Protocol B5061004

A PHASE 3, DOUBLE-BLIND, RANDOMIZED SAFETY AND EFFICACY STUDY COMPARING MULTIPLE ADMINISTRATIONS OF IBU 250 MG/APAP 500 MG (ADMINISTERED AS TWO TABLETS OF IBU/APAP 125 MG/250 MG) TO PLACEBO IN THE TREATMENT OF POST SURGICAL DENTAL PAIN IN ADULT SUBJECTS

Statistical Analysis Plan
(SAP)

Version: 1.0

Date: 03-Mar-2017

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1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study B5061004 is based on the protocol amendment 1 dated on 09 February 2017.

Table 1 Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B5061004. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Note: in this document text taken directly from the protocol is *italicized.*

2.1. Study Objectives

The objective of the study is to compare the analgesic efficacy and safety of FDC IBU/APAP 250 mg/500 mg every 8 hours compared to placebo in a 48-hour period following extraction of ≥3 third molar teeth.

2.2. Study Design

This will be a Phase 3, 48-hour, single-center, in-patient, multiple-dose, fixed dosing interval, randomized, placebo-controlled, sex- and baseline pain severity-stratified, double-blind, parallel group trial. Subjects will be adult males and females (18 to 40 years of age, inclusive) who are experiencing post-operative pain following surgical extraction of 3 or more third molar teeth. Following extraction of 3 or more third molar teeth, subjects will rest quietly at the study center until they experience post-surgical pain of at least moderate severity. At that time, subjects will be asked to assess their pain intensity and severity using categorical, numerical, and/or visual scales. Subjects with a qualifying baseline pain threshold within approximately 5 hours of completion of surgery will be entered into the study.

Upon completion of the baseline scales, eligible subjects will receive an oral dose of investigational product at 0 hours (baseline) and at 8, 16, 24, 32, and 40 hours post-baseline under randomized, double-blind conditions. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 32, 40, and 48 hours post-baseline, subjects will provide self-ratings of pain severity using the categorical and numerical PSRs. Subjects will also provide a self-rating of pain relief at each time point (except at baseline) using a categorical CCI [redacted] *. At 24 and 48 hours, or at the first rescue medication administration on the respective day, subjects will also complete a* CCI [redacted] *of the investigational product. Additionally, subjects will also evaluate the time to first perceptible relief and time to meaningful relief using a double stopwatch method up to 8 hours post-baseline (ie, up to the second dose administration), or until the time of first rescue*

medication use, whichever is sooner. A review of any reported adverse events will also be completed.

2.2.1. Study Treatments

Study treatments will be: A) FDC IBU/APAP 250 mg/500 mg and B) Placebo.

2.2.2. Schedule of Important Activities

The schedule of baseline, efficacy, safety, and treatment activities across the study visits are listed in the following table. For details of scheduled visit activities, refer to the protocol section of "Schedule of Activities".

Schedule of Activities

			Time (hours)												
	Screen[a]	Surgery	0	0.25	0.5	1.0	1.5	2.0, 3.0, 4.0, 5.0, 6.0, 7.0	8.0	9.0, 10.0, 11.0, 12.0	16.0	24.0	32.0	40.0	48.0
Informed Consent	x														
Medical History	x														
Physical Examination	x														
Screening Laboratory Tests[b]	x														
Hematology	x														
Blood Chemistry	x														
Urinalysis	x														
Coagulation	x														
Serum Pregnancy Test	x														
Urine Pregnancy Test[c]		x													
Surgical Procedure		x													
Surgical Trauma Scale		x													
Vital Signs (HR, BP, T, RR)			x						x						x
Randomization[d]			x												
Dosing			x						x		x	x	x	x	
Pain Evaluations															
VAS Pain Severity Rating[e]			x												
Categorical Pain Severity Rating[f]			x	x	x	x	x	x	x	x	x	x	x	x	x
Numerical Pain Severity Rating[g]			x	x	x	x	x	x	x	x	x	x	x	x	x
CCI [h]			x	x	x	x	x	x	x	x	x	x	x	x	x
CCI [i]				→											
Time to 'Meaningful' Relief[j]				→											
CCI [k]												x			x
Subjects taking a rescue medication during this time will be considered:			Discontinued						Treatment Failure						
Concomitant Medications	→														
Adverse Events	Recorded at any time during the study as they occur.														

a. Screening must be within 21 days of surgery; it may occur on the morning of surgery. Pregnancy test must be performed morning of surgery.

b. Screening laboratory tests include complete blood count (CBC) with differential count, prothrombin time (PT), parital thromboplastin time (PTT), international normalized ratio (INR), chemistry panel including liver function tests, and urinalysis. In addition, females of child bearing potential will be given a serum pregnancy test at screening.
c. Females of child bearing potential must be given a urine pregnancy test on the morning of surgery.
d. Those subjects meeting all inclusion/exclusion criteria, including at least moderate baseline pain on the Categorical Pain Severity Rating Scale confirmed by a score of at least 50 mm on a 100 mm Visual Analog Pain Severity Rating Scale.
e. 100 mm Visual Analog Pain Severity Rating Scale: none=0 to severe=100.
f. CCI: none=0, mild=1, moderate=2, and severe=3. Completed at each time point and immediately before rescue medication use.
g. 11 point Numerical Pain Severity Rating Scale: none=0 to 10 = Worst Possible Pain. Completed at each time point and immediately before rescue medication use.
h. CCI: none=0, a little=1, some=2, a lot=3, and complete=4. Completed at each time point and immediately before rescue medication use.
i. Subject is instructed to stop the first stopwatch “when you first begin to feel any pain relieving effect whatsoever of the drug”
j. Subject is instructed to stop the second stopwatch “when you have meaningful relief, that is, when the relief from the pain is meaningful to you”.
k. CCI: very poor=0, poor=1, fair=2, good=3, very good=4, excellent=5. Completed at the designated time points or immediately before taking rescue medication.
Abbreviations: → = ongoing/continuous event; BP = blood pressure; HR = heart rate; multiple-admin. = multiple administrations; RR = respiration rate; T = temperature

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

The following definitions and conventions will be used in the derivation of endpoints described in this document.

- Baseline pain intensity measure is defined as the last such measure when subjects experience post surgical pain of at least moderate severity following extraction of 3 or more third molar teeth prior to the administration of the first study medication. Other baseline variables are those last collected prior to the administration of the first study medication.
- Time of dosing with the first study medication will be considered time 0.
- Pain intensity difference from baseline (at each assessment timepoint) is defined as the baseline pain intensity minus the post baseline pain intensity so that a higher positive value is indicative of a greater improvement.
- The time-weighted sum of pain intensity differences from baseline and sum of pain relief over time interval 0-T will be derived as $\sum_1^T (t_i - t_{i-1}) * x_i$, where t_0 is the time of baseline assessment and $x_1, x_2, \ldots x_n$ are either the pain intensity difference from baseline or pain relief at scheduled on-treatment assessments time $t_1, t_2, \ldots, t_n$.
- Teeth surgery duration is the time from starting the surgery till stopping the surgery.
- Concomitant medications and concomitant non-drug treatments administrated in teeth surgery period are these medications and treatments administrated in the day of teeth surgery that were prior to the administration of the first study medication.
- None treatment-emergent adverse events in teeth surgery period are these adverse events occurred during the day of teeth surgery that were prior to the administration of the first study medication.

3.1. Primary Endpoint

The primary efficacy endpoint is time-weighted *sum of pain intensity difference scores based on the 11 point numerical Pain Severity Rating [PSR] scale from 0-24 hours* (SPID[11](0-24))

Time-weighted sum of SPID[11](0-24) will be derived using the pain intensity difference (imputed PID[11] per Section 5.3) from baseline to each post-dosing assessment time point through 24 hours (i.e. 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, and 24 hours post-dose assessments).

3.2. Secondary Endpoints

The secondary efficacy endpoints are:

- *Time weighted sum of Pain Intensity Difference scores PID[11] based on the 11 point Numerical PSR scale from 0-8, 6-8, 0-16, 8-16, and 0-48 hours* SPID[11](0-8), SPID[11](6-8), SPID[11](0-16), SPID[11](8-16), and SPID[11](0-48);

- *Duration of relief after first dose, as measured by the time from first dose to rescue medication or second dose whichever occurs first;*

- *Time to onset of "meaningful" relief for the first dose.*

Time-weighted sum of pain intensity difference scores: SPID[11](0-8), SPID[11](6-8), SPID[11](0-16), SPID[11](8-16), and SPID[11](0-48) will be derived using the pain intensity difference from baseline (imputed PID[11] per Section 5.3) through 48 hours assessments, i.e. during 0-8 hours, 6-8 hours, 0-16 hours, 8-16 hours, and 0-48 hours post first dose assessments respectively.

Time from first dose to rescue medication or second dose (duration of relief after first dose): The "duration of relief after first dose" will be computed as the minutes from the time of first dose to the time a subject first took a rescue medication (censoring is No), time to dropout due to lack of efficacy or AE (censoring is No), or the time of taking the second dose (censoring is Yes) whichever occurs first. If prior to taking rescue medication or secondary dose, a subject early discontinued from the study due to other reasons, the time will be censored at time when the subject last performed a study evaluation (censoring is Yes) prior to the dropout.

Time to onset of "meaningful" relief for the first dose: Time to onset of "meaningful" relief for the first dose will be computed as the minutes from the time a subject taking the first dose of study medication to the time of the subject stopping the stopwatch labeled for "meaningful" relief prior to the administration of the second dose of the study medication. If prior to onset of "meaningful" relief or the second dose, a subject took a rescue medication or early discontinued the study, the time will be censored at rescue medication onset time or the last time when the subject performed a study evaluation whichever occurs first. Otherwise if onset of "meaningful" relief did not occur prior to the second dose the time would be censored at time of the second dose. If time of onset of "meaningful" relief is missing then the subject will be censored at the time of taking second dose, rescue medication, or performed a study evaluation (if the subject early terminated) whichever occurs first.

3.3. Other Endpoints

3.3.1. Other Efficacy Endpoints

- CCI [redacted];

- CCI ;
- CCI ;
- CCI ;
- CCI

  CCI ;
- CCI ;
- CCI
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- CCI ;
- CCI
- CCI

CCI

CCI [redacted]

CCI [redacted]

CCI [redacted]

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CCI [redacted].

3.4. Baseline Variables

Unless otherwise specified, baseline variables are those latest assessments collected prior to the first dosing of the study medication and can occur at screening, surgery or post-surgery at day of tooth surgery prior to the administration of the study medication (see Table 2).

3.4.1. Demographic Data, Tooth Extraction and Surgery Details, Baseline Pain Evaluations, and other Background Information

Demographic Data: Sex, race, ethnicity, and age will be collected at screening. These variables will be summarized as described in Section 6.5.1.1.

Tooth Extraction and Surgery Details: the duration of surgery, number of teeth removed, and surgical trauma will be collected during the surgery. These variables, in addition to the time to study medication since the end of surgery will be summarized as described in Section 6.5.1.1. No treatment comparability will be assessed. All tooth extraction and surgery details including the date of surgery and information on the tooth removed will be listed appropriately.

Baseline Pain Evaluations: the following will be collected prior to the first dosing of the study medication, post-surgery at hour 0 during the study period. They will be summarized as described in Section 6.5.1.1.

- CCI [redacted].

- 100 mm Visual Analog Scale Pain Severity Rating Scale (VAS-PSR). A minimum score of 50 mm is required to verify that the subject has at least moderate pain at baseline.

- 11-point numerical PSR scale (None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible Pain.)

Background Information: Past and current medical history will be collected at screening and will be summarized by treatment and total in a similar manner as adverse events (AEs) using

the MedDRA system organ class (SOC) and preferred term. The corresponding listing will be also produced. .

3.4.2. Concomitant Medications and Non-Drug Treatment

During the study, all concomitant medications and non-drug treatments used during the study will be recorded in the case report form. Concomitant medications will be coded using WHO Drug Dictionary. Non-drug treatments will be coded using MedDRA Dictionary.

3.4.2.1 Concomitant Medications (except Rescue Medication) and Non-Drug Treatment for Tooth Surgery

Concomitant medications and non-drug treatment for tooth surgery are those that were administered at any time from prior to tooth surgery till the administration of the first study medication on Day 1.

3.4.2.2 Concomitant Medications and Non-Drug Treatment Administrated Post Study Dose

Concomitant medications (except rescue medication) and non-drug treatment administrated post study dose are those that were administered at any time point from the first dose of the study medication (about 2 hours after tooth surgery) on Day 1 to the end of study (48 hours post-dose).

3.5. Safety Endpoints

3.5.1. Adverse Events

An adverse event (AE) is considered treatment emergent relative to a given treatment if:

- the event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- the event was seen prior to the start of treatment but increased in severity during treatment.

The effective duration of treatment is determined by the lag time which for this study is 14 days. Any event occurring within the lag time, whether this occurs during a break in treatment or at the end of treatment, is attributed to the corresponding treatment.

For serious adverse events (SAEs), the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product.

If the date or time of onset of an AE is missing, the following rules will be used in determining whether an AE was treatment emergent or not:

a. If the onset time is missing but the date is not missing, the onset date will be compared with the first dose date: if onset date is on or after the dose date such AEs will be considered treatment emergent;

b. If both the date and the time of onset are missing, whether the AE was treatment emergent or not cannot be determined and such AEs will be considered treatment emergent.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's *Safety Review Plan* (SRP) listed in Appendix 1 for the complete list of treatment emergent AEs. For this study treatment emergent AEs in the SRP are considered as Tier-1 events.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA preferred term (PT) is defined as a tier-2 event if there are at least *2%* in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events. Tier-3 events will not be summarized separately from all adverse events.

3.5.2. Vital Signs

Each subject's vital signs (ie, pulse, heart rate, blood pressure, respiratory rate and temperature) will be measured at baseline (screening period prior to start surgery), at 8 hours post first dose and again at the end of study (48 hours post first dose) or at the time of rescue medication (if needed) or early termination of the study. The change from baseline vital signs will be calculated as post baseline value minus the baseline value. If multiple values at a scheduled time point are measured the last one of repeated values will be used in analysis for the time point.

3.5.3. Laboratory Data

Laboratory assessments such as hematology, coagulation, blood chemistry, urinalysis, and pregnancy will be performed at screening and results will be used for inclusion purposes only. The results will not be entered in the database.

Urine pregnancy tests will be also administered to female subjects before the investigational product administration prior to surgery and results will be used for inclusion purposes only. The results will not be entered into the database. Physical Examination

Physical exam will be only performed at screening period prior to surgery. If multiple exams are assessed, the latest one will be used in the analysis. .

3.5.4. Electrocardiogram

In this study no ECG exam will be conducted.

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

The full analysis set (primary population) is the intent to treat (ITT) subject population, defined as all randomized subjects who dosed with the study medication and provided a baseline assessment.

CCI

[redacted]

4.3. Safety Analysis Set

The safety analysis set will include all subjects who received at least once dose of the study product.

4.4. Other Analysis Sets

No additional analysis sets are planned.

5. GENERAL METHODOLOGY AND CONVENTIONS

All analyses will be performed upon the database lock following completion of the study.

In the efficacy analysis, subjects will be assigned to the randomized treatment regardless of what treatment they actually received. In the safety analysis, subjects will be analyzed according to the treatment they received, regardless of the randomized treatment assigned.

5.1. Hypotheses and Decision Rules

For the analysis of all endpoints, the statistical hypothesis to be tested is that FDC IBU/APAP 250 mg/500 mg is significantly better than Placebo.

5.2. General Methods

All computations will be performed using SAS® version 9.2 or higher *(SAS Institute, Cary, NC). Statistically significant treatment differences will be declared if the probability of random occurrence between treatments, p, is ≤0.05 (two-sided). Treatment differences will be considered marginally significant if 0.05< p ≤0.10*. All tests will be two sided.

The primary efficacy analyses will be based on the full analysis set (Intent to treat). For all endpoints, summary statistics will be provided by treatment group.

5.2.1. Analyses for Continuous Data

An analysis of covariance (ANCOVA) model will be used with endpoints derived from the 11-point numerical PSR such as SPID[11] as well as the pain intensity difference (PID[11]) scores. The primary model will include treatment group, sex, and the baseline categorical PSR as classification variables, and the baseline numerical PSR as a continuous covariate. For each comparison, the treatment difference based on the least squares means (LSM), the p-value and the associated 95% confidence intervals (CI) based on the main effects model will be presented. *Primary efficacy endpoint SPID[11] 0-24 will be analyzed by ANCOVA model with treatment, categorical baseline PSR, baseline numerical PSR, and sex terms*.

The treatment-by-baseline categorical PSR and treatment-by-sex interaction effects will be additionally assessed for the primary endpoint SPID[11](0-24) only by adding each of these terms, one at a time to the main effects model. If any of the interaction terms are significant at the 0.05 level of significance, additional analyses may be conducted as appropriate.

An analysis of variance (ANOVA) model will be used with the summary scores based on the C [redacted], and CCI [redacted] CCI [redacted] as well as CI the pain relief, CCI [redacted], and CCI [redacted] scores. The ANOVA model will include treatment, baseline categorical PSR, and sex terms in the model. For each comparison, the treatment difference based on the LSM and the associated 95% CI based on the main effects model will be presented.

Descriptive statistics, including the sample size, mean, standard deviation, median, minimum, and maximum values, will be provided for continuous efficacy endpoints.

5.2.2. Analyses for Time to Event Data

Time to event endpoints will be analyzed using the Gehan-Wilcoxon test for testing difference between the two treatment groups, stratifying by categorical baseline PSR and sex term, and be displayed graphically using the survival curves based on the Kaplan-Meier estimates. The

median survival time and its corresponding 95% CI will be estimated using the method of Simon and Lee (1982) method.

5.2.3. Analyses of Ordinal Categorical Endpoint

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[redacted]

5.2.4. Analyses of Proportion

All analyses of binary endpoints (such as proportional of responders) will be analyzed using a CMH general association test controlling for baseline categorical PSR and sex, using table scores. The confidence limits for the treatment differences will be derived based on the adjusted proportions (the CMH weighted average of proportions within each sex-by-baseline pain severity stratum) and the standard error for the difference in adjusted proportions. For all proportions the number and percentages of subjects will be presented for each treatment group.

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[redacted]

- CCI [redacted]
- CCI [redacted]

- CCI [redacted]

  CCI [redacted]
- CCI [redacted]
- CCI [redacted].

6. ANALYSES AND SUMMARIES

The endpoints described below will be analyzed using the full analysis set (Section 4.1). Selected endpoints may also be analyzed using the 'per-protocol' analysis set (Section 4.2) provided that the per-protocol population does not constitute at least 90% of the full analysis set.

6.1. Primary Endpoint

6.1.1. Primary Analysis

The primary efficacy endpoint of time-weighted sum Pain Intensity Difference Scores based on the 11 point numerical PSR Scale from 0-24 hours (SPID[11](0-24)) will be analyzed using the model described in Section 5.2.1 with treatments of FDC IBU/APAP 250 mg/500 mg and Placebo. Difference between the two treatment groups will be tested using the main

effects ANCOVA model (specified in Section 5.2.1). This is considered the primary analysis. The full analysis set will be used.

Reporting of Results:

- The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm as well as the LSM and standard error based on the main effects ANCOVA model. The root mean square of error (RMSE) based on the main effects model will be presented. The LSM for difference between the two treatments, its corresponding 95% CI and p-value based on the main effects model will also be presented.

- The p-values from the addition of the interaction terms treatment-by- categorical baseline PSR, and treatment-by-sex, one at a time, to the main effects model, will be tabulated.

- The LSM of SPID[11](0-24) for each treatment groups and its standard error will be presented in a vertical bar graph based on the main effects model.

6.1.2. Per-Protocol Analysis

If the per protocol population consists of less than 90% of the ITT subject population, a per protocol analysis will be performed. In per protocol analysis, the primary efficacy endpoint SPID[11](0-24) based on per protocol analysis population will be analyzed using the model described in Section 5.2.1 with treatments of FDC IBU/APAP 250 mg/500 mg and Placebo. Difference between the two treatment groups will be tested using the main effects model.

Reporting of Results:

The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm as well as the LSM and standard error based on the main effects ANCOVA model. The root mean square of error (RMSE) based on the main effects model will be presented. The LSM for difference between the two treatments, its corresponding 95% CI and p-value based on the main effects model will also be presented.

6.2. Secondary Endpoints

6.2.1. Time weighted sum of Pain Intensity Difference scores SPID[11] based on the 11 point Numerical PSR scale from 0-8, 6-8, 0-16, 8-16, and 0-48 hours - SPID[11](0-8), SPID[11](6-8), SPID[11](0-16), SPID[11](8-16), and SPID[11](0-48) – Secondary Endpoints in Continue Data Format

These secondary endpoints will be analyzed using the main effects ANCOVA model described in Section 5.2.1.

Reporting of Results:

- The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm as well as the LSM and standard error. The root mean square of error (RMSE) based on the main effects model will be presented. The LSM for difference between the two treatments, its corresponding 95% CI and p-value based on the main effects model will also be presented.

- The LSM of SPID[11](0-8), SPID[11](6-8), SPID[11](0-16), SPID[11](8-16), and SPID[11](0-48) for each treatment groups and its standard error will be presented in a vertical bar graph.

6.2.2. Time to Onset of "Meaningful" Relief for the First Dose and Duration of Relief after First Dose - Secondary Endpoints in Time-to-Event Data Format

Time to first onset of "meaningful" relief for the first dose and time duration of relief after first dose (as measured by the time from first dose to first use of rescue medication or second dose whichever occurs first) will be analyzed using the model described in Section 5.2.2 with treatments of FDC IBU/APAP 250 mg/500 mg and Placebo.

Reporting of Results: The sample size, estimated median time (in minutes) and its 95% CI calculated using the Simon and Lee method (1982), percentage of subjects with event for each treatment, and the p-value from difference between the two treatments by the Gehan-Wilcoxon test. Kaplan-Meier plot of time to "meaningful" relief or duration of relief after first dose will be presented respectively by treatment group.

6.3. Other Endpoint(s)

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[redacted]

CCI [redacted]:

- CCI [redacted]

CCI

- CCI
- CCI

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6.4. Subset Analyses

Subgroup analyses may be conducted for selected endpoints among subjects in the full analysis set who had moderate baseline pain and severe baseline pain. Similar analysis models as described above will be used, except that the baseline pain severity may be excluded from each model as appropriate.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographics and Baseline Characteristics

Demographic data and baseline characteristics will be summarized by treatment group and overall.

Continues variables (age, body weight, BMI, etc.) will be summarized using sample size, mean, median, standard deviation, minimum and maximum by treatments. Categorical variables (sex, race, ethnicity, etc.) will be summarized using frequencies and proportions by treatments. All randomized subjects will be included.

Baseline numerical scores of Pain Severity Rating and VAS Pain Severity Rating will be summarized using sample size, mean, median, standard deviation, minimum and maximum by treatments. Baseline categorical scores of Pain Severity Rating will be summarized using frequencies and proportions by treatments. The full analysis set may be used.

Number of tooth extraction and categorical trauma rating score will be summarized using frequencies and proportions by treatments. Duration of surgery and time from end of surgery to the administration of the first study dose will be summarized using sample size, mean, median, standard deviation, minimum and maximum by treatments. Both safety population and full analysis set will be used if they are different.

No treatment comparability will be assessed.

6.5.1.2. Prior Medical Conditions and Medical History

Frequency and percentage of subjects with prior medical conditions and medical history will be tabulated by treatment group and overall for the safety analysis set based on the MedDRA dictionary preferred term.

6.5.1.3. Concomitant Medications and Concomitant Non-Drug Treatment for Tooth Surgery

Frequency and percentage of subjects who took concomitant medications (based on the MedDRA dictionary preferred term) and/or concomitant non-drug treatment for tooth surgery (based on WHO Drug dictionary term) will be tabulated by treatment group and overall for the full analysis set and the safety analysis set (if different from the full analysis set) .

6.5.2. Study Conduct and Subject Disposition

The number and proportions of subjects who were randomized, completed or withdrew from the study, by reason for withdrawal will be summarized by treatment group and overall. The number and proportions of subjects who were screened and enrolled into the study will be summarized for overall.

The numbers of subjects in the full analysis set and safety analysis set will also be summarized by treatment group and overall.

6.5.3. Concomitant Medications and Non-Drug Treatments

Frequency and percentage of subject taking concomitant medications (except rescue medication) post the first study dose will be tabulated by treatment group and overall for the safety analysis set based on the WHO Drug dictionary term.

Frequency and percentage of subject taking non-drug treatment post the first study dose will be tabulated by treatment group and overall post first dose, respectively, for the safety analysis set based on the MedDRA dictionary preferred term. Time of taking Ice will be listed by subjects.

6.6. Safety Summaries and Analyses

Safety analyses will be performed using the safety analysis set (Section 4.3).

6.6.1. Adverse Events

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment. Adverse events will be summarized by the MedDRA SOC and preferred term and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the worst relationship.

Non- treatment emergent AEs will be summarized.

Adverse events will be presented by overall incidence of at least one event, incidence by SOC and preferred term, and by severity and relationship to study product. Each subject will contribute only once regardless of the number of occurrences (events) the subject experiences.

Tier-1 and Tier-2 adverse events (Section 3.5.1) and all AEs will be tabulated separately.

Serious adverse events (SAE) occurred within 48 hours after first dosing of the first study medication will be listed as in study treatment period. SAE reported after 48 hours post first dose till 28 calendar days after the last dose of study mediation via the follow-up telephone call will be listed as in study follow-up period.

6.6.2. Laboratory Data

Screening laboratory exam data will not be entered into the database. No analysis of Laboratory data is planned.

6.6.3. Vital Signs

Post-treatment vital signs at 8 and 48 hours post-treatment, and at time of taking rescue medication or early termination, and their change from baseline values will be tabulated in summary statistics (n, mean, SD, media, and range) by treatment group and overall for the safety analysis set. No statistical test will be conducted.

6.6.4. Electrocardiogram

In this study no ECG exam will be conducted.

6.6.5. Physical Examination

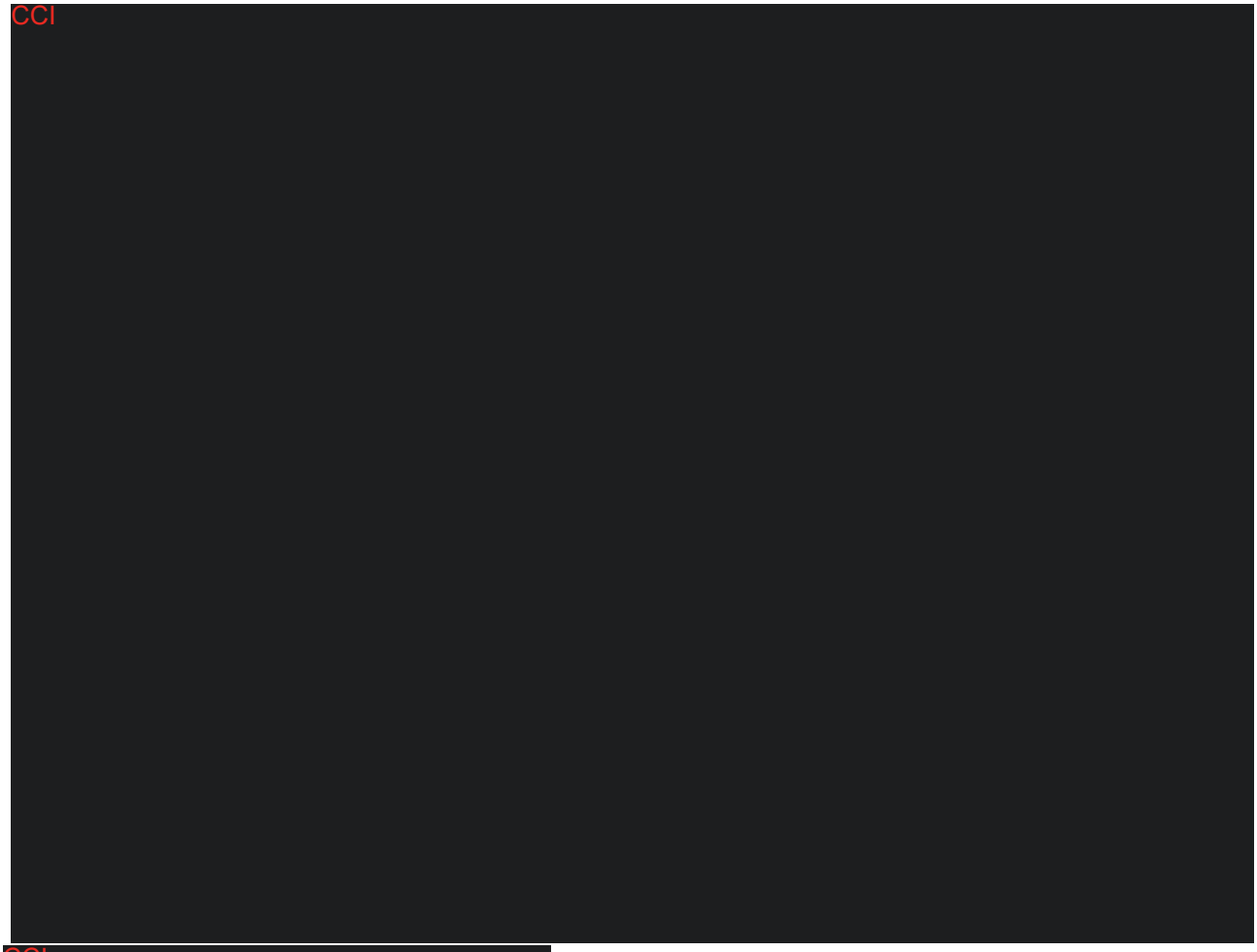
Screening physical exam will be only listed by subjects.

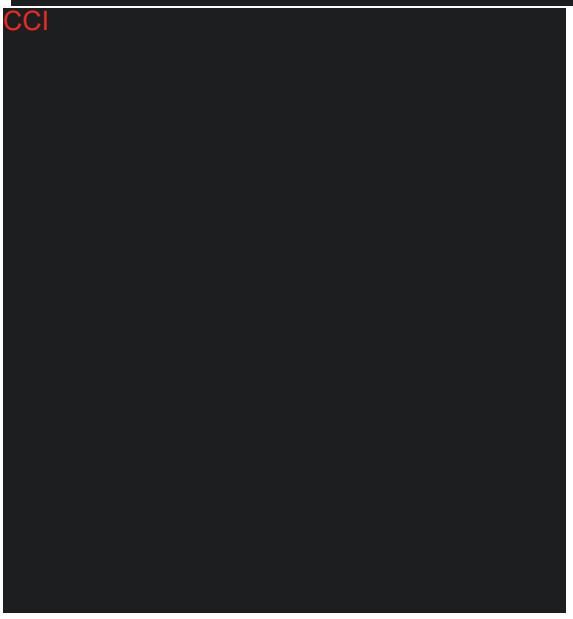
7. INTERIM ANALYSES

No interim analysis is planned.

8. REFERENCES

Ricahrd Simon & Young Jack Lee (1982): Nonparametric Confidence Limits for Survival probabilities and Median Survival Time, *Cancer Treat Rep 66:37-42*.





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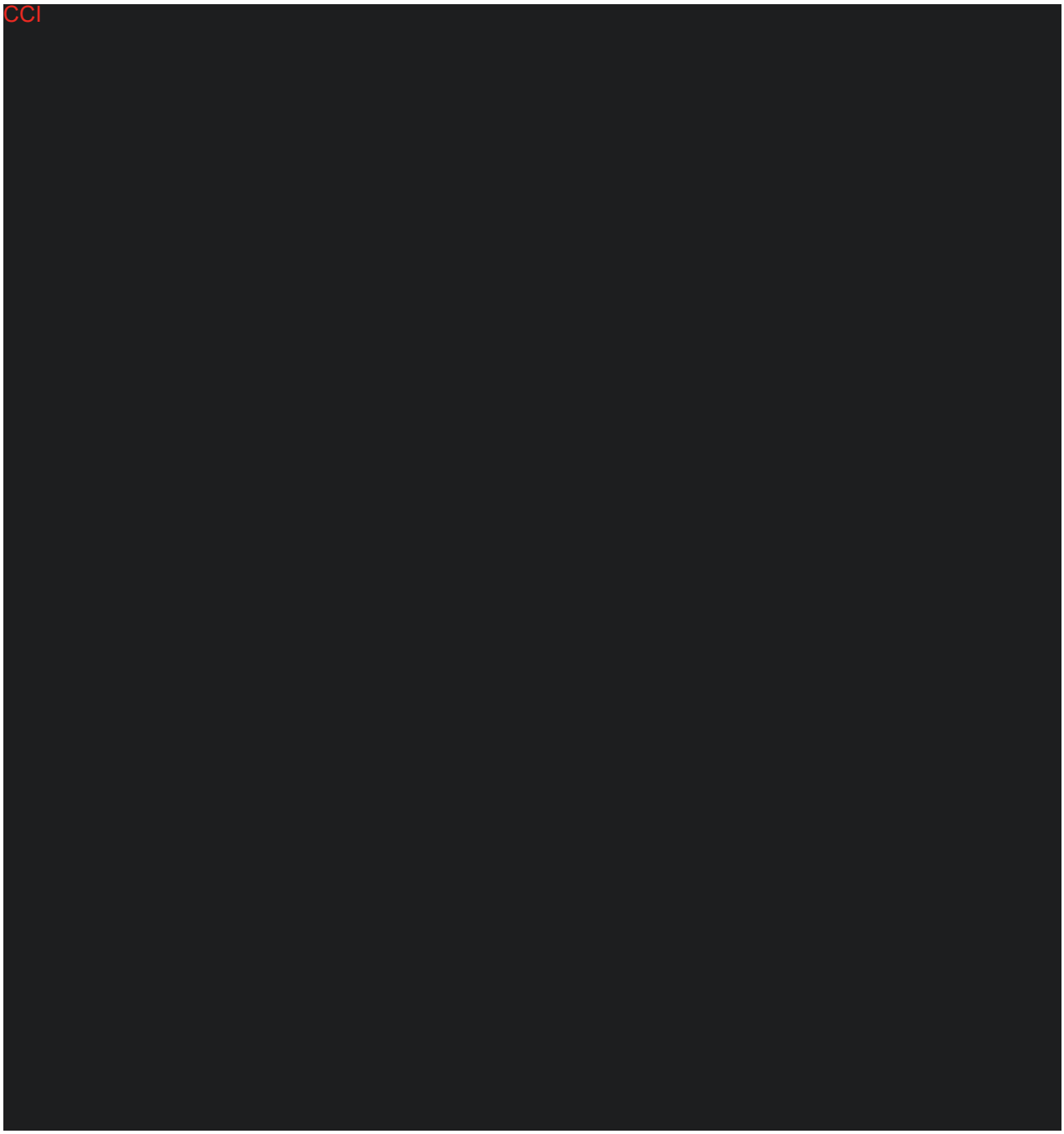

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