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Number of plates: 4
Names of plates: "(Cyan) (Magenta) (Yellow) (Black) "

Environment

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Protocol CCSPAA001068

A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE- CONTROLLED, PROOF OF CONCEPT STUDY TO EVALUATE TWO STRENGTHS OF CONCOMITANTLY DOSED NAPROXEN SODIUM WITH ACETAMINOPHEN, COMPARED WITH NAPROXEN SODIUM, HYDROCODONE/ACETAMINOPHEN AND PLACEBO IN POSTOPERATIVE DENTAL PAIN

Statistical Analysis Plan (SAP)

Version Date: December 3rd, 2019

CONTENTS

1 INTRODUCTION

As stated in the protocol:

The combination of naproxen sodium and acetaminophen (paracetamol) is not marketed in the United States. The investigational product will involve concomitantly administered commercial formulations of naproxen sodium and acetaminophen.

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, naproxen sodium 220 mg 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 [1]. 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, 220 mg naproxen sodium is approximately equivalent to 200 mg naproxen [2].

Acetaminophen has been available in the United States (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 [3,4].

There are currently no fixed combination products containing acetaminophen and naproxen sodium available on the US market. Fixed combinations of acetaminophen and naproxen sodium are available in countries outside of the US, including the Dominican Republic, Ecuador, India, Mexico, Peru, and countries in Central America.

The current study will evaluate the analgesic efficacy, safety, onset and duration of concomitantly administered naproxen sodium 440 mg with acetaminophen 1000 mg and naproxen sodium 220 mg with acetaminophen 650 mg, compared to a fixed combination of hydrocodone 10 mg + acetaminophen 650 mg, naproxen sodium 440 mg and placebo.

1.1 Study Objectives

As stated in the protocol:

Primary Objective:

- *To evaluate relative efficacy of two strengths of concomitantly administered naproxen sodium and acetaminophen versus hydrocodone 10 mg + acetaminophen / 650 mg, on self-assessed pain over 12 hours.*

Secondary Objective:

- *To evaluate relative efficacy of two strengths of concomitantly administered naproxen sodium and acetaminophen versus naproxen sodium, on self-assessed pain over 12 hours.*

[redacted]

1.2 Study Design

As stated in the protocol:

This is a randomized, double-blind, placebo- and active- controlled, parallel-group study to evaluate the analgesic efficacy, and safety profile of the following strengths of naproxen sodium (NPX) /acetaminophen (APAP) administered concomitantly as a single dose:

- *440 mg of naproxen sodium with 1000 mg acetaminophen*
- *220 mg of naproxen sodium with 650 mg acetaminophen*

Subjects will undergo surgical removal of up to four third molars, of which, two must be mandibular impactions. Both maxillary third molars may be removed regardless of impaction level. Supernumerary teeth may also be removed. The mandibular third molars must meet one of the following criteria and must not result in an overall surgical trauma rating of severe on a mild, moderate, or severe scale:

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

For the purposes of this study, a full impaction is being defined as at least 90% imbedded in the alveolar bone of the mandible. The oral surgeon will make this judgement by visual examination of the panorex x-ray.

Approximately 288 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 five treatment groups in a 2:2:2:2:1 allocation ratio:

- *440 mg of naproxen sodium with 1000 mg acetaminophen* [redacted]
- *220 mg of naproxen sodium with 650 mg acetaminophen* [redacted]
- *10 mg hydrocodone + 650 mg acetaminophen (administered as two hydrocodone and acetaminophen tablets 5 mg/325 mg and two placebo tablets)*
- *naproxen sodium 440 mg* [redacted]
- *Placebo (administered as four placebo tablets)*

All treatments will be administered as a single dose. Rescue analgesic medication (tramadol 50 mg, 1-2 tablets every 6 hours as needed for pain) will be available for subjects as needed. Subjects who do not experience pain relief after dosing will be encouraged but not required to wait at least 1.5 hours before using rescue medication.

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. 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, and hourly from 2 through 12 hours (± 5 minutes) post dose as well as at the time of rescue [redacted]

Subject global evaluation of the investigational product will be collected at 12 hours or at the time of rescue medication (whichever occurs first), or at the time of subject withdrawal with a 0-4 rating scale: (0) poor, (1) fair, (2) good, (3) very good, and (4) excellent.

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 day 7 and 10.

Table 1: Schedule of Activities

	Screening	Baseline (Day of Surgery)	Hours Post-Dose	Follow-Up Call
Procedures	**Day -30 to 1**	**Day 1**	**0 to 12 hours**	**Days 7 - 10**
Written informed consent and/or assent	X			
Demography (including age)	X			
Inclusion / Exclusion Assessment	X[1]	X		
Significant medical history	X[1]	X		
Vital signs[2]	X[1]	X		
Physical Exam (Height, weight and BMI)	X			
Urine pregnancy test[3]	X[1]	X		
Urine drug screen[11]	X[1]	X		
Serology[4]	X			
Dental extraction surgery		X		
Categorical and Numerical Pain Intensity		X[5]		
Randomization criteria		X		
Investigational product administration		X		
[redacted]			[redacted]	
Pain intensity and pain relief ratings[6]			X	
Pulse Oximetry[12]	X	X	X	
[redacted]			[redacted]	
Rescue therapy			X[7]	
Subject Global Evaluation			X[8]	
Prior and Concomitant Therapy	X	X	X	X
Safety monitoring	X	X[9]	X[9]	X[9]
Subject Disposition			X[10]	
Follow up interview				X

[1] Baseline assessments collected on Electronic Case Report Form (eCRF);
[2] Blood pressure, heart rate, respiratory rate, oral temperature;
[3] Females of childbearing potential;
[4] HIV antibody, hepatitis B surface antigen (HBsAg) , hepatitis C virus antibody (anti-HCV);
[5] Scored within 4.5 hours after last stitch from dental surgery;
[6] Pain intensity and pain relief ratings collected: 0.25, 0.5, 0.75, 1, 1.25, 1.5, and hourly 2 - 12 hours (± 5 minutes) post dose. If subject requests rescue medicine, ratings will be collected before administration. [redacted]
[7] Subjects encouraged to wait at least 1.5 hours after investigational product administration before using rescue medicine;
[8] Evaluation at 12 hours or time of rescue medication (whichever occurs first), or at time of early termination; if subject is discontinued or withdrawn <12 hours after dosing;
[9] Collection of AEs and report of pregnancy (subject instructed to report pregnancy to PI within 30 days post dose)
[10] End of Study is at the time of follow up call or at time of subject withdrawal;
[11] Minimum requirements for urine drug testing for screening & day of surgery: cocaine, tetrahydrocannabinol, opioids (e.g., buprenorphine, oxycodone, methadone, and morphine), benzodiazepines, and amphetamines.

[12] Pulse oximetry will be performed at baseline and when pain ratings are collected (0.25, 0.5, 0.75, 1, 1.25, 1.5, and hourly 2 - 12 hours (± 5 minutes) post dose).

[redacted]

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 set by at least 5% of the subjects. The per-protocol set will exclude subjects who took rescue medication within 90 minutes after dosing, 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 Pain Intensity Difference from 0 to 6 hours (SPID 6)
- Time weighted Pain Intensity Difference from 0 to 12 hours (SPID 12)

Secondary Efficacy Endpoint

- Time weighted sum of pain relief from 0 to 6 hours (TOTPAR 6)
- Time weighted sum of pain relief from 0 to 8 hours (TOTPAR 8)
- Time weighted sum of pain relief from 0 to 12 hours (TOTPAR 12)
- Time weighted of Pain Intensity Difference from 0 to 8 hours (SPID 8)
- Pain relief (PAR) and pain intensity difference (PID) scores at individual time points
- Subject Global Evaluation at 12 hours or time of rescue medication, whichever occurs first

[redacted]

4.2 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 Investigator [redacted]. Pulse oximetry will be monitored and recorded at baseline and when pain ratings are collected.

- 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

4.3 Covariates

Baseline pain (moderative or severe) score, gender and treatment group will be used as covariates in the model for analysis related to SPID 6, SPID 8, SPID 12, [redacted] TOTPAR 6, TOTPAR 8, TOTPAR 12, PAR and PID scores and subject global evaluation.

4.4 DATA COMPUTATIONS AND DATA IMPUTATIONS

4.4.1 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 0-6, 0-8, 0-12[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.

[redacted]

5 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

5.1 Statistical Hypotheses

The primary hypothesis for each of the primary endpoints is

H_0: $\mu_1 = \mu_2$
H_1: $\mu_1 \neq \mu_2$

where μ_1 and μ_2 are the means for each investigational product, respectively. These same hypotheses apply to other endpoints based on pain intensity scores, pain relief scores, or global evaluation.

[redacted]

5.2 Statistical Decision Rules

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

1. NPX 440 mg/APAP 1000 mg vs. placebo
2. NPX 220 mg/APAP 650 mg vs. placebo
3. Hydrocodone 10 mg/APAP 650 mg vs. placebo
4. NPX 440mg vs. placebo
5. NPX 440 mg/APAP 1000 mg vs. Hydrocodone 10 mg/APAP 650 mg
6. NPX 220 mg/APAP 650 mg vs. Hydrocodone 10 mg/APAP 650 mg
7. NPX 440 mg/APAP 1000 mg vs. NPX 440mg
8. NPX 220 mg/APAP 650 mg vs. NPX 440mg
9. NPX 440 mg/APAP 1000 mg vs. NPX 220 mg/APAP 650 mg

Given the exploratory nature of the study, no multiple comparisons procedure will be applied. All statistical tests of hypotheses will be two-sided and employ a significance level of α=0.05.

5.3 STATISTICAL METHODS

5.3.1. Pain Intensity Difference, Pain Relief and Subject Global Evaluation

For pain intensity difference, analysis will be performed for SPID 6, SPID 8, SPID 12, [redacted] and pain intensity difference (PID) at each time-point. For pain relief scores, analysis will be performed for TOTPAR 6, TOTPAR 8, TOTPAR 12, [redacted] and pain relief scores (PAR) at each time point.

Each of these variables (SPID 6, SPID 8, SPID 12, [redacted] TOTPAR 6, TOTPAR 8, TOTPAR12, [redacted] PID, PAR and subject global evaluation) 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. Missing data will not be imputed for subject global evaluation.

The following is sample SAS code for analysis of variance:

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

[redacted]

[redacted]

5.3.4. Subgroup Analyses

Primary endpoints (SPID 6 and SPID 12) will be analysed 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.

[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. 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 12-hour assessment period. In addition, those medications taken after the 12-hour assessment

period through the follow-up interview for an AE will be considered concomitant medications.

Medications taken after the 12-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, pulse, respiratory rate, and blood pressure) collected at baseline will be summarized (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

5.6.3 Pulse Oximetry

Pulse oximetry (oxygen saturation) collected at baseline and post-baseline will be summarized (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

6. CHANGES FROM PROTOCOL

For secondary efficacy endpoints based on TOTPAR, analysis will also be performed for TOTPAR 4-12, 6-12 and 8-12.

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	Time weighted Pain Intensity Difference (SPID)	All Randomized Subjects
Table 14.2.2	Time Weighted Total Pain Relief Scores (TOTPAR)	All Randomized Subjects
Table 14.2.3	Pain Intensity Difference (PID) from baseline At Each Time Point	All Randomized Subjects
Table 14.2.4	Pain Relief Score (PAR) At Each Time Point	All Randomized Subjects
Table 14.2.5	Subject Global Evaluation of Study Medication	All Randomized Subjects
[redacted]		
Table 14.2.9	Time weighted Pain Intensity Difference (SPID) – Age < 18 Years Old	All Randomized Subjects
Table 14.2.10	Time weighted Pain Intensity Difference (SPID) – Age >= 18 Years Old	All Randomized Subjects

Table 14.2.11	Time weighted Pain Intensity Difference (SPID) – Female	All Randomized Subjects
Table 14.2.12	Time weighted Pain Intensity Difference (SPID) – Male	All Randomized Subjects
Table 14.2.13	Time weighted Pain Intensity Difference (SPID) – Whites	All Randomized Subjects
Table 14.2.14	Time weighted Pain Intensity Difference (SPID) – Non-Whites	All Randomized Subjects
Table 14.2.15	Time weighted Pain Intensity Difference (SPID) – Moderate Baseline Pain	All Randomized Subjects
Table 14.2.16	Time weighted Pain Intensity Difference (SPID) – Severe Baseline Pain	All Randomized Subjects
Table 14.2.17	Time weighted Pain Intensity Difference (SPID)[a]	Per Protocol Analysis Set
[redacted]	[redacted]	[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

Table 14.3.12	Summary of Pulse Oximetry	Safety Analysis Subjects

FIGURES:

Figure 14.1	SPID by Treatment	All Randomized Subjects
Figure 14.2	TOTPAR by Treatment	All Randomized Subjects
Figure 14.3	Pain Intensity Difference (PID) from Baseline at Each Time Point	All Randomized Subjects
Figure 14.4	Pain Relief Score (PAR) at Each Time Point	All Randomized Subjects
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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
[redacted]	[redacted]	[redacted]
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
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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
16.2.6.8	Pulse Oximetry	All Randomized
16.2.7	Follow-up Interview	All Randomized

[redacted]