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Protocol CCSPAA005199

A Full Factorial, Randomized, Double Blind, Placebo Controlled, Parallel Group, Single Dose Efficacy and Safety Study of an Acetaminophen/Naproxen Sodium Fixed Combination, Acetaminophen, and Naproxen Sodium in Postoperative Dental Pain

Statistical Analysis Plan (SAP)

Date: 25-Jun-2024
Version: 3.0

Status : Approved

Version History

Version	Date	Description
1.0	07-Feb-2022	Initial version
2.0	08-Mar-2023	Same information but the year was incorrect on the document, not 2022 but 2023
3.0	25-Jun-2024	Updated based on protocol amendment #5 (Version 6.0, 24-Jun-2024), and findings from blinded data review

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

As stated in the protocol:

Primary Objective(s):
To evaluate the analgesic efficacy of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium and placebo over 12 hours.

Secondary Objective(s):
To evaluate the duration of analgesic effect of a fixed combination of acetaminophen/naproxen sodium.

Safety Objective(s)
To evaluate the safety of a fixed combination of acetaminophen/naproxen sodium.

1.2 STUDY DESIGN

As stated in the protocol:

This will be a randomized, double-blind, placebo-controlled study to evaluate the analgesic efficacy and safety of a fixed combination of acetaminophen/naproxen sodium, compared with acetaminophen, naproxen sodium, and placebo.

Subjects will undergo dental extraction of three or four third molars. Supernumerary teeth may also be removed. Judgment of impaction level will be made by the oral surgeon based on visual examination of the panorex x-ray. Maxillary third molars may be removed regardless of impaction level. The mandibular extractions must meet one of the following scenarios:

- *Two full bony impactions*
- *Two partial bony impactions*
- *One full bony impaction in combination with one partial bony impaction*

Post-surgery trauma assessment determined by the surgeon will be done on the day of surgery (Baseline visit). Subjects will be excluded from the study if the mandibular extraction results in a trauma rating of "severe" on a mild, moderate, or severe scale.

Approximately 440 subjects who meet the randomization criteria (post-surgical pain of moderate to severe on the four-point categorical pain scale, and at least a score of 5 on the 11 point [0-10] pain intensity numerical rating scale [PI-NRS] at Baseline within 4.5 hours of last stitch from dental extractions) will be randomized. No less than approximately 30% of randomized subjects will be either male or female.

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To maintain the double-blind nature of the study, all tablets in the study will be over-encapsulated and placebo (an inert powder) will be encapsulated in identical opaque capsules to ensure that they are indistinguishable.

Upon randomization, subjects will be assigned to one of the following treatment groups, with 4:4:2:1 allocation:

- *Acetaminophen* [redacted] */Naproxen Sodium* [redacted]
- *Naproxen Sodium* [redacted]
- *Acetaminophen* [redacted]
- *Placebo* [redacted]

All treatments will be administered as a single dose.

Rescue analgesic medications include:

• First-line rescue analgesic medication (celecoxib 400 mg initial dose, which can be followed by celecoxib 200 mg 12 hours after the initial dose, if needed; not to exceed 600 mg in 24 hours) will be available for subjects as needed for intolerable pain.

• Second-line rescue analgesic medication (oxycodone immediate release 5 mg every four to six hours as needed; not to exceed 30 mg in 24 hours) will be available for subjects as needed for intolerable pain only during the 12-hour therapeutic window after any dose of the first-line rescue medication. If intolerable pain occurs beyond 12 hours after the initial dose of the first-line rescue medication, then the second dose of first-line rescue medication will be administered before proceeding with any additional doses of second-line rescue medication that may be needed.

Self-reported pain intensity will be collected using a four-point categorical pain scale and a 0-10 PI-NRS at Baseline (Time 0). Pain intensity (using PI-NRS) [redacted] *will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post dose as well as* [redacted] *prior to each use of rescue analgesic (if applicable).* [redacted]

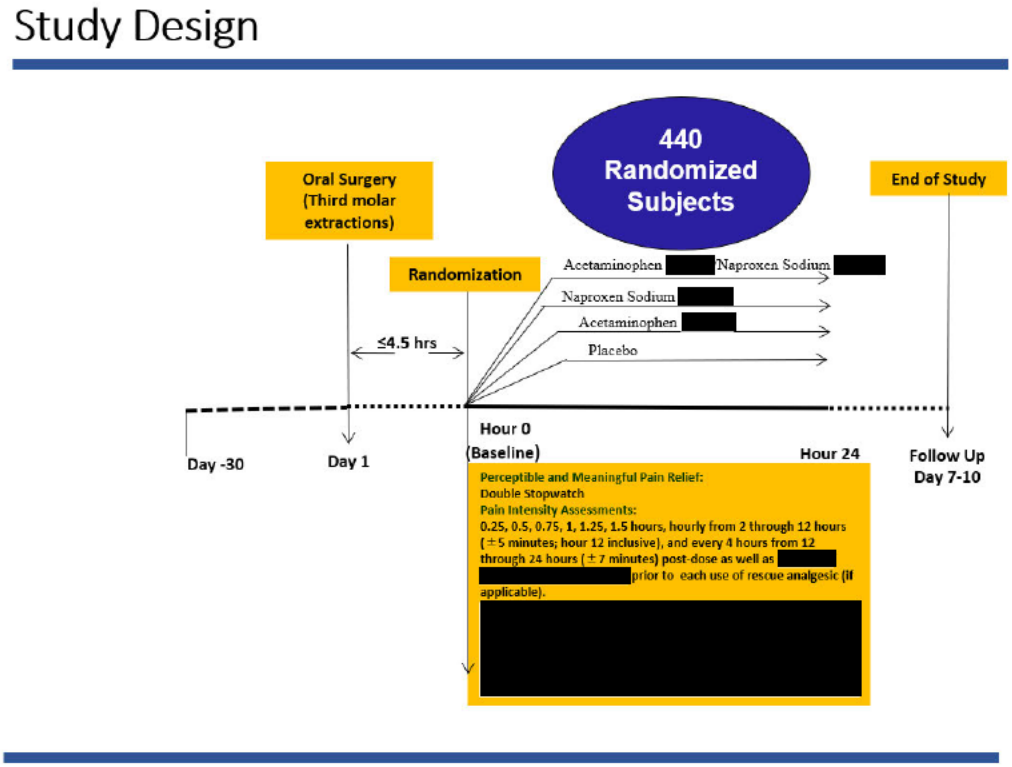
[redacted]

After completion of all study assessments, subjects will be discharged from the study site. Subjects will be interviewed by telephone to follow up on appropriate post-surgical medical

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care and changes in their health, including any emergent or existing adverse events (AEs). The interview will occur between the sixth and ninth day after the dental surgery (Days 7 to 10 of the study).

Figure 1. Schematic Study Design



2. INTERIM ANALYSES

No interim analysis is planned. Final analyses will be performed at the official database release.

3. ANALYSIS SETS

The primary efficacy analyses will be based on the Intent-to-Treat analysis set (ITTS), which will include all randomized subjects. As a secondary analysis, the primary endpoint will be analyzed based on the per-protocol analysis set (PPS), if the per-protocol analysis set differs from the Intent-to-Treat analysis set by at least 5% of the subjects. The per-protocol analysis set will include all randomized subjects excluding subjects who vomited within 60 minutes after dosing, and those with major protocol deviations (The final per-protocol analysis set will be determined before unblinding).

The Safety Analysis Set (SS) will include all subjects who were randomized and took IP.

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4. ENDPOINTS

4.1 PRIMARY ENDPOINTS

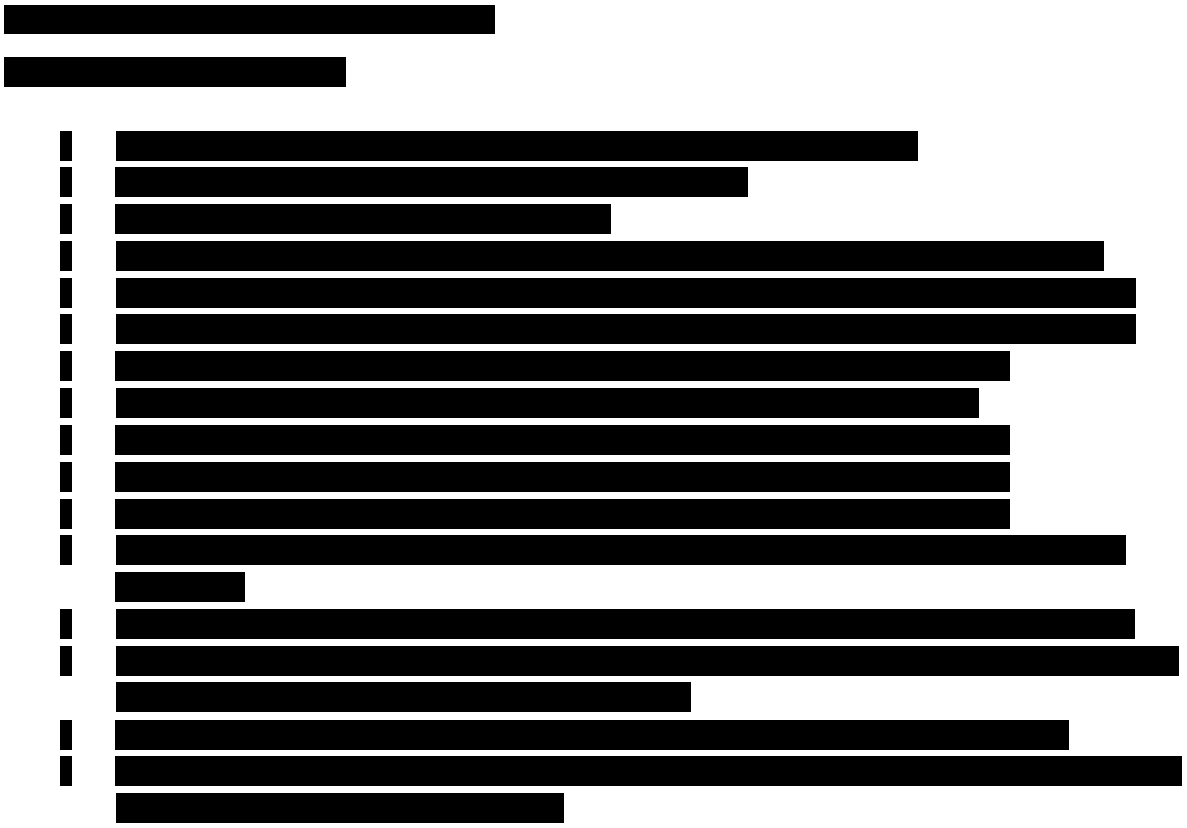
The primary endpoint is:

- Time weighted sum of pain intensity difference from 0 to 12 hours after dosing (SPID 0-12)

4.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first request for rescue analgesic
- Proportion of subjects who request rescue analgesic during the first 12 hours



5. DATA COMPUTATIONS AND HANDLING OF MISSING VALUES

5.1 ENDPOINTS RELATING TO PAIN INTENSITY

Pain intensity score for each time-point is the pain intensity score which is the closest valid score to the target time-point within ± 5 minutes for time-points up

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to 90 minutes post-dose, and ± 15 minutes for the remaining timepoints, among scheduled pain assessments, pain assessments prior to rescue [redacted]. In case more than one pain intensity [redacted] scores are the same distance from the target time-point, the scheduled pain assessment score will be used. Only pain intensity [redacted] that are not within any rescue medication's therapeutic window, are considered to be valid scores. Pain intensity [redacted] scores provided at times differing from the intended times by more than ±5 minutes for the scores up to 90 minutes post-dose, and by more than ±15 minutes for the remaining measurements will be estimated by linear interpolation.

5.1.1 Imputation for Pain Intensity

For subjects who use rescue medications, the last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue medication respectively. [redacted]

For subjects who discontinue the treatment due to lack of efficacy or adverse event during the 24-hour period, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted]

For subjects who withdraw from the study due to reasons other than lack of efficacy or adverse event during the 24-hour period, or are missing data without withdrawal from the study, multiple imputation method will be used for such missing time-points, under the Missing at Random assumption. [redacted]

5.1.2 Therapeutic Window of Rescue Medications

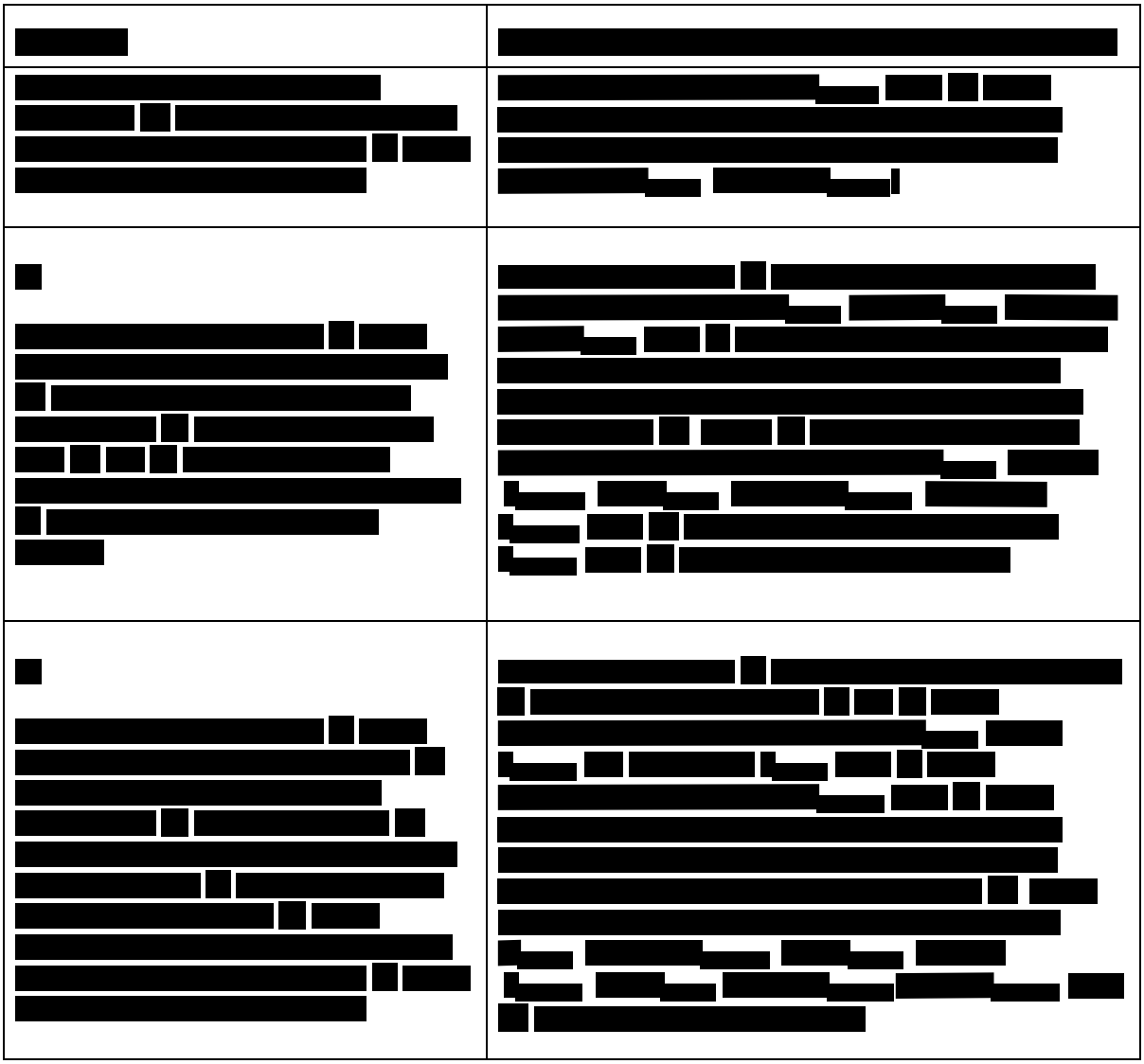
For subjects who use multiple rescue medications during the 24-hour observation period, time-points that are within any rescue medication's therapeutic window will be imputed using the last reported pain intensity score before taking first rescue medication, when imputing for pain intensity. [redacted]

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[redacted]

[redacted]

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For subjects who used rescue, but did not have documented time of rescue taken, the start time of therapeutic window for that rescue will be considered as the time of pain assessment prior to that rescue.

5.1.3 Derivation of SPID Scores

The PID at each time point will be derived by subtracting the pain intensity at that time point from the baseline pain intensity.
The SPID scores will be derived by first multiplying each PID score by the time from the previous time point and adding these time-weighted PID scores together over the intervals from 0-6, 0-12, 4-12, 6-12 or 0-24 hours. Rescue medication will be accounted for by carrying forward the pain intensity just prior to the first rescue medication forward from the current time of rescue to the current time of rescue plus the therapeutic window. Through this approach, rescue at all possible time points will be adequately accounted for. Following are examples taking into account the therapeutic window of rescue medication when deriving SPID scores:

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[redacted]

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[redacted]

5.2 TIME TO FIRST REQUEST FOR RESCUE

Time to first request of rescue medication will be measured as the elapsed time from when IP was given until the time rescue medication was first requested. For request for rescue medication, subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, will be considered as having requested rescue, and their time of rescue request is the time of discontinuation. Subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to lack of efficacy or adverse event, will be censored at the time of study withdrawal. Subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to lack of efficacy or adverse event, and do not withdraw from the study before 24 hours, will have their time to first request for rescue set to 24 hours and will be censored at 24 hours.

[redacted]

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[redacted]

6. SAMPLE SIZE DETERMINATION

The total sample size of 440 subjects (160 for Acetaminophen/Naproxen Sodium Fixed Combination, 160 for Naproxen Sodium, 80 for Acetaminophen, and 40 for Placebo) is based on, for SPID 0-12, a population standard deviation of 28. [redacted]

The assumed population standard deviation is based on previous studies using the same clinical model and study site, and the assumed differences between treatment means were based on extrapolation from a previous dose-ranging study.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL HYPOTHESES AND DECISION RULE

For endpoints based on pain intensity (such as SPID), [redacted] Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments by testing the following hypotheses:

$H_0: \mu_1 = \mu_2$
$H_A: \mu_1 \neq \mu_2$

Where μ_1 is the population mean for Acetaminophen [redacted] / Naproxen [redacted] and μ_2 is the population mean for Placebo, Acetaminophen [redacted], or Naproxen [redacted].

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For time-to-event endpoints (time to first request for rescue analgesic, [redacted]), Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments by testing the following hypotheses:

$H_0 : S_1(t) = S_2(t)$ (all t)
$H_A : S_1(t) \neq S_2(t)$ (at least some t)

where $S_1(t)$ is the survival function for Acetaminophen [redacted] / Naproxen [redacted] and $S_2(t)$ is the survival function for Placebo, Acetaminophen [redacted], or Naproxen [redacted].

For the proportion of subjects requesting rescue Acetaminophen [redacted] / Naproxen [redacted] will be compared with each of the other three treatments by testing the following hypotheses:

H_0: $\pi_1 = \pi_2$
H_A: $\pi_1 \neq \pi_2$

where π_1 is the population proportions for Acetaminophen [redacted] / Naproxen [redacted] and π_2 is the population proportion for Placebo, Acetaminophen [redacted], or Naproxen [redacted].

All statistical comparisons will be performed at the 5% significance level, two-sided. For primary and secondary endpoints, statistical testing will be carried out in a fixed-sequence approach as follows:

1. The following comparisons will be tested for SPID 0-12:

   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted]
   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted]/Naproxen Sodium [redacted] will meet efficacy requirements for SPID 0-12, and testing will proceed to secondary endpoints, only if the mean for Acetaminophen [redacted]/Naproxen Sodium [redacted] is statistically significantly higher than the means for Placebo, Naproxen Sodium [redacted], and Acetaminophen [redacted]. [redacted]

2. The following comparisons will be tested for SPID 6-12:

   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Testing will proceed to the next secondary endpoint only if the mean for Acetaminophen [redacted]/Naproxen Sodium [redacted] is statistically significantly higher than the means for Placebo, and Acetaminophen [redacted]. [redacted]

3. The following comparisons will be tested for Time to First Request for Rescue Analgesic:

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- Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo.
- Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted]/Naproxen Sodium [redacted] will meet efficacy requirements for Time to First request of Rescue Analgesic only if the distribution for Acetaminophen [redacted]/Naproxen Sodium [redacted] is statistically significantly different from the distributions for Acetaminophen [redacted] and Placebo, in favor of Acetaminophen [redacted]/Naproxen Sodium [redacted]. [redacted]

4. The following comparisons will be tested for proportion of subjects requesting rescue within 12 hours:

   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo.
   - Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]

Acetaminophen [redacted]/Naproxen Sodium [redacted] will meet efficacy requirements for proportion of subjects requesting rescue within 12 hours only if Acetaminophen [redacted]/Naproxen Sodium [redacted] has a statistically significantly lower proportion than Acetaminophen [redacted] and Placebo.

The above fixed-sequence procedure will provide strong familywise error rate control at 5% for the family of comparisons including primary and secondary endpoint pairwise comparisons, with the exception of comparisons between Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted] for SPID 6-12 and rescue-related endpoints. [redacted] The rationale for excluding these comparisons from familywise error rate control is as follows: [redacted] The proposed dosing interval of the fixed combination product is no longer than the maximum labeled interval for existing OTC naproxen sodium products. [redacted]

7.2 STATISTICAL ANALYSIS

The Global Biostatistics Department at the sponsor will be responsible for statistical analyses. For continuous distributions, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum and maximum values. Distributions of categorical variables will be summarized by presenting the number and percent of subjects in each response category.

7.2.1 Subject Disposition

Subjects disposition will be presented using descriptive summaries overall for all screened subjects and by treatment group for all randomized subjects, respectively. Disposition

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summary will include screened subjects, subjects discontinued before randomization, randomized subjects, subjects completed the first 12-hour observation period, subjects completed the 24-hour observation period, treatment discontinuation during the 24-hour observation period, reasons for treatment discontinuation, study withdrawal during the 24-hour observation period, reasons for study withdrawal and completion status of follow-up interview.

7.2.2 Demographic and Baseline Characteristics

Baseline and demographic characteristics will be presented by treatment group for each analysis set. For continuous variables, descriptive summaries will include number of subjects, mean, standard deviation, median and range (min, max). For categorical variables, the number and percent of subjects in each response category will be presented.

Vital signs (temperature, respiratory rate, heart rate, and blood pressure) collected at Baseline will be summarized (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

7.2.3 Previous and Concomitant Medications

Previous and concomitant medications will be coded. Previous medications will be those that were discontinued before the surgery day. Concomitant medications will be those continued through, or started on, the surgery day and up through the 24-hour assessment period. In addition, those medications taken after the 24-hour assessment period through the follow-up interview for an AE will be considered concomitant medications. Medications taken after the 24-hour assessment through the follow-up call that were not taken for an AE will not be collected on the eCRF or summarized. Previous medications and concomitant medications will be summarized by treatment in separate tables. Number and percentage of subjects receiving each coded medication will be presented by treatment. Additionally, concomitant medications taken by greater than or equal to 5% of subjects in at least one treatment group will be presented.

7.2.4 Protocol Deviation

The major protocol deviation will be summarized by treatment group and all protocol deviation will be listed.

7.2.5 Analysis of Primary Endpoint

The primary estimand is the main clinical quantity of interest relative to pain relief over 0-12 hours after dosing and is defined according to the attributes in Table 2.

Table 2. Attributes of Primary Estimand

Treatment being compared:	The following comparisons will be tested for SPID 0-12: • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo

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	• Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Naproxen Sodium [redacted] • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time weighted sum of pain intensity difference from 0-12 hours after dosing (SPID 0-12)
Intercurrent events:	<u>Rescue Medication during the 12-hour evaluation period</u> For subjects who use rescue medication during the 12-hour evaluation period, the composite variable strategy will be used. The last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue medication, respectively. [redacted] <u>Treatment discontinuation due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period</u> For subjects who discontinue the treatment due to lack of efficacy or adverse event during the 12-hour evaluation period, the composite variable strategy will be used. To account for uncertainty, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted]

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Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event during the 12-hour evaluation period, or are missing data without withdrawal from the study, to account for uncertainty, a regression based multiple imputation method will be used for the subsequent missing time-point, under the Missing at Random (MAR) assumption. [redacted] The justification of MAR assumption including detailed narrative are given in Appendix 3.
Population level summary:	Differences in least square means of SPID 0-12 between treatment groups.

Statistical Model

As the primary analysis, pairwise comparisons of SPID 0-12 will be made using single analysis of variance (ANOVA) model with baseline pain (moderate or severe) score, gender (male or female), and treatment group (with 4 treatment groups as 4 levels) as factors, using imputation methods defined in section 5.1. The difference of least-square means, and its 95% confidence interval and p-value will be reported. The SAS procedure MIXED will be used to implement ANOVA analysis. The SAS procedure MI will be used to generate imputed datasets. The SAS procedure MIANALYZE will be used to combine analysis results, using standard methods (Little & Rubin, 2002). Appendix 4 provides the details of implementation of multiple imputation using SAS for primary analysis.

Supplementary and Sensitivity Analyses

As supplementary analysis, the pairwise comparisons of SPID 0-12 will be analyzed based on the per-protocol analysis set, if the per-protocol analysis set differs from the Intent-to-Treat analysis set by at least 5% of the subjects.

As the first sensitivity analysis, for subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event during the 12-hour evaluation period, or are missing data without withdrawal from the study, multiple imputation of the last reported pain

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score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach (the same method used for treatment discontinuation due to Lack of Efficacy or Adverse Event in primary analysis) will be used for subsequent missing time-points.

As the second sensitivity analysis, for subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period, multiple imputation of baseline observation carrying forward approach will be used for subsequent time-points. [redacted]

7.2.6 Analysis of Secondary Endpoints

7.2.6.1 SPID 6-12

The secondary estimand #1 is the main clinical quantity of interest relative to pain relief over 6-12 hours after dosing and is defined according to the attributes in Table 3.

Table 3. Attributes of Secondary Estimand #1

Treatment being compared:	The following comparisons will be tested for SPID 6-12: • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time weighted sum of pain intensity difference from 6-12 hours after dosing (SPID 6-12).
Intercurrent events:	<u>Rescue Medication during the 12-hour evaluation period</u> For subjects who use rescue medication during the 12-hour evaluation period, the composite variable strategy will be used. The last reported pain intensity score before taking first rescue medication will be carried forward from the time of each rescue medication to the subsequent time points within the therapeutic window for each rescue

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	medication, respectively. [redacted] Treatment discontinuation due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period For subjects who discontinue the treatment due to Lack of Efficacy or Adverse Event during the 12-hour evaluation period, the composite variable strategy will be used. To account for uncertainty, multiple imputation of the last reported pain score before taking first rescue medication or baseline pain score, whichever is worse, carrying forward approach will be used for subsequent time-points. [redacted]
Missing data handling:	For subjects who withdraw the study due to reasons other than lack of efficacy or Adverse Event during the 12-hour evaluation period or are missing data without withdrawal from the study, to account for uncertainty, the regression based multiple imputation method will be used for the subsequent missing time-point, under the Missing at Random assumption. [redacted]
Population level Summary:	Differences in least square means of SPID 6-12 between treatment groups.

Statistical Model

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SPID 6-12, will also be analyzed using single ANOVA model with baseline pain (moderate or severe), gender, and treatment group (with 4 treatment groups as 4 levels) as factors, using imputation methods defined in Section 5.1. The difference of least-square means, and its 95% confidence interval and p-value will be reported. The same multiple imputation method will be used, as specified for the primary estimand.

Acetaminophen [redacted]/Naproxen Sodium [redacted] and NPX [redacted] will also be compared for exploratory purposes.

Sensitivity Analysis

As a sensitivity analysis, for subjects who discontinue the treatment due to lack of efficacy or adverse event during the 12-hour evaluation period for subsequent time-points, multiple imputation of baseline observation carried forward will be used for subsequent missing time-points. [redacted]

7.2.6.2 Time to First Request for Rescue

The secondary estimand #2 is the main clinical quantity of interest relative to Time to first request for rescue analgesic and is defined according to the attributes in Table 4.

Table 4. Attributes of Secondary Estimand #2

Treatment being compared:	The following comparisons will be tested for time to first request for rescue: • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery, as reflected in subject inclusion/exclusion criteria.
Variable:	Time to first request for rescue analgesic.
Intercurrent events:	Treatment discontinuation due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication

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	A composite variable strategy will be used, and subjects will be considered as having requested rescue, and their time of rescue request is the time of treatment discontinuation.
Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to Lack of Efficacy or Adverse Event, subjects will be censored at the time of study withdrawal, considering a non-informative censoring. For subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to Lack of Efficacy or Adverse Event, and do not withdraw from the study before 24 hours, subjects will be censored at the time of 24 hours, considering a non-informative censoring. [redacted]
Population level Summary:	Proportion of subjects who requests for rescue analgesic estimated by Kaplan-Meier method.

Statistical Model

Time to first request for rescue analgesic will be analyzed using Kaplan-Meier method and censored according to section 5.2. The cumulative percentage of subjects requesting rescue will be presented by treatment group in tabular and graphical formats. The median, Q1 and Q3 time to first request for rescue will be tabulated. The survival functions will be compared between the fixed combination and placebo/monotherapy using the Wilcoxon test stratified by baseline pain (moderate or severe) and gender. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis and statistical testing.

Acetaminophen [redacted]/Naproxen Sodium [redacted] and NPX [redacted] will also be compared for exploratory purposes.

[redacted]

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[redacted]

7.2.6.3 Proportion of subjects who request rescue analgesic up to 12 hours

The secondary estimand #3 is the main clinical quantity of interest relative to Proportion of subjects who request rescue analgesic during the first 12 hours and is defined according to the attributes in Table 5.

Table 5. Attributes of Secondary Estimand #3

Treatment being compared:	The following comparisons will be tested for proportion of subjects who request rescue during the first 12 hours: • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Placebo • Acetaminophen [redacted]/Naproxen Sodium [redacted] vs. Acetaminophen [redacted]
Population:	Males and females who are 16 to 50 years of age (inclusive) with at least moderate pain on the categorical pain scale AND at least a score of 5 on NRS at Baseline within 4.5 hours of the last stitch from oral surgery.
Variable:	Proportion of subjects who request rescue analgesic during the first 12 hours at each treatment group
Intercurrent events:	Treatment discontinuation due to Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication. A composite variable strategy will be used, and subjects will be considered as having event, and their event time is the time of treatment discontinuation due to Lack of Efficacy or Adverse Event.

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Missing data handling:	For subjects who withdraw from the study due to reasons other than Lack of Efficacy or Adverse Event before 24 hours, but do not request rescue medication, and do not discontinue the treatment due to Lack of Efficacy or Adverse Event, subjects will be censored at the time of study withdrawal, considering a non-informative censoring. For subjects who do not request rescue medication during the 24-hour study period, do not discontinue the treatment due to Lack of Efficacy or Adverse Event, and do not withdraw from the study before 24 hours, subjects will be censored at the time of 24 hours, considering a non-informative censoring. [redacted]
Population level Summary:	Proportion of subjects who request for rescue analgesic during the first 12 hours

Statistical Model

Proportion of subjects requesting rescue medication up to 12 hours, will be estimated using the Kaplan-Meier method and censored according to section 5.2. The standard errors will be approximated using the Greenwood method. This method will be used for this endpoint due to the censoring that may occur at times between 0 and 12 hours. The complementary log-log transformed proportion differences between the fixed combination and placebo/monotherapy will be tested for statistical significance using Wald test stratified by baseline pain (moderate or severe) and gender. The SAS procedure LIFETEST will be used to conduct Kaplan-Meier analysis. The statistical details for stratified Wald test are in Appendix 6.

Acetaminophen [redacted]/Naproxen Sodium [redacted] and NPX [redacted] will also be compared as exploratory.

[redacted]

Status : Approved

[redacted]

Status : Approved

[redacted]

Status : Approved

8. REFERENCES

Little R.J. & Rubin D.B. (2002). Statistical Analysis with Missing Data. New Jersey: Wiley.

Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med. 2007 Oct 30;26(24):4505-19. Doi: 10.1002/sim.2864. PMID: 17348080.

Lipkovich, I., Ratitch, B., & O'Kelly, M. (2016). Sensitivity to censored-at-random assumption in the analysis of time-to-event endpoints. Pharmaceutical statistics, 15(3), 216–229. https://doi.org/10.1002/pst.1738

Status : Approved

APPENDIX 1 ACTIVITY SCHEDULE

	Screening	Baseline (Day of Surgery)	Hours Post-dose	Follow-up Call
Procedures	**Day -30 to 1**	**Day 1**	**0 to 24 hours**	**Days 7 – 10**
Written informed consent and/or assent	X			
Demography (including age)	X			
Inclusion and Exclusion assessment	X[1]	X[1]		
Significant medical history	X[1]	X[1]		
Vital signs[2]	X[1]	X[1]		
Physical exam (height, weight and BMI)	X			
Urine pregnancy test[3]	X[1]	X[1]		
Urine drug screen[4]	X[1]	X[1]		
Serology[5]	X			
Dental extraction surgery		X		
Post-surgery trauma assessment[6]		X		
Categorical and numerical pain intensity		X[7]		
Randomization criteria		X		
Investigational product administration		X		
[redacted]			[redacted]	
Pain intensity [redacted] ratings[8]			X	
Rescue therapy			X	
[redacted]			[redacted]	
Prior and concomitant therapy	X	X	X	X
Safety monitoring	X	X[10]	X[10]	X[10]
Subject disposition	X[11]	X[11]	X[11]	X[11]
Follow-up interview				X

Abbreviations: AE=adverse events; BMI=body mass index; eCRF=electronic case report form; HIV=human immunodeficiency virus
Note: Admission and surgery of subjects will occur on Day 1. Discharge of the subjects will occur on Day 2 (24-hours post dose).
[1] Only Baseline assessments will be collected on eCRFs.
[2] Blood pressure, heart rate, respiratory rate, oral temperature.
[3] Females of childbearing potential.
[4] Minimum requirements for urine drug testing for Screening & day of surgery: cocaine, tetrahydrocannabinol, opioids (e.g., buprenorphine, oxycodone, methadone, and morphine), benzodiazepines, and amphetamines.
[5] HIV antibody, hepatitis B surface antigen (HbsAg), hepatitis C virus antibody (anti-HCV).
[6] Subjects will be excluded from the study if the mandibular extraction results in a trauma rating of "severe" on a mild, moderate, or severe scale.
[7] Scored within 4.5 hours after last stitch from dental surgery.
[redacted]

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[redacted]

[10] Collection of Aes and report of pregnancy.
[11] Only collected at end of study. End of Study is at the time of follow-up call or at time of subject early termination, which will be documented in the source documents and Subject Disposition eCRF. In addition, for randomized subjects, early discontinuation during the 0 to 24- hour post-dose period will be documented in the source documents and the 24-hour post-dose observation status eCRFs.

Status : Approved

APPENDIX 2 EFFICACY ASSESSMENTS

The PI or designated study staff will ensure the subjects complete the pain intensity and pain relief assessments at 0.25, 0.5, 0.75, 1, 1.25, 1.5 hours, hourly from 2 through 12 hours (±5 minutes; hour 12 inclusive), and every 4 hours from 12 through 24 hours (±7 minutes) post-dose as well as at time of meaningful pain relief and prior to each use of rescue analgesic (if applicable). Subjects will record their pain intensity and pain relief directly onto the respective source worksheet. Evaluations will include the following parameters:

• Pain intensity

  - Four-point categorical scale collected at Baseline: (0) no pain; (1) mild pain; (2) moderate pain; (3) severe pain

  - 0-10 PI-NRS collected at Baseline and at each time point as well as at time of meaningful pain relief and prior to each use of rescue analgesic (if applicable).

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• Time to first request for rescue medication; time when first rescue medication was requested

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APPENDIX 3 JUSTIFICATIONS OF MISSING AT RANDOM ASSUMPTION

In the analysis of primary endpoint SPID 0-12 and secondary endpoint SPID 6-12, the missing pain intensities after study withdrawal due to reasons other than Lack of Efficacy or Adverse Event are handled under Missing at Random assumption. During blinded data review, below randomized subjects were found to have withdrawn from the study due to reasons other than Lack of Efficacy or Adverse Event:



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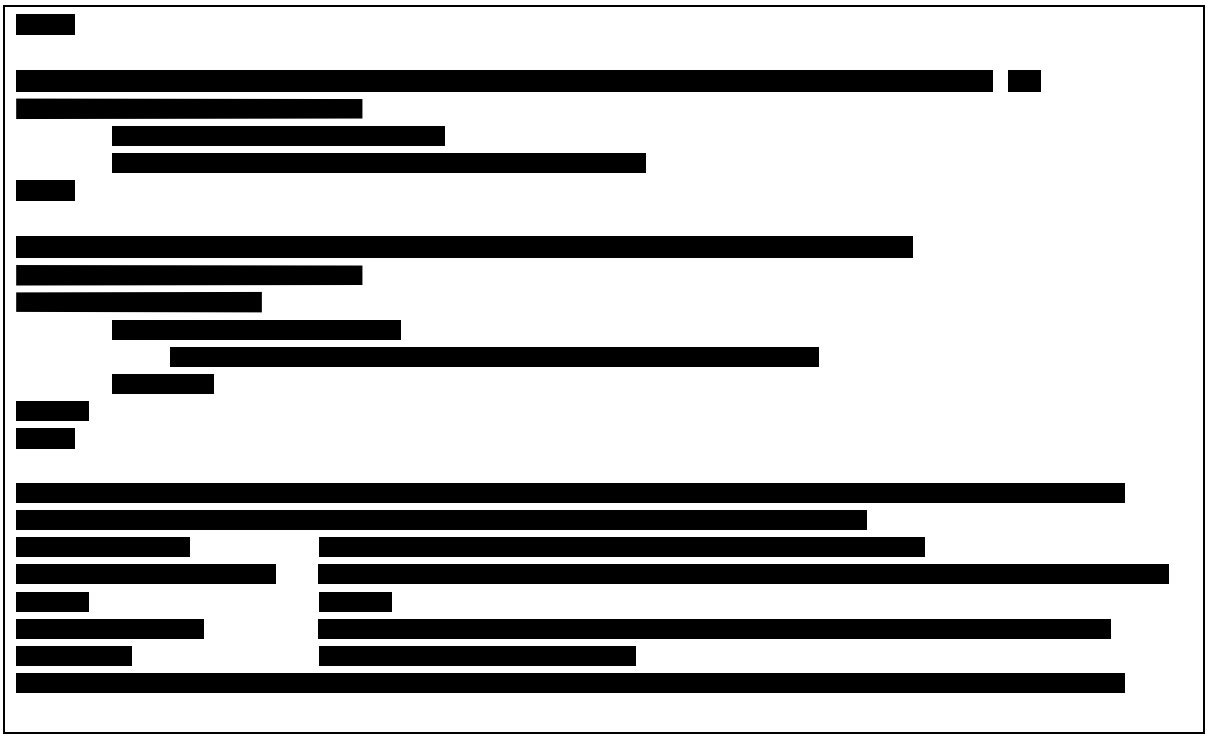
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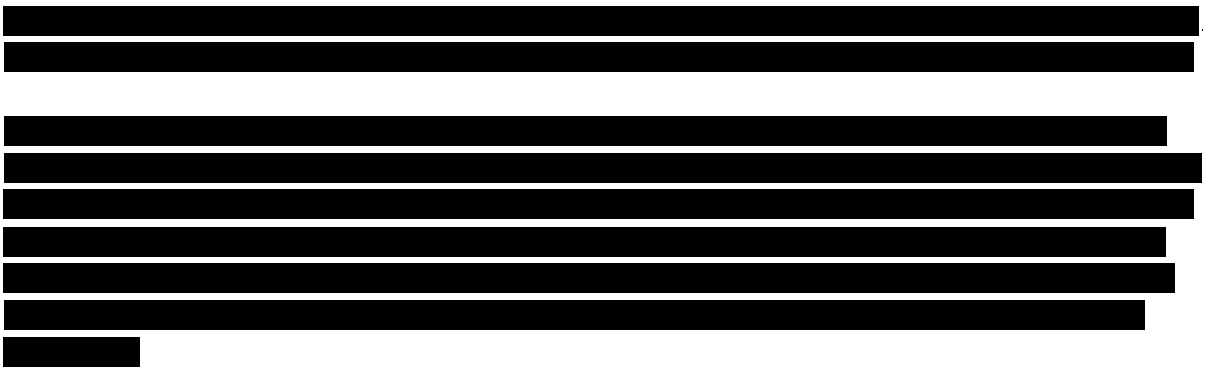
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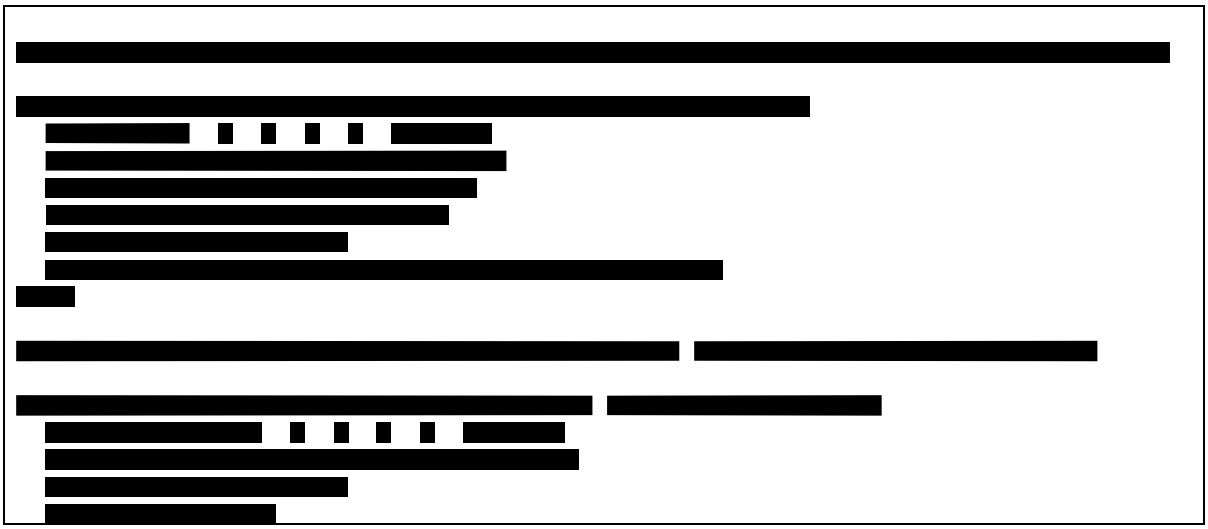
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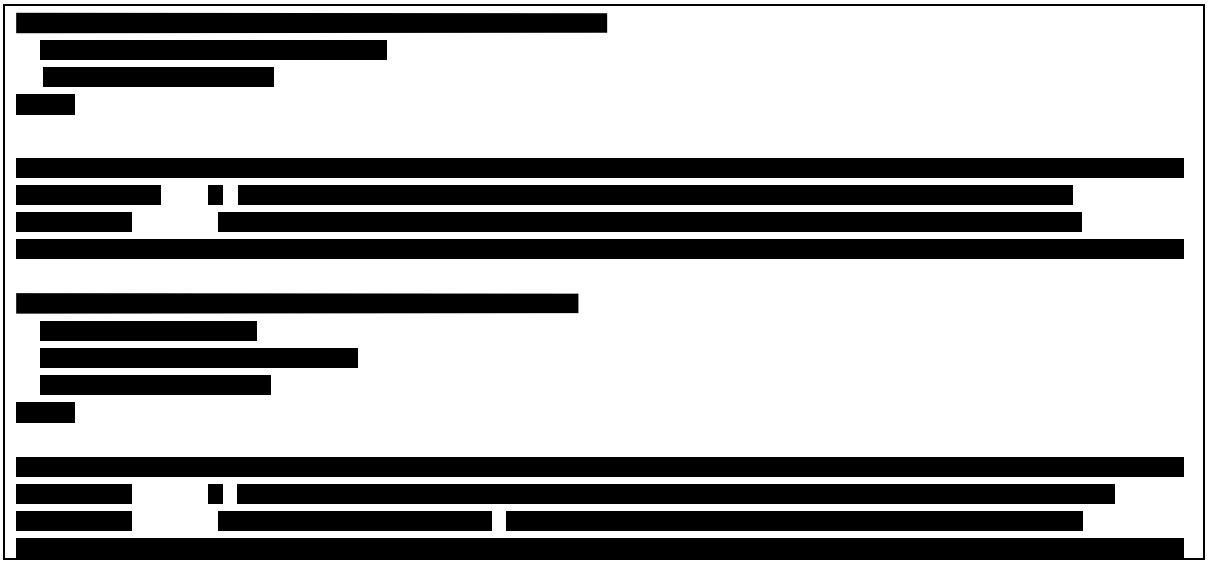
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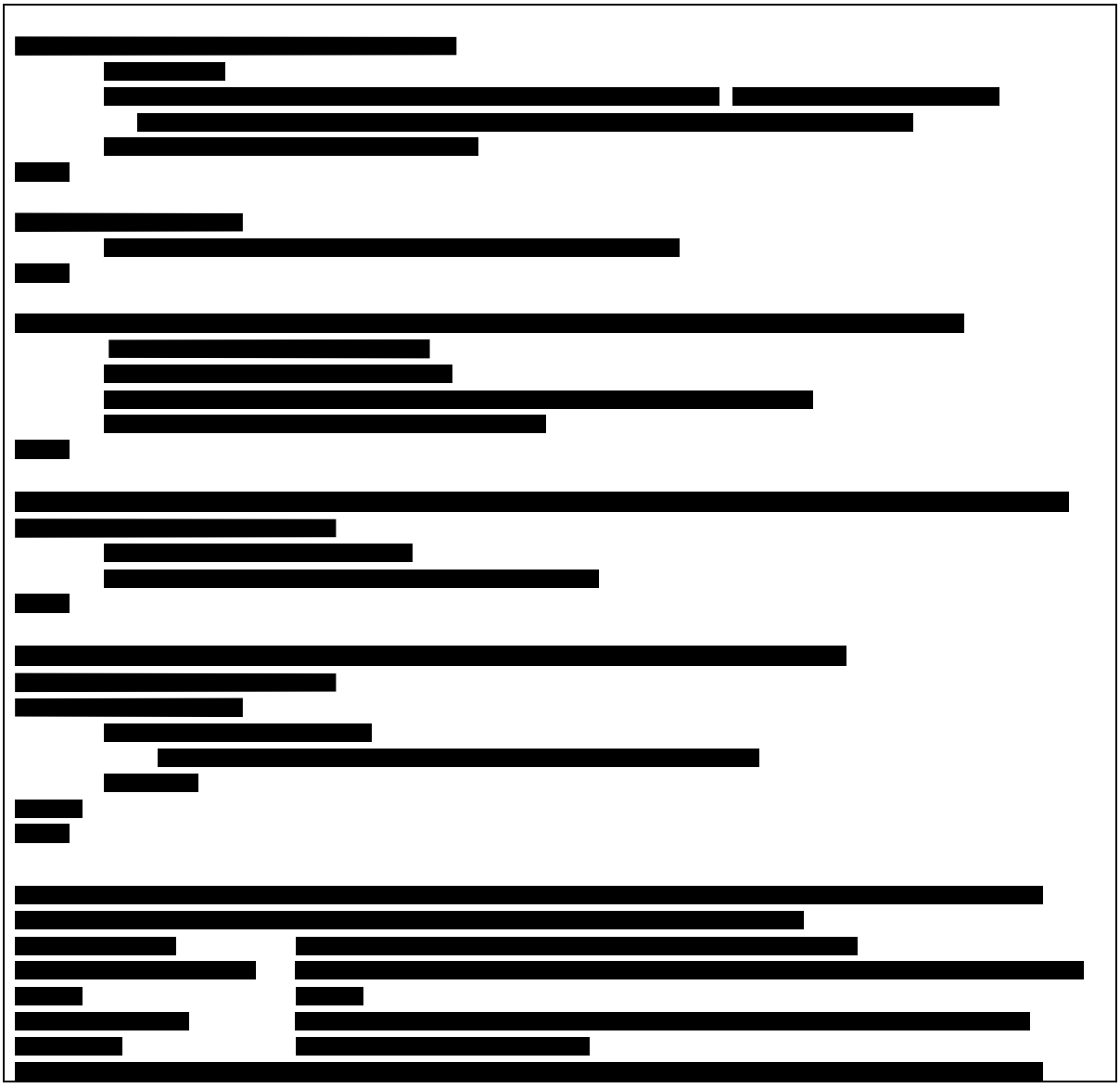
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APPENDIX 6 WALD TEST

Let $\hat{p}_{1s}$ and $\hat{p}_{2s}$ denote the Kaplan-Meier estimator of proportion of first requesting using analgesic at the first 12 hours for treatment group 1 and 2 at stratum s, where $s = 1,2, \dots m$. $\widehat{Var}(\hat{p}_{1s})$ and $\widehat{Var}(\hat{p}_{2s})$ denote the square of standard errors accordingly. n_s denote the total number of subjects in stratum s for treatment groups 1 and 2, and let $n = \sum_{s=1}^{m} n_s$ equal the total number of subjects for treatment group 1 and 2.

By taking complementary log-log transformation, the test statistics outperform the original test statistics (Klein 2007). Let $\hat{\phi}_{1s}$ and $\hat{\phi}_{2s}$ denote the transformation of $\hat{p}_{1s}$ and $\hat{p}_{2s}$,

$$\hat{\phi}_{1s} = log\big(-log(1-\hat{p}_{1s})\big)$$

$$\hat{\phi}_{2s} = log\big(-log(1-\hat{p}_{2s})\big)\,.$$

Therefore, using Greenwood's formula, the estimated variance of $\hat{\phi}_{1s}$ and $\hat{\phi}_{2s}$ are

$$\widehat{Var}\big(\hat{\phi}_{1s}\big) = \widehat{Var}\big[log\big(-log(1-\hat{p}_{1s})\big)\big] = [(1-\hat{p}_{1s})log(1-\hat{p}_{1s})]^{-2}\widehat{Var}[\hat{p}_{1s}]$$

$$\widehat{Var}\big(\hat{\phi}_{2s}\big) = \widehat{Var}\big[log\big(-log(1-\hat{p}_{2s})\big)\big] = [(1-\hat{p}_{2s})log(1-\hat{p}_{2s})]^{-2}\widehat{Var}[\hat{p}_{2s}].$$

The test statistics Z_s for stratum s,

$$\frac{\hat{\phi}_{1s} - \hat{\phi}_{2s}}{\sqrt{\widehat{Var}\big(\hat{\phi}_{1s}\big) + \widehat{Var}\big(\hat{\phi}_{2s}\big)}}$$

has a standard normal distribution under the null hypothesis.

Using the number subjects in each stratum as weighting scheme, the weighted test statistics Z,

$$\frac{\sum_{s=1}^{m} \frac{n_s}{n}\big(\hat{\phi}_{1s} - \hat{\phi}_{2s}\big)}{\sqrt{\sum_{s=1}^{m}\left(\frac{n_s}{n}\right)^2\Big(\widehat{Var}\big(\hat{\phi}_{1s}\big) + \widehat{Var}\big(\hat{\phi}_{2s}\big)\Big)}}$$

has a standard normal distribution under the null hypothesis.

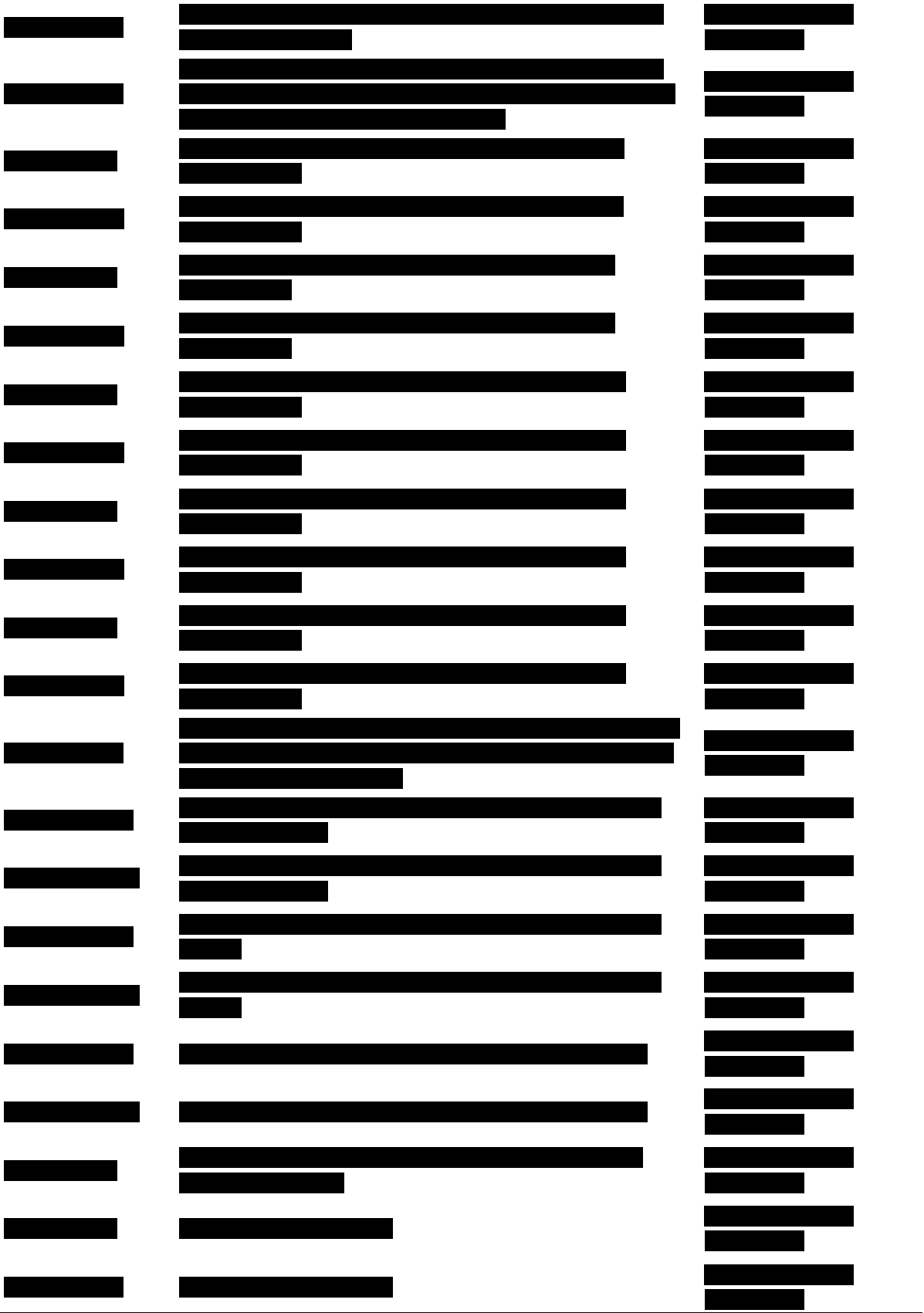
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