Trial Statistical Analysis Plan

c09625501-02

BI Trial No.:	1358.1
Title:	A randomized, controlled multi-centre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain Including Protocol Amendment 1 [c03317678-02]
Test Substance:	Diclofenac + Capsaicin
Responsible trial statistician:	[redacted] Phone [redacted] Fax [redacted]
Date of statistical analysis plan:	06 October 2017 REVISED
Version:	Revised

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[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANCOVA	Analysis of Covariance
[redacted]	[redacted]
ASS	Acetyl salicylic acid
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BMI	Body Mass Index
BRPM	Blinded Review Planning Meeting
CI	Confidence Interval
cm	Centimetre
CRA	Clinical Research Assistant/Associate
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBLM	Database Lock Meeting
DBP	Diastolic Blood Pressure
[redacted]	[redacted]
eCRF	Electronic Case Report Form
EoT	End of Text
FAS	Full Analysis Set
g	Gram
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IDEA	International Document Management and Electronic Archiving System
IMP	Investigational Medicinal Product
IPV	Important Protocol Violation
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]

Term	Definition / description
MMRM	Mixed Model Repeated Measures
MQRM	Medical Quality Review Meeting
N	Newtons
NSAID	Non-steroidal Anti-Inflammatory Drug
[redacted]	[redacted]
PA	Pressure Algometry
POM	Pain on movement
POM_{WP}	Pain on movement of worst procedure
$POM_{WP}AUC_{72}$	Area Under the Curve of POM_{WP} assessed until Day 4 morning
$POM_{WP}AUC_{120}$	Area Under the Curve of POM_{WP} assessed until Day 6 morning
[redacted]	[redacted]
PR	Pulse Rate
[redacted]	[redacted]
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
REML	Restricted Maximum Likelihood
REP	Residual Effect Period
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
PDL	Patient Data Listing
SOC	System Organ Class
TMM	Trial Member Medicine
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
VAS	Visual Analog Scale
WHO-DD	World Health Organization-Drug Dictionary

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 trial statistical analysis plan (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, randomisation.

SAS® Version 9.4, or a later version, will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The following changes to CTP v1 were made and approved in CTP v2, dated 21-Jun-2016

Global Amendment 1:

1. The two endpoints, number of patients with a decrease in POM_{WP} from baseline of at least 30% and 50% respectively were planned to be analysed at the timepoint, before drug application in the morning of day 2 (Visit 2), however no such analysis will be performed as there is no POM assessment scheduled at this timepoint.

In addition, the following changes are made in the TSAP

- Contrary to the protocol, all analyses pertaining to change from baseline were programmed as

  Change in endpoint = Endpoint at time x – endpoint at baseline

  rather than

  Change in endpoint = Endpoint at baseline - Endpoint at time x

  To minimize the risk of error by re-programming it was decided not to reverse the calculation. Additionally it was felt that, for the POM assessments in particular, it would be intuitively preferable to show any decrease from baseline as a negative value thus providing an indication of treatment effect.

[redacted]

- The initial TSAP stated the planned treatment application date/time for Day 6 was to be included in the calculation of the time intervals used in the derivation of the key secondary endpoint, $POM_{WP}AUC_{120}$. However as there is no treatment application scheduled at Day 6, the POM assessment time for Day 6 will be imputed as the actual treatment application date/time for Day 5 evening + 12 hours or alternatively, Day 5 morning + 24 hours if the former is missing.

[redacted]

- Some sites in Germany, during the conduct of the trial, did not have sufficient POM booklets in stock which led to photocopies of the VAS scale being used in the POM assessments. Unfortunately some of these copied VAS scales were not exactly 10cm in length. Similarly for Russian sites, the VAS scale displayed in the POM booklets, printed in Russia, were not always exactly 10cm. As a consequence,
    - all POM measurements will be normalised, prior to analysis, to a 10cm scale.
    - [redacted]

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary efficacy endpoint is the change in pain on movement (POM) between baseline and day 2 evening, 1 hour after drug application (Visit 3), with regard to the POM of the procedure which gave the highest score at baseline ("POM of worst procedure", POM_{WP}).

$$Change\ in\ POM_{WP} = POM_{WP,day\ 2\ evening\ post\ application} - POM_{WP,baseline}$$

POM is assessed by the patient on one standardized movement by using a Visual Analog Scale (VAS) ranging from 0 mm = 'no pain' to 100 mm = 'worst pain possible for this condition'.

For definition of study baseline please refer to section 6.7.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

- $POM_{WP}AUC_{72}$ and $POM_{WP}AUC_{120}$

  AUC will be calculated as area under the curve from zero to approximately 72 hours (corresponding to $POM_{WP,\ day\ 4\ morning\ post\ application}$) or to approximately 120 hours (corresponding to $POM_{WP,\ day\ 6\ morning}$) using the trapezoidal rule divided by the observation time.

$$POM_{WP}AUC_{72} = \frac{1}{t_6}\sum_{i=1}^{6}\frac{1}{2}(POM_{WP}(t_{i-1}) + POM_{WP}(t_i)) * (t_i - t_{i-1})$$

$$POM_{WP}AUC_{120} = \frac{1}{t_7}\sum_{i=1}^{7}\frac{1}{2}(POM_{WP}(t_{i-1}) + POM_{WP}(t_i)) * (t_i - t_{i-1})$$

Study drug application date/times will be the basis for the calculation of respective time intervals.

$t_0 = 0$,

for i=1 to 6,

t_i = ([actual date of application of POM_{WP} assessment i+1] – [actual date of first application (visit 1)]) * 24 + [actual time of application of POM_{WP} assessment i+1] – [actual time of first application (visit 1)] + $1_{post\text{-}value}$.

t_7 = ([actual date of application on Day 5 evening] – [actual date of first application (visit 1)]) * 24 + [actual time of application on Day 5 evening – actual time of first application (visit 1)] + 12.

where

$$1_{post-value} = \begin{cases} 0, if\ pre-application\ POM_{WP}\ value \\ 1, if\ post-application\ POM_{WP}\ value \end{cases}$$

Planned assessment times are:

Assessment	$\mathbf{t_i}$
1 (Baseline)	$t_0 = 0$
2 (Day 1 morning, 1 hour after application)	$t_1 = 1$
3 (Day 2, morning, 1 hour after application)	$t_2 = 25$
4 (Day 2 evening, before application)	$t_3 = 36$
5 (Day 2 evening, 1 hour after application)	$t_4 = 37$
6 (Day 3, morning, 1 hour after application)	$t_5 = 49$
7 (Day 4, morning, 1 hour after application)	$t_6 = 73$
8 (Day 6, morning)	$t_7 = 120$

For AUC calculation, one or more missing assessments in between POM assessments will be imputed using the planned assessment time and a linear interpolation of the last available assessment before (including baseline, if applicable) and the first available assessment after the missing assessment. If there is no evaluable assessment after the planned time of the missing assessment, planned assessment time and LOCF will be used to impute the value.

For example, if assessment 3 is missing but assessments 2 and 4 are available, imputation will use the planned assessment time of 25 hours and linear interpolation using the data from assessments 2 and 4. If assessment 4 was also missing but assessment 5 was available that would be used instead.

5.2.2 Other secondary endpoints

- Number of patients with a decrease in POM_{WP} of at least 30% from baseline on day 2 evening, 1 hour after drug application (Visit 3)

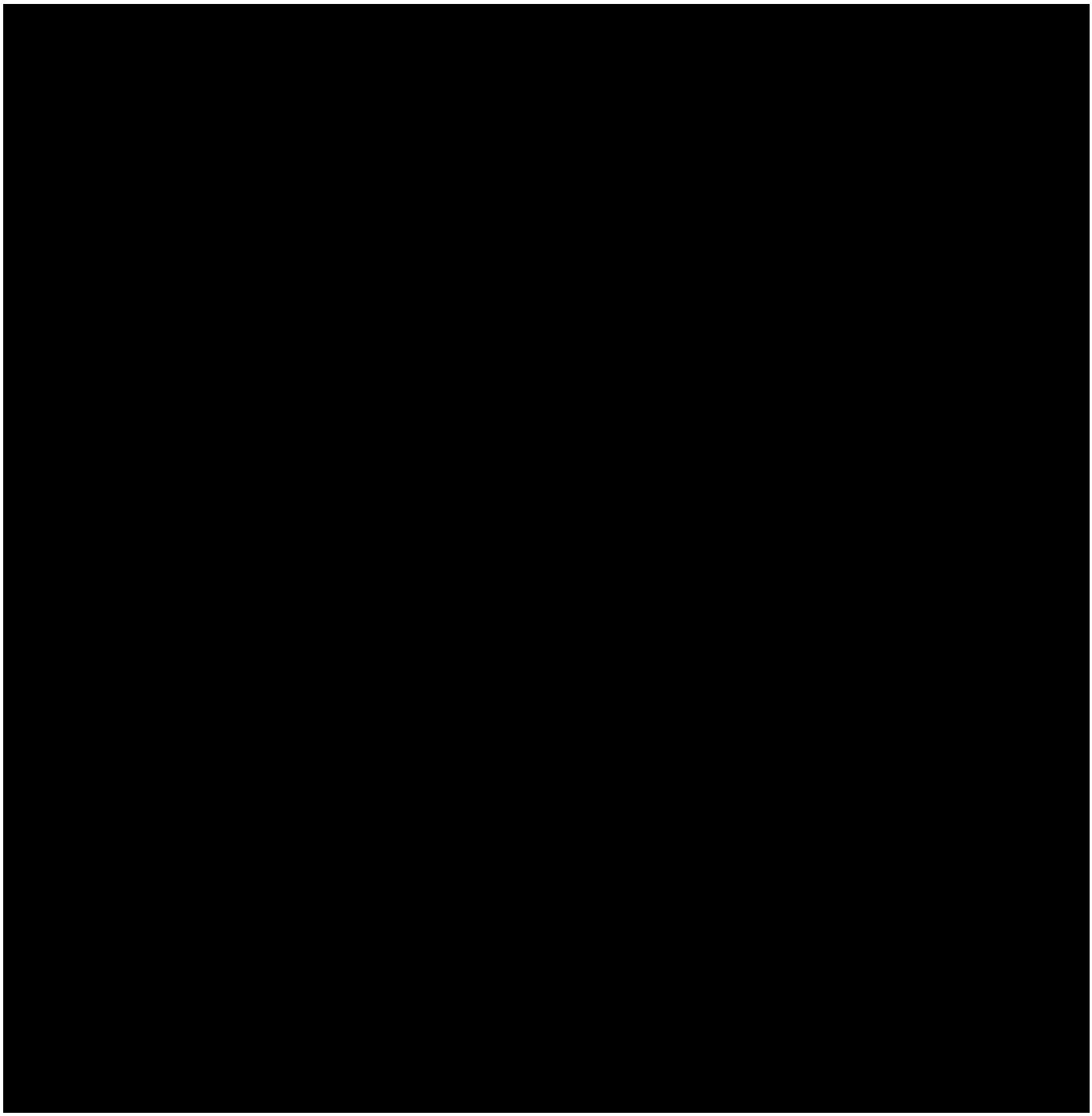
- Number of patients with a decrease in POM_{WP} of at least 50% from baseline on day 2 evening, 1 hour after drug application (Visit 3)

- Change in POM_{WP} between baseline and the morning of day 6 (Visit 6)

- Change in Pressure Algometry (PA) $[N/cm^2]$ between baseline and day 2 evening, before drug application (Visit 3)

- Change in PA $[N/cm^2]$ between baseline and the morning of day 6 (Visit 6)

[redacted]



5.4 OTHER VARIABLES

- Assessment of skin reactions as assessed by Dermal Response Score (DRS) at visits 1, 2, 3, 4, 5 and 6.

    - Observed values
      The DRS is a scale ranging from 0 (no evidence of irritation) to 7 (strong reaction spreading beyond test site).

- Responders

  A responder analysis will be performed; the categorisation of changes will be as follows:

  Positive is defined as any score ≥3

  Negative is defined as any score <3

- Overall assessment of tolerability at visit 6
  - Overall tolerability as assessed by the patient
    Tolerability is assessed on a scale ranging from 0 (poor) to 3 (very good).
  - Overall tolerability as assessed by the investigator

- Physical examination
- Vital signs
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - Pulse rate (PR)
- Safety laboratory parameters
- Adverse events

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Table 6.1: 1 shows the treatments which are planned to be investigated and the treatment order to be displayed in the tabulations:

Table 6.1: 1 Planned treatments

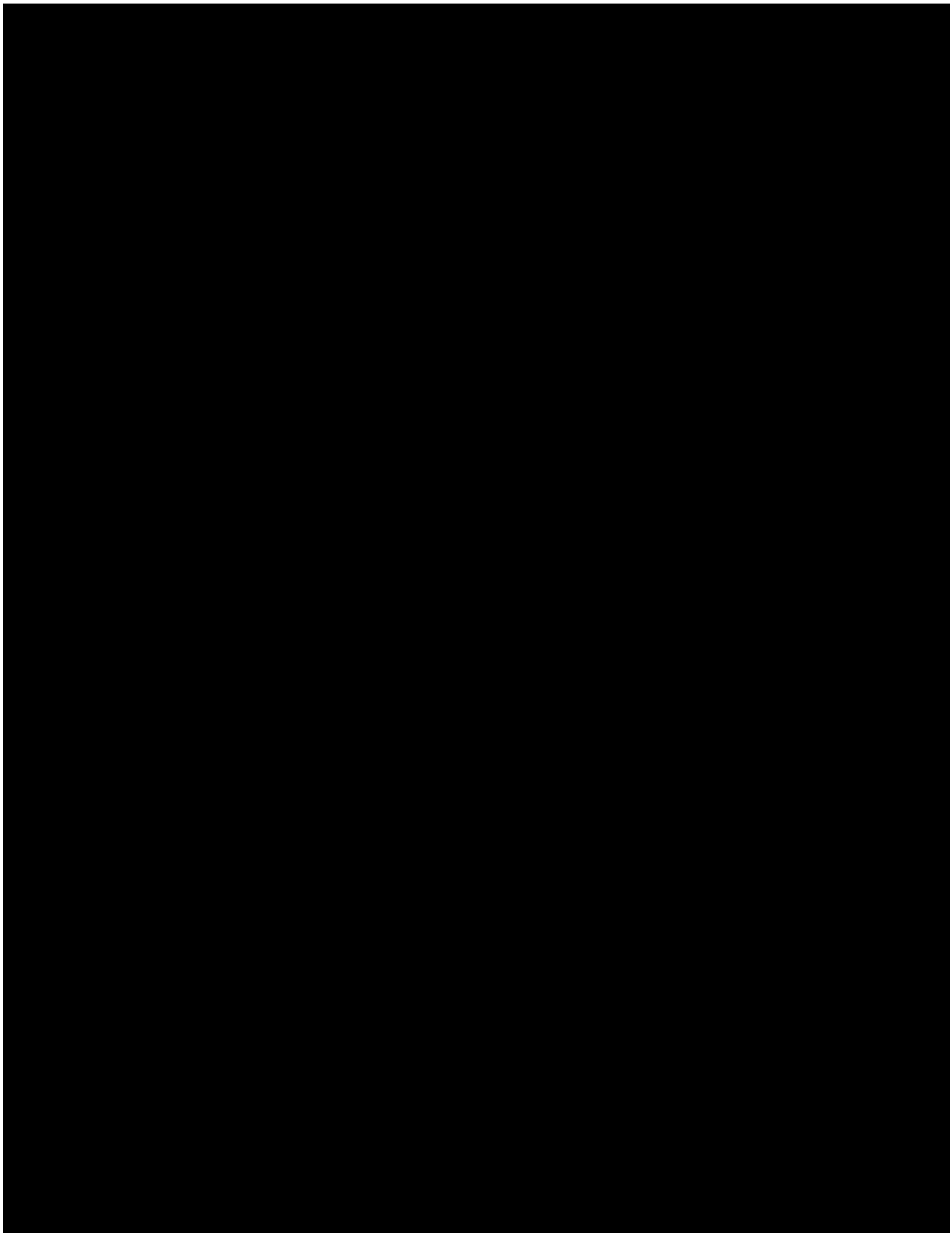
Treatment Order	**Treatment**	**Short label**	**Administration timing**
1	Placebo gel administered twice daily	Placebo	Morning and evening
2	Capsaicin 0.075% gel administered twice daily	Capsaicin	Morning and evening
3	Diclofenac 2% gel administered twice daily	Diclofenac	Morning and evening
4	Diclofenac 2% + Capsaicin 0.075% gel administered twice daily	Diclofenac + capsaicin	Morning and evening

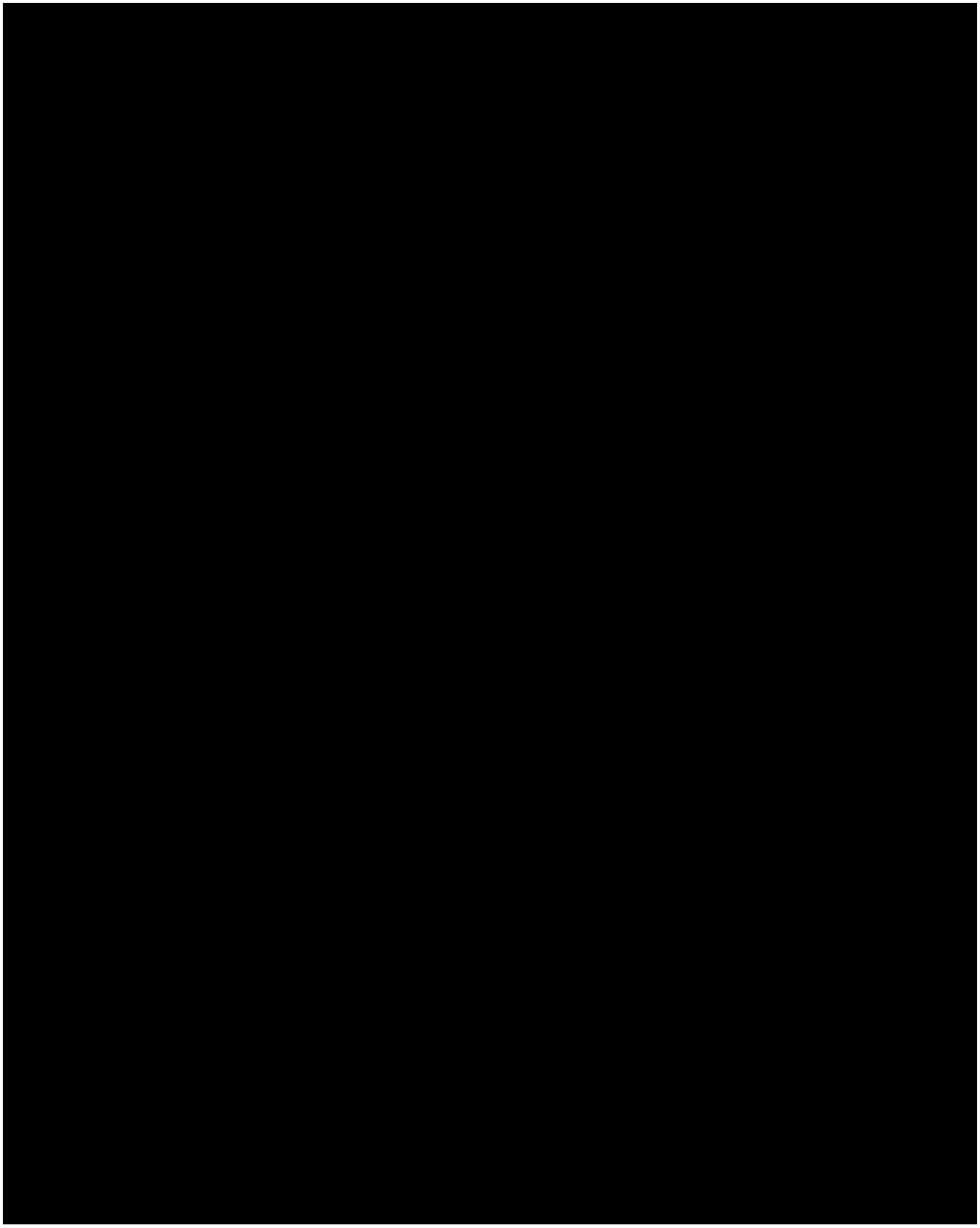
If a patient receives the wrong treatment the patient will be analysed within the planned (randomised) treatment group in the efficacy analysis and within the actual treatment group in the safety analysis.

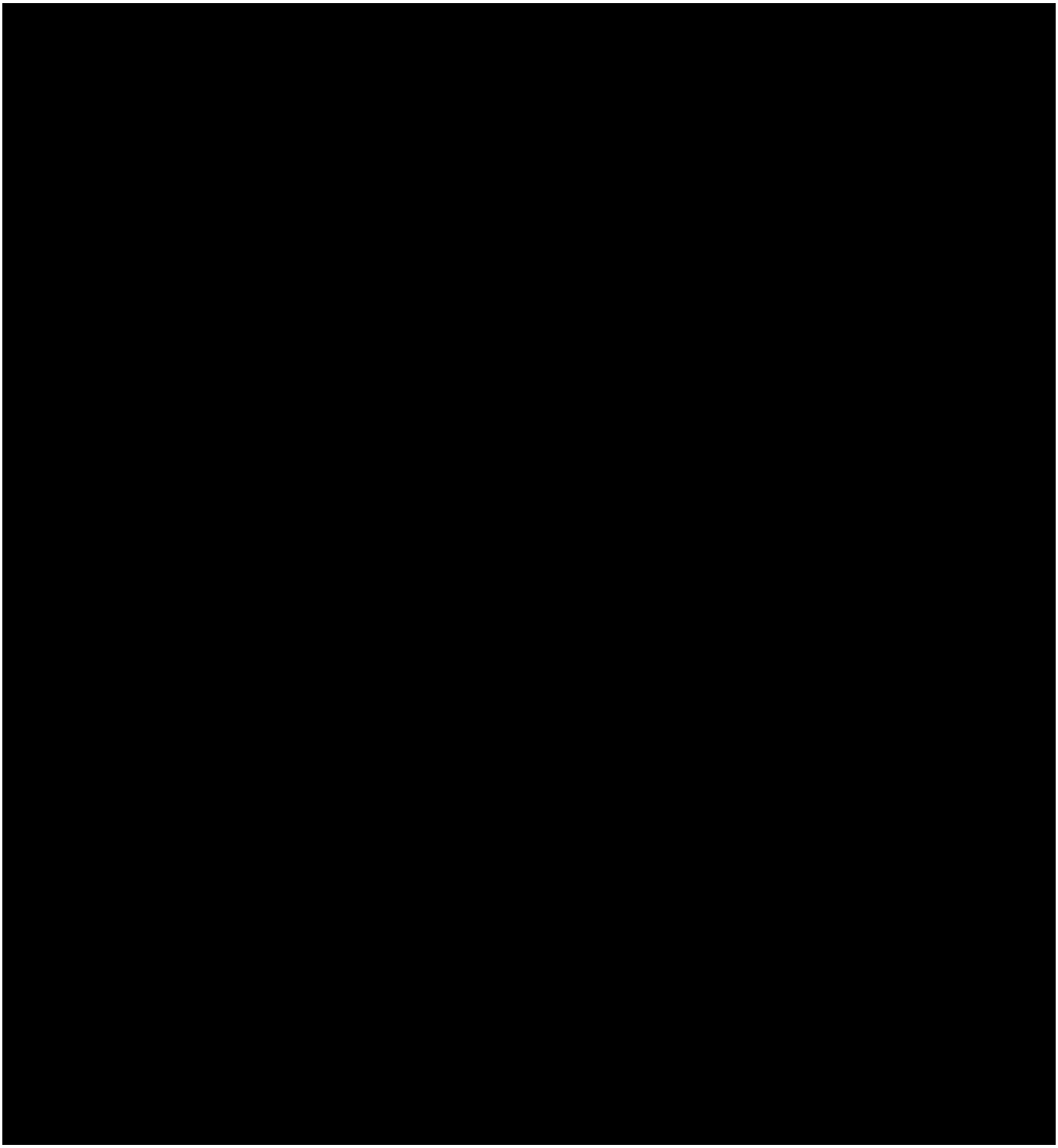
The study periods of interest are displayed in Table 6.1: 2.

Table 6.1: 2 Study periods of interest

Study period	**Definition**
Screening	From screening until informed consent is obtained
On-treatment	From first application of trial drug until last application of trial drug plus 2 days (inclusive).
Post-treatment	From date of last application of trial drug plus 2 days until trial termination date
Post-study	Post-trial termination date







[redacted]

6.3 PATIENT SETS ANALYSED

The patient sets of treated set (TS), full analysis set (FAS) [redacted] as defined in the CTP will be used [redacted]

The randomised set is defined as all randomised patients, whether treated or not.

Patients having received the wrong treatment will be analysed within the planned (randomised) treatment group in the efficacy analysis (TS as randomized) and within the actual treatment group in the safety analysis (TS as treated).

Patients who are incorrectly randomised into the stratum not containing the POM_{WP} will be included in the patient set TS as randomised but will be allotted to the stratum with the POM_{WP} for efficacy analyses.

Table 6.3: 1 shows which analysis set is used for each class of endpoint.

Table 6.3: 1 Patient sets for planned analyses

Planned analysis	**Patient set**
Disposition	Enrolled patients
Analysis sets	Randomised set
IPVs, demographic and other baseline characteristics, concomitant therapies and treatment compliance	TS (as randomised)
Efficacy analysis: primary, secondary [redacted]	TS (as randomized) FAS (primary endpoint only) [redacted]
Safety analysis	TS (as treated)

Note that the number of patients with available data may differ between endpoints. For details, see Section 6.6 “Handling of missing data”.

[redacted]

6.5 POOLING OF CENTRES

Country will be included in the statistical models therefore no pooling of centres is planned.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Every effort should be made to collect complete data for each time point at each test day.

6.6.1 Missing or partial dates

According to the guideline, if only the year of birth is known, the day and month of birth will be imputed as 01 January. For other incomplete date information, the midpoint of the possible interval will be used. If only the year is present, the day and month will be imputed as 01 July; if year and month are present, the day will be imputed as 15. If the year is missing, the date will be considered missing.

For partial start and stop dates for background medication, concomitant therapies, and additional treatments, the following derivations will be used to impute "worst case" values:

- If the day of the end date is missing, then the end date is set to last day of the month.
- If the day and month of the end date are missing, then the end date is set to 31st December of the year.
- If the day of the start date is missing, then start date is set to first day of the month.
- If the day and month of the start date are missing, then the start date is set to 1st January of the year.

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

6.6.2 Missing efficacy data

Every effort should be made to collect complete data for each time point at each test day, independent whether it is related to POM_{WP} endpoint data or any other endpoint data.

For missing baseline data, no imputation will be implemented.

For the analyses utilising a likelihood-based repeated measures model, no imputation of missing values will be performed.

For details on the handling of missing data for the AUC calculation see section 5.2.1.

[redacted]

Missing patient assessments of [redacted] resulting from early discontinuation that was clearly unconnected to treatment will not be imputed.

6.6.3 Safety

With regard to the safety analysis, no imputation of safety data is foreseen (observed case analysis) except for missing or incomplete adverse event (AE) dates. Missing or incomplete AE dates are imputed according to BI standards ("Handling of missing and incomplete AE dates") [2].

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Definition of baseline

Baseline values are defined as the last morning assessment prior to randomization and the first drug application on day 1 (Visit 1).

Time windows

Time windows for visits are shown in the Flow Chart in the CTP. Visits 1-5 must be carried out on the specified days, for Visit 6 there is a time window of -1/+2 days, for Visit 7T there is a time window of +4 days.

Calculated visits

Visits which occur outside of the defined visit window are flagged as PVs.

If a single scheduled visit is completed outside of the visit window, as defined in the CTP, that visit will be assigned to the scheduled visit. For example, if a patient completes a visit in the afternoon of day 3, the visit would be assigned to visit number 4.

If two consecutive scheduled visits are missed, but a single visit completed between the visit for both scheduled (but missed) visits, the completed visit will be assigned to the closest scheduled visit. However, the final assignment of the visit should be agreed at a medical quality review meeting (MQRM) or BRPM.

Unscheduled visits are not expected for this study. However, should unscheduled visits occur between non-missed scheduled visits, they are assigned separate visit numbers according to BI convention, but will not be included in the summary statistics and will not be used in any inferential analysis.

7. PLANNED ANALYSIS

For End-of-Text (EoT) tables, for continuous variables, the set of summary statistics is: Number of patients with non-missing values / Mean / standard deviation (SD) / Minimum / Q1 (lower quartile) / Median / Q3 (upper quartile) / Maximum.

Tabulations of frequencies for categorical and ordinal 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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Patient sets for the planned analyses are displayed in Table 6.3: 1. Patient data listings (PDLs) will be based on the randomised set. If any AEs/SAEs are reported for screening failures, these will be summarised in the AE listing "Adverse event overall summary" and described in the Clinical Trial Report (CTR) if considered related to the screening procedures.

For all efficacy analyses pertinent to application site and applicable only to the FAS and [redacted] any patient who is incorrectly randomised into the stratum not containing the POM_{WP} will be included in the stratum with the POM_{WP}.

As detailed in Section 4 all analyses pertaining to POM will be performed on the normalised POM scores derived as:

$$\text{Normalised POM score (cm)} = \frac{\text{POM score}}{\text{VAS scale length}} \times 10$$

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be presented for the treated set for the following demographic and baseline characteristics, by treatment group and all patients combined:

Demographic data

- Age [years]
- Age class (≥18 to <65, ≥65 years)
- Age class (≥18 to <65, 65 to <85, ≥85 years)
  (required only for the 'Disposition of patients for data disclosure by age groups' table)
- Sex (Male, Female)
- Race (American Indian/Alaska Native, Asian, Black/African American, Hawaiian/Pacific Islander, White)

- Ethnicity (Not Hispanic/Latino, Hispanic/Latino)

Baseline disease characteristics

- Time since onset of acute pain (days)
- POM (each assessment and POM_{WP})
- PA [N/cm^2]
- Pain intensity at rest
- Average pain intensity

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive analysis is planned for this section of the report, using the treated set.

Concomitant medication taken in the 4 weeks before the treatment period and at baseline or during the treatment period will be summarised by World Health Organization-Drug Dictionary (WHO-DD) name and preferred term (PT), and presented by treatment group and all patients combined. Concomitant analgesic medication taken at baseline or during the treatment period will be summarized separately from both rescue medication and from all other concomitant medication.

Baseline conditions / concomitant diagnoses will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and PT, and presented by treatment group and the total of all subjects.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be assessed by calculating the weight difference of the tubes after being returned at Visit 6 from the pre-dose weight at Visit 1. In addition, the mean weight per gel application will be calculated based on the total number of gel applications. Descriptive statistics will be calculated for these parameters.

Weight difference will be calculated by:

$Weight_{Diff}$ [g] = $Weight_{Pre}$ [g] – $Weight_{Post}$ [g]

The mean weight per gel application will be calculated by:

Mean weight per gel application = $Weight_{Diff}$ [g] / total number of gel applications

Compliance will be presented by treatment group and in total, using the treated set.

7.4 PRIMARY ENDPOINTS

7.4.1 Primary analysis

The primary endpoint will be analysed as described in the CTP, using the FAS.

Differences between the combination treatment (diclofenac and capsaicin) and individual treatments or placebo will be estimated at visit 3 (day 2 evening, 1 h after application), differences should be calculated as the combination treatment minus the individual treatment or placebo, meaning negative differences favour the combination treatment. Adjusted least squares means (with standard errors) as well as treatment contrasts and their 95% confidence intervals (CIs) and two-sided (α=0.05) p-values will be presented.

The SAS code to be used for this analysis is given in section 9.1.

In addition, the primary endpoint will be summarized by treatment group using descriptive statistics.

[redacted]

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

The key secondary endpoints will be analysed using the treated set.

$POM_{WP}AUC_{72}$ and $POM_{WP}AUC_{120}$ will be analysed using an ANCOVA model as described in the CTP. Adjusted means (with standard errors) as well as treatment contrasts will be presented together with 95% confidence intervals. The analysis will be performed using the treated set.

In addition $POM_{WP}AUC_{72}$ and $POM_{WP}AUC_{120}$ will be summarised by treatment group using descriptive statistics.

[redacted]

7.5.2 Other secondary endpoints

All other secondary endpoints will be analysed using the treated set.

7.5.2.1 Endpoints from POM_{WP}

The number of patients with a decrease in POM_{WP} of at least 30% from baseline until day 2 evening, 1h after drug application, will be analysed using a logistic regression model as described in the CTP. Treatment differences will be analysed using adjusted odds ratios which will be presented together with 95% confidence intervals, the combination treatment (diclofenac and capsaicin) will be used as the reference treatment. Odds ratios will be

calculated as combination treatment/individual treatments or placebo, meaning an odds ratio >1 would indicate better responses for the combination treatment.

[redacted]

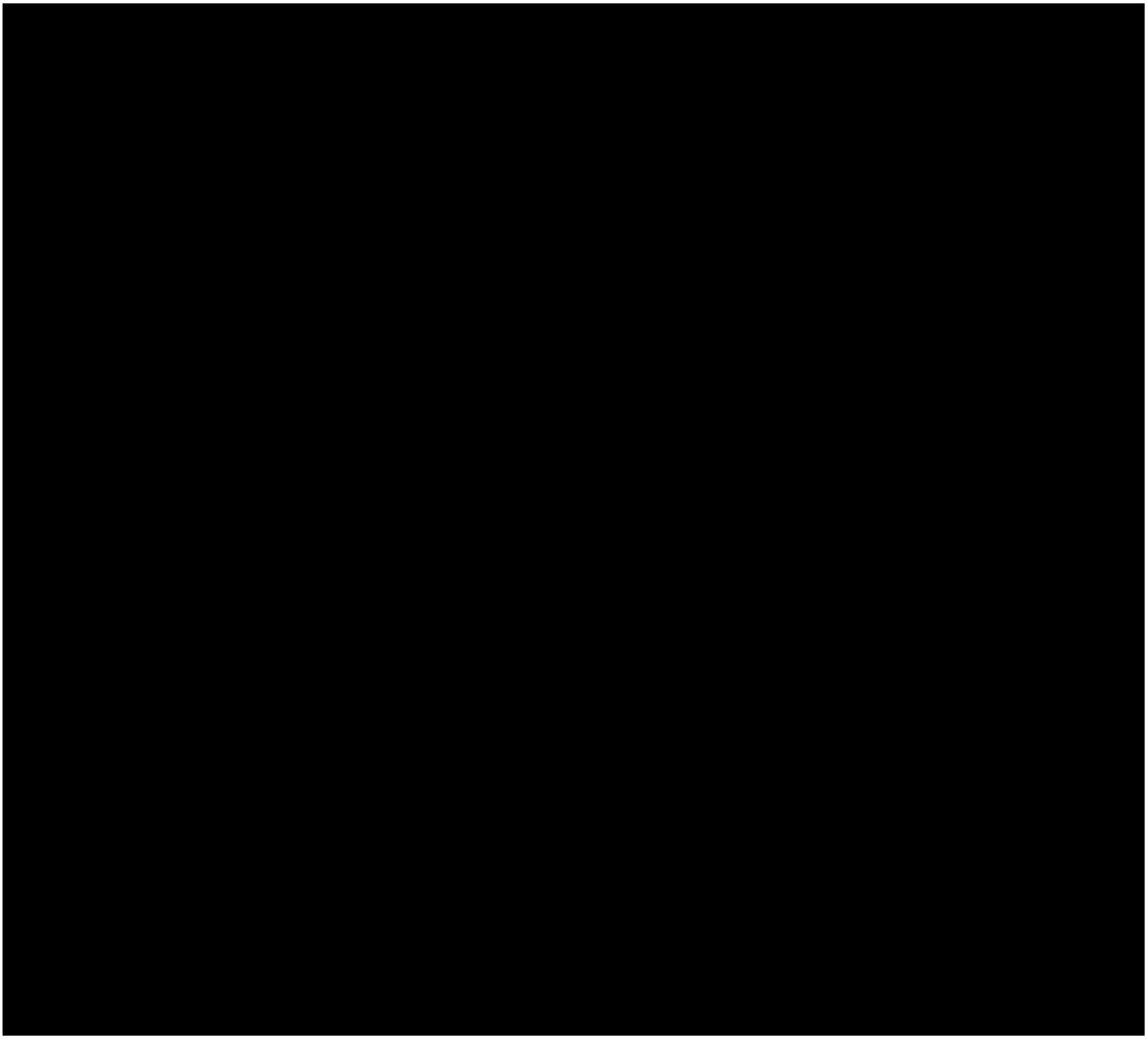
The number of patients with a decrease in POM_{WP} of at least 50% from baseline until day 2 evening, 1h after drug application, will be analysed similarly.

Change in POM_{WP} between baseline and the morning of day 6 will be analysed analogously to the primary endpoint, using all available data points as described in CTP section 7.3.2.

7.5.2.2 Endpoints from pressure algometry

Change in PA between baseline and day 2 evening before drug application and change in PA between baseline and the morning of day 6 will all be analysed analogously to the primary endpoint, using all available data points as described in CTP section 7.3.2.

[redacted]



7.7 EXTENT OF EXPOSURE

Duration of treatment exposure will be determined for each patient during the randomised treatment period. The basis for the treatment exposure will be the duration of exposure counted in days on treatment.

Duration of treatment exposure will be calculated as:

Number of days on treatment = treatment discontinuation date – treatment start date + 1

Extent of exposure will be summarised using descriptive statistics. A frequency table showing the number of gel applications, per day and in total, as recorded in the patient diary, will be presented. Descriptive statistics will be calculated and displayed by treatment group as well as all patients combined.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the Treated set (as treated).

7.8.1 Adverse events

Adverse events will be coded using the most recent version of MedDRA.

AE data will be handled according to the current version of the BI AE guideline [2].

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not the number of AEs. For this purpose, AE data will be combined in a 2-step procedure into AE records:

In the first step, AE occurrences, i.e. AE entries on the eCRF, will be collapsed into AE episodes provided that all of the following apply:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

In the second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level. For further details on summarisation of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' [3].

Other significant AEs will be reported and summarized according to ICH E3 criterion. Thus, AEs classified as ‘other significant’ will include those non-serious adverse events with:

(i) ‘action taken = discontinued from study’, or
(ii) marked hematological and other lab abnormalities, or lead to significant concomitant therapy as identified by the Clinical Monitor / Investigator at a MQRM or a BRPM.

An overall summary of adverse events will be presented by treatment group.

The frequency of patients with adverse events will be summarised by treatment group, primary SOC and PT. Separate tables will be provided for patients with other significant adverse events, for patients with adverse events of special interest (AESI), for patients with serious adverse events, for patients with AEs leading to discontinuation, for patients with drug-related AEs and for patients with drug-related serious adverse events.

The SOCs will be sorted alphabetically; PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

Laboratory data will be analysed and summarised as described in the CTP.

Clinically significant findings will appear under “Baseline condition” or “Adverse events” and will be analysed accordingly.

Where repeat measurements are taken for a patient, the worst value according to BI standards will be presented.

7.8.3 Vital signs

Vital signs (systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate (PR)) will be summarised by treatment group using descriptive statistics for observed values and changes from baseline.

7.8.4 Others

7.8.4.1 Assessment of skin reactions

Assessment of skin reactions will be analysed descriptively only.

Two tables will be presented, by treatment group and in total. The first table will be a frequency count of the individual dermal response scores (range 0-7) and the second a responder analysis table, categorised as positive for scores ≥3 and negative for scores <3.

7.8.4.2 Assessment of tolerability

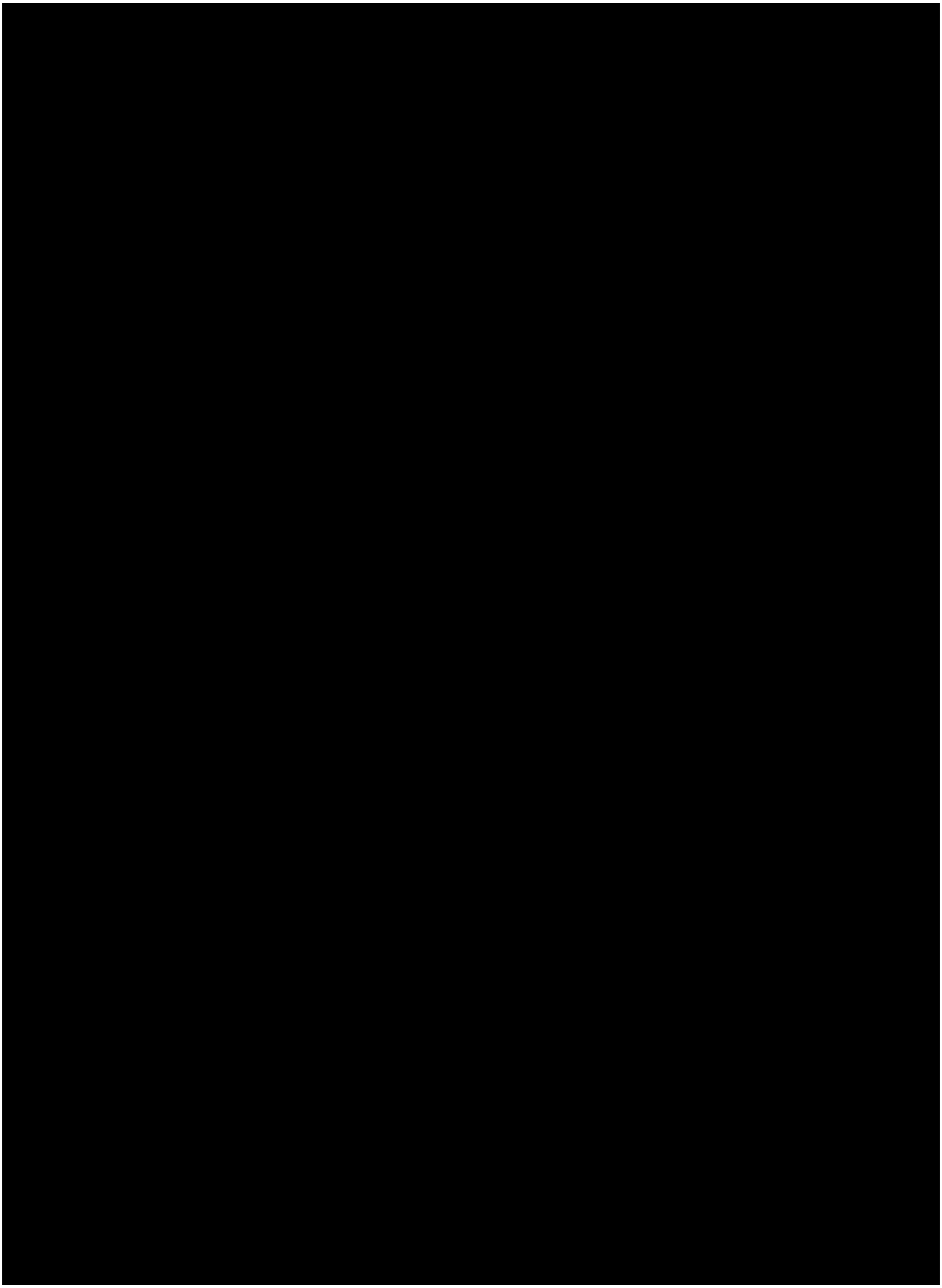
Final overall patient assessment of tolerability and final overall investigator assessment of tolerability will be analysed [redacted]

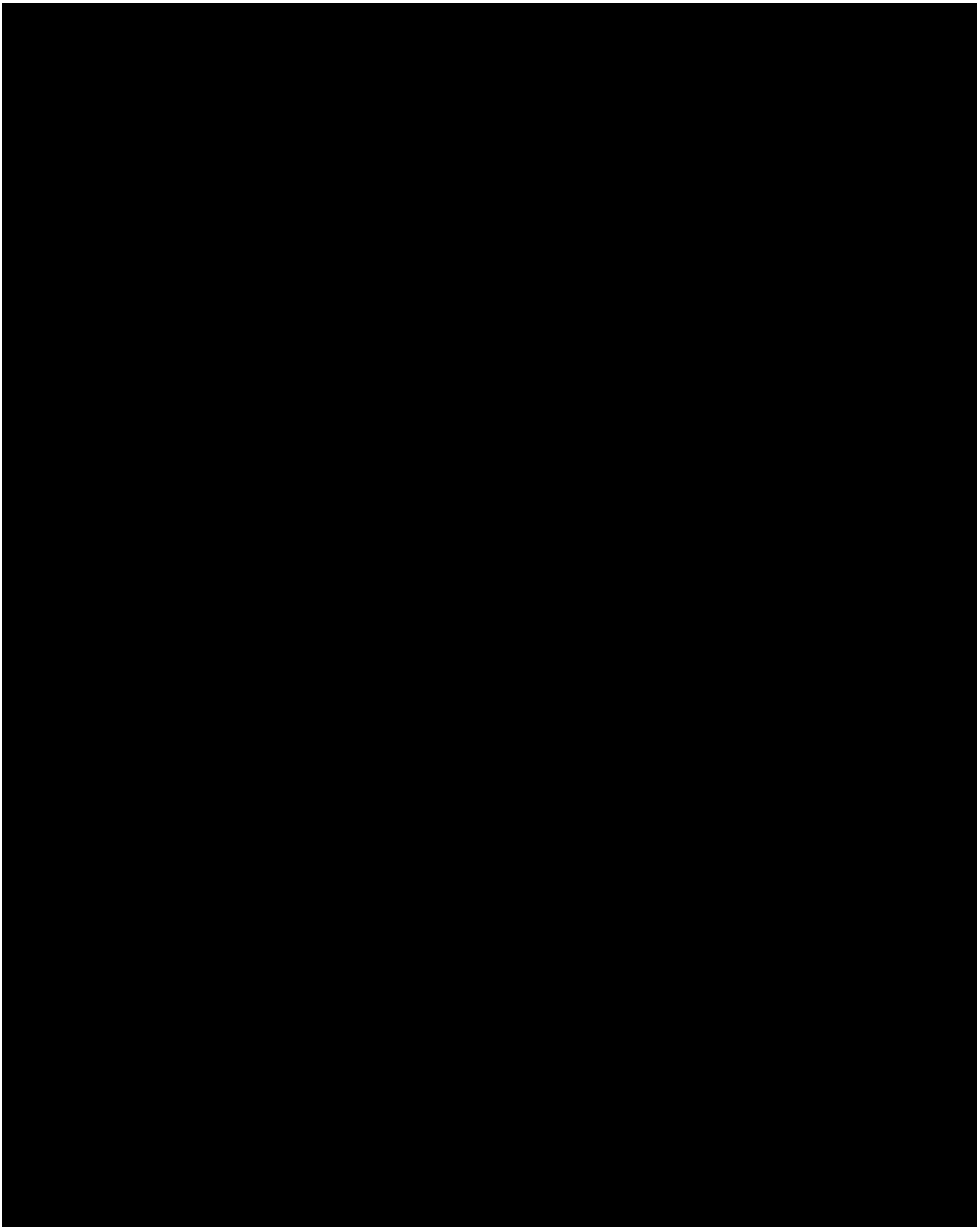
8. REFERENCES

[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.

[2] 001-MCG-156_RD-01: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

[3] 001-MCG-156: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", version 5.0; IDEA for CON.





10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10:1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Final	29-Jun-17	[redacted]	None	This is the final TSAP without any modification
Revised	06-Oct-17		Refer to Section 4	Refer to Section 4