Protocol CCSPAA002398

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE FIVE STRENGTHS OF A FIXED COMBINATION OF ACETAMINOPHEN/NAPROXEN SODIUM IN POSTOPERATIVE DENTAL PAIN

Statistical Analysis Plan (SAP)

Version Date: 5/17/2021

CONTENTS

1 INTRODUCTION

As stated in the protocol:

The investigational product (IP) will involve a fixed combination tablet of immediate release (IR) acetaminophen and naproxen sodium [redacted] Currently there are no fixed combination products containing acetaminophen and naproxen sodium marketed in the United States (US).

Acetaminophen has been available in the US for over-the-counter (OTC) adult analgesic use since the 1960s. In the US, adult single-ingredient OTC acetaminophen products are indicated for the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache, for the minor pain of arthritis, for the pain of premenstrual and menstrual cramps and for the reduction of fever. Acetaminophen is a para aminophenol derivative with analgesic and antipyretic properties. Although the precise mechanism of action has not been definitively established, it is believed that acetaminophen produces its analgesic and antipyretic effects by inhibiting prostaglandin synthesis centrally and elevating the pain threshold.2,3

Naproxen sodium has been available in the US for OTC analgesic use since 1994. Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. In the US, [redacted] naproxen sodium is available as an OTC medication for the temporary relief of minor aches and pains due to minor pain of arthritis, muscular aches, backache, menstrual cramps, headache, toothache, and the common cold, and for the temporary reduction of fever.[4] The therapeutic effects of naproxen are produced through nonselective inhibition of cyclooxygenase enzymes (COX-1 and COX-2) resulting in inhibition of prostaglandin synthesis. Naproxen sodium salt has similar therapeutic properties as comparable doses of naproxen free acid based on molecular weight, but with more rapid systemic absorption. In this respect, [redacted] naproxen sodium is approximately equivalent to [redacted] naproxen.[1]

The fixed combination of acetaminophen/naproxen sodium is not currently marketed in the United States (US).

The current study will evaluate relative efficacy of five strengths of a fixed combination of acetaminophen and naproxen sodium to help inform selection of dose(s) for further development and to evaluate the safety of a fixed combination of acetaminophen and naproxen sodium.

1.1 Study Objectives

As stated in the protocol:

Primary Objective:

- *To evaluate the relative analgesic efficacy of five strengths of a fixed combination of acetaminophen/naproxen sodium over 12 hours.*

Secondary Objective:

- *To evaluate the relative analgesic duration of five strengths of a fixed combination of acetaminophen/naproxen sodium.*

[redacted]

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 profile of the following doses of a fixed combination of acetaminophen/naproxen sodium (Figure 1):

- [redacted] *mg Acetaminophen/[redacted] mg Naproxen sodium*
- [redacted] *mg Acetaminophen/[redacted] mg Naproxen sodium*
- [redacted] *mg Acetaminophen/[redacted] mg Naproxen sodium*
- [redacted] *mg Acetaminophen/[redacted] mg Naproxen sodium*
- [redacted] *mg Acetaminophen/[redacted] mg Naproxen sodium*
- *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 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 on the categorical and numerical pain intensity scale.

Approximately 300 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 assigned to one of the following six treatment groups, with equal allocation among the treatment groups:

- *[redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])*
- *[redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])*
- *[redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])*
- *[redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])*
- *[redacted] mg Acetaminophen/[redacted] mg Naproxen sodium (administered as two tablets of Acetaminophen/Naproxen sodium [redacted])*
- *Placebo (administered as two placebo tablets)*

All treatments will be administered as a single dose. Rescue analgesic medication (oxycodone IR 5 mg every four to six hours as needed for pain; not to exceed 30 mg in 24 hours) will be available for subjects as needed.

No less than approximately 30% of randomized subjects will be either male or female. To maintain the double-blind nature of the study, an independent third party will administer study drug to blindfolded subjects.

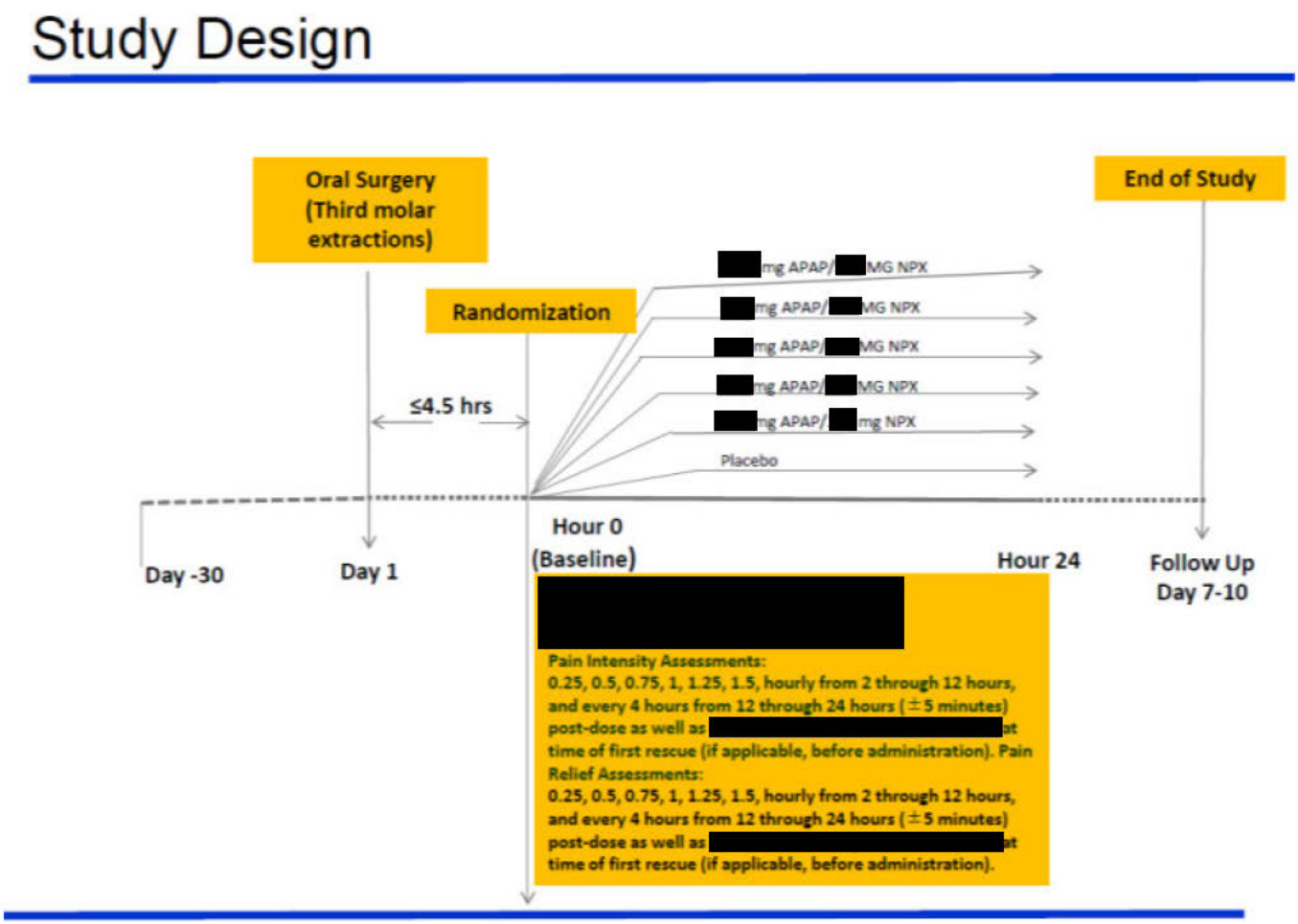
Self-reported pain intensity will be collected using a 0-10 NRS at Baseline (Time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24 hours (±5 minutes) post-dose as well as [redacted] at the time of first rescue (if applicable, before administration). [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 postsurgical medical care and changes in their health, including any emergent or existing (AEs). The interview will occur between the sixth and ninth day after the dental surgery (Days 7-10 of the study).

The total study duration for an individual subject will be 10 days, including Baseline (Day 1 [day of surgery]) and follow-up (Days 7 to 10), and excluding Screening (Day -30 to Day 1).

Figure 1: Schematic Study Design



Key: APAP=acetaminophen; NPX=naproxen sodium

Table 1: Schedule of Activities

Table 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 and pain relief ratings[8]			X	
[redacted]			[redacted]	
Rescue therapy			X	
[redacted]			[redacted]	
Prior and concomitant therapy	X	X	X	X
Safety monitoring	X	X[11]	X[11]	X[11]
Subject disposition	X[12]	X[12]	X[12]	X[12]
Follow-up interview				X

Abbreviations: AE=adverse events; BMI=body mass index; eCRF=electronic case report form; HIV=human immunodeficiency virus

Note: Admission and discharge of the subjects will occur on Day 2 (24 hours).

[1] Only Baseline assessments were collected on eCRF.

[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 on the categorical and numerical pain intensity scale.

[7] Scored within 4.5 hours after last stitch from dental surgery.

[8] Pain ratings collected: 0.25, 0.5, 0.75, 1, 1.25, 1.5, hourly from 2 through 12 hours, and every 4 hours from 12 through 24hours (±5 minutes) post-dose. If subject requests rescue medicine, ratings will be collected before administration.

[redacted]

[11] Collection of AEs and report of pregnancy.

[12] Only collected at end of study. End of Study is at the time of follow-up call or at time of subject withdrawal.

2 INTERIM ANALYSES

No interim statistical analysis is planned for this trial.

3 ANALYSIS SETS

3.1 Primary Analysis Set

The primary analysis set will be based on the Intent-to-Treat analysis set, which will include all randomized subjects

3.2 Per-Protocol Set

As a secondary analysis, the primary endpoint 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. The final per protocol analysis set will be determined before unblinding. The per-protocol set will exclude subjects who vomited within 60 minutes after dosing, and those with major protocol deviations. The final per-protocol set will be determined before unblinding.

3.3 Safety Analysis Set

The Safety Analysis Set will include all subjects who are randomized and take investigational product. Safety analysis will be based on the actual received treatment.

4 EFFICACY ASSESSMENTS AND ENDPOINTS

4.1 Efficacy Assessments

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoint

- Time weighted sum of pain relief from 0 to 12 hours (TOTPAR 0-12)
- Time weighted sum of pain intensity difference from 6 to 12 hours (SPID 6-12)
- Time to first use of rescue analgesic (duration of relief after dosing)
- Proportion of subjects who require rescue analgesic

[redacted]

[redacted]

4.1.1 Safety Assessments and Endpoints

Safety will be monitored and assessed by reviewing the collection, evaluation, and analysis of adverse events (AEs). Any causally related AE that is unresolved upon completion of the last study visit will be followed by the study staff until the event, or its sequelae, resolves or stabilizes at a level acceptable to the medically qualified Investigator or designee, and recorded on the electronic case report form.

- Number and percentage of subjects with treatment-emergent adverse event (AE)
- Number and percentage of subjects who discontinued the study due to an AE
- Number and percentage of subjects experiencing a serious AE
- Number and percentage of subjects with treatment-related AEs
- Number and percentage of subjects with treatment-emergent AE by severity and relationship to treatment

4.2 Covariates

Baseline pain (moderative or severe) score and gender and will be used as covariates in the model for analysis related to [redacted] SPID 0-12, SPID 6-12, [redacted] TOTPAR 0-12, [redacted] and rescue medication.

4.3 DATA COMPUTATIONS AND DATA IMPUTATIONS

4.3.1 Endpoints Relating to Pain Intensity and Pain Relief

The pain intensity difference (PID) at each time point will be derived by subtracting the pain intensity from the baseline pain intensity. A higher value is indicative of a greater improvement.

Time-weighted sum of the pain intensity difference scores (SPID) 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 [redacted] 0-12, 6-12[redacted] hours. Time-weighted total pain relief (TOTPAR) for each specified interval will be similarly derived.

Pain intensity and pain relief ratings 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. For subjects who use rescue medication, the last reported pain score before taking rescue medication or baseline pain score, whichever is worse, will be carried forward to the remaining time points; pain relief scores after rescue medication will be set to zero. For subjects who discontinue the study early, the same imputation approach will be used.

4.3.2 Time to Rescue

Time to first use of rescue medication will be measured as the elapsed time from when the investigational product was given until the time rescue medication was first given. Subjects who discontinue from the study before 24 hours, but do not use rescue medication, will be censored at the time of discontinuation. Subjects who do not use rescue medication during the 24-hour study period will have their time to rescue set to 24 hours and be censored at 24 hours.

4.3.3 [redacted]

[redacted]

5 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

5.1 Statistical Hypotheses

For the primary endpoint, SPID 0-12, each strength of the fixed combination will be compared with the corresponding monotherapy doses by fitting the following regression model to the observed data:

$\mu_{xy} = f(x,y) = \alpha + \beta_1 x + \beta_2 y + \beta_3 xy$ where:

x = (continuous) acetaminophen dose
y = (continuous) naproxen dose
μ_{xy} = SPID 0-12 as a function of acetaminophen dose x and naproxen dose y
α = intercept
β_1 = slope term associated with acetaminophen dose
β_2 = slope term associated with naproxen dose
β_3 = interaction slope term

Comparisons based on this model will test the following hypothesis for each tested strength of the fixed combination:
H_0:: $\mu_{xy} = \max(\mu x0, \mu 0y)$
H_1:: $\mu_{xy} > \max(\mu x0, \mu 0y)$

For endpoints based on pain intensity (such as SPID), endpoints based on pain relief (such as TOTPAR), [redacted] each strength of the fixed combination will be compared with placebo by testing the following hypotheses:

H_0:: $\dot{\eta}_1 = \dot{\eta}_2$
H_1:: $\dot{\eta}_1 \neq \dot{\eta}_2$

where $\dot{\eta}_1$ is the population mean for the strength of the fixed combination and $\dot{\eta}_2$ is the population mean for placebo.

For time-to-event endpoints (time to first use of rescue analgesic[redacted]), each fixed combination will be compared with placebo by testing the following hypotheses:

H_0: $S_1(t) = S_2(t)$ (all t)
H_1: $S_1(t) \neq S_2(t)$ (at least some t)

where $S_1(t)$ is the survival function for the fixed combination and $S_2(t)$ is the survival function for placebo.

Each pairwise comparison with placebo will be performed at α=0.05, two-sided.

5.2 Statistical Decision Rules

For SPID 0-12, combinations will be compared with corresponding monotherapy doses using the regression methodology specified in section 5.1.

Each comparison of fixed combination with monotherapy will be tested at α=0.01, one-sided, in order to control the familywise error rate at approximately 10%, one-sided.

For each of the endpoints, the following pairwise comparisons will be performed:

1. APAP[redacted] mg/NPX[redacted] mg vs. placebo
2. APAP[redacted] mg/NPX[redacted] mg vs. placebo
3. APAP[redacted] mg/NPX[redacted] mg vs. placebo
4. APAP[redacted] mg/NPX[redacted] mg vs. placebo
5. APAP[redacted] mg/NPX[redacted] mg vs. placebo

Each statistical test comparing APAP/NPX vs. placebo will be two-sided and employ a significance level of α=0.05.

5.3 STATISTICAL METHODS

5.3.1. [redacted] SPID 0-12, SPID 6-12, [redacted] TOTPAR 0-12, [redacted]

For the primary endpoint, SPID 0-12, the dose response will be assessed by fitting a linear regression model with SPID 0-12 as the response variable, including terms for acetaminophen dose, naproxen dose, and acetaminophen by naproxen interaction, as further described in Section 5.1. Based on this regression model, the model-based means for each strength of fixed combination and corresponding monotherapy doses will be estimated and statistically compared. Pairwise comparisons will be made using an analysis of variance (ANOVA) with baseline pain (moderate or severe) score, gender, and treatment group.

The following is sample SAS code for fitting regression model:

```
proc glm data=DATASET;
  model outcome = apap npx apap*npx;
[redacted]
run;
```

The above SAS code includes, as an example, the ESTIMATE statements that will provide the point estimate for [redacted] naproxen / [redacted] acetaminophen, and the estimate and statistical testing for this combination dose versus each monotherapy.

The following is sample SAS code for analysis of variance for pairwise comparisons of APAP/NPX vs. placebo:

```
proc mixed data=DATASET;
  class basepain gender trt;
  model outcome = basepain gender trt;
  lsmeans trt;
run;
```

Each of the endpoints [redacted] SPID 6-12, [redacted] TOTPAR 0-12 [redacted] will be analyzed with an analysis of variance with baseline pain (moderate or severe) score, gender, and treatment group in the model using imputation methods defined in Data Imputations Section 4.4. [redacted]

The following is sample SAS code for analysis of variance:

```
proc glm data=DATASET;
  class pain gender trt;
  model outcome = basepain gender trt;
  lsmeans trt;
run;
```

5.3.2. Time to Rescue

Kaplan-Meier estimates of cumulative percentage of subjects using rescue medication will be presented by treatment group in tabular and graphical formats. The survival function (cumulative proportions of subjects at each time point) and the median time to first rescue will be estimated by the Kaplan-Meier method for each treatment. The survival functions will be compared between fixed combinations and placebo using the Wilcoxon test stratified by baseline pain (moderate or severe) and gender. The following sample SAS code compares survival functions between the treatment groups using the Wilcoxon test.

```
proc lifetest data=DATASET method=KM outsurv=predict;
strata basepain gender / group=trt diff=all;
  time TIME*censor(x);
run;
```

5.3.3. [redacted]

[redacted]

5.3.4. Proportion of subjects who require rescue analgesic

The proportion of subjects requiring rescue medication through 24 hours will be estimated by treatment group using the Kaplan-Meier method, and 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 24 hours.

The differences between naproxen/acetaminophen combination levels and placebo will be tested for statistical significance, and approximate two-sided 95% CIs of the differences in cumulative incidences between the treatment groups in 24 hours will be calculated, using the Wald method as:

$$\hat{d} \pm z_{\alpha/2}\sqrt{(\widehat{Var}(\hat{p}_1) + \widehat{Var}(\hat{p}_2))}$$

where

$\hat{d}$ = estimated Kaplan-Meier estimated cumulative incidence difference, and

$\widehat{Var}$ (p_i) = estimated variance of the Kaplan-Meier estimated cumulative incidence in treatment group i, based on Greenwood's formula

$z_{\alpha/2}$ is the 100 ×(1 – α/2)th percentile of the standard normal distribution for α = 0.05.

The corresponding p-values will be calculated with reference to the standard normal distribution, from the following test statistic:

$$Z = \frac{\hat{d}}{\sqrt{\widehat{Var}(\hat{p}_1) + \widehat{Var}(\hat{p}_2)}}$$

The following sample SAS code can be used to obtain information for performing cumulative incidence analysis:

```
proc lifetest data=DATASET method=KM outsurv=predict;
  strata trt;
  time TIME*censor(x;
run;
```

Note: The protocol-specified analysis includes adjustment for baseline pain and gender, and the intention was to combine across strata using inverse variance weighting. However, based on the high overall proportion of subjects requiring rescue analgesics based on the blinded data, and the relatively small number of subjects per stratum, there was concern with the risk that the variance for the treatment difference within a stratum could be zero, which would result in division by zero for the weighting for that stratum. For this reason, stratification by gender and baseline pain was removed from the Kaplan-Meier analysis method.

As a sensitivity analysis, Cochran-Mantel-Haenszel tests will be used, stratifying by baseline pain (moderate or severe) and gender, and considering as having received rescue those subjects who discontinued prior to the end of the 24-hour observation period and did not have rescue medication usage recorded.

The following SAS sample code provides the Cochran-Mantel-Haenszel test:

```
proc freq data=dataset;
   tables Gender*Basepain*trt*response / cmh;
run;
```

In the event that computation difficulties arise in the Kaplan-Meier approach, the Cochran-Mantel-Haenszel test will serve as the primary method for analyzing proportion of subjects requiring rescue analgesics.

5.3.5. [redacted]

[redacted]

[redacted]

5.3.6. Subgroup Analyses

The primary endpoint (SPID 12) will be analyzed based on the following subgroups: age group (<18 years, ≥18 years), gender, race (white, non-white) and baseline categorical pain (moderate, severe). Each will be analysed with an analysis of variance with treatment group in the model using imputation methods defined in Data Imputations Section 4.4.1.

5.3.7. [redacted]

[redacted]

5.4 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.

5.5 PREVIOUS AND CONCOMITANT MEDICATIONS

Previous and concomitant medications will be summarized by treatment group. 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 CRF 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.

5.6 SAFETY ANALYSIS

5.6.1 Adverse Events

Treatment-emergent AEs are those with a start date and time at or after the time of study drug administration. All summaries described below are for treatment-emergent AEs except where noted. Non- treatment-emergent AEs will be provided in a listing.

The number and percentage of subjects experiencing AEs will be tabulated by treatment, system organ class and preferred term using the MedDRA coding dictionary. The number and percentage of subjects experiencing treatment-related AEs will also be presented by system organ class and preferred term. Treatment-related AEs will include events marked as being at least possibly related to study treatment. The number and percentage of subjects with AEs will be presented by severity. Subjects will be counted only once for each system organ class and preferred term by selecting the most severe event. The number of subjects with the most commonly reported adverse events (those reported by 5% or more in any one treatment group) will be summarized by treatment, system organ class and preferred term. The number of subjects with adverse events will also be summarized by demographic characteristics: age group (<18 years, ≥18 years), gender, and race.

The number and percentage of subjects experiencing SAEs or who discontinued the study due to an AE will be presented by system organ class and preferred term. These displays will include all AEs, not just treatment-emergent AEs.

5.6.2 Vital Signs

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.

6. CHANGES FROM PROTOCOL

For proportion of subjects requiring rescue analgesics, the protocol-specified analysis includes adjustment for baseline pain and gender, and the intention was to combine across strata using inverse variance weighting. However, based on the high overall proportion of subjects requiring rescue analgesics based on the blinded data, and the relatively small number of subjects per stratum, there was concern with the risk that the variance for the treatment difference within a stratum could be zero, which would result in division by zero for the weighting for that stratum. For this reason, stratification by gender and baseline pain was removed from the Kaplan-Meier analysis method.

Cochran-Mantel-Haenszel tests were added as a sensitivity analysis, and as the primary methodology in the event of computational difficulties using the Kaplan-Meier method. The CMH tests will stratify by baseline pain (moderate or severe) and gender, and consider as having received rescue those subjects who discontinued prior to the end of the 24-hour observation period and did not have rescue medication usage recorded.

7. REFERENCES

None.

APPENDICES

APPENDIX 1: SUMMARY TABLES AND FIGURES

The following tables and figures are planned for the Clinical Study Report. The numbering and titles of tables and figures in this document serves as guidance; the exact numbers and titles may be modified as appropriate.

Section / Table No	Title	Population / Analysis Sets
14.1 Subject Disposition, Demographics, and Baseline Information		
Table 14.1.1	Subjects Disposition and Analysis Sets	All Enrolled Subjects
Table 14.1.2	Summary of Protocol Deviations	All Randomized Subjects
Table 14.1.2.1	Summary of Major Protocol Deviations	All Randomized Subjects
Table 14.1.2.2	Summary of Minor Protocol Deviations	All Randomized Subjects
Table 14.1.3.1	Demographic and Baseline Characteristics	All Randomized Subjects
Table 14.1.3.2	Demographic and Baseline Characteristics	Safety Analysis Subjects
Table 14.1.3.3	Demographic and Baseline Characteristics	Per-Protocol Subjects
Table 14.1.4	Previous Medications	All Randomized Subjects
Table 14.1.5	Concomitant Medications	All Randomized Subjects
Table 14.1.5.1	Concomitant Medications Taken By >= 5% of Subjects in One or More Treatment Groups	All Randomized Subjects
Table 14.1.6	Vital Signs at Baseline	All Randomized Subjects
14.2 Efficacy		
Table 14.2.1.1	Regression Analyses of SPID 0-12 on APAP and NPX Doses	All Randomized Subjects
Table 14.2.1.2	Time weighted Pain Intensity Difference (SPID[redacted] 0-12, 6-12[redacted])	All Randomized Subjects
Table 14.2.2	Time Weighted Total Pain Relief Scores (TOTPAR[redacted] 0-12[redacted])	All Randomized Subjects
Table 14.2.3	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects Using Rescue Medication	All Randomized Subjects
Table 14.2.4	Kaplan-Meier Comparison of the Cumulative Percentage of Subjects Using Rescue Medication	All Randomized Subjects
14.2.4.1	Sensitivity Analysis for Percentage of Subjects Using Rescue Medication	All Randomized Subjects
Table 14.2.5	[redacted]	All Randomized Subjects
Table 14.2.6	[redacted]	All Randomized Subjects

Table 14.2.7	[redacted]	All Randomized Subjects
Table 14.2.8	[redacted]	All Randomized Subjects
Table 14.2.9	[redacted]	All Randomized Subjects
Table 14.2.10	[redacted]	All Randomized Subjects
Table 14.2.11	[redacted]	All Randomized Subjects
Table 14.2.12	[redacted]	All Randomized Subjects
Table 14.2.13	Time weighted Pain Intensity Difference (SPID) – Age < 18 Years Old	All Randomized Subjects
Table 14.2.14	Time weighted Pain Intensity Difference (SPID) – Age >= 18 Years Old	All Randomized Subjects
Table 14.2.15	Time weighted Pain Intensity Difference (SPID) – Female	All Randomized Subjects
Table 14.2.16	Time weighted Pain Intensity Difference (SPID) – Male	All Randomized Subjects
Table 14.2.17	Time weighted Pain Intensity Difference (SPID) – Whites	All Randomized Subjects
Table 14.2.18	Time weighted Pain Intensity Difference (SPID) – Non-Whites	All Randomized Subjects
Table 14.2.19	Time weighted Pain Intensity Difference (SPID) – Moderate Baseline Pain	All Randomized Subjects
Table 14.2.20	Time weighted Pain Intensity Difference (SPID) – Severe Baseline Pain	All Randomized Subjects
Table 14.2.21	Time weighted Pain Intensity Difference (SPID)[a]	Per Protocol Analysis Set
Table 14.2.22.1	[redacted]	All Randomized Subjects [redacted]
Table 14.2.22.2	[redacted]	All Randomized Subjects [redacted]
Table 14.2.23.1.1	[redacted]	All Randomized Subjects [redacted]
14.2.23.1.2	[redacted]	All Randomization Subjects [redacted]
Table 14.2.23.2	[redacted]	All Randomized Subjects [redacted]

a. Provided if the per-protocol analysis set differs from the Intent-to-Treat set by at least 5% of the randomized subjects.

14.3 Safety

Section / Table No	**Title**	**Population / Analysis Sets**

Table 14.3.1	Summary of Adverse Events	Safety Analysis Subjects
Table 14.3.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects
Table 14.3.3	Summary of Treatment-Emergent Adverse Events by Demographic Characteristics	Safety Analysis Subjects
Table 14.3.4	Summary of Treatment-Emergent Adverse Events by Severity	Safety Analysis Subjects
Table 14.3.5	Most Commonly Reported (>=5% of Subjects in One or More Treatment Groups) Treatment-Emergent Adverse Events	Safety Analysis Subjects
Table 14.3.6	Summary of Treatment-Related Adverse Events	Safety Analysis Subjects
Table 14.3.7	Most Commonly Reported (>=5% of Subjects in One or More Treatment Groups) Treatment-Related Adverse Events	Safety Analysis Subjects
Table 14.3.8	Summary of Treatment-Related Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects
Table 14.3.9	Summary of Treatment-Related Adverse Events By Severity	Safety Analysis Subjects
Table 14.3.10	Summary of Serious Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects
Table 14.3.11	Summary of Subject Discontinuation from Study Due to Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects

FIGURES:

Figure 14.1.1	Regression of SPID 0-12 on APAP and NPX Dose	All Randomized Subjects
Figure 14.1.2	SPID by Treatment	All Randomized Subjects
Figure 14.2	TOTPAR by Treatment	All Randomized Subjects
Figure 14.3.1	[redacted]	All Randomized Subjects
Figure 14.3.2		All Randomized Subjects
Figure 14.4.1		All Randomized Subjects
Figure 14.4.2		All Randomized Subjects
Figure 14.5	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects Using Rescue Medication	All Randomized Subjects
Figure 14.6	[redacted]	All Randomized Subjects

Figure 14.7	[redacted]	All Randomized Subjects
Figure 14.8		All Randomized Subjects
Figure 14.9		All Randomized Subjects
Figure 14.10.1		All Randomized Subjects
Figure 14.10.2		All Randomized Subjects [redacted]

APPENDIX 2: DATA LISTINGS

The following listings are planned for Clinical Study Report. The numbering and titles of data listings in this document serve as guidance; the exact numbers and titles may be modified as appropriate.

Listing No.	Title	Population
16.1.7	Randomization Schedule	All Randomized
16.2.1	Subject Disposition	All Randomized
16.2.2.1	Discontinued Subjects	All Randomized
16.2.2.2	Subjects with Protocol Deviations	All Randomized
16.2.2.3	Subjects Excluded from Per Protocol Population	All Randomized
16.2.3.1	Demographic and Baseline Characteristics	All Randomized
16.2.3.2	Significant Medical History	All Randomized
16.2.3.3	Previous and Concomitant Medications	All Randomized
16.2.3.4	Non-Drug Therapy/Procedure	All Randomized
16.2.4.1	Surgery Information and Baseline Pain Measurement	All Randomized
16.2.4.2	Tooth Extractions	All Randomized
16.2.4.3	Dosing Time of Study Medication	All Randomized
16.2.5.1	[redacted]	All Randomized
16.2.5.2	Pain Intensity and Pain Relief Assessments	All Randomized
16.2.5.3	Pain Intensity and Pain Relief Assessments Out of Assessment Window and Imputed Values	All Randomized
16.2.5.4	Time to Rescue Medication and Pain Intensity and Pain Relief Prior to Rescue	All Randomized
16.2.5.5	[redacted]	All Randomized [redacted]
16.2.6.1	Subjects with Treatment-Emergent Adverse Events	All Randomized
16.2.6.2	Subjects with Non-Treatment-Emergent Adverse Events	All Randomized
16.2.6.3	Subjects with Adverse Events that Resulted in Subject Discontinuation From Study	All Randomized
16.2.6.4	Subjects with Serious Adverse Events	All Randomized
16.2.6.5	MedDRA Preferred Terms for Adverse Events	All Randomized
16.2.6.6	Self-Reported Pregnancy	All Randomized
16.2.6.7	Vital Signs	All Randomized
16.2.7	Follow-up Interview	All Randomized

APPENDIX 3: [redacted]

[redacted]