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STATISTICAL ANALYSIS PLAN

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Sponsor Contact:	
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Authored by: PPD

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Bayer HealthCare LCC

Revisions to the Statistical Analysis Plan described herein must be approved through a formal written amendment with the exception of minor editorial changes to tables, figures, or listing shells, and any necessary textual clarifications for programmers that do not affect the stated analysis variables, study endpoints, or statistical methods.

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE(s)	adverse event(s)
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
CI	confidence interval
COX	Cyclooxygenase
FDA	Food and Drug Administration
hr(s)	hour(s)
ITT	intent-to-treat
LOCF	last observation carried forward
LSMean	Least squares mean
LSSD	Least squares standard deviation
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
n	number of observations
N	number of subjects (sample size)
NSAID	Nonsteroidal Anti-inflammatory Drug
OTC	over-the-counter
PID	Pain Intensity Differences
PP	per-protocol
PT	preferred term
CCI	[redacted]
RNR	randomization number
SAE(s)	serious adverse event(s)
SAS®	Statistical Analysis System (SAS® Institute Inc., Cary, NC)
SD	standard deviation
SOC	system organ class
SPID	Summed Pain Intensity Difference
TEAE(s)	treatment-emergent adverse event(s)
TOTPAR	Total Pain Relief
US	United States
WHO-DDE	World Health Organization Drug Dictionary Enhanced

2. INTRODUCTION

2.1 Background

Naproxen sodium and ibuprofen are nonselective cyclooxygenase (COX) inhibitors. They are propionic acid derivatives and members of a drug class s known as nonsteroidal anti-inflammatory drugs (NSAIDs). Both naproxen and ibuprofen inhibit COX-1 and COX-2 isoenzymes. COX enzymes play a key role in the inflammatory response and the production of prostaglandins. Specifically, COX-1 is expressed in the gastrointestinal epithelium, vascular endothelium and kidney, while COX-2 plays a role in induction of inflammation. COX-2 inhibition reduces prostaglandin synthesis, leading to pain relief.

In the United States, naproxen has been marketed as a prescription medication since 1976 under the brand name Naprosyn®. Its sodium salt, naproxen sodium, was first sold under the trade name Anaprox® in 1980. In 1994, the US FDA approved naproxen sodium tablets (using the brand name Aleve®), 220 mg for over-the-counter (OTC) use. Aleve is indicated for the temporary relief of minor aches and pains due to: minor pain of arthritis, muscular aches, backaches, menstrual cramps, headaches, toothaches, and the common cold. It also temporarily reduces fever. As an OTC medication, Aleve should not be taken for longer than 10 days for pain or 3 days for fever unless otherwise directed by a physician. Similarly, Advil® (a branded form of ibuprofen) has been available OTC since 1984. It carries the same indications and duration of use labeling as Aleve.

The labelled dosing interval for over-the-counter naproxen sodium is 8-12 hours due to its long elimination half-life (approximately 14 hours) and documented long duration of action.[1,2] In contrast, ibuprofen, another propionic acid nonsteroidal anti-inflammatory drug available over-the-counter, has a labeled dosing interval of 4-6 hours and a short elimination half-life, 2-4 hours.[2] These two agents have been compared in single dose dental pain studies.[3,4] The analgesic effectiveness of naproxen sodium was greater than ibuprofen at later time points in both of these 12 hour studies but the duration of the studies was relatively short and the evaluations were performed at home. The ability to assess relative differences in the later hours may have been limited by the outpatient nature of those earlier studies which used at-home diaries.

The duration of analgesia in acute pain studies is generally assessed by the time to remedication.[5] At both low OTC doses and high OTC doses, naproxen sodium showed a numerically longer duration of action compared to ibuprofen although the difference did not achieve the level of statistical significance.[3,4] However, the sample size in these two studies was not estimated based on this secondary outcome parameter.

2.2 Rationale of the Study

The post-impaction dental pain model chosen for this study has been widely used in the evaluation of OTC and prescription analgesics for a number of reasons. Dental surgical procedures can be easily standardized, and the population of subjects undergoing a given procedure is usually relatively healthy and homogeneous. In addition, there is extensive data substantiating the usefulness of the dental pain model in predicting the relative efficacy of a wide range of analgesic medications. The model has been found to be very useful for comparing several measures of analgesic efficacy, including onset, peak effect, and duration of analgesic activity. [6,7,8] Therefore, the purpose of this investigation is to use the post-impaction dental pain model to compare the duration of action of naproxen sodium to ibuprofen at over-the-counter doses.

3. STUDY OBJECTIVES

The primary objective of this trial is:

- To compare the duration of analgesic efficacy as determined by the time to rescue medication of a single oral dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo (2 x tablets) over 24 hours in subjects experiencing moderate to severe post-impaction surgery dental pain.

The secondary objectives of this trial are:

- To compare the overall analgesic effect (SPID 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo;
- To compare the overall relief from starting pain (TOTPAR 0-24) of a single dose of naproxen sodium 440 mg (2 x 220 mg tablets) relative to ibuprofen 400 mg (2 x 200 mg tablets) and placebo.

Other objectives of this trial are:

- To compare the efficacy of naproxen 440 mg, ibuprofen 400 mg, and placebo for the following measures:
    - SPID 0-4, SPID 0-8, SPID 0-12, SPID 6-12;
    - TOTPAR 0-4, TOTPAR 0-8, TOTPAR 0-12, and TOTPAR 6-12;
    - Peak Pain Intensity;
    - Peak Pain Relief;
    - Sum of Observations with Pain Half Gone;

- Duration of Pain Relief At Least Half Gone;
- Total amount of time that subject reported at least a 2-point PID;
- Global Pain Assessment.

4. STUDY DESIGN

4.1 Overall Study Design

This is a single center, randomized, double-blind, parallel, placebo-controlled study, stratified by baseline pain, in subjects experiencing moderate to severe postoperative dental pain. The study will consist of a Prescreening telephone call, a Screening Visit, a two day Treatment Period and a Post-Operative visit. Eligible subjects who have undergone surgical extraction of at least 2 mandibular partial or full bony impacted third molars will be kept in-house and evaluated for efficacy and safety at the study site overnight.

The study consists of a Screening Phase, Treatment Phase and a Follow-Up Phase. During Treatment Phase, subjects will be kept in-house at the study site for one overnight stay. Qualified subjects will then be randomized into one of three treatments. Approximately 397 will have surgery and approximately 385 will be randomized to a specific treatment.

The duration of each subject's participation will be approximately 38 days. For an overview on the study design and study procedures see Figure 1.

Figure 1 – Design Overview

	Screening Phase	**Treatment Phase**					**Follow up Phase**
Trial Days	**Day -28 to -1**	**Day 1 Presurgery**	**Day 1 Surgery**	**Day 1 Postsurgery**	**Day 1**	**Day 2**	**Days 6-10**
		Check-in to study site (if needed)	Surgical teeth extraction	Categorical pain ✸ NRS pain	NRS pain Pain relief Pain half gone	NRS pain Pain relief Pain half gone Global assessment	Phone call or visit

✸ = randomized to either naproxen (440 mg), ibuprofen (400 mg), or placebo

The schedule of assessments can be found in Section 16.1 of the protocol.

4.1.1 Method of Assigning Subjects to Treatment Groups

At the beginning of the first treatment period, after completion of the pre-treatment baseline procedures/assessments, subjects who meet the entry criteria will be sequentially assigned to a

unique number in sequential order (randomization number [RNR]) according to the randomization schedule 3:3:1 (naproxen sodium: ibuprofen: placebo) prepared prior to the study.

Subjects will be numbered according to the following scheme, which is a different number than the RNR:

14001XXXX

Whereas the "Xs" will be replaced with a four digit sequentially assigned number as each subject enters the study (e.g. first subject number will be 140011001).

The unique subject identifier number will be assigned in numerical order stratified by baseline 2 or 3 categorical pain level (moderate or severe) prior to dosing. Subjects who designate their baseline pain as ***moderate*** will use the lowest RNR available with subsequent moderate randomizations using the next available lowest RNR. Subjects who designate their baseline pain as ***severe*** will use the highest RNR available with subsequent severe randomizations using the next available highest RNR. Subjects who characterize their pain severity as ***mild*** and <5 on the NRS will not receive treatment and be withdrawn from the study.

Once a number has been assigned to a subject, it cannot be reassigned to another subject.

Subjects completing the Screening Visit, if not scheduled for surgery the same day, will return to the trial site within 28 days, and if they continue to meet inclusion/exclusion criteria postsurgery will be randomized to one of three treatment groups:

- Naproxen sodium tablets (220 mg x 2 tablets)
- Ibuprofen tablets (200 mg x 2 tablets)
- Placebo tablets (2 tablets)

Subjects will be assigned to treatment groups in accordance with the randomization schedule. The Sponsor or designee will provide a randomization schedule to the study site.

4.1.2 Blinding

Subjects enrolled in the trial, investigators and their staff involved in protocol procedures or who are involved in data collection, data entry and data analysis will be blinded to the identity of the treatments until the database is locked. The study monitor will conduct product accountability after database lock. To preserve blinding, subjects will be blindfolded. Study drug will be dispensed by an unblinded study team member based on the randomization schedule. That team member may have no other role in the study conduct and may not reveal the study drug's identity to any members of the blinded study team.

Sponsor will supply study medication in bulk containers. Selection of the proper dose for an individual subject will be performed by an unblinded study team member using the provided

randomization schedule. The unblinded study team member will withdraw the appropriate study medication from the bulk container and transfer it to a dispensing cup. The unblinded study team member will then bring the study medication to the treatment room where it will be dispensed to the subject by the unblinded study team member. The unblinded study team member should have no other responsibilities in the study.

5. EFFICACY AND SAFETY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

The primary efficacy analyses population will be based on the PP population.

The primary efficacy endpoint is the time to first use of rescue medication.

5.1.2 Secondary Efficacy Endpoints

The secondary endpoints are as follows:

- SPID 0-24;
- TOTPAR 0-24.

5.1.3 Other Efficacy Endpoints

Other efficacy endpoints are as follows:

- SPID 0-4, SPID 0-8, SPID 0-12, SPID 6-12;
- TOTPAR 0-4, TOTPAR 0-8, TOTPAR 0-12, and TOTPAR 6-12;
- Peak Pain Intensity Difference;
- Peak Pain Relief;
- Cumulative proportion taking rescue medication by timepoint;
- Proportion of subjects with Pain Half Gone by 24 hours;
- Proportion of subjects with pain at least half gone at each time point;
- Duration of time that subjects reported their pain was at least half gone;
- Total amount of time that subjects reported at least a 2-point PID;

- Global Pain Assessment.

5.2 Safety Endpoints

Safety will be assessed by reports of adverse events (AEs) and absolute and change from baseline in vital signs.

6. STATISTICAL AND ANALYTICAL PLANS

6.1 General Methodology

All statistical processing will be performed using SAS® Version 9.3 or higher unless otherwise stated. No interim analyses are planned. Except where noted, all statistical tests will be two-sided and will be performed at the 0.05 level of significance. No adjustments for multiplicity will be made.

Descriptive statistics will be used to provide an overview of the efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum (min), and maximum (max). Appropriate inferential statistics will be used for the primary and other efficacy variables.

The efficacy analysis performed on the Per-Protocol (PP) population is considered the primary analysis. The efficacy analysis performed on the Intent-to-Treat population is considered a supportive analysis.

Reported AEs, medical history terms, and prior and concomitant procedures and therapies will be classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Prior and concomitant medications as well as rescue medication will be classified on the basis of World Health Organization Drug Dictionary Enhanced (WHO-DDE) terminology.

6.1.1 Statistical Analysis

All analyses will be performed by CCI [redacted] using SAS® Version 9.3 or later. All summary tables and data listings will be prepared utilizing SAS® software.

The standard operating procedures of CCI will be followed in the creation and quality control of all data displays and analyses.

6.1.2 Baseline Definition

Baseline is from the last measurement prior to study treatment.

6.1.3 Visit Windowing

Visits will not be windowed. Visits will be summarized and listed by their nominal value.

6.1.4 Adjustments for Covariates

Baseline pain intensity will be used as a covariate for the efficacy analysis where appropriate.

6.1.5 Handling of Dropouts or Missing Data

A LOCF method will be used to extrapolate efficacy data that are missing beyond the last observation. Missing scheduled pain and relief scores prior to the last observation will be imputed using the weighted average of adjacent evaluations as follows:

$$S_i = (S_{i+1} - S_{i-1})*(t_i - t_{i-1})/(t_{i+1} - t_{i-1}) + S_{i-1}$$

Where S_{i-1} and S_{i+1} are scheduled nonmissing adjacent evaluations at t_{i-1} and t_{i+1}, respectively, where t_i is the scheduled time postdose in hours, and t_{i-1} and t_{i+1} are actual hours postdose of scheduled evaluations.

If a partial date is reported where the day is missing, then the day will be imputed as the first day of the month unless the month is the same month as the first dose then the day will be that of first dose with the month and year remaining the same. If a partial date is reported where the month is missing, then the month will be imputed to January unless the year is the same year as the first dose then the month will be that of first dose with the year remaining the same. If a partial date where both the day and month is missing, follow details as stated previously.

Missing AE start dates will be imputed using partial date imputation rules as previously described in this Section. Missing data for other parameters will not be imputed for analysis unless otherwise defined.

6.1.6 Interim Analyses and Data Monitoring

No interim analysis or data monitoring is planned for this study.

6.1.7 Multicenter Studies

Not applicable; this is a single center study.

6.1.8 Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

6.1.9 Use of an Efficacy Subset of Subjects

The PP population will be used for the primary analysis.

6.1.10 Active-Control Studies Intended to Show Equivalence

Not applicable to this study.

6.1.11 Examination of Subgroups

Not applicable to this study.

6.2 Disposition of Subjects

The number of subjects enrolled, randomized, completed, and discontinued (including the reasons for discontinuation) will be summarized for each treatment group.

6.3 Protocol Deviations

Protocol deviations will not be entered into the database. Deviations leading to exclusion from analysis populations will be identified and summarized.

6.4 Analysis Sets

The number of subjects included in each analysis population will be summarized by treatment group. Subjects who are excluded from an analysis population will be summarized by the reasons for exclusion.

6.4.1 Safety Population

All subjects who are randomized and take at least one dose of investigational product will be included in the safety population and analyzed according to the treatment they actually received. All safety analyses will be performed using the Safety population.

6.4.2 Intent-to-Treat (ITT) Population

All subjects in the Safety population who provide at least one pain assessment after the first dose of the investigational product will be included in the ITT population and analyzed according to

the treatment they were randomized to. All efficacy analyses will be presented using the ITT population for supportive purposes.

6.4.3 Per-Protocol (PP) Population

All subjects in the ITT population who do not have any major protocol violations will be included in the PP population and analyzed according to the treatment they actually received.

Major protocol violations include:

- Inclusion / Exclusion Criteria violations
- Took prohibited medications
- Were noncompliant with study medication
- Use of rescue medication at or prior to 60 minutes after ingesting study medication
- Vomiting at or prior to 60 minutes after ingesting study medication

Evaluability for inclusion in the PP population will be reviewed and finalized prior to database lock.

The primary efficacy analysis will be performed using the PP population. The ITT population will be used as supportive.

6.5 Demographic and Other Baseline Characteristics

All baseline summaries will be done on the ITT, PP, and Safety populations.

Sex, race, and ethnicity will be summarized by counts and percentages. Age, height (cm), weight (kg), and BMI will be summarized with descriptive statistics by treatment group and overall.

Oral surgery site will be presented by frequency counts and percentages for each treatment group and overall. Number of teeth extracted, impaction scores, and duration of surgery (first incision to last suture) will be summarized with descriptive statistics by treatment group and overall. All dental surgery information and oral examination data will be presented in by-subject listings.

Baseline pain score will be summarized with frequency counts and percentages as well as with descriptive statistics by treatment group and overall.

Social history (drug, alcohol, tobacco, and caffeine use) will be summarized with frequency counts and percentages by treatment group and overall. Social history will also be presented in a by-subject listing.

Medical histories / surgeries will be coded using the MedDRA dictionary and presented in a by-subject listing. Inclusion / exclusion criteria will also be presented in by-subject listings.

6.6 Prior and Concomitant Medications

Concomitant medications will be coded to preferred name and Anatomical Therapeutic Chemical (ATC) classification of ingredients using the WHO-DDE.

Medications which start prior to first dose will be considered prior medications. Ongoing medications and medications ending after the date of first dose will be considered concomitant medications. Incomplete start and end dates which could be either prior to first dose or after first dose will be considered prior to first dose.

A by-subject listing of all prior and concomitant medications will be presented. Concomitant medications will be summarized by drug class and preferred name by treatment group and overall for each population.

6.7 Rescue Medications

Rescue medications will be coded to preferred name and ATC classification of ingredients using the WHO-DDE.

Rescue medications will be summarized by drug class and preferred name by treatment group and overall for each population.

A by-subject listing of all rescue medications will be presented.

6.8 Analysis of Efficacy

All statistical tests will be 2-sided at the significance level of 5% and no multiplicity adjustment will be made.

In all analyses, for subjects who take rescue medication, all pain intensity scores after intake of rescue medication will be replaced by the worse of the baseline or the score assessed immediately before taking rescue medication. All pain relief after intake of rescue medication will be replaced by “no relief” (0).

For the purposes of analysis, dates of the subject assessments for efficacy will be populated programmatically when the time indicates a date change, i.e., the collection time of the time point went past midnight.

6.8.1 Primary Efficacy Analysis

Time to first use of rescue medication during the treatment period is the primary efficacy endpoint. If a subject did not take the rescue medication during the treatment period, the subject will be considered censored at the time of last assessment. Time to first use of rescue medication will be estimated and plotted using Kaplan-Meier method and analyzed using a log-rank test

stratified by baseline pain intensity. Time to first use of rescue medication will be measured and presented in hours.

Time to first use of rescue medication will be summarized by count and percentage of subjects taking the rescue medication and count and percentage of subjects censored. Kaplan-Meier 25^{th}, 50^{th}, and 75^{th} percentiles, as well as minimum and maximum times observed, will be determined and summarized and Kaplan-Meier curves will be plotted. Elapsed times will be computed from the date and time of first dose of study medication. Subjects not taking any rescue medication by the time of study completion (24 hours post-surgery) will be right-censored. The date and time of the last recorded non-missing assessment will be used as the censoring date. Log-rank tests will be used to compare naproxen sodium to ibuprofen and naproxen sodium to placebo.

The primary efficacy analysis will be presented using the PP population. The ITT population will be presented as supportive.

Time to first use of rescue medication will also be presented in a by-subject listing.

6.8.2 Secondary Efficacy Analysis

For each postdose time point, PIDs will be derived by subtracting the pain intensity at the postdose time point from the baseline intensity score (baseline score – post-baseline score). A positive difference is indicative of improvement. Time-weighted sum of pain intensity differences (SPIDs) will be calculated for 4, 8, 12, 6-12, and 24 hours by multiplying the PID score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values over 4, 8, 12, 6-12, and 24 hours, respectively. Similarly, total pain relief scores (TOTPARs) will be calculated by multiplying the pain relief score at each postdose time point by the duration (in hours) since the preceding time point and then summing these values. Nominal times as recorded by the site will be used for timepoints mentioned above.

SPID 0-24 and TOTPAR 0-24 will be analyzed using an analysis of covariance model (ANCOVA) with treatment as fixed effect and baseline pain intensity score as the covariate. The least squares mean (LSMean), least squares standard deviation (LSSD), and 95% confidence intervals (CIs) for the treatment differences (naproxen-placebo; naproxen-ibuprofen; ibuprofen-placebo) will be calculated based on the above mentioned model.

6.8.3 Other Efficacy Analysis

The SPID 0-4, 0-8, 0-12, and 6-12 will be analyzed using an ANCOVA model with treatment as fixed effect and baseline pain intensity score as the covariate. The LSMean, LSSD, and 95% CIs for the treatment differences will be calculated from the above mentioned model as well.

The TOTPAR 0-4, 0-8, 0-12, and 6-12 will be analyzed using the same method as stated above.

Peak PID and peak pain relief will be summarized using descriptive statistics for each treatment group. PIDs and pain relief scores at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, and 24 hour postdose will be summarized using descriptive statistics for each treatment group. In addition line graphs showing the time effect curves will also be presented by treatment group for both PID and the pain relief scores. In addition, pain intensity scores will be summarized by timepoint including pre-dose.

The cumulative proportion of subjects taking rescue medication by each time point will be summarized and Chi-square tests will be presented to compare treatments. In addition, the cumulative proportion of subjects taking rescue medication will be plotted at every time point for each treatment group to show the time-effect. The number of times a subject took a rescue medication over the 24 hour period will be summarized using frequency counts and percentages by treatment group.

The percent of subjects with pain half gone by 24 hours will be summarized using frequency counts and percentages by treatment group. Subjects reporting at least one time point as pain half gone, regardless of response at 24 hours will be considered to have pain half gone by 24 hours. In addition, the proportion of subjects with pain at least half gone at each time point will be summarized using frequency counts and percentages by treatment group. The proportion of subjects with pain at least half gone will be plotted at every time point for each treatment group.

The duration of time (in hours) that subjects reported their pain was at least half gone will be summarized using descriptive statistics by treatment group. The start of any period of reporting pain half gone will be the reported time of the first "Yes" response and the end of the period will be the time of the first "No" response after the "Yes" response. For example, if a subject reported pain half gone at 1 hr, 2 hr, 3 hr, and 4 hr and reported pain not half gone at 5 hr time point then the duration of time pain was at least half gone would be (exact time of 5 hr assessment) – (exact time of 1 hr assessment). A subject may have more than 1 period of time in which they reported their pain half gone. All periods of time will be summed together per subject. Only assessments taken prior to rescue medications will be considered.

The total amount of time (in hours) a subject reported at least a 2-point PID will be summarized using descriptive statistics by treatment group. The PID at each time point is calculated as the pain intensity numerical rating score (NRS) – baseline pain intensity NRS. A subject may have more than 1 period of time of reporting at least a 2-point PID. Each period of time will be summed together. Only assessments taken prior to rescue medications will be considered.

The global assessment score will be summarized using frequency counts and percentages as well as with descriptive statistics. The treatments will be compared using CMH method with modified ridit score (SCORES=MODRIDIT option). An overall CMH test with modified ridit score will also be presented.

6.9 Safety Evaluation

Only descriptive analyses will be presented for the Safety population. No imputation will be made for missing safety data. Quantitative data for safety variables will be described by summary statistics for the original data as well as for the differences to baseline when it is appropriate. Frequency tables will be provided for qualitative data.

6.9.1 Extent of Exposure

Study treatment administration data will be presented with a by-subject listing.

6.9.2 Adverse Events

All AEs that occur during the study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after the date of the first study drug administration. AEs noted prior to the first study drug administration that worsen after baseline will also be reported as AEs and included in the summaries.

TEAEs will be summarized by treatment group, the number of subjects reporting a TEAE, system organ class, preferred name, severity, relationship to study treatment (causality), and seriousness. When summarizing TEAEs by severity and relationship, each subject will be counted once within a system organ class or a preferred term by using the event with the highest severity and greatest relationship within each classification.

Serious AEs (SAEs) will be summarized.

The number and percent of subjects who experience any event, by System Organ Class (SOC), and by Preferred Term (PT) will be displayed by treatment group for the Safety population.

All adverse events and all serious adverse events will be presented in individual listings. In addition, a list of subjects who prematurely discontinue from the study due to an AE will be provided.

6.9.3 Clinical Laboratory Evaluation

Urine pregnancy tests will be presented in a by-subject listing.

Urine drug screens and cotinine tests taken during screening and presurgery will be presented in a by-subject listing.

6.9.4 Other Observations Related to Safety

6.9.4.1 Vital Signs

Vital signs data for blood pressure, pulse rate, and respiratory rate will be summarized using descriptive statistics by treatment group for both the observed values and change from baseline values.

A by-subject listing will be presented of all vital signs data.

6.9.4.2 Physical Examination

Physical examination data will be presented in a by-subject listing.

6.9.4.3 ECG Measurements

Not applicable to this study.

7. DETERMINATION OF SAMPLE SIZE

The objective of this study is to establish superiority of naproxen sodium 440 mg over 24 hours compared to ibuprofen 400 mg over 24 hours with respect to the time to rescue medication.

CCI [redacted] A total of 385 subjects will be randomized into the study if a drop-out rate of 5% is assumed.

8. CHANGES IN THE PLANNED ANALYSES

There are no changes in the planned analyses.

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