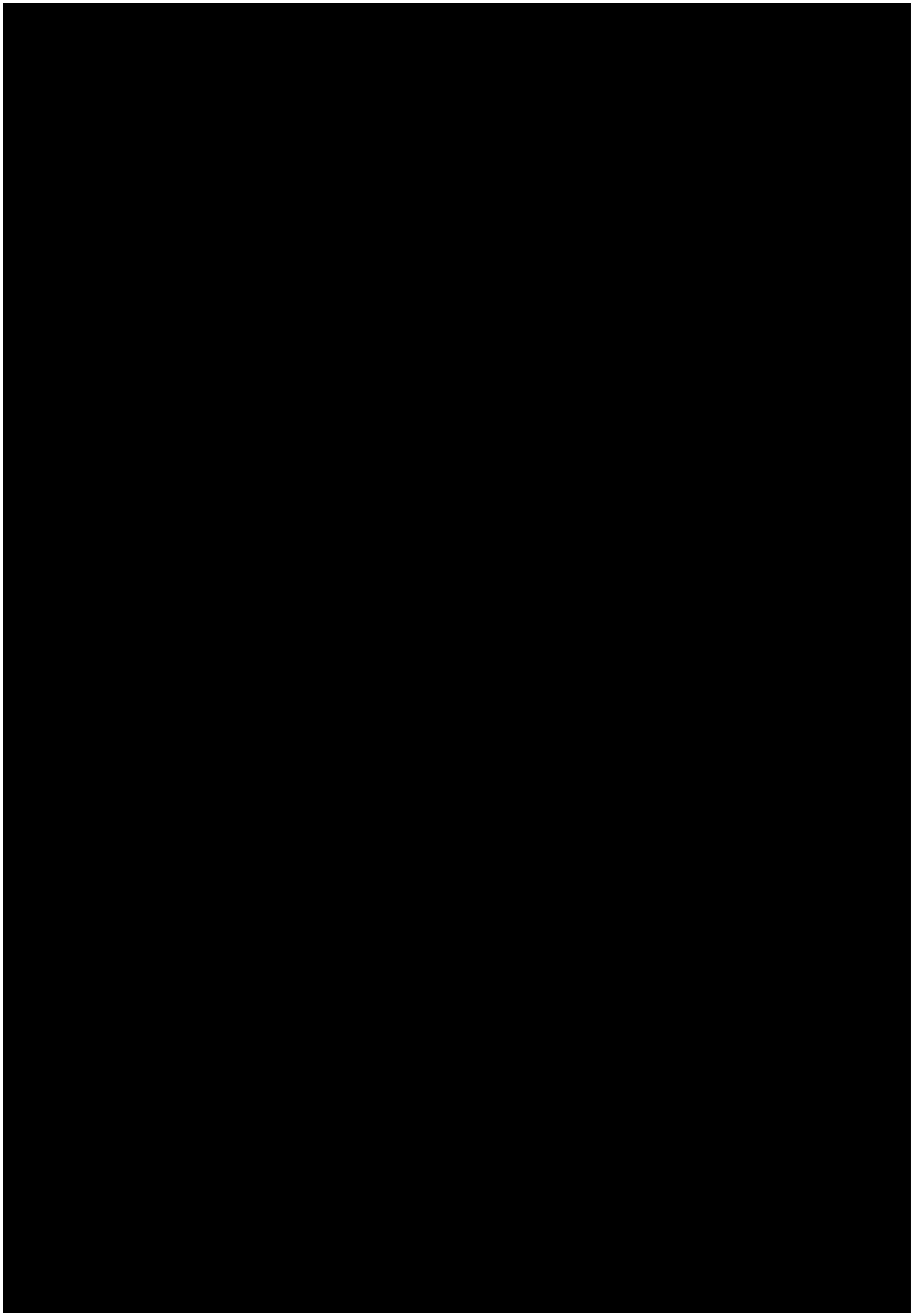
Not applicable.

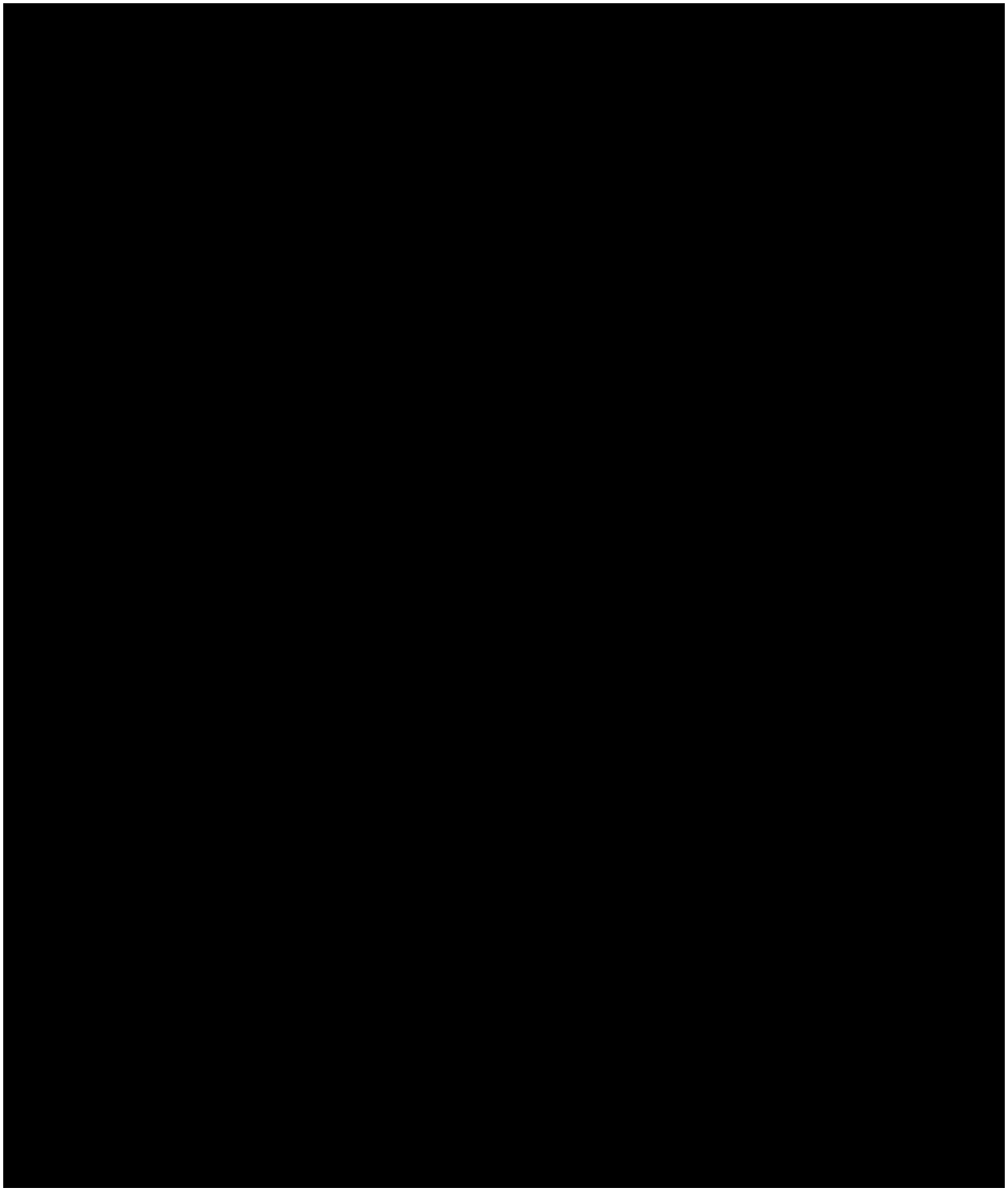
7.8.5 Others

CSS-R
The individual items and categories of suicidal ideation and behavior from the C-SSRS will be summarized through descriptive statistics.

8. 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]	
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]	
7.	Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat. 2006; 16:5. 639-656.[R10-1424]
8.	Pinheiro J, Bomkamp B, Glimm E, et al. Model-based dose finding under model uncertainty using general parametric models. Stat Med 2014; 33 (10): 1646-1661 [R15-4293]
9.	Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding' (February 19, 2015). Comprehensive R Archive Network. 2015 [R15-2001]





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**08-Nov -2018**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**06-Sept-2019**	[redacted]	None	This is the final TSAP, approved before unblinding of the week 4 interim analysis. It is also intended to be the TSAP for primary analysis at week 12 and final database lock.

APPROVAL / SIGNATURE PAGE

Document Number: c25658163 **Technical Version Number:2.0**

Document Name: 8-01-tsap-core

Title: Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	06 Sep 2019 20:08 CEST
Approval-Biostatistics		06 Sep 2019 20:28 CEST
Approval-Medical Writer		09 Sep 2019 07:55 CEST
Approval-Clinical Trial Leader		09 Sep 2019 11:14 CEST
Approval-Team Member Medicine		09 Sep 2019 22:02 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

TRIAL STATISTICAL ANALYSIS PLAN

c35536779-01

BI Trial No.:	1407-0030 Part 2
Title:	Phase II evaluation of safety, tolerability, and efficacy of BI 730357 in patients with moderate-to-severe plaque psoriasis Including revised protocol amendment (c20414608-08)
Investigational Product(s):	BI 730357
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	12 May 2021 SIGNED
Version:	1

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

A list of all abbreviations used in this TSAP

Term	Definition / description
AE	Adverse Event
BRPM	Blinded Report Planning Meeting
BES	Biopsy Evaluable Set
CTC	Common Terminology Criteria
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
IPD	Important Protocol Deviation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
MMRM	Mixed Effect Model Repeated Measurement
PASI	Psoriasis Area Severity Index
PK	Pharmacokinetics
PKS	Pharmacokinetics Set
PPS	Per Protocol Set
PSTAT	Project Statistician
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
REP	Residual Effect Period
SA	Statistical Analysis

Term	Definition / description
SD	Standard Deviation
SMQ	Standardised MedDRA Query
SOC	System Organ Class
sPGA	Static Physician's Global Assessment
TOM	Trial Oversight Meeting
ToC	Table of Contents
TS	Treated Set
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. To be precise, this trial statistical analysis plan intends to describe the statistical analysis strategy for the part 2 of study 1407-0030 in detail.

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 analyses.

R Version 4.0.1 (2020-06-06) with “RBesT” package (Version 1.6.1) will be used for the Bayesian analysis.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

A fast-track approach will be taken in order to expedite decision making and for preparation of the planned phase III trials, see more details in Section 8.

Details surrounding the assessment of the impact of the COVID-19 pandemic on the trial, are specified in Section 10.1.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The co-primary endpoints are:

- Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 12
- Achievement of a sPGA score 0 or 1 at Week 12

The summary measures for the co-primary endpoints are the proportion of patients achieving PASI 75 at Week 12 and achieving sPGA 0/1 at Week 12, respectively, by treatment group.

Details for scoring Psoriasis Area and Severity Index (PASI) and static Physician Global Assessment (sPGA) are described in Section 10.1 and 10.2 of the CTP.

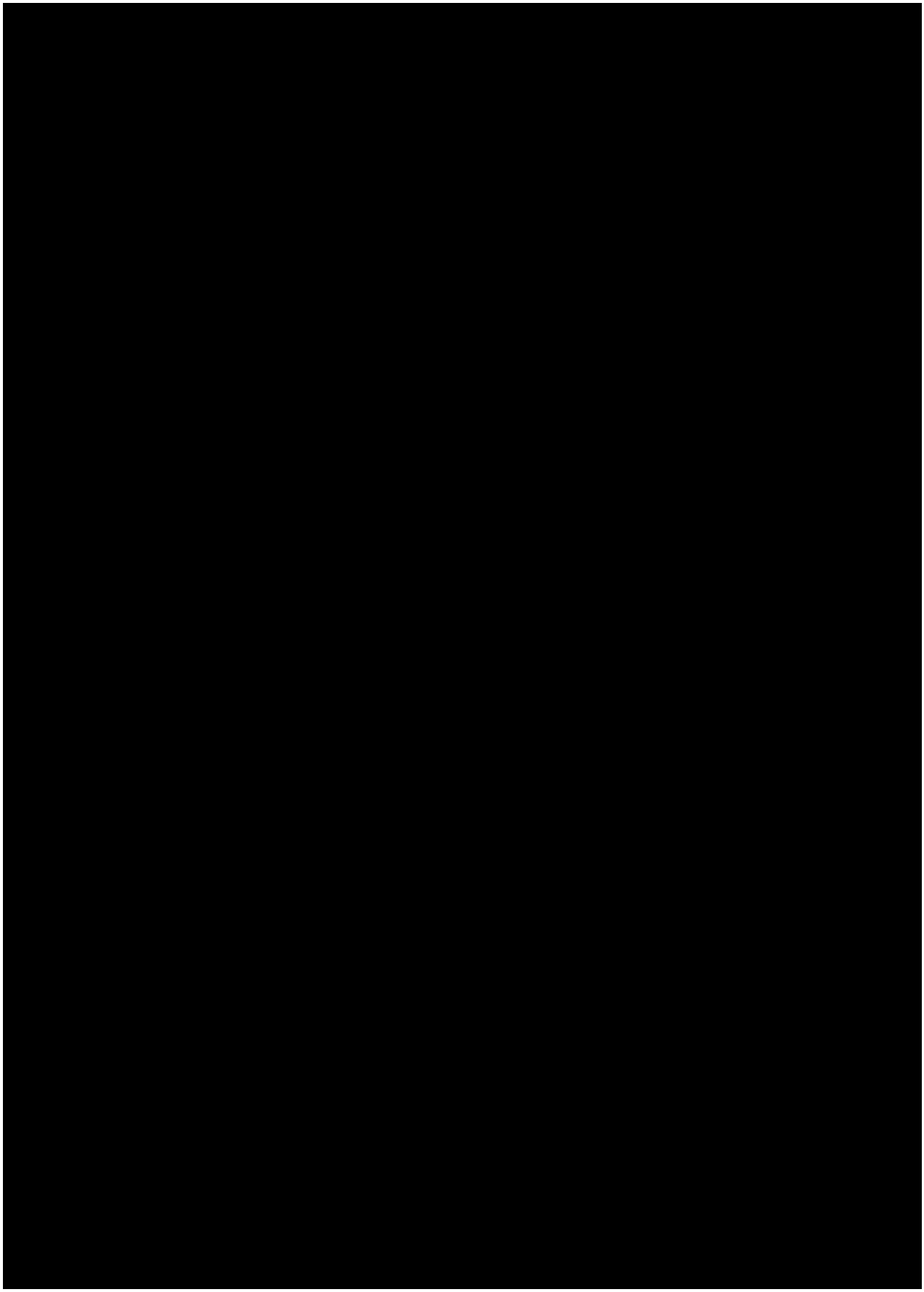
5.2 SECONDARY ENDPOINT(S)

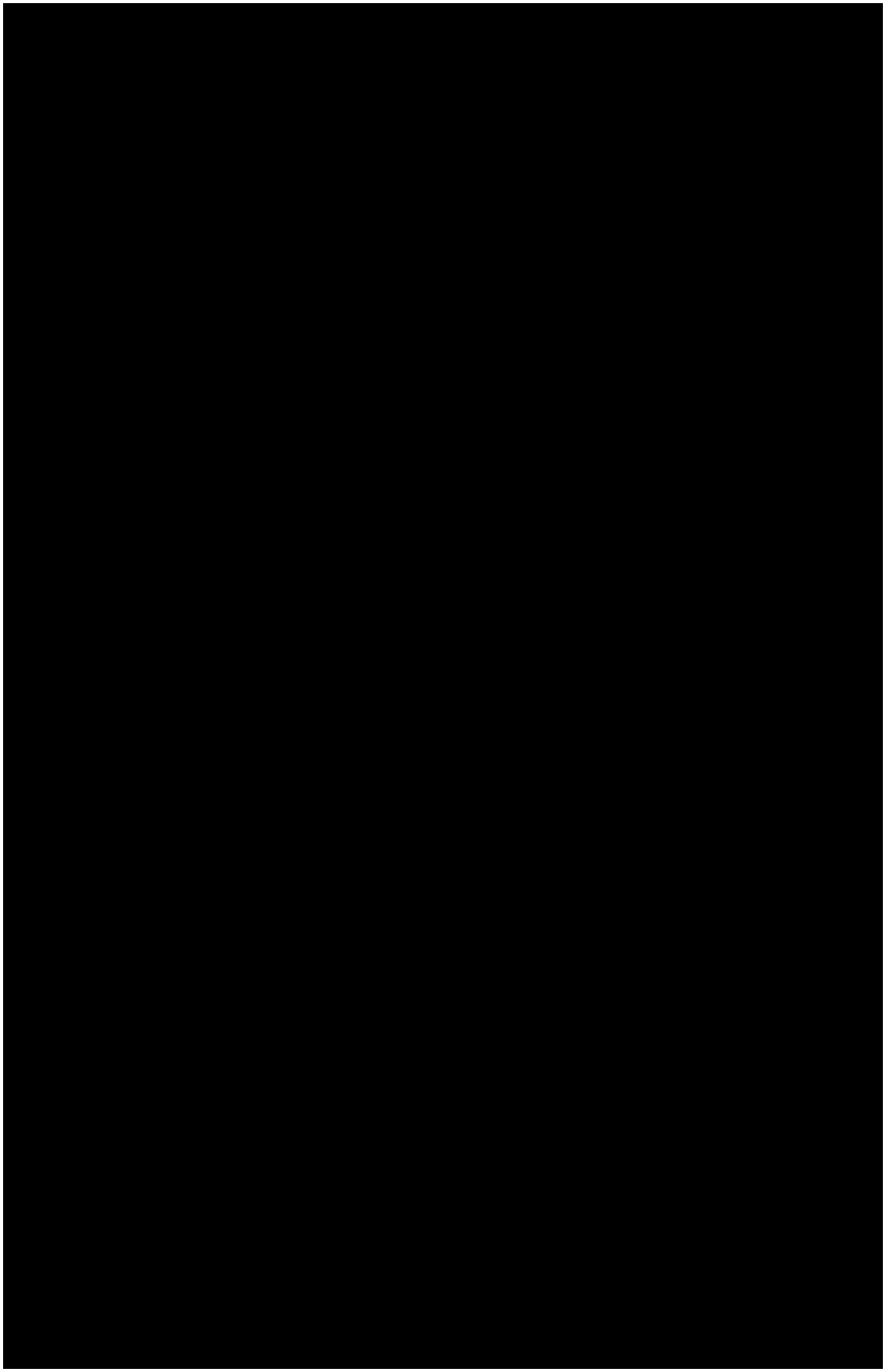
5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

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





5.4.5 Variables related to safety

In this trial, no endpoint of safety will be analyzed. However, safety and tolerability will be assessed in a descriptive way based on:

- Vital signs (blood pressure (BP), pulse rate (PR), body weight)
- Clinical laboratory tests (hematology, clinical chemistry and urinalysis)
- Suicidality (as captured in the Columbia-Suicide Severity Rating Scale(C-SSRS))
- Adjudicated cerebrocardiovascular events
- Adverse events (note that clinically significant physical examinations and pathological ECG findings are reported as AE/SAE)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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.

Patients will be analyzed according to the treatment to which they were randomized. The following study periods based on actual start and stop dates of study treatment administration are defined:

Table 6.1: 1 Definition of treatment periods

Analysing Treatment Period	**Start Date (including)**	**Stop Date (excluding)**
Screening	Date of informed consent	Date of medication randomization -1 day
On-treatment period	Date of medication randomization	Date of last study medication intake + 7 days
Follow-up	Date of last study medication intake +8 days	Last contact date

For the main safety analyses, Adverse Events (AEs) will be classified to one of the following time periods: “screening”, “on-treatment”, 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 are listed below:

- If date of informed consent ≤AE onset date <date of first drug administration, then the AE is assigned to “screening”;
- If date of first drug administration ≤AE onset date ≤date of last intake +7 days, then the AE is assigned to “on-treatment”;
- If AE onset date > date of last drug administration+7 days, then the AE is assigned to “follow-up”.

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.

6.2 IMPORTANT PROTOCOL DEVIATIONS

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. Handling of iPDs in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in the electronic Document Management System (eDMS).

6.3 SUBJECT SETS ANALYSED

The following patient analysis sets are defined:

- Screened set:

  This screened set includes all patients who signed the informed consent form.

- Randomised set (RS):
  The RS includes all patients who signed the informed consent form and were also randomised, regardless whether the patient was treated with trial medication or not.

- Treated set(TS):
  The TS includes all patients in the RS who were documented to have taken at least 1 dose of trial medication. Patients will be grouped based on the actual treatment received at the randomization visit and week 12 visit, if applicable.

- Full analysis set (FAS):

  The FAS includes all patients in the RS who received at least 1 dose of trial medication and provided baseline and at least 1 post-randomisation measurement of PASI. Patients will be grouped according to the treatment to which they were randomized by IRT at the start of the trial.

[redacted]

The FAS will be used for the analyses of demographics, baseline characteristics and all efficacy endpoints. The efficacy analyses will follow the intention-to-treat (ITT) principle in assigning patients to treatment groups, i.e., efficacy analyses will be analysed as randomised using the FAS.

The TS will be used for the analyses of concomitant medication use, medical history, PsO therapy history, treatment exposure, compliance, and safety (including adverse events, laboratory measurements, vital signs, and ECG). Safety analyses will assign patients to the treatment group based on the actual treatment received.

If a patient erroneously receives the wrong dose of trial drug, the patient's efficacy data will be analysed using the randomized treatment group and the patient's safety data will be analysed using the actual treatment group.

[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

6.6.1 Efficacy data

General imputation rules for continuous and binary endpoints are described in protocol section 7.5. Every effort should be made to collect complete data at all visits.
The following rules will be used to impute for missing data:

- For all non-binary endpoints, LOCF (Last Observation Carried Forward) will be used to impute missing values.
- For all binary endpoints (i.e., endpoints that are either 1 (patient responded) or 0 (patient did not respond)):
  - If no data after that visit*, then impute as failure (NRI [No Response Imputation])
  - If data at visits* before and after, only impute as success if both visits are successes; else impute as failure.

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

If at any time a patient uses an inappropriate concomitant medication, then all future data will be treated as failure for binary variables and LOCF (using the last on-treatment observation prior to inappropriate concomitant medication use) for continuous variables. As part of the LOCF technique, baseline values will be carried forward if no post-baseline value is available.

If a patient is missing items from a questionnaire measured at a visit, these will be handled according to the instructions given in Section 10 of the protocol specific to each questionnaire. Missing items from the Quality of Life questionnaires will be handled according to the measure instructions (cf. CTP Appendix 10.6). If there is no data for a particular visit, then it will be imputed following the same rules as described in the protocol.

For the NAPSI, PSSI, and PPASI assessment, if the CRF is marked as “No” indicating that the patient does not have nail, scalp, palmo-plantar disease, then exclude such patients from the analysis for NAPSI, PSSI, and PPASI.

For efficacy endpoints which are continuous in nature, a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will be used for inferential analysis, if applicable. No imputation will be performed for data used in MMRM.

6.6.2 Safety data and other data

With respect to safety evaluations, it is not planned to impute missing values; and only observed values will be analysed.

Missing or incomplete AE dates will be imputed according to BI standards “Handling of missing and incomplete AE dates” (2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For efficacy endpoints, baseline is defined as the pre-treatment observation at Visit 2. If Visit 2 is missing, then Visit 1 will be used for baseline.

For laboratory safety measurements, the last measurements taken prior to the treatment start 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 1 in the protocol. 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 6 is planned on Day

29 and Visit 7 is planned on Day 57. Therefore, the window of Visit 6 reaches until Day 42 while the window of Visit 7 starts on Day 43. The visit schedule with corresponding windows is given in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of on-treatment efficacy, safety lab, vital signs, and biomarker measurements to visits for statistical analysis

Window No.	Window label	Nominal visit	Nominal day	Interval
0	Baseline	VISIT 2	1	N/A
1	Week 1	VISIT 3	4	[2,5]
2	Week 1	VISIT 4	8	[6,11]
3	Week 2	VISIT 5	15	[12,21]
4	Week 4	VISIT 6	29	[22,42]
5	Week 8	VISIT 7	57	[43,70]
6	Week 12	VISIT 8/EOT visit	84	[71,98]
7	Week 16	EOS	113	[99,∞]

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.

The same visit windows will be used for safety laboratory and vital sign assessments. If there are multiple safety or laboratory values in one time window on treatment, the worst value will be selected for the by-visit analyses.

Analysis of AE data, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Frequency tables for these data will be using on-treatment data only. Therefore, no assignment to time windows will be necessary for such data.

While the nominal times listed in this section should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

For visits without an assigned value based on time windows, a value will thereafter be imputed as defined in Section 6.6. LOCF imputation of efficacy endpoints, when applicable,

will be performed based on all available observations obtained during the on-treatment period, irrespective of whether the observation was selected in any time window.

7. PLANNED ANALYSIS

For End-Of-Text (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.

Planned treatment is defined as the treatment to which one patient has been assigned by IVRS at randomization visit (visit2).

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 will be summarized by treatment ongoing patients, patients complete planned treatment period and patients who are prematurely discontinued, by reason. Disposition will be listed by country.

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] (continuous)
- Weight Group (>100kg vs. ≤ 100 kg)
- Body mass index [kg/m^2] (defined as weight [kg]/(height [cm]/100)$^{2)}$
- Body mass index category (≥30 kg/m^2 vs. <30 kg/m^2)
- Smoking history (Never-smoked, Former-smoker, Currently smokes)
- Alcohol History (Never-drinker, Former-drinker, Current-drinker)
- Region and country
- Prior biologic use for psoriasis (Yes/No)

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

- BSA (Visit 1)
- PASI score
- sPGA
- NAPSI, PPASI, PSSI
- Pain VAS
- PSS total score
- DLQI
- Duration of Psoriasis [years]
- PsA history (diagnosed, suspected, no PsA)

For NAPSI, PPASI, PSSI and pain-VAS, report is only based on patients who have such applicable measurements per protocol, e.g. pain VAS is reported only among patients with psoriatic arthritis.

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, based on the treated set.

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. 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. Depending on if concomitant medication stops before trial treatment starts or not, medication information collected from eCRF pages will be classified as historical medication or on-treatment concomitant medication, and a summary table will be provided for each of the two categories. Historical medication is defined as medication taken prior to the start of trial treatment and stopped before trial treatment starts. There are two scenarios for on-treatment concomitant medications:

- Scenario 1: medication start date or stop date is between first dose of trial treatment and last dose of trial treatment plus 7-day REP;

or

- Scenario 2: medication stop date is after ‘last dose of trial treatment plus 7-day REP’, and medication start date is before ‘last dose of trial treatment plus 7-day REP’.

7.3 TREATMENT COMPLIANCE

Treatment non-compliance, as one type of important protocol deviations (iPDs), is defined as any randomized patients having taken at least one dose of study medication with an overall compliance rate not between 80% and 120% inclusive. Overall compliance rate is calculated based on unweighted average of study drug compliance rate across all visits during the treatment period. For patients who discontinued the study treatment prematurely, only the visits on or before premature discontinuation will be used for the calculation of overall compliance rate.

Treatment compliance will be reported from baseline to Week 12 based on calculation as described in CTP section 4.3. When presenting the compliance rate of study medication by visit, if patients discontinue treatment prematurely, then their compliance data collected at EOT visit is mapped to the next originally planned visit per protocol for reporting. For example, if one patient prematurely discontinues the study treatment at Week 10 and comes to site for EOT visit, then his/her compliance data collected at EOT visit is mapped to Week 12 for reporting purpose. That compliance rate should be interpreted as the compliance rate for his/her participation days in the window between planned Week 8 and Week 12.

Only descriptive statistics are planned for this section of the report. Summary statistics of 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 co-primary endpoint ‘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.

For Part 2 of 1407-0030, the primary analysis on PASI 75 at week 12 will be based on a Bayesian borrowing approach. An informative prior is derived for the placebo control group based on historical placebo data. 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 mentioned in the protocol is now updated based on additional historical information being available to:

[redacted]

Non-informative beta prior Beta(1, 1) is used for BI 730357 active treatment arms.

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 arm is higher than that for patients on placebo arm; and (2) relevance: a posterior probability of at least 50% that the PASI 75 response rate for patients on BI 730357 arm is higher than that for patients on placebo arm by various boundary values. If at least one dose satisfies both criteria based on PASI 75 response rate, 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. When falling in ‘consider zone’ based on PASI 75 response rate, sPGA 0/1 at week 12 will be jointly evaluated.

The calculations for the Bayesian posterior probability calculation are based on R-package RBesT Version 1.6.1 and R version 4.0.1(2020-06-06).

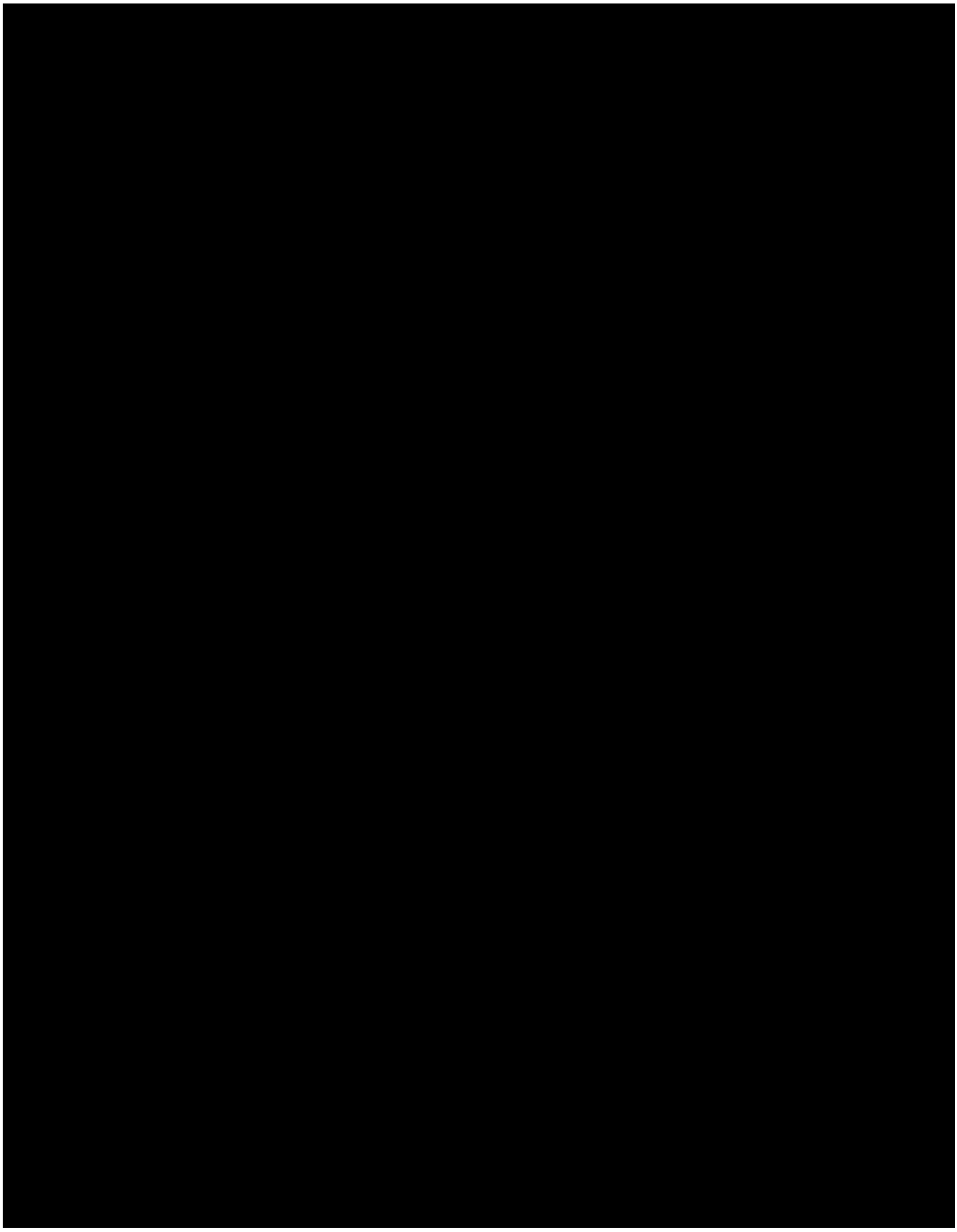
The primary analysis for sPGA clear or almost clear at week 12 will be summarizing the proportion of responders in each arm together with 90% and 95% exact confidence intervals.

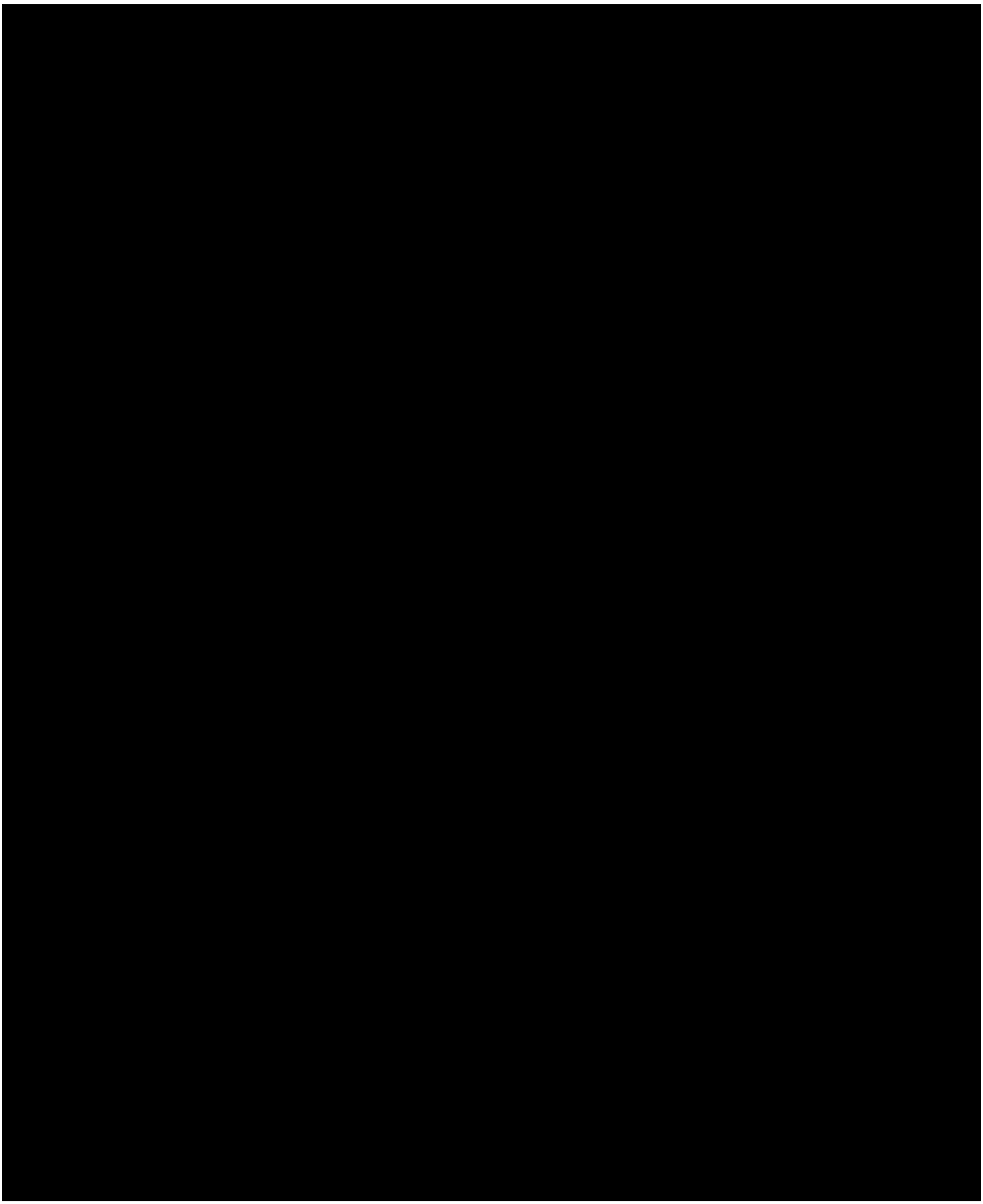
7.4.2 Secondary analyses for the co-primary endpoints

The secondary analyses for PASI 75 at week 12 include:

- summarizing the proportion of responders in each arm together with 90% and 95% exact confidence intervals.
- Calculating the unadjusted absolute difference in proportion between active treatment group and placebo group, 90% and 95% confidence intervals together with a corresponding p-value to investigate if the active treatment group has a different response rate from the placebo group based on Chi-square distribution;

The secondary analysis for sPGA clear or almost clear at week 12 is calculating the unadjusted absolute difference in proportion between active treatment group and placebo group, 90% and 95% confidence intervals together with a corresponding p-value to investigate if the active treatment group has a different response rate from the placebo group based on Chi-square distribution.





[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)

The same methods as discussed previously for the secondary analyses for the summary measure of the co-primary endpoint 'PASI 75 at week 12' will be used to analyse clinical binary secondary endpoints for each treatment group as well as treatment comparison.

Psoriasis Area and Severity Index (PASI)
Treatment comparison for unadjusted absolute difference in proportion between active groups and placebo group will be performed for achievement of 50% (PASI50), 90% (PASI90), 100% (PASI 100) at week 12.

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

Details for scoring sPGA and its components are described in Section 10.2 of the CTP.

Treatment comparison for unadjusted absolute difference in proportion between active groups and placebo group will be performed for sPGA equals to 0 at week 12.

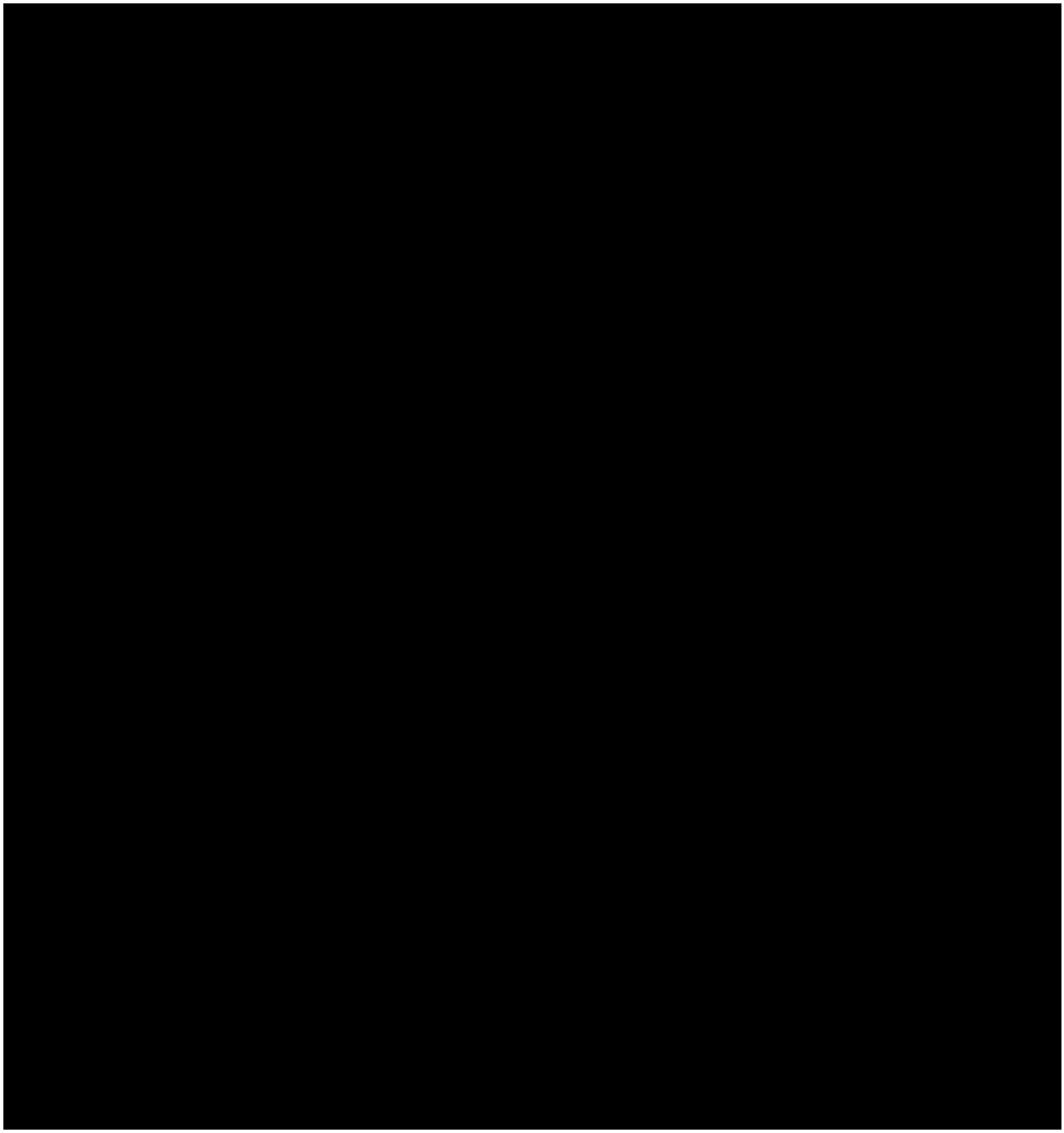
PSS total score change from baseline at week 12

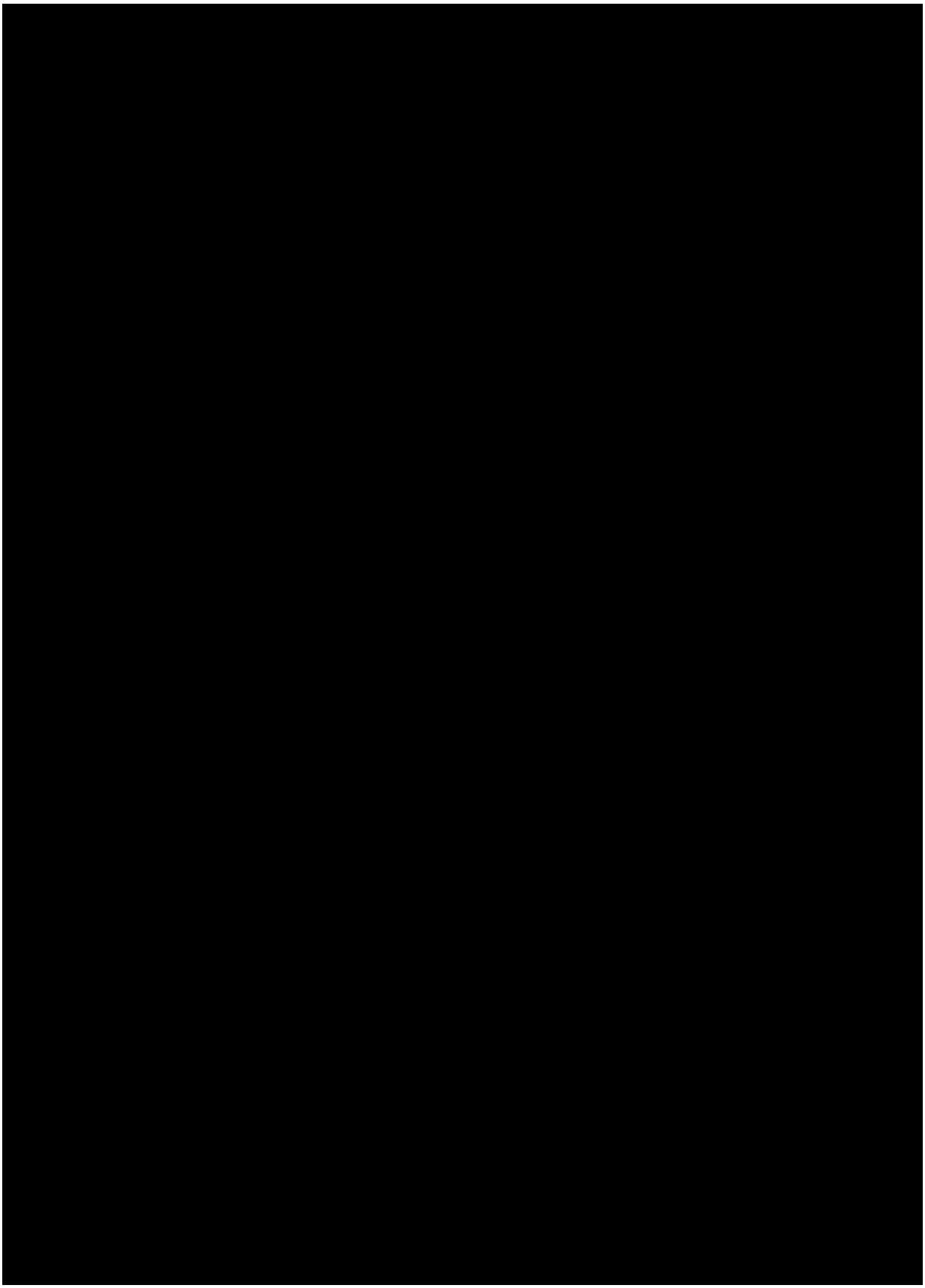
For change from baseline in PSS total score at Week 12 and treatment comparison, a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will be used. The analyses will include the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline PSS total score and baseline PSS score-by-visit interaction. Patient will be considered as a random effect. An unstructured covariance structure for within subject variation will be used.

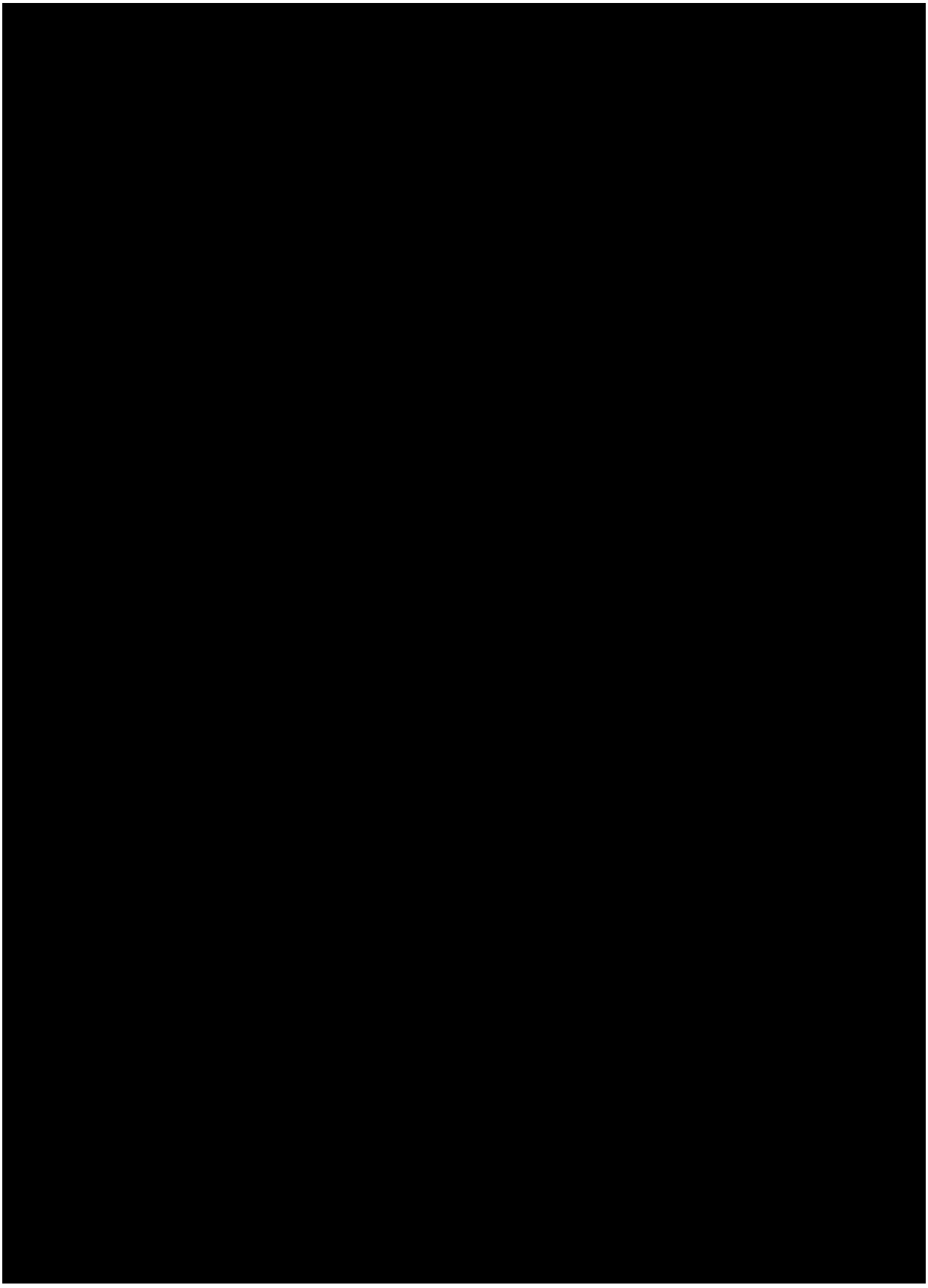
DLQI score of 0 or 1 at week 12

For DLQI, if one question is left unanswered, this is scored 0 and then the total score is summed and expressed as usual out of a maximum of 30.

Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at week 12 will be analysed by treatment comparison of unadjusted absolute difference in proportion between active groups and placebo group with 90% and 95% confidence intervals.







7.7 EXTENT OF EXPOSURE

Exposure will be presented as categorized period of "1-28", "29-56", "57-84" and "≥85" days based on dose received for total study medication intake. Exposure will be summarized and presented for first 12 weeks of treatment.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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).

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug administration and within 7 days after last drug administration will be assigned to the assigned treatment. 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.

All adverse events 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).

According to ICH E3 (6), 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' (7).

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

AESIs need to be reported to the sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAEs.

The AESI have been defined in section 5.2.6.1 of the protocol.

Other user-defined special adverse event grouped term for BI 730357 specified in Table 7.8.1:1 will be reported.

Table 7.8.1:1 Other user-defined special groupings of adverse events

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 - 20000235)
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 – MedDRA (soc code 10021881 mppath=1)
5	Gastritis related terms	• BIcMQ Gastritis (broad) [32008061]
6	Malignancies including all sub-SMQs	- SMQ broad (20000090) Merge medbase by mptcd to all HLT terms

This column indicates whether the Term(s) provided in the first column are MedDRA

preferred terms (PT), Standardised MedDRA Queries (SMQ) or BI customised MedDRA Queries (BIcMQ).
In addition, the adjudication outcome of Cerebro-cardiovascular events from the vendor, [redacted], will be summarized by indication, treatment, primary system organ class and preferred term.

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:

- Investigator defined drug-related AEs
- Investigator defined drug-related serious AEs
- AESIs
- AEs leading to discontinuation
- Serious AEs
- Other significant AEs
- AE by worst RCTC intensity
- Special AE grouped term (or called "user-defined AE category") specified in Table 7.8.1:1

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards.

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 with possibly clinically significant abnormalities will be identified within the initial on-treatment period by study treatment.

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 parameter within each treatment period, and treatment group. For these shift tables, only the double blind period will be considered. Parameters using categorised values, such as the urinalysis parameters, will show the shift table among those values in a similar manner to the RCTC graded values.

A graphical summary highlighting potential cases of Hy's Law within each treatment

group 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 randomized study drug will be considered as on-treatment.

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

Listing and descriptive statistics of laboratory values over time as well as median and interquartile range (IQR) of changes between baseline and extreme abnormal value on treatment will be provided. Baseline is understood as the last available measurement before study drug administration. Extreme abnormal value on treatment is understood as the on treatment laboratory value which is most significantly away from the reference range.

Frequency of patients with transitions relative to reference range and listing of patients with significant abnormal laboratory values will be presented as well.

In cases of repeated measurements performed for the same visit the last observation will be used for tabulations.

7.8.3 Vital signs

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

7.8.4 ECG

Relevant findings at baseline were reported as baseline conditions, and other findings on ECGs were reported as AEs and analyzed accordingly.

7.8.5 Others

C-SSRS
The individual items and categories of suicidal ideation and behaviour from the C-SSRS will be summarized through descriptive statistics.

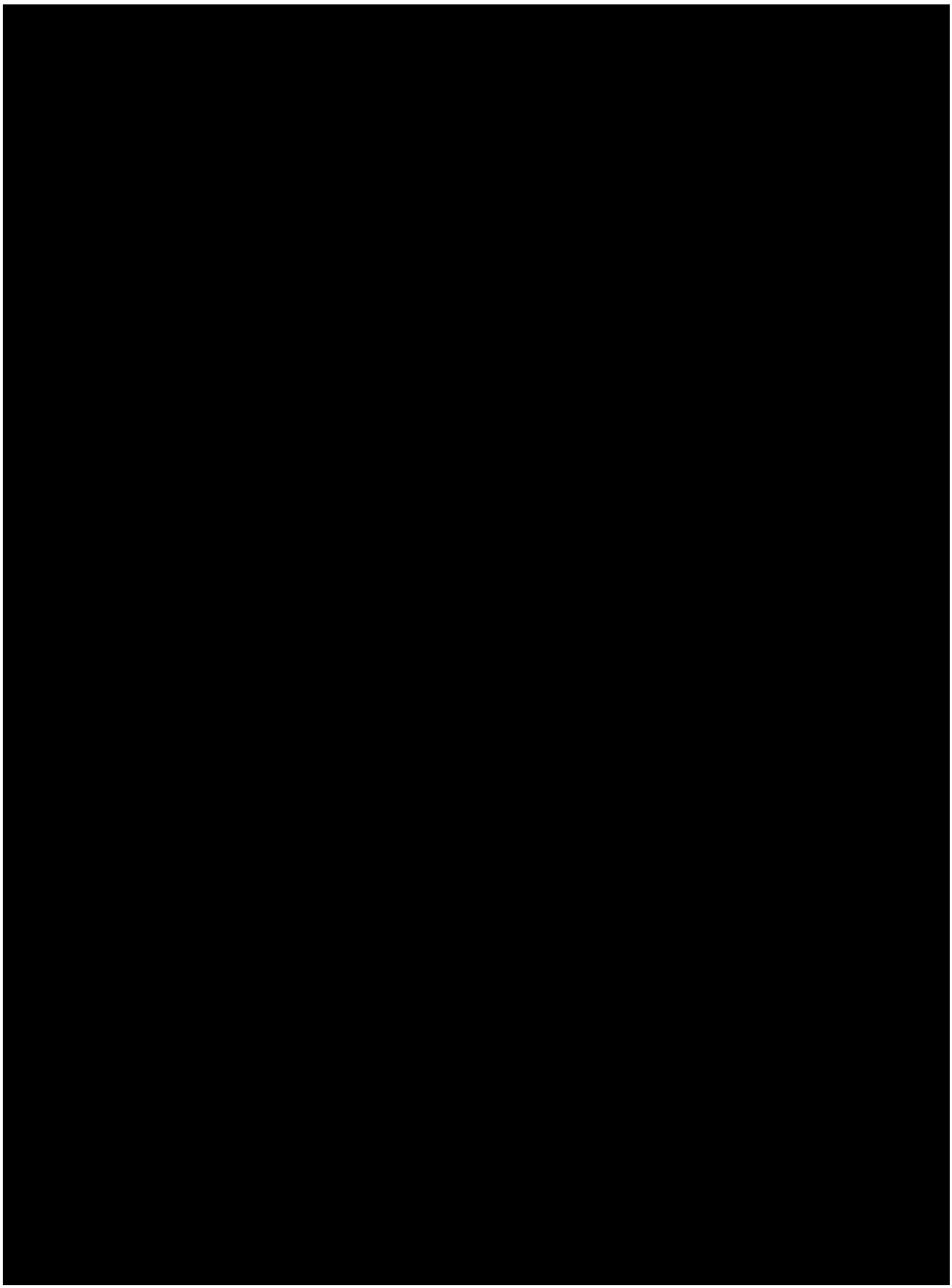
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

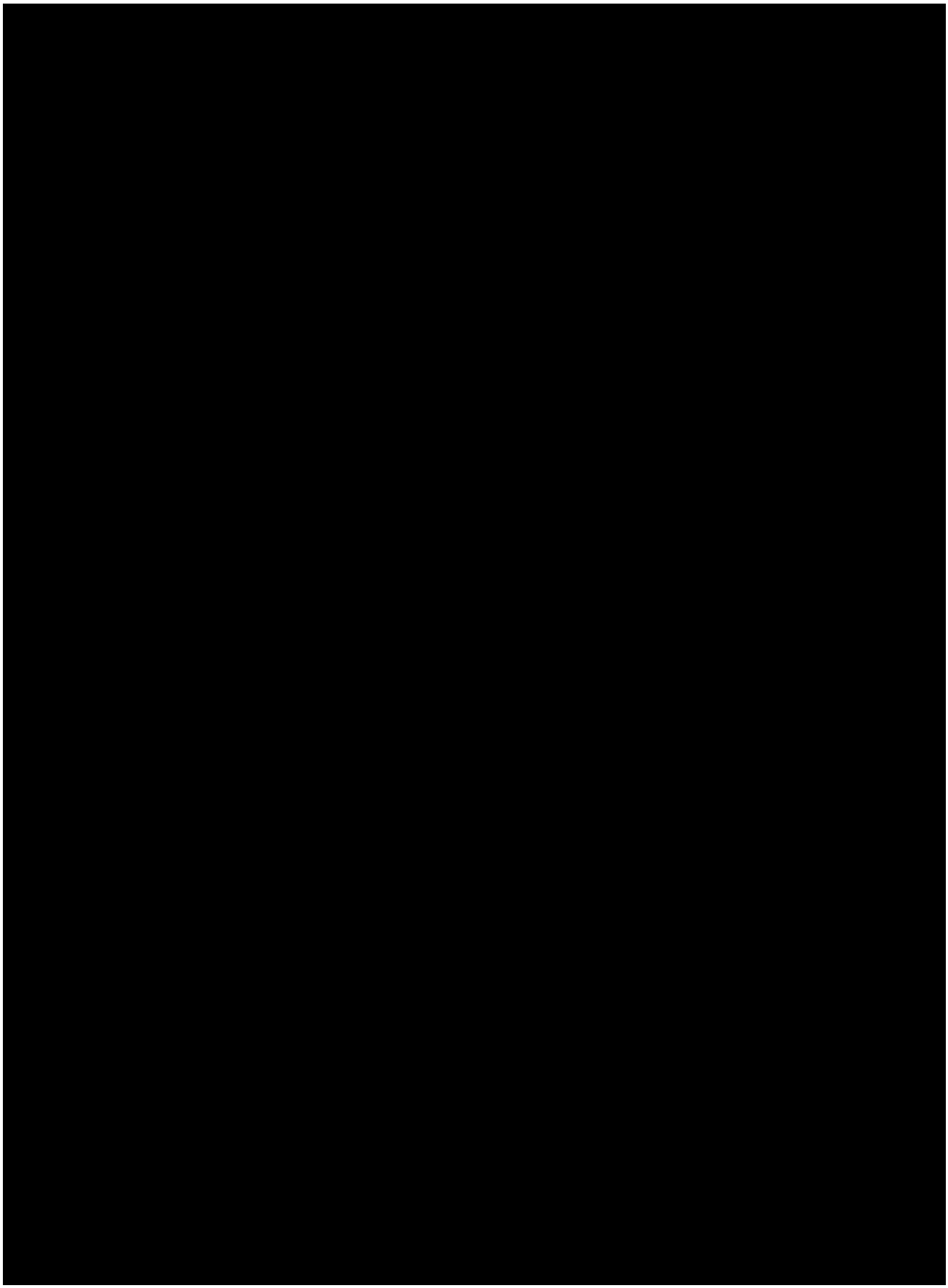
Fast-track approach:

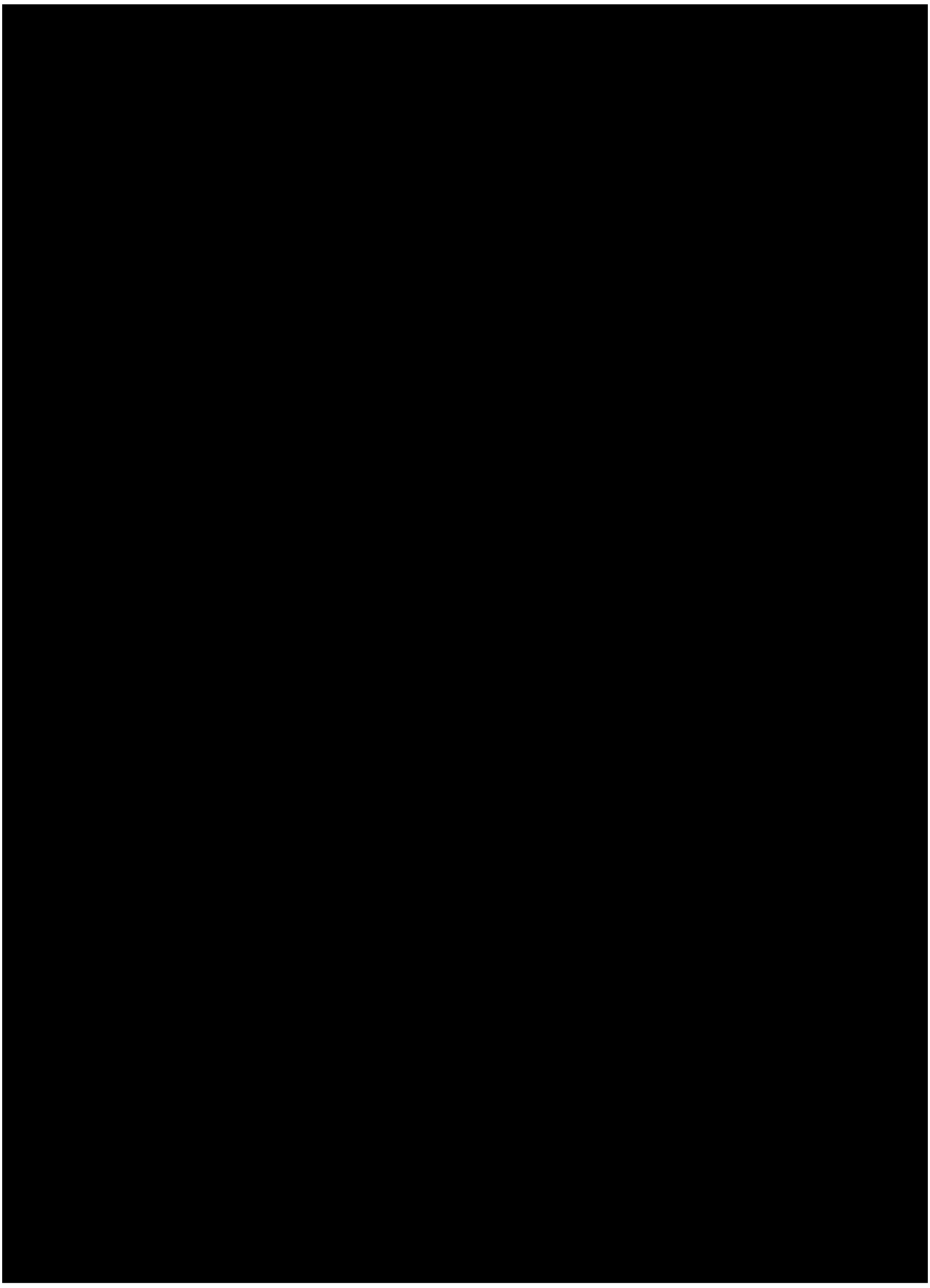
Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.
The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.
After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit will be documented and summarized in the CTR.

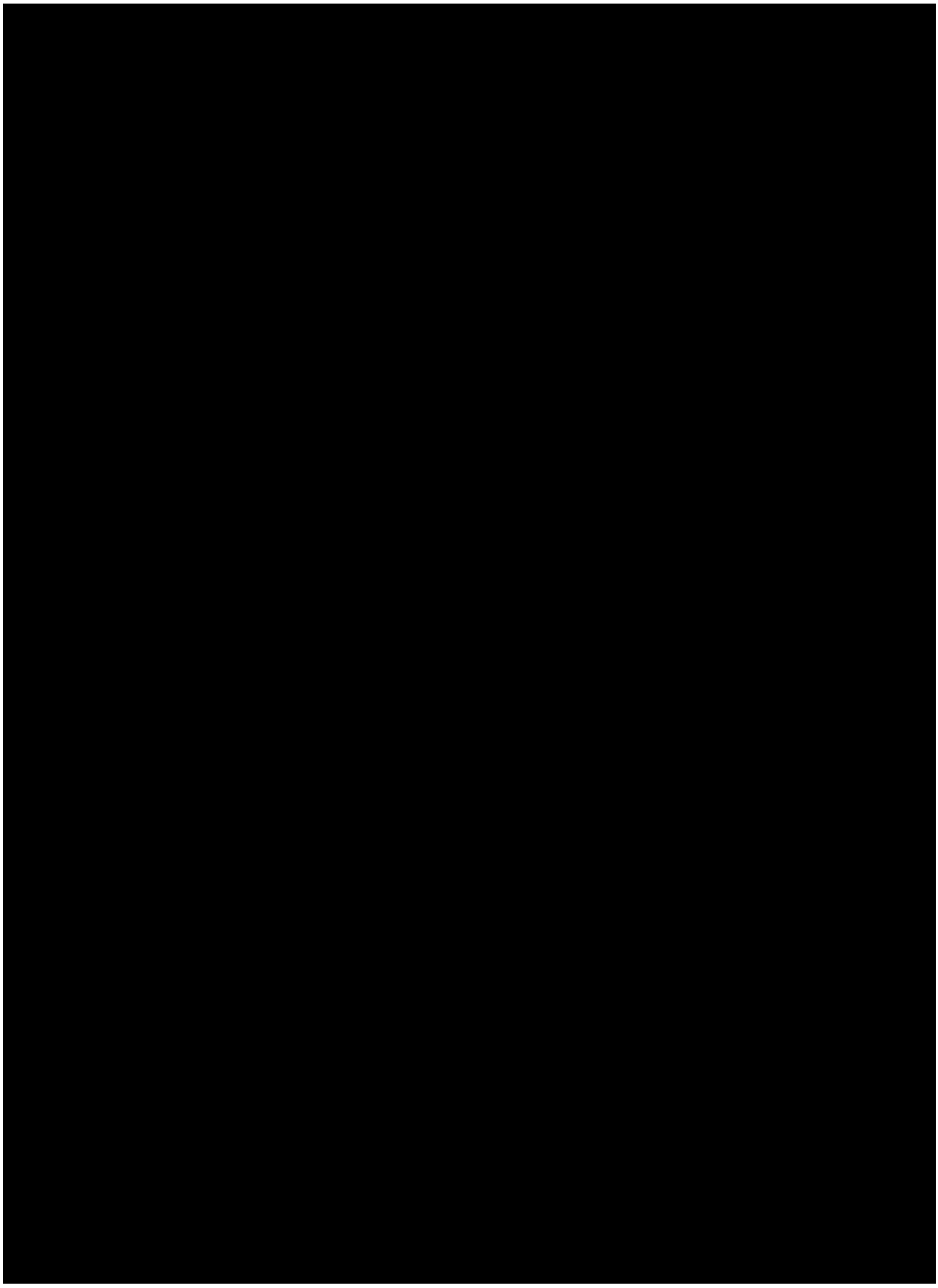
9. REFERENCES

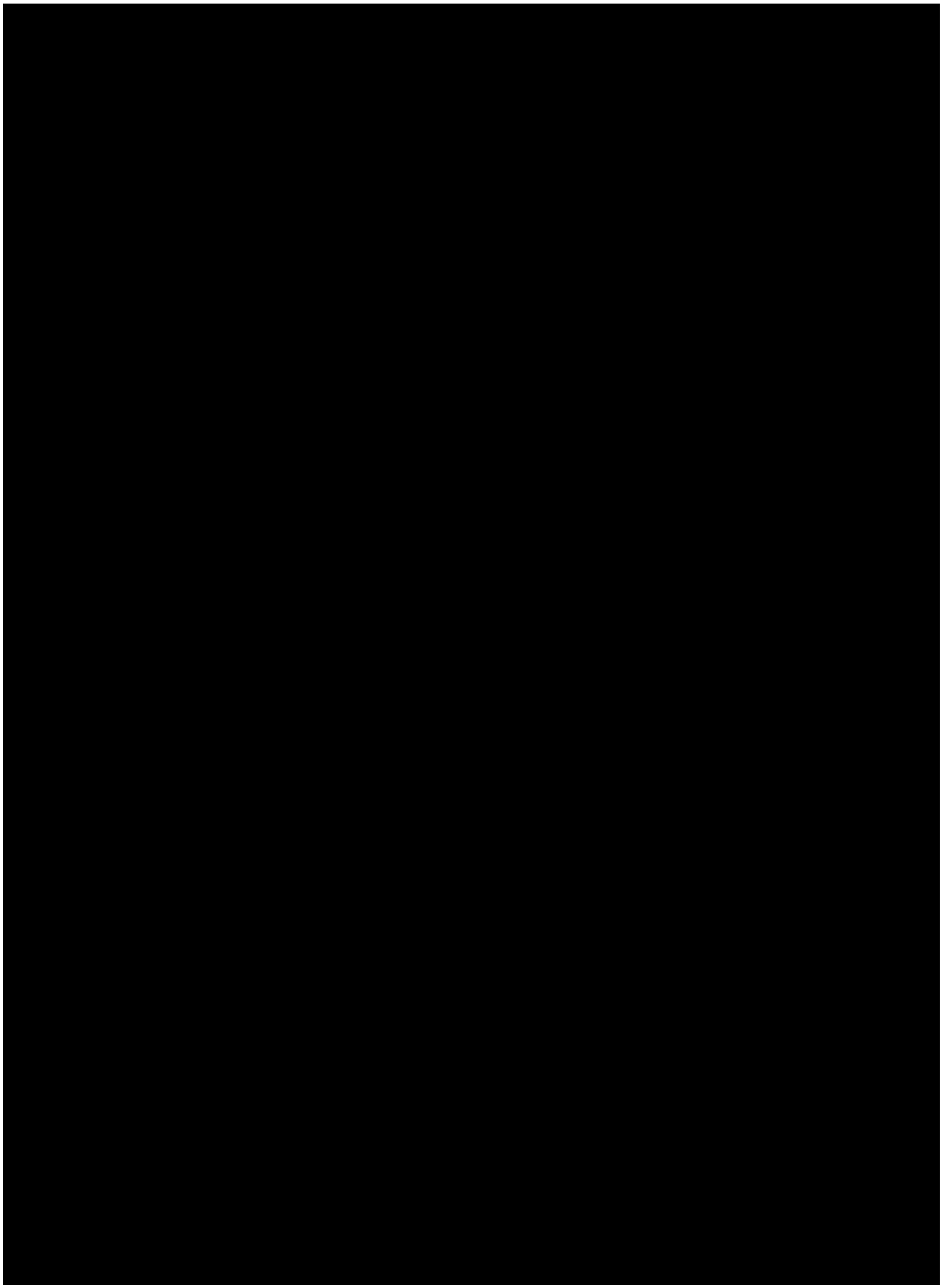
1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
[redacted]	
4.	Bias reduction of maximum likelihood estimates. Firth, D. Biometrika. 1993; 80 (1): 27-38. [R20-2291]
5.	Ge, M., Durham, L. K., Meyer, R. D., Xie, W., & Thomas, N. (2011). Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. Drug information journal: DIJ/Drug Information Association, 45(4), 481-493 [R16-5360]
6.	*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, EMA webpage.
[redacted]	

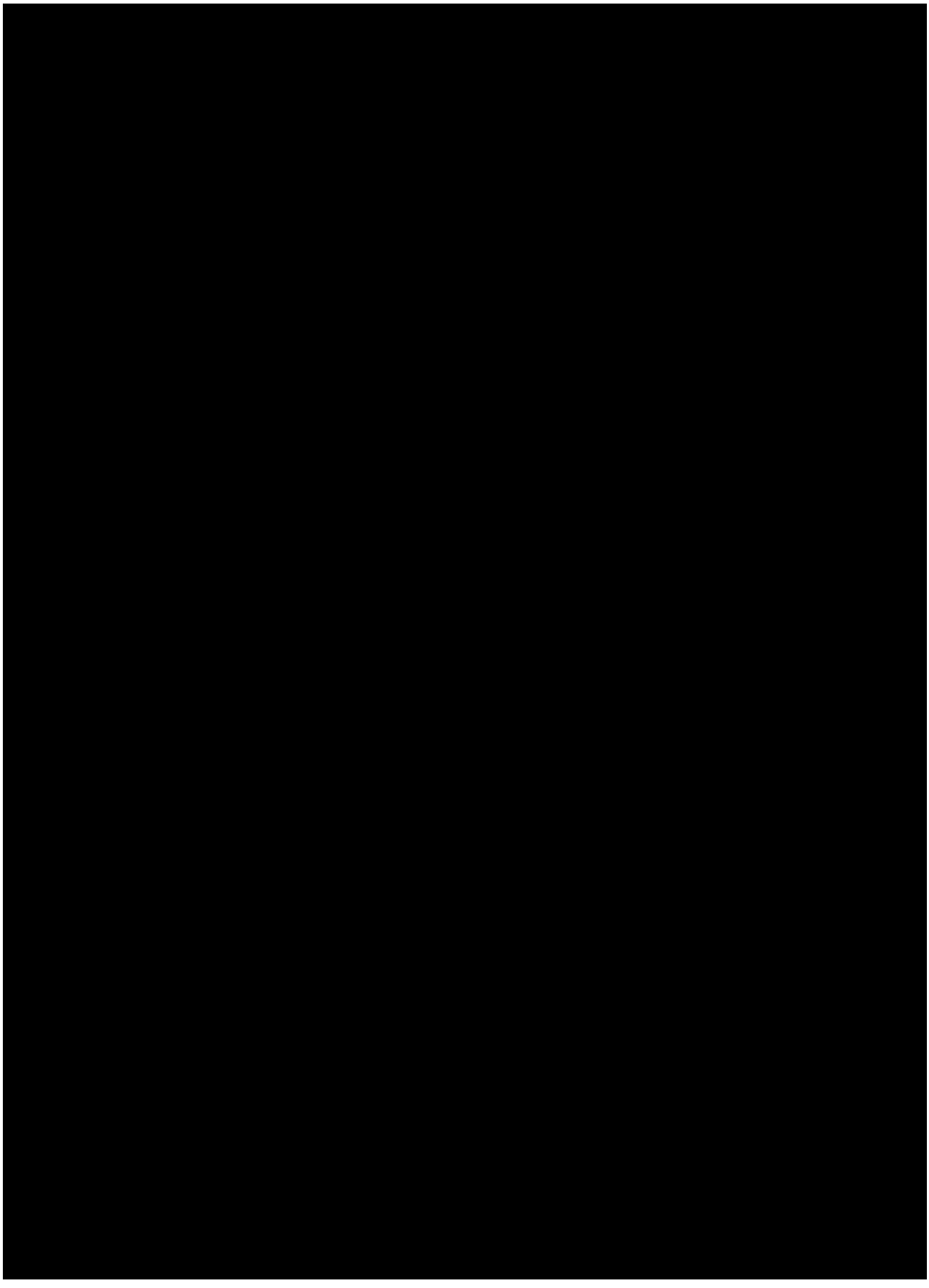


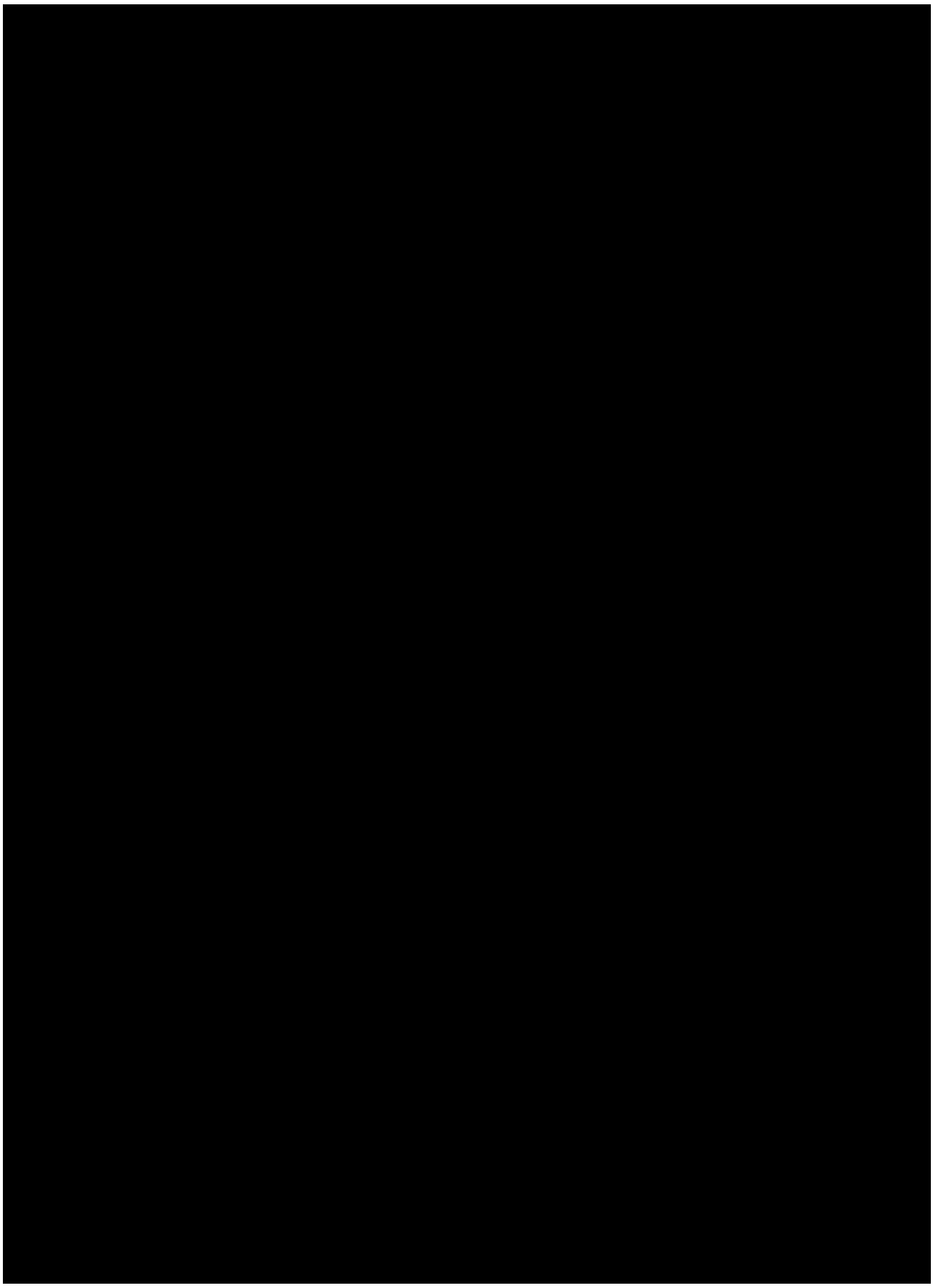












11. HISTORY TABLE

Table 11: 1 History table

Version	Date	Author	Sections changed	Brief description of change
1	**12-May-2021**	[redacted]	None	This is the final TSAP