Protocol CO-170317095828-PACT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE- CONTROLLED, SINGLE-DOSE, EFFICACY AND SAFETY STUDY OF [redacted] IN POSTOPERATIVE DENTAL PAIN

Statistical Analysis Plan (SAP)

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CONTENTS

1 INTRODUCTION

Acetaminophen is a para-aminophenol derivative with analgesic and antipyretic properties, and is thought to produce analgesia by inhibiting prostaglandin synthesis centrally and elevating the pain threshold. Acetaminophen is available as an over-the-counter (OTC) analgesic and antipyretic in many global markets. In the US, TYLENOL® is commercially available in extra strength (500 mg) and regular strength (325 mg) dosage forms marketed under the Internal Analgesic, Antipyretic and Antirheumatic Drug Products for OTC Human Use Tentative Final Monograph. TYLENOL® Regular Strength 325 mg is dosed 2 dosage units every 4 to 6 hours and TYLENOL® Extra Strength 500 mg is dosed 2 dosage units every 6 hours. It is labeled for the temporary relief of minor aches and pains due to the common cold, headache, backache, toothache, premenstrual and menstrual cramps, minor pain of arthritis, muscular aches and for the temporary relief of fever.

The overall purpose of this study is to evaluate the analgesic onset, efficacy, and safety of a single dose of [redacted] compared with a single dose of 1000 mg acetaminophen administered as two commercial acetaminophen 500 mg caplets (ACM), a single dose of 400 mg ibuprofen administered as two commercial ibuprofen 200 mg liquid-filled capsules (IBU), and placebo (PBO) over 4 hours. [redacted] The dental pain model, a validated model of acute pain widely used to study analgesic efficacy of compounds, will be used in this study [1, 2]. Reference Safety Information (RSI) for the [redacted] and ACM commercial product is the Drug Facts labeling for the ACM commercial product in the US, and the RSI for the IBU commercial product is the associated Drug Facts Label in the US.

1.1 Study Objectives

To evaluate analgesic onset, efficacy, and safety of [redacted]) compared with 1000 mg acetaminophen administered as two commercial acetaminophen 500 mg caplets (ACM) and 400 mg ibuprofen administered as two commercial ibuprofen 200 mg liquid-filled capsules (IBU) in the dental pain model following third-molar extractions.

1.2 Study Design

This is a single-dose, randomized, double-blind, placebo- and active- controlled, parallel-group study to evaluate the analgesic onset, efficacy, and safety profile of [redacted] compared with two commercial products over a four-hour period after third-molar extractions. Subjects will undergo dental extraction of three or four third molars. Maxillary third molars may be removed regardless of impaction level. The mandibular

extractions must meet one of the following scenarios and must not result in a trauma rating of severe in a mild, moderate, or severe scale:

- two full bony impactions
- two partial bony impactions
- one full bony impaction in combination with one partial bony impaction

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 four treatment groups. Approximately 660 subjects will receive a single dose of either [redacted], ACM 1000 mg, IBU 400 mg, or PBO in a 4:4:2:1 allocation ratio, and will be stratified according to gender and baseline pain rating (moderate or severe). No less than approximately 30% of randomized subjects will be either male or female. In addition, no more than approximately 30% of subjects will be 17 years of age at the time of screening. Self-reported pain intensity will be collected at baseline (time 0). Pain intensity and pain relief will be collected at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, and 4 hours (± 5 minutes) after the dose. Perceptible pain relief and meaningful pain relief will be collected using two separate stopwatches. Subjects who do not experience any pain relief after dosing will be encouraged, but not required, to wait at least 1 hour before using rescue therapy.

2 INTERIM ANALYSES

No interim analysis is planned for this trial.

3 ANALYSIS SETS

3.1 Primary Analysis Set

The primary analysis set for the efficacy analyses will be the intent-to-treat population which includes all randomized subjects.

Subjects who received different treatment from their assigned treatment will be analyzed based on the actual received treatment.

3.2 Per-Protocol Set

The per protocol set will exclude subjects who took rescue medication within 60 minutes after dosing, vomited within 60 minutes after dosing, and those with major protocol deviations. The major protocol deviation and the per-protocol set will be determined before the database lock.

3.3 Safety Analysis Set

The Safety Analysis Set will include all subjects who are randomized and take investigational product.

4 EFFICACY ASSESSMENTS AND ENDPOINTS

4.1 Efficacy Assessments

- Time to perceptible pain relief – recorded using perceptible pain stopwatch
- Time to meaningful pain relief (TMPR) – recorded using meaningful pain stopwatch
- Time to confirmed perceptible pain relief (TCPR) - defined as the time to perceptible pain relief provided that the subject subsequently stopped the meaningful pain stopwatch
- Pain intensity

  Categorical 4-point scale: 0 – no pain, 1 – mild pain, 2 – moderate pain and 3 – severe pain, collected at baseline.

  Numerical 0 – 10 scale (PI): 0 – no pain to 10 – very severe pain, collected at Baseline, 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h and 4h (± 5min) after dosing
- Pain relief

  Numerical 0 – 10 scale (PAR): 0 – no relief to 10 – complete relief, collected at 0.25h, 0.5h, 0.75h, 1h, 1.25h, 1.5h, 2h, 3h and 4h (± 5min) after dosing (including at time of rescue and at time of meaningful relief)
- Time to rescue – time when rescue medication was administered
- Subject global evaluation – subject overall impression of the investigational product, collected at Hour 4, at time of rescue, or at the time of early termination, using the 5-point scale: 0 – poor, 1 – fair, 2 – good, 3 – very good and 4 – excellent.

4.2 Efficacy Endpoints

Primary efficacy endpoint

- Time to confirmed perceptible pain relief (TCPR)

Secondary efficacy endpoints

- Time to meaningful pain relief (TMPR)

- Percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments ([redacted] versus PBO)

Tertiary efficacy endpoints

- Percentage of subjects with meaningful pain relief at 35, 40, and 45 minutes ([redacted] versus ACM)
- Percentage of subjects with confirmed perceptible relief at 15, 20, and 25 minutes
- Time weighted sum of pain intensity difference from 0 to 4 hours (SPID0-4)
- Time weighted sum of pain relief from 0 to 4 hours (TOTPAR0-4)
- Pain relief (PAR) and pain intensity difference (PID) scores at individual time points;
- Time to rescue medication
- Subject Global Evaluation

4.3 Safety Assessments and Endpoints

- Number and percentage of subjects with treatment-emergent adverse event (AE)
- Number and percentage of subjects who discontinued the trial 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

4.4 Covariates

No covariate variable will be adjusted in the analyses.

5 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

5.1 Statistical Hypotheses

The comparison between the active treatments will be based on the median survival times. The following hypothesis will be tested using the bootstrap re-sampling method

$$H_0 : M_1 = M_2 \text{ vs } \quad H_A : M_1 \neq M_2$$

where M_1 and M_2 are the median survival times of the two active treatments to be compared, respectively.

The comparison between the active treatments and PBO will be based on the survival functions. The following hypothesis will be tested using the Wilcoxon test

$$H_0 : S_{Active}(t) = S_{PBO}(t) \text{ (all t)} \quad \text{versus} \quad H_A : S_{Active}(t) \neq S_{PBO}(t) \text{ (at least some t)}$$

where $S_{Active}(t)$ and $S_{PBO}(t)$ are the survival functions of the active treatments and the PBO, respectively.

5.2 Statistical Decision Rules

In order to control the family-wise Type I error rate at 0.05 level for primary and secondary endpoints, the fixed sequence testing with fallback method will be used. Table 1 presents the order of the tests and the assigned α values for each ordered test. The comparison of [redacted] to IBU in TMPR is not included in the fixed testing sequence. Testing will commence with an assigned α = 0.049 and an α value of 0.001 will be reserved for the comparison of [redacted] and PBO on the percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments.

Table 1: Fixed Test Sequence and Assigned α-value

	Pre-Assigned α-value	**α-value available if previous test positive**	**α-value available if previous test(s) negative**
TCPR [redacted] vs PBO	0.049	---	---
TMPR [redacted] vs PBO	0.000	0.049	0.000
TCPR [redacted] vs ACM	0.000	0.049	0.000
TCPR [redacted] vs IBU	0.000	0.049	0.000
TMPR [redacted] vs ACM	0.000	0.049	0.000

	Pre-Assigned α-value	α-value available if previous test positive	α-value available if previous test(s) negative
Percentage of subjects with confirmed perceptible relief from 30 minutes to successively earlier minutes in one-minute increments [redacted] vs PBO	0.001	0.05	0.001

The six tests in the above family will be conducted as follow: The survival functions in TCPR between [redacted] and PBO will be compared. If it is non-significant at the 0.049 level, then the first test and the following 4 tests will be failed, and the last test (the percentage of subjects in TCPR) will be tested at the 0.001 level. If the first test is significant at the 0.049 level, then the second test, the survival functions in TMPR between [redacted] and PBO, will be compared at the 0.049 level and the following tests will follow the same pattern as for the first test. If all previous 5 tests are significant at the 0.049 level, the last test, the percentage of subjects in TCPR, will be tested at the 0.05 level.

5.3 Statistical Methods

5.3.1 Time to Confirmed Perceptible Pain Relief and Meaningful Pain Relief

The time to meaningful pain relief is defined as the time (in minutes) elapsed from dosing until the subject stopped the second stopwatch. Time to confirmed perceptible pain relief is defined as the time (in minutes) to perceptible pain relief as indicated on the first stopwatch, provided that the subject also stopped the second stopwatch indicating meaningful pain relief.

For subjects who do not have both perceptible and meaningful pain relief by 4 hours, their values of the TCPR and the TMPR will be censored at 4 hours. For subjects who have perceptible pain relief but do not have meaningful pain relief by 4 hours, their values of TCPR and TMPR will be censored at 4 hours. For subjects who discontinue before having relief, their values of TCPR and TMPR will be censored at 4 hours. For subjects who take rescue medication before having relief, their values of the TCPR and TMPR will be censored at 4 hours.

TCPR and TMPR will be analyzed using the survival data analysis. The survival function (cumulative proportions of subjects with pain relief at each time point) and the median survival time will be estimated by the Kaplan-Meier (KM) method for each treatment. The survival functions of the active treatments will be compared with the survival

function of PBO using the Wilcoxon test. The median survival time of [redacted] will be compared with the median survival times of ACM and IBU using the bootstrap re-sampling method.

The estimation of the survival functions and the comparison of the survival functions between the active treatments and PBO will be performed by the following SAS codes

```
proc lifetest data=DATASET method=KM outsurv=predict;
  strata trt;
  time TIME*censor(x);
  ods output Quartiles=output1(where=(percent=50));
run;
```

The median survival time is used as an endpoint to evaluate the onset of pain relief. The median survival times of the active treatments can be estimated by the KM method. The median survival time of [redacted] will be compared with the median survival times of ACM and IBU by the bootstrap re-sampling method using the following procedure:

1) Independently take B=2000 bootstrap samples from each active arm. Each bootstrap sample is obtained by sampling with replacement from the original observed time-to-event (TTE) data (ie, $\{t_{i1}^b,\Lambda\ ,t_{in_i}^b : i=1,2,\ b=1,\Lambda\ ,B\}$).

2) Within each bootstrap sample, estimate the median survival time using the KM method (ie, $\{\hat{m}_i^b : i=1,2,\ b=1,\Lambda\ ,B\}$).

3) Calculate the difference in median survival times $\hat{\tau}^b = \hat{m}_1^b - \hat{m}_2^b,\ b=1,\Lambda\ ,B$.

4) The dataset $\{\hat{\tau}^b :\ b=1,\Lambda\ ,B\}$ constitutes a bootstrap sampling distribution of the difference in median survival times. The cumulative probability function of this distribution is given by $F_B(t) = \#\{\hat{\tau}^b < t\}/B$.

5) From the cumulative probability function of the bootstrap sampling distribution, $F_B(t) = \#\{\hat{\tau}^b < t\}/B$, the 2-sided bootstrap percentile p-value for testing the hypothesis of $H_0 : M_1 - M_2 = 0$ vs $H_A : M_1 - M_2 \neq 0$ is given by

$$p = 2 * F_B(0)$$

and the 95% bootstrap percentile confidence interval for the difference in median survival times is given by

$$(F_B^{-1}(0.025), F_B^{-1}(0.975))$$

5.3.2 Earliest Separation of [redacted] and PBO on Percentage of Subjects with Confirmed Perceptible Relief

The earliest time of separation between [redacted] and PBO will be established by comparing the percentage of subjects with confirmed perceptible pain relief starting from 30 minutes to successive earlier minutes in one minute increment, until statistical significance is no longer achieved. The time to confirmed perceptible pain relief will be dichotomized to binary response at each time point and analyzed using the logistic regression analysis.

The following is the sample SAS code for the logistic regression analyses:

```
proc GENMOD data=DATASET ;
  class trt;
  model responder = trt / dist=BIN link=LOGIT;
  lsmeans trt / diff cl exp;
run;
```

5.3.3 Percentage of Subjects with Meaningful Pain Relief at 35, 40 and 45 minutes ([redacted] versus ACM)

The percentage of subjects with meaningful pain relief at 35, 40 and 45 minutes in the [redacted] and ACM groups will be analyzed using the logistic regression analysis.

5.3.4 Percentage of Subjects with Confirmed Perceptible Pain Relief at 15, 20, and 25 minutes

The percentage of subjects with confirmed perceptible pain relief at 15, 20 and 25 minutes will be analyzed using the logistic regression analysis. Each active treatment will be compared to PBO, and [redacted] will be compared to ACM and IBU.

5.3.5 Pain Intensity and Pain Relief

For subjects who use rescue medication, the last reported pain intensity score or baseline pain intensity score, whichever is worse, will be carried forward to the remaining time points; the 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.

Pain intensity and pain relief scores collected outside the window $\pm$ 5 minutes of scheduled time prior to 90 minutes post-dose and outside the window $\pm$ 15 minutes of scheduled time $\geq$ 90 minutes post-dose will be replaced by the linear interpolation.

The pain intensity difference (PID) at each post-baseline time point will be derived by

the baseline PI score minus the post-baseline PI score. A positive value indicates a reduction in pain intensity.

PID and PAR will be analyzed at each post-baseline time point separately using analysis of variance with baseline pain level (moderate or severe) and treatment as the factors in the model. Summary statistics (number of subjects, least square mean, standard error and 95% confidence interval) will be tabulated by treatment group.

Time-weighted sum of the pain intensity difference scores (SPID0-4) will be derived by first multiplying each PID score by the time difference (in hours) from the previous time point (in nominal time), and adding them together for each scheduled time point from 0.25 to 4 hours.

Time-weighted total pain relief (TOTPAR0-4) will be derived by first multiplying each PAR by the time difference in hours from the previous time point (in nominal time), and adding them together from 0.25 to 4 hours.

SPID0-4 and TOTPAR0-4 will each be analyzed using analysis of variance with baseline pain level (moderate or severe) and treatment as the factors in the model. Summary statistics (number of subjects, least square mean, standard error and 95% confidence interval) will be tabulated by treatment group.

5.3.6 **Time to Rescue Medication**

Time to rescue medication will be measured as the elapsed time from the time of dosing to the time of the rescue medication. Subjects who discontinue from the study before 4 hours, but do not use rescue medication, will be censored at the time of discontinuation. Subjects who do not use rescue medication during the 4-hour study period will be censored at 4 hours.

The cumulative percentage of subjects who used rescue medication will be estimated by the Kaplan-Meier method, the survival functions of active treatment groups will be compared with the survival function of PBO and the survival function of [redacted] will be compared with the survival functions of ACM and IBU using the Wilcoxon test.

5.3.7 **Subject Global Evaluation**

Subject global evaluation score will be analyzed using analysis of variance with the baseline pain level (moderate or severe) and treatment as the factors. The adjusted means will be compared for the pairwise comparisons, each active treatment will be compared to PBO, and [redacted] will be compared to ACM and IBU.

5.3.8 Subgroup Analyses

TCPR will be analyzed within the following subgroups: age (<18 years, ≥18 years), gender (male, female), race (white, non-white) and baseline pain level (moderate, severe).

The survival functions and the median survival time of each treatment will be estimated by the Kaplan-Meier method within each subgroup.

The protocol stated that the TCPR and the TMPR will be analyzed within the above subgroups. It was determined after the protocol finalization that subgroup analyses are only needed for the primary efficacy endpoint of TCPR.

5.4 DEMOGRAPHIC AND BASELINE CHARACRISTICS

Summary statistics (number of subjects, mean, standard deviation, median, minimum and maximum) will be provided by treatment group for numerical variables.

Frequency summary statistics (number and percentage of subjects) will be provided by treatment group for categorical variables.

Number and percentage of subjects receiving previous medication, concomitant medication and non-drug therapy/procedure will be provided by treatment group. Medications that were stopped before the date and time the study medication was taken will be considered previous medications. All other medications will be considered concomitant medications.

Concomitant medications taken by greater than or equal to 5% of subjects in one or more treatment groups will be provided by treatment group.

5.5 SAFETY ANALYSIS

5.5.1 Adverse Events

Number and percentage of subjects with treatment-emergent AE will be summarised by treatment group, MedDRA system organ class and preferred term. The most commonly reported treatment-emergent AE (≥5% in one or more treatment groups) will also be provided. Treatment-emergent adverse events are those with a start date and time on or after the date and time of study dose administration, or those AEs that start before the dose administration but worsen after dosing.

Number and percentage of subjects who discontinued the trial due to an AE will be summarised by treatment group, MedDRA system organ class and preferred term. This display will include subjects who discontinued due to an AE whether or not it was a treatment-emergent AE.

Number and percentage of subjects with serious AEs will be summarised by treatment group, MedDRA system organ class and preferred term. This display will include subjects who discontinued due to an AE whether or not it was a treatment-emergent AE.

Number and percentage of subjects with treatment-related AEs will be summarised by treatment group, MedDRA system organ class and preferred term. Treatment-related AEs are events evaluated by the investigator as possible, probable or very likely related to study medication.

The number of subjects with treatment-emergent adverse events will be summarized by gender (male, female), age group (<18 years, ≥18 years), and race (white, non-white).

Number and percentage of subjects with treatment-emergent AEs will be summarised by severity (mild, moderate and severe) for all AEs and also for treatment-related AEs. Subjects will be counted only once for each system organ class and preferred term by selecting the most severe event.

5.5.2 **Vital Signs**

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

6. REFERENCES

1. Averbuch M, Katzper M. Baseline pain and response to analgesic medications in the postsurgery dental pain model. J Clin Pharmacol 2000;40:133-137.

2. Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. In: Max M, Portenoy R, Laska E, eds. Advances in pain research and therapy. Vo l 18. New York, NY: Raven Press, Ltd., 1991:117-24.

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 Deviation	All Randomized Subjects
Table 14.1.3	Demographic and Baseline Characteristics	All Randomized Subjects
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Table 14.1.4	Previous Medications	All Randomized Subjects
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Table 14.1.6	Non-Drug/Therapy	All Randomized Subjects
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14.2 Efficacy		
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Table 14.2.1.3	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Severe Baseline Pain	Intent-to-Treat Subjects
Table 14.2.1.4	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Male	Intent-to-Treat Subjects
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Table 14.2.1.6	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age < 18 Years Old	Intent-to-Treat Subjects
Table 14.2.1.7	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age >= 18 Years Old	Intent-to-Treat Subjects
Table 14.2.1.8	Kaplan-Meier Estimates of The Cumulative	Intent-to-Treat Subjects

	Percentage of Subjects with Confirmed Perceptible Pain Relief – White Subjects	
Table 14.2.1.9	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Non-White Subjects	Intent-to-Treat Subjects
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Table 14.2.3	Percentage of Subjects with Confirmed Perceptible Pain Relief at Specified Times – [redacted] vs Placebo	Intent-to-Treat Subjects
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Table 14.2.5	Percentage of Subjects with Confirmed Perceptible Pain Relief at 15, 20 and 25 Minutes	Intent-to-Treat Subjects
Table 14.2.6	Time Weighted Sum of Pain Intensity Difference 0 – 4 Hours (SPID0-4)	Intent-to-Treat Subjects
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Table 14.2.8	Pain Intensity Difference (PID) from Baseline At Each Time Point	Intent-to-Treat Subjects
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Table 14.2.10	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects Using Rescue Medication	Intent-to-Treat Subjects
Table 14.2.11	Subject Global Evaluation of Study Medication	Intent-to-Treat Subjects

14.3 Safety

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

	Term	
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 Withdrawals Due to Adverse Events	Safety Analysis Subjects

FIGURES:

Figure 14.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief	Intent-to-treat subjects
Figure 14.1.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Moderate Baseline Pain	Intent-to-treat subjects
Figure 14.1.2	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Severe Baseline Pain	Intent-to-treat subjects
Figure 14.1.3	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Male	Intent-to-treat subjects
Figure 14.1.4	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Female	Intent-to-treat subjects
Figure 14.1.5	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age < 18 Years Old	Intent-to-treat subjects
Figure 14.1.6	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age >= 18 Years Old	Intent-to-treat subjects
Figure 14.1.7	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – White Subjects	Intent-to-treat subjects
Figure 14.1.8	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Non-White Subjects	Intent-to-treat subjects
Figure 14.2	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Meaningful Pain Relief	Intent-to-treat subjects
Figure 14.3	SPID by Treatment	Intent-to-treat subjects
Figure 14.4	TOTPAR by Treatment	Intent-to-treat subjects
Figure 14.5	Pain Intensity Difference (PID) from Baseline at Each Time Point	Intent-to-treat subjects
Figure 14.6	Pain Relief Score (PAR) at Each Time Point	Intent-to-treat subjects
Figure 14.7	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects Using Rescue Medication	Intent-to-Treat Subjects

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	Perceptible Pain Relief, Meaningful Pain Relief and Subject Global Evaluation	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
16.2.6.1	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 Study Discontinuation	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