Study Title: A Randomized, Double Blind, Placebo-Controlled, Parallel Group, Dose-Response Study of Meloxicam Co-Crystal in The Treatment of Post-Surgical Dental Pain

Protocol Number: MECC-TBZ-2001

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:

A RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, DOSE-RESPONSE STUDY OF MELOXICAM CO-CRYSTAL IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN

PROTOCOL NUMBER:

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IND NUMBER: [redacted]
PREPARED BY: [redacted]

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VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
0.0	2020-10-05	Initial draft	
1.0	2021-02-05	Various updates and clarifications	See section 11.2

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BDR	Blinded Data Review
BID	Twice daily
BMI	Body Mass Index
BOCF	Baseline observation carried forward
CI	Confidence interval
CRF	Case Report Form
CSR	Clinical study report
CV	Cardiovascular
ECG	Electrocardiogram
ET	Early termination
GCP	Good Clinical Practice
GI	Gastrointestinal
HR	Heart rate
ICH	International Council for Harmonization
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IP	Investigational product
ITT	Intent-to-treat
IWRS	Interactive Web Response system
LOCF	Last observation carried forward
LS	Least squares
MAR	Missing at Random
MCMC	Markov Chain Monte Carlo
MCP-Mod	Multiple Comparison Procedure – Modeling
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
mITT	Modified Intent-to-treat
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random

NPRS	Numeric Pain Rating Scale
PD	Pharmacodynamic
PGA	Patient Global Assessment
PI	Pain intensity
PID	Pain intensity difference
PK	Pharmacokinetic
PP	Per Protocol
PPK	Population Pharmacokinetic
QD	Once daily
RM	Rescue medication
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SID	Subject Identification
SOC	System organ class
SPID	Summed Pain Intensity Difference
SS	Safety Analysis Set
TEAE	Treatment Emergent Adverse Events
TIA	Transient ischemic attack
TOTPAR	Total pain relief
W2LOCF	2-hour windowed last observation carried forward
W4LOCF	4-hour windowed last observation carried forward
WHO-DD	World Health Organization Drug Dictionary

2. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) provides a detailed description of the strategy and statistical methodology to be used for analysis of data from the MECC-TBZ-2001 protocol, version 5.0 (amendment 4), dated 15SEP2020.

The purpose of the SAP is to describe the pre-specified statistical approaches to the analysis of study data prior to database lock. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Any deviations from this plan will be described in the Clinical Study Report.

3. PROTOCOL SUMMARY

This will be a randomized, double-blind, placebo-controlled, parallel group, dose-response study, randomizing approximately 110 male or female subjects who have had dental surgery (removal of ≥2 third molars) performed. Subjects will receive study drug on Day 1.

The study design is consistent with research design recommendations of the IMMPACT (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials) group for trials involving subjects with short-duration acute pain.

Subjects will attend screening at Visit 1, to occur within 30 days prior to the planned dental surgery.

The subjects will have the operation performed on Day 1 using appropriate local anesthesia and sedation (performed using nitrous oxide and a local injection of lidocaine with epinephrine). Subjects will also receive prophylactic antibiotics post-surgically.

Pain Intensity (PI) (using a 0-10-point numeric pain rating scale (NPRS) where 0 is no pain and 10 is the worst pain imaginable) will be assessed during the 5 hours following surgery. If the subject scores a NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.

A diary will be used to record the pain scores.

Subjects will be randomized to receive either MECC-SA (10 mg QD, 15 mg QD, 10 mg BID or 15 mg BID) or placebo.

Dosing of study medication must be within 15 minutes of the eligible pain score. PI scores (NPRS) will be measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, as well as immediately before any rescue medication and/or at the time of early termination.

Pain relief assessment (using a 5-point scale - none = 0, slight = 1, moderate = 2, good or a lot = 3, and complete = 4) will be measured at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, as well as immediately before any rescue medication and/or at the time of early termination.

A Patient Global Assessment (PGA) of pain control will be made at 24 hours post dose, rated on a 5-point scale, ranging from 0 to 4, where 0-poor, 1-fair, 2 good, 3-very good, or 4-excellent and/or at the time of early termination.

The times to first perceptible relief and meaningful pain relief will be determined using the double-stopwatch technique. The time to onset of first perceptible relief (time that the first watch is stopped) is defined as the post dose time at which the subject first begins to feel pain relief. The time to meaningful pain relief (time that the second watch is stopped) is defined as the post dose time at which the subject begins to feel meaningful pain relief.

Rescue medication of immediate release hydrocodone/acetaminophen will be allowed at any time, but subjects will be encouraged to wait until at least 1 hour post-dose if possible. A PI score assessment will be made immediately prior to any rescue medication.

Pharmacokinetic (PK) samples will be taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose at Day 1.

Subjects will be discharged from the clinic following the 24-hour assessments; if the subject requires a longer duration of in-patient assessment due to reasons associated with the surgery this is acceptable.

A final follow-up telephone call will occur approximately 5 days after the last dose of study drug administration.

Safety will be assessed via recording of adverse events (AEs), safety laboratory testing and pre and post-dose 12-lead electrocardiogram (ECGs) and vital signs.

Adverse events of special interest will include those related to gastrointestinal (GI) AEs, particularly bleeds and those related to serious cardiovascular (CV) events.

Unless consent is withdrawn, subjects who prematurely terminate study drug will have discharge procedures performed at that time or at an early termination (ET) visit scheduled as soon as possible.

4. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies will be described, if applicable, in the appropriate sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

For categorical variables, summary statistics will consist of the number and percentage of subjects in each category; percentages will be out of the number of subjects in the population being reported, unless otherwise noted. All percentages will be rounded to one decimal point. The number and percentage of subjects will always be presented in the form XX (XX.X%) where the percentage is in parentheses. To ensure completeness, all summaries for categorical and discrete variables will include all categories, even if none of the subjects had a response in a particular category. Denominators for each analysis will be based on the population of interest (e.g., safety population; subjects with non-missing data).

For continuous variables, summary statistics will consist of the number of subjects with data, mean, median, standard deviation (SD), minimum, and maximum values. The summary statistic n will be the number of subjects with non-missing values. All means and medians will be reported to one more significant digit than the values being analyzed. Standard errors (SE) and SDs will be reported to two more significant digits than the values being analyzed. The minimum and maximum will be reported to the same number of significant digits as the values being analyzed.

For tests of hypothesis of treatment group differences, the associated p-value will be reported. All p-values will be rounded to three decimal places; p-values that round to 0.000 will be presented as "<0.001". P-values are descriptive for outcomes and analyses other than the primary endpoint.

In general, the baseline value will be considered the last non-missing measurement observed prior to the first dose of study treatment.

For efficacy, subjects will be analyzed according to randomized treatment. For safety analyses, subjects will be analyzed according to the actual treatment received.

Data will be listed by treatment and subject. In general, listings will be sorted in the order that columns are displayed, starting with the first column on the left (treatment). Subject listings of data will be presented for all randomized subjects unless specified otherwise.

Unless otherwise specified, summaries will include the following study arms:

- MECC-SA 15 mg QD
- MECC-SA 10 mg QD
- MECC-SA 15 mg BID
- MECC-SA 10 mg BID
- Placebo

SAS statistical software, version 9.4 or higher, will be used for all analyses.

4.1. Assessment Time Windows

Assessments should be performed within the windows stated in the protocol and will be analyzed by the visit/time point under which they are entered into the case report form (CRF). For assessments other than the NPRS pain, if an assessment is missing and an unscheduled or early termination assessment falls within the protocol-specified window, it will be assigned to that visit/time point for the purposes of summarization. If more than one unscheduled visit/ early termination visit falls into a window, the one closest to the scheduled time point will be used (with the earlier one used in case of a tie); again, scheduled visits will always take precedence, regardless of timing.

NPRS assessments will use the actual times of collection; see section 8.2.1 for additional details.

5. ANALYSIS SETS

The following 6 analysis populations are planned for this study:

- All Subjects Analysis Set: This includes all subjects consented and screened and will be used for the reporting of subject populations and dispositions.
- Safety Analysis Set: The safety analysis set (SS) will include all subjects who received at least one dose of study drug. Data will be summarized according to the treatment a subject actually received.
- Modified Intent-to-treat (mITT) Analysis Set: The mITT analysis set includes all randomized subjects who received study drug and report at least one post-baseline pain intensity, including subjects who discontinued study treatment or received protocol allowed rescue medication. This will be used for all efficacy analyses; data will be summarized and analyzed according to the treatment a subject was randomized to receive.
- Intent-to-treat (ITT) Analysis Set: The ITT analysis set includes all randomized subjects who received study drug, including subjects who discontinued study treatment or received protocol allowed rescue medication. Data will be summarized and analyzed according to the treatment a subject was randomized to receive. This population is the anticipated phase III population and will be utilized for planning and power calculations for the phase III studies.
- Per Protocol Analysis Set: The per protocol analysis set (PP) will include all subjects in the ITT who had no major protocol violation that would impact on the primary efficacy endpoint. Significant protocol deviations are defined in Section 9.4 of the protocol. The list of major protocol deviations will be finalized prior to database lock and unblinding as part of the final blinded data review (BDR). Data will be summarized and analyzed according to the treatment a subject actually received at randomization.
- PK Analysis Set: The pharmacokinetic analysis set (PK) will include all subjects who receive a dose of study medication and who provide at least one post dose concentration sample for the Population PK analysis.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

The number and percentage of subjects screened, enrolled (marked as meeting inclusion criteria and not a screen failure), randomized, received treatment, completed the study, and discontinued from the study, will be reported, along with the reason for discontinuation (counts only will be reported for screened and enrolled subjects). Percentages will be out of the number of subjects randomized. Additionally, the number and percentage of subjects that complete the in-clinic portion (through day 2) will be reported. Subjects screened and enrolled will be reported overall; the remaining items will be reported by treatment group and overall. Subjects randomized will include all subjects for whom randomization is checked on the CRF; subjects receiving treatment will include all subjects that had any IP administered; subjects completing the study will be based on the recorded disposition; subjects completing the confinement period will include those that have a termination date on or after day 2.

Reasons for discontinuation include the following:

- Adverse Event
- Death
- Lack of Efficacy
- Lost to Follow-Up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Protocol Deviation
- Site Terminated by Sponsor
- Study Terminated by Sponsor
- Withdrawal by Subject
- Other

Additionally, the number and percent of subjects in each analysis population will be reported by treatment. Screen failures will also be included in a by-subject listing.

6.2. Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be collected during the Screening Visit.

Descriptive statistics will be provided for all demographic and baseline characteristics based on the Safety Population; if the mITT population is different, demographics will be presented for it as well. For categorical variables, the number and percentage of subjects in each category will be presented. For continuous variables, summaries will include the number of subjects with data, mean, median, standard deviation, minimum, and maximum.

Variables to be summarized include:

- Age at screening (years) as recorded on the CRF
- Sex
- Ethnicity
- Race
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

All demographic and other baseline characteristics will be provided in a listing. Additionally, the substance use and surgery info collected will be provided in a listing.

6.3. Prior and Concomitant Medications

All concomitant medications taken during the study (from signing informed consent to post-study follow-up) must be recorded with indication, daily dose, and start and stop dates of administration in the CRF. All subjects will be questioned about concomitant medication at each clinic visit and at follow up.

Medications taken prior to dosing with study medication will be documented as a prior medication. Medications taken after dosing with study medication will be documented as concomitant medications. All medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) Version GLOBALB3Sep20.

Rescue medication of immediate release hydrocodone/acetaminophen (5/500 mg) will be allowed to treat breakthrough pain, subjects will be encouraged to refrain from rescue medication until at least 1-hour post-dose. A dose of rescue medication will be allowed as needed up to once every two hours. A maximum of 6 tablets (equivalent to 3000 mg acetaminophen) will be allowed; if a subject requires greater than this the subject should be withdrawn from the study.

Pain Intensity will be measured immediately before any rescue medication is administered. Rescue medications and the associated pain intensities will be recorded on a separate CRF page.

6.3.1. Prior Medications

Prior medications are defined as all medications recorded in the CRF initiated prior to the administration of IP. Prior medications will be summarized in a table by treatment group using the Safety Analysis Set. Medications will be reported by drug class (Anatomical Therapeutic Chemical [ATC] Level 3) and preferred term; a subject will be counted only once for each medication.

6.3.2. Concomitant Medications

Concomitant medications are defined as all medications recorded in the CRF taken after the administration of IP, including those that were initiated prior to administration of IP and ongoing. Concomitant medications will be summarized in a table by treatment group using the Safety Analysis Set. Medications will be reported by drug class (Anatomical Therapeutic Chemical [ATC] Level 3) and preferred term; a subject will be counted only once for each medication.

6.4. Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1. Conditions will be listed, including the verbatim investigator description of the relevant medical condition, the coded terms (system organ class, preferred term), start date, end date, and whether or not the condition is ongoing.

7. STUDY OPERATIONS

7.1. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan.

Protocol deviations will be identified by site staff, through medical reviews, and by clinical research associates during site monitoring. Deviations will be classified as minor or major prior to the database lock. Major protocol deviations are defined as those that result in harm to the study patients or significantly affect the scientific value of the reported results of the study. Other deviations will be considered minor.

Major protocol deviations will be summarized in a table; all deviations will be presented in a listing, including their assigned severity (major/minor).

7.2. Randomization

Assignment of Subject Identification (SID) number, randomization number and study medication, as well as site drug inventory control will be managed by an automated Interactive Web Response system (IWRS). A manual containing complete instructions for internet or telephone access and use will be provided to each site prior to study start. At their first clinic visit, the IVRS/IWRS will assign a SID. Each SID will be unique and serve as the primary subject identifier throughout all phases of the study. The SID must appear on all CRF pages, source documents, laboratory data, ECG and diary data. Subjects qualifying to enter the study drug treatment phase, will be assigned an additional "randomization number" by the IWRS at randomization.

A total of 110 subjects are planned to be randomized in a 1:1:1:1:1 ratio of 22 subjects to each of the five study arms:

- MECC-SA 15 mg QD
- MECC-SA 10 mg QD
- MECC-SA 15 mg BID
- MECC-SA 10 mg BID
- Placebo BID

A by-subject listing of randomized treatment group and randomization number will be presented.

7.3. Measures of Treatment Compliance

Subjects will receive a two doses in the clinic on Visit 2 (Day 1); the first will be denoted time zero; the second will occur 12 hours later. A visual check of the subject's mouth and hands will be made to ensure compliance of dosing. The number and percentage of subjects in the safety population that received first dose, the second dose and both doses will be reported. Additionally, the date and time of the first and second doses will be presented in a

listing and the target date and time for the second dose will be listed. First doses that do not occur within 15 minutes of the baseline pain assessment will be flagged on the listing.

8. ENDPOINT EVALUATION

8.1. Overview of Efficacy Analysis Methods

8.1.1. Multicenter Studies

This is a single-center study and no special considerations are required for pooling of data.

8.1.2. Timing of Analyses

All final, planned analyses will be performed after the last participant has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post-hoc, exploratory analyses completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post-hoc) will also be clearly identified in the text of the CSR.

8.1.3. Multiple Comparisons/Multiplicity

All hypotheses will be tested at a two-sided significance level of 0.05. Nominal p-values will be presented for all secondary endpoints without adjustment for multiple comparisons (since this is a Phase 2 study).

8.2. Primary Efficacy Endpoint

The primary endpoint is the summed pain intensity difference (SPID) over 0 to 24 hours ($SPID_{0-24}$).

8.2.1. Computation of the Primary Endpoint

First, the pre-dose NPRS will be subtracted from each pain score for a pain intensity difference (PID). The SPID will be calculated using these values and actual times of collection with the trapezoidal rule; the primary analysis will include the NPRS scores recorded at the time of perceptible pain relief and at the time of meaningful pain relief. Due to the short duration of the study, missing data is expected to be minimal.

Missing data will be imputed based on the reason for missingness:

- Missing pain assessments for subjects who discontinued early due to lack of efficacy (including subjects that discontinue as a result of requiring more than 6 tablets of rescue medication), or an AE will be imputed using a baseline observation carried forward (BOCF) approach. These values will be placed at the planned times of assessments for the purpose of computing the SPID.
- Missing pain assessments due to other reasons for discontinuing will be imputed using a last observation carried forward (LOCF) approach. These values will be placed the planned times of assessments for the purpose of computing the SPID. Subjects that discontinue while in a period of censoring for rescue will have the pre-rescue value carried forward.
- Intermittent missing pain assessments between two non-missing scores will be imputed using linear interpolation.

Additionally, NPRS scores will be recorded just prior to administration of rescue medications. For the primary analysis of the primary efficacy endpoint a 2-hour windowed last observation carried forward (W2LOCF) approach will be used whereby the NPRS score obtained before a given rescue medication will be carried forward to replace the NPRS scores collected at each observation time point within 2 hours following the rescue dose. For the purposes of calculating the SPID, these values will be placed at the time of the assessments that they are replacing. If there is no assessment at a planned time point that falls within the censoring period, then the W2LOCF value will be placed at the planned time. If a NPRS score is not obtained as planned just prior to the rescue administration, then the last NPRS value available prior to the rescue will be utilized.

Once the above imputation process is complete, it is expected that there will be slight variations in the time contributing to the SPID; these will all be normalized to be precisely 24 hours.

8.2.2. Primary Analysis of the Primary Endpoint

A 3-parameter Emax model will be fitted to the $SPID_{0\text{-}24}$ standardized means (observed mean for each dose and placebo divided by the pooled standard deviation) for placebo and each dose of MECC-SA, using SAS proc NLMIXED. Standardized effect sizes will be estimated from the Emax model together with their 95% confidence intervals and p-values. Baseline pain intensity score (PI) will be used as a covariate in the Emax model; it will be centered by subtracting the mean baseline across all treatment groups from each subject's baseline.

The model will take the following form:

$$SPID_{0-24hr} = NPRS_0 + E_0 + \frac{E_{max}Dose}{ED_{50}+Dose} + \varepsilon$$

Where E_0 is the placebo response, E_{max} is the asymptotic maximum dose effect and ED_{50} is the dose that produces 50% of the maximal effect and ε is the random error term.

For the purposes of fitting the Emax model, the doses assigned will reflect the actual dose the subject received and dose will be considered as a numerical (not class) variable. This departure from the ITT principle will apply solely to fitting of the Emax model and reporting results based on the model. The numerical dose values will be 10, 15, 20, 30 and 0 for 10 mg QD, 15 mg QD, 10 mg BID, 15 mg BID and placebo respectively.

Descriptive statistics and other analyses of the SPIDs on the mITT population will analyze subjects based on the randomized treatment group.

If the Emax model fails to converge, additional models will be investigated using a Multiple Comparison Procedure – Modeling (MCP-Mod) approach (Branson, 2003). If no other suitable models are identified using MCP-Mod, an Analysis of covariance (ANCOVA) will be used to assess the difference between treatment groups for $SPID_{0\text{-}24}$. The ANCOVA model will include treatment as a fixed effect and baseline PI score as a covariate. The difference between MECC-SA and placebo will be estimated from the least squares means (LS means) along with the 95% confidence interval (CI) and associated 2-sided p-values. In addition, the standardized effect sizes for each dose will be calculated by dividing the differences in LS means for each dose and placebo by the pooled standard deviation.

8.2.3. Sensitivity Analyses of the Primary Analysis

As a sensitivity analysis of the W2LOCF approach, a W4LOCF will also be used whereby the PI score obtained before a given rescue medication will be carried forward to replace the PI scores collected at each observation within 4 hours following the rescue dose. The analysis will be conducted in both the mITT and the PP analysis sets.

In addition to the BOCF/LOCF approaches outlined above, missing data may be imputed using multiple imputation (MI) methods. This will be executed in three stages:

- Censoring and replacement of values within the two-hour rescue window will be performed via W2LOCF.
- Intermittent missing values will be imputed assuming missing at random with 20 replicates; covariates will include all non-missing NPRS assessments (including the pre-dose value) and imputation will be done within treatment arm.
- For the third stage subjects who discontinued early due to lack of efficacy or an AE related to study drug will be imputed using the pre-dose distribution by sampling from a trimmed normal that has the mean and standard deviation of the baseline values across all arms. The distribution will be trimmed to a value of 5-10. For subjects that discontinue for any other reason, values will be imputed assuming missing at random with 20 replicates; covariates will include all non-missing NPRS assessments (including the pre-dose value) and imputation will be done within treatment arm.

For the multiple imputation stages, values will be imputed using the Markov Chain Monte Carlo (MCMC) method implemented with the SAS MI procedure. If the missing data is minimal, this analysis may not be performed. This MI analysis will be performed on both the mITT and ITT populations (if they differ).

Additionally, the primary analysis will be repeated excluding the NPRS scores recorded at the time of perceptible pain relief and at the time of meaningful pain relief.

8.3. Secondary Endpoints

All hypotheses will be tested at a two-sided significance level of 0.05. Since this is a phase 2 study, nominal p-values will be presented for all secondary endpoints without adjustment for multiple comparisons.

8.3.1. Secondary SPID Endpoints

An approach identical to the primary computation for the $SPID_{0-24}$ above will be employed for the cumulative SPID for hours 0-2, 0-4, 0-8, and 0-12. Additionally, the interval 12-24 will be calculated by subtracting the 0-12 SPID from the 0-24 SPID.

For each, summary statistics will be presented as well as the ANCOVA LS means model results from a model identical to the one specified for the primary. If it converges, results from the 3 parameter Emax model will also be presented for each interval.

8.3.2. Total Pain Relief (TOTPAR)

TOTPAR will have AUCs calculated in a manner identical to the primary SPID analysis with the exception that it is not collected pre-dose, therefore, there is no comparison to the pre-dose value. AUCs will be calculated for the intervals 0-2, 0-4, 0-8, 0-12, 0-24 and 12-24.

For each, summary statistics will be presented as well as the ANCOVA LS means model results from a model identical to the one specified for the primary. If it converges, results

from the 3 parameter Emax model will also be presented for each interval. Note that these models will utilize the baseline pain intensity NPRS value as a covariate.

8.3.3. Pain Intensity Differences over Time

Summary statistics will be presented for the pain intensity differences (pre-dose value minus NPRS) at each collection time point. Additionally, a longitudinal mixed model for repeated measures (MMRM) with fixed effects for treatment, time, treatment by time interaction and baseline PI score will be fit. No imputations will be performed and data will be assumed to be missing at random. An unstructured covariance matrix will be fit to the subjects' repeated measures; if this fails to converge, compound symmetric will be used instead. Degrees of freedom will utilize the DDFM=KR option in Proc MIXED. Least square means for each time point and 95% CIs will be presented for each study arm and the MECC-SA arms pooled (via an estimate statement). Likewise, the differences from placebo at each time point will be presented for the individual MECC-SA arms and overall with LS means, 95% CIs and p-values.

Least squares means will be plotted by time to show the pain-relieving efficacy of both MECC-SA and placebo over 24 hours.

8.3.4. Time to Event outcomes

The three time to event outcomes will be analyzed in an identical manner. These include:

- Time to perceptible relief (as measured by double-stopwatch technique) after first dose.
- Time to meaningful pain relief (as measured by double-stopwatch technique) after first dose.
- Elapsed time from the start of study medication to first rescue medication administration.

Each will be analyzed using the Kaplan-Meier method with strata for all arms to present quantiles (25%, median, 75%), if estimable. The log-rank test will be used to test the hypothesis of overall treatment difference, pooling the MECC-SA arms. If significant, the individual arms will be compared to placebo in a pairwise manner.

Plots of the Kaplan-Meier curves will also be presented.

8.3.5. Responder endpoints

The four responder endpoints will be analyzed in an identical manner. These include:

- Proportion of subjects with overall pain reductions from baseline of ≥30% and ≥50% within 4 hours following the first dose based on the PI scores. Both these analyses will be presented for both methods of handling rescue medication use (W2LOCF and W4LOCF approaches). This will include the 4-hour nominal time point, even if it falls slightly after four hours.
- Proportion of subjects using rescue medication during 0-24 hours. This will be cut off at precisely 24 hours from first dose.
- Proportion of subjects using rescue medication prior to second dose. Subjects that do not have a second dose will be cut off at precisely 12 hours from first dose. This analysis will be repeated pooling the matching first dose for BID and QD treatments.

- Patient's Global Assessment of pain control for 0-24 hours after the initial dose scored on the 5-point scale will be dichotomized and the percentage of subjects reporting a PGA score of 2 (good) or better defined as a responder. This will include the 24-hour nominal time point, even if it falls slightly after 24 hours.

The number and percentage of responders in each treatment group will be summarized. Comparisons between MECC-SA and placebo will be evaluated with the odds ratio and corresponding 95% CI from a logistic regression model with treatment group and baseline PI as a covariate. Pairwise tests will be performed via an estimate statement. For the proportion of subjects using rescue medication prior to second dose, an additional analysis of treatment groups combined vs. Placebo will be performed.

8.3.6. Frequency of Rescue Medication Use

The frequency of rescue medication use in the 0-24 hours period after the first dose of study treatment will be summed for each subject and this will be summarized and graphically presented. A Wilcoxon Test Rank Sum will perform pairwise comparisons of the rescue use in each arm versus placebo.

8.3.7. Pharmacokinetics

For all pharmacokinetic data analyses, the PK population will be used.

Samples for PK determination of drug concentrations of meloxicam and salicylic acid, in plasma will be determined by a bioanalytical laboratory using validated bioanalytical methods. Details of the validated bioanalytical method used will be provided in a separate bioanalytical report.

The plasma concentration data for meloxicam will be listed, summarized on the basis of time intervals, and plotted using a scatter plot with time relative to the preceding meloxicam dosing time. Actual times will be displayed in listings, when plotting individual data, and for the derivations of PK parameters; summaries by time point will group values by the nominal times. Summary statistics (mean, standard deviation, minimum, maximum, number of subjects, and coefficient of variation) will be calculated for plasma concentrations for each time interval and by treatment group.

Additional population PK (PPK) analyses of meloxicam concentrations will be performed; these analyses will be conducted and reported separately. These analyses may include explorations of:

- Plasma AUCs and corresponding SPIDs for matching time periods (AUC_{0-4} vs $SPID_{0-4}$, for example)
- Rescue medication use through 24hr and AUC_{0-24}
- T_{max} and time to perceptible relief/time to meaningful pain relief
- Scatter plots of pain intensity vs corresponding plasma concentration at the same time
- Scatter plots of time to perceptible relief/time to meaningful pain relief vs corresponding plasma concentration at nearest collection
- Additional PK:PD relationships

Full details of the PPK model building will be described in a separate PPK analysis plan.

8.4. Examination of Subgroups

There are no preplanned analyses of subgroups; exploratory analyses of subgroups may be performed, but will be post-hoc.

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

Analysis of all safety data will be performed on the Safety Population and will be presented by the treatment received.

9.2. Adverse Events

Subjects will be routinely queried in regard to the presence or absence of AEs using open ended questions. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms. The clinic will provide documentation of any adverse events in the subject's CRF. The AE source documentation will minimally include the following information: date and time of assessment, the outcome of the response, and identification of the clinic staff member collecting the information.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency or severity, or a change in the quality, of the disease or condition. (Worsening of a pre-existing condition is considered an AE.)

Events that occur in subjects treated with placebo are also considered AEs.

An AE is considered to be a treatment-emergent adverse event (TEAE) if the first onset or worsening is after administration of the IP (MECC-SA or placebo) and not more than 30 days after administration of IP.

All AEs will be coded using MedDRA Version 23.1.

An AE summary table presenting the total number of AEs will be presented for the following:

- TEAEs
- TEAEs by severity
- TEAEs leading to study discontinuation
- TEAEs by relationship
- Serious AEs (defined below)

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System organ class (SOC) and preferred term will be prepared. Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and TEAEs by strongest relationship to study drug. If missing, severity will be imputed as severe and relationship will be imputed as related.

Each participant will be counted only once within each summation level (SOC; preferred term). If a participant experiences more than one TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

In the AE data listings, all AEs will be displayed. AEs that are treatment-emergent will be flagged.

9.3. Deaths, Serious Adverse Events (SAE), and Other Significant Adverse Events

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- Fatal
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization

Section 7.3.1 of the protocol provides additional detail and exceptions to the above criteria.

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, SOC, and preferred term will be prepared for the Safety Population. A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF. Likewise, AEs resulting in study discontinuation and AEs resulting in death will be listed separately.

Adverse events of special interest given that MECC-SA is an NSAID will include the following:

- Myocardial Infarction/Unstable Angina
- Stroke/transient ischemic attack (TIA)
- Heart Failure
- Cardiac Arrhythmia (Atrial & Ventricular)
- Gastrointestinal haemorrhages NEC
- Gastrointestinal ulceration and perforation

Additionally, a summary of incidence rates (frequencies and percentages) of adverse events of special interest by treatment group, SOC, and preferred term will be prepared for the Safety Population.

9.4. Clinical Laboratory Evaluation

Clinical laboratory values will be collected at the Screening Visit and after the final pain assessment (24 hours post-dose). Values collected at Screening will serve as the baseline.

Clinical laboratory results will be listed only. Only laboratory values that are outside the normal range will be flagged in the data listings and presented with the corresponding normal ranges. The original units for normal ranges provided the study's local lab will be utilized in determining whether parameters are in range; that is, no conversions or rounding will be performed prior to this determination. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

Pregnancy tests, and urine drug screens will be presented in separate listings.

9.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1. Vital Signs

Blood Pressure and pulse rate will be listed and descriptively summarized (N, mean, SD, minimum and maximum) by treatment group and visit. Baseline (defined as the pre-dose value collected on Visit 2 (Day 1) and changes from baseline will be similarly summarized.

9.5.2. ECGs

ECG data; QT, QTcF (Fridericia's), heart rate (HR), QRS duration, PR and RR interval will be listed.

Baseline (defined as the pre-dose value collected on Visit 2 (Day 1)) and change from baseline for QT, QTcF, HR, QRS, RR and PR will be summarized using descriptive statistics (N, mean, SD, minimum and maximum) by treatment and time point.

For QTcF a classification of absolute values and increases from baseline will be performed. The number of subjects with maximum absolute QTcF <450 msec, 450 msec ≤QTcF <480 msec, 480 msec ≤QTcF <500 msec and QTcF values ≥500 msec will be tabulated by treatment and visit. The number of subjects with maximum increase from baseline QTcF <30 msec, 30 msec ≤QTcF <60 msec and QTcF ≥60 msec will be tabulated by treatment and time point.

All ECG results will be presented in a listing, including the interpretation.

9.5.3. Physical Exams

Physical Exam findings are recorded in medical history or adverse events CRFs as appropriate; dates they were performed and whether significant findings were present will be presented in a listing.

10. INTERIM ANALYSES AND DATA MONITORING

No interim analyses are planned.

11. CHANGES TO THE ANALYSES

11.1. Changes to the Analyses Planned in the protocol

The following are changes from the protocol-planned analyses:

The protocol specifies an ITT set for the efficacy analyses; in the context of the objectives of this study, subjects with no post baseline data do not inform the dose-response relationship and are excluded from the mITT population that this SAP specifies for the efficacy analyses. However, it is expected that an ITT population will be used in the phase III and dropouts prior to the first efficacy assessment there may be informative of the effectiveness of the drug; hence, it is planned to use the ITT population for phase III study planning and calculation of effect sizes for power and sample size.

The protocol includes a site covariate in many of the model descriptions; since this is a single-site study, it is not necessary.

The protocol described several models as ANOVA; these have been updated to ANCOVA.

For the protocol's MMRM model for the analysis of pain intensity over time included a random effect for subject; instead, subject correlated data will be handled via a repeated statement.

Intolerance to study drug was listed among the reasons for withdrawal that would result in BOCF imputation; this is not among the choices for reason for withdrawal, but should be recorded as an AE withdrawal.

[redacted]

A test comparing the number of RM uses was added.

[redacted]

Laboratory results are to be listed only.

11.2. Analyses Changed or Added from the Initial Draft

[redacted]

A test comparing the number of RM uses was added.

[redacted]

Laboratory results are to be listed only.

Minor editorial corrections for typos and grammar.

12. REFERENCES

Branson, M., J. Pinheiro, and F. Bretz, Searching for an adequate dose: Combining Multiple Comparisons and Modeling Techniques in Dose-Response Studies. Novartis Biometrics Technical Report, 2003. Number 2003-08-20.

13. APPENDIX

13.1. Schedule of Events

VISIT	1 (Screen)	2 (In-clinic)	2 (In-clinic)	Follow up Telephone Call
DAY	-30 to -2	1	2	5-7
Written informed consent	X			
IVRS/IWRS registration	X			
Demography and medical history	X			
Review concomitant medications	X	X	X	X
General physical examination[1]	X		X[15]	
Height	X			
Weight	X			
Temperature		X[2]		
Vital Signs (supine/semi-recumbent blood pressure, pulse rate)	X	X[3]	X[15]	
12-lead ECG (supine/semi-recumbent)	X	X[4]	X[15]	
Serum or urine pregnancy test[5]	X	X[2]	X[15]	
Urinalysis[6]	X		X[15]	
Urine drug screen	X	X[2]		
Blood safety labs (hematology, chemistry) including FSH (V1)[7]	X		X[15]	
PK Sample[8]		X	X	
Diary training		X[2]		
Review AEs[9]	X	X	X	X
Inclusion/exclusion criteria	X	X		
Dispense diary for pain assessment recordings		X		
Subject records AEs at home	X			X
Subject records AEs in the clinic		X	X	
Perform dental surgery		X		
Pain Assessments (Pain Intensity, Categorical Pain Rating) (prior to randomization)		X[10]		
Randomize to study via IVRS/IWRS		X		
Dispense study drug		X[11]		
Administer study drug (within 15 minutes of eligible pain assessments)		X[12]		
Administer study drug (12 hours after first dose)		X		
Pain Intensity Assessments (post-randomization)		X[13]	X[13]	
Pain Relief Assessments (post-randomization)		X[13]	X	
Patient Global Assessment of Pain Control			X[14]	
Record Rescue Medication Use		X	X	X

[1] Including respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological systems, lymph nodes, skin, extremities, head, ears, eyes, nose, and thyroid gland.

[2] Prior to surgery.

[3] Vital signs (blood pressure and pulse rate) are taken prior to surgery, pre-dose and 24 hours post-dose performed after ECG measurements taken at the same nominal time.

[4] 12-lead ECG will be performed both pre-dose and 24 hours post-dose as single measures.

[5] Serum pregnancy test at screening, urine at other visits.

[6] Urinalysis for blood, protein, nitrites, leukocyte esterase, pH, glucose and ketones. If positive for blood, protein, nitrites or leukocytes esterase a sample for microscopy/culture should be analyzed by the central laboratory.

[7] FSH to be measured in females who have been amenorrheic for at least 2 years, to confirm non-child bearing potential.

[8] PK sample taken pre-dose and 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication.

[9] All AEs will be recorded from time of consent until the telephone follow up/End of Study (EOS) Visit. The Investigator is also responsible for notifying the sponsor if they become aware of any AE after the study period has ended and it is considered related to the study medication. When assessing AEs, the subject will be specifically asked regarding the presence of any GI symptoms.

[10] Pain assessments (Pain Intensity and Categorical Pain Rating) performed for up to 5 hours post completion of surgery. Subjects with NPRS ≥5 and a rating of moderate or severe pain on a 4-point categorical pain rating scale (i.e., none, mild, moderate, severe) during this time they will be eligible for randomization.

[11] Drug is dispensed at 'time zero' and 12 hours later.

[12] Dosing of study medication must be within 15 minutes of the eligible pain assessments.

[13] Post-dose pain assessments made at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 14, 16, 20 and 24 hours after the first dose of study medication, and immediately before any dose of rescue medication. Assessments will also be made immediately following the time of first relief and time of meaningful relief.

[14] Patient's Global Assessment of Pain Control measured at 24 hours post-dose, or at time of early termination if applicable.

[15] Procedures performed after the final pain assessment (24 hours post-dose).

13.2. Random Seeds

The following list of number will be used in order for programming tasks that require random seeds. If additional numbers are required, programming will return to the start of the list and add one to each value for additional seeds.

95757437
73846758
65831589
86284444
90876999
43543977
78974612
22334268
66674922
78467583

14. ATTACHMENTS