A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED, EFFICACY AND SAFETY STUDY OF A TEST NAPROXEN SODIUM 220 MG TABLET IN POSTOPERATIVE DENTAL PAIN

CCSPAA000457

Statistical Analysis Plan (SAP)

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CONTENTS

1 INTRODUCTION

Naproxen is a propionic acid derivative and nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The mechanism of action of naproxen involves inhibition of cyclooxygenase enzymes resulting in decreased prostaglandin synthesis. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen. Naproxen sodium products have been available over-the-counter (OTC) for the indications of fever reduction and relief of minor aches and pains in several countries for many years. According to the Drug Facts for [redacted], dosing for adults and children 12 years of age and older is one 220 mg dosage unit (e.g., tablet, caplet, capsule) every 8-12 hours, and for the first dose, may take two 220 mg units within the first hour. [redacted]

Clinical efficacy and safety studies have not yet been conducted on the [redacted] formulation of naproxen sodium. The current study will evaluate the analgesic onset, efficacy and safety of a single 440 mg dose of [redacted] naproxen sodium (administered as two 220 mg tablets) compared to two currently marketed [redacted] formulations of naproxen sodium and placebo after third molar dental extractions. The postoperative dental pain model is a validated model of acute pain that is widely used to study analgesic efficacy of compounds.

1.1 Study Objectives

To evaluate analgesic onset, efficacy, and safety of a single dose of 440 mg of naproxen sodium administered as two Test Naproxen Sodium 220 mg tablets (Test NPX) compared with two commercial naproxen sodium products (two [redacted] 220 mg tablets and two [redacted] 220 mg [redacted] capsules) and placebo 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 440 mg of naproxen sodium administered as two Test NPX 220 mg tablets compared with two commercial products and placebo over a 12-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

Pain assessments will be based on subject self-report. Subjects who meet the randomization criteria (post-surgical pain of moderate to severe on the four-point categorical pain scale [0-no pain, 1-mild pain,2-moderate pain, 3-severe pain], 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. This PI-NRS will be within 5 minutes prior to study medication dosing and will be considered the time 0 pain intensity assessment.

Approximately 500 subjects will receive a single 440 mg dose of either Test NPX, [redacted] tablets, [redacted] capsules, or placebo in a 3:3:3:1 allocation ratio and will be stratified according to gender and baseline pain rating (moderate or severe). To maintain the double-blind nature of the study, an independent third party will administer study drug to blindfolded subjects. 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). [redacted] 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 1.5 hour before using rescue therapy. [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 Day 6 – 10 of the study.

Table 1: Schedule of Activities

	Screening	Baseline (Day of Surgery)	Hours Post-Dose	Follow-Up Call/End of Study
Procedures	**Day -30 to 1**	**Day 1**	**0 to 12 hours**	**Day 6 - 10**
Written informed consent and/or assent	X			
Demography (including age)	X			
Inclusion / Exclusion Assessment	X	X		
Significant medical history	X	X		
Vital signs	X	X		
Physical Exam (Height, weight and BMI)	X			
Urine pregnancy test (Females of childbearing potential)	X	X		
Urine drug screen	X	X		
Serology	X			
Dental extraction surgery		X		
Baseline Pain Assessments (Categorical and PI-NRS)		X[1]		
Randomization criteria		X		
Investigational product administration		X		
Stopwatch Assessments (perceptible & meaningful pain relief)			X	
[redacted]			X	
Rescue therapy			X[3]	
[redacted]			X[4]	
Prior and Concomitant Therapy	X	X	X	X[5]
Safety monitoring[6]	X	X	X	X
Subject Disposition				X[7]

[1]Scored within 4.5 hours after last stitch from dental surgery; [redacted]; [3]Subjects encouraged to wait at least 1.5 hours after investigational product administration before using rescue medicine; [redacted] [5] Medications and other treatments taken after 12-hour assessment period through follow-up interview will be captured on source documents and only those taken for or associated with an AE will be recorded in the CRF; [6] Collection of AEs and report of pregnancy; [7] End of Study for each subject is defined as the follow-up phone call or early termination.

2 INTERIM ANALYSES

No interim statistical analysis is planned for this trial.

3 ANALYSIS SETS

3.1 Primary Analysis Set

The primary analysis set for the efficacy analyses will be all randomized subjects.

Subjects who received different treatment from their assigned treatment according to the sponsor-intended treatment decodes will be analyzed based on the actual received treatment.

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 primary analysis 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 having potential substantial impact on the efficacy evaluation. The 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

- Time to perceptible pain relief (TPPR)– recorded using perceptible pain relief 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 relief 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

-
-
-

4.2 Efficacy Endpoints

Primary efficacy endpoint

- Time to confirmed perceptible pain relief (TCPR)

Secondary efficacy endpoints

- Percentage of subjects with confirmed perceptible pain relief from 45 minutes to successively earlier minutes in one-minute increments (Test NPX versus PBO)

Tertiary efficacy endpoints

-
-
-
-
-
-

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 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

4.4 Covariates

No covariate variable will be adjusted in the analyses.

5 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

5.1 Statistical Hypotheses

The primary hypothesis is

$H_0 : S_1(t) = S_2(t)$ (all t)

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

where S_1(t) and S_2(t) are the survival functions of each compared treatment, respectively. For the primary endpoint TCPR [redacted] survival functions will be compared between Test NPX and [redacted], between Test NPX and [redacted] Tablet, and between each naproxen product and placebo.

5.2 Statistical Decision Rules

To control the family-wise Type I error rate at 0.05 for primary and secondary endpoints, the fixed sequence testing with fallback method will be used [Wiens 2003]. Table 2 presents the order of the tests and the assigned α values for each ordered test. Testing will commence with an assigned alpha = 0.049 and an alpha value of 0.001 will be reserved for the comparison of Test NPX and placebo on the percentage of subjects with confirmed perceptible relief from 45 minutes to successively earlier minutes in one-minute increments.

Table 2: Order of Tests and Assigned Alpha Values

	Pre-Assigned α-value	**α-value available if previous test positive**	**α-value available if previous test(s) negative**
TCPR: Test NPX vs PLACEBO	0.049	Not Applicable	Not Applicable
TCPR: Test NPX vs [redacted]	None	0.049	None
TCPR: Test NPX vs [redacted]	None	0.049	None
Percentage of subjects with confirmed perceptible pain relief from 45 minutes to successively earlier minutes in one-minute increments: Test NPX vs Placebo	0.001	0.05	0.001

The four tests in the above family will be conducted as follows: The survival functions for TCPR will be compared between Test NPX and PBO. If it is non-significant at the 0.049 level, then the first test and the following two tests will be failed and the last test (the percentage of subjects with CPR) will be tested at the 0.001 level. If the first test is significant at the 0.049 level, then the second test, the comparison of survival functions for TCPR between Test NPX and [redacted], will be compared at the 0.049 level and the following tests will follow the same pattern as for the first test. If the first 3 tests are significant at the 0.049 level, the last test, the percentage of subjects with CPR, will be tested at the 0.05 level.

5.3 Statistical Methods

5.3.1 **Time to Confirmed Perceptible Pain Relief (TCPR)** [redacted] 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. [redacted] subjects who do not have relief by 12 hours, who take any type of rescue medication before having relief, or who discontinue before having relief will have time to relief set to 12 hours and be censored at 12 hours. Subjects who take rescue medication after confirmed perceptible pain relief will not be censored Subjects who received lidocaine 2% after dosing will be treated as subjects taking rescue medication.

[redacted] TCPR[redacted] will be analysed using 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 method for each treatment. The survival functions will be compared using the Wilcoxon test.

The estimation of the survival functions and the comparison of the survival functions between treatments 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;
```

Sensitivity analyses will be conducted for TCPR to assess the impact of different censoring.

- To assess the impact of censoring at the time of rescue medication for subjects not having meaningful relief, the following approach will be used: For subjects taking rescue medication before having confirmed perceptible pain relief, TCPR will be censored at the time of rescue medication. For those subjects who discontinue before having confirmed perceptible pain relief, TCPR will be censored at the time of discontinuation, approximated using the last observed timepoint [redacted]. For subjects having perceptible relief but not meaningful relief, TCPR will be censored at 12 hours.
- To assess the impact of censoring at the time of perceptible relief for subjects not having meaningful relief, the following approach will be used: For subjects having perceptible relief but not meaningful relief, TCPR will be censored at the time of perceptible relief. For subjects not experiencing TCPR who discontinue before 12 hours, TCPR will be censored at the time of discontinuation, [redacted]. For subjects not experiencing TCPR who receiving rescue medication, TCPR will be censored at 12 hours.

5.3.2 Earliest Statistically Significant Separation of Test NPX and Placebo on Percentage of Subjects with Confirmed Perceptible Relief

The earliest time of separation between Test [redacted] and PBO will be established by comparing the percentage of subjects with confirmed perceptible pain relief starting from 45 minutes to successive earlier minutes in one-minute increments, until statistical significance is no longer achieved. At each one-minute increment, each subject will be categorized as either having experienced confirmed perceptible pain relief by that time or not. The resulting binary response at each time point will be analyzed using logistic regression analysis.

The following is 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 [redacted]

[redacted]

5.3.5 [redacted]

[redacted]

5.3.6 [redacted]

[redacted]

5.3.7 [redacted]

[redacted]

5.3.8 **Subgroup Analyses**

Time to confirmed perceptible relief 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). The survival function and the median survival time will be estimated by the Kaplan-Meier method within each subgroup.

5.4 DEMOGRAPHIC AND BASELINE CHARACRISTICS

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 coded. Previous medications will be those that were discontinued before the surgery day. Concomitant medications will be those continued through, or started on, the surgery day and up through the 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 summarised (number of subjects, mean, standard deviation, median, minimum and maximum) by treatment group.

6. REFERENCES

1. Wiens, BL. A fixed sequence Bonferroni procedure for testing multiple endpoints. Pharmaceutical Statistics 2003; 2:211-215.

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	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief	All Randomized Subjects
Table 14.2.1.1	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief	Per-Protocol Subjects
Table 14.2.1.2	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Moderate Baseline Pain	All Randomized Subjects
Table 14.2.1.3	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Severe Baseline Pain	All Randomized Subjects
Table 14.2.1.4	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Male	All Randomized Subjects
Table 14.2.1.5	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Female	All Randomized Subjects
Table 14.2.1.6	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age < 18 Years Old	All Randomized Subjects
Table 14.2.1.7	Kaplan-Meier Estimates of The Cumulative	All Randomized Subjects

	Percentage of Subjects with Confirmed Perceptible Pain Relief – Age >= 18 Years Old	
Table 14.2.1.8	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – White Subjects	All Randomized Subjects
Table 14.2.1.9	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Non-White Subjects	All Randomized Subjects
Table 14.2.1.10	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Sensitivity Analysis 1	All Randomized Subjects
Table 14.2.1.11	Kaplan-Meier Estimates of The Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Sensitivity Analysis 2	All Randomized Subjects
Table 14.2.1.12	[redacted]	All Randomized Subjects
Table 14.2.2	[redacted]	All Randomized Subjects
Table 14.2.3	Percentage of Subjects with Confirmed Perceptible Pain Relief at Specified Times – Test NPX vs Placebo	All Randomized Subjects
Table 14.2.4	[redacted]	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

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	Safety Analysis Subjects

	One or More Treatment Groups) Treatment-Emergent Adverse Events	
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 Withdrawals Due to Adverse Events By System Organ Class and MedDRA Preferred Term	Safety Analysis Subjects

FIGURES:

Figure 14.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief	All Randomized Subjects
Figure 14.1.1	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Moderate Baseline Pain	All Randomized Subjects
Figure 14.1.2	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Severe Baseline Pain	All Randomized Subjects
Figure 14.1.3	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Male	All Randomized Subjects
Figure 14.1.4	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Female	All Randomized Subjects
Figure 14.1.5	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age < 18 Years Old	All Randomized Subjects
Figure 14.1.6	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Age >= 18 Years Old	All Randomized Subjects
Figure 14.1.7	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – White Subjects	All Randomized Subjects
Figure 14.1.8	Kaplan-Meier Estimates of the Cumulative Percentage of Subjects with Confirmed Perceptible Pain Relief – Non-White Subjects	All Randomized Subjects
Figure 14.2	[redacted]	All Randomized Subjects

Figure 14.3	[redacted]	All Randomized Subjects
Figure 14.4	[redacted]t	All Randomized Subjects
Figure 14.5	[redacted]	All Randomized Subjects
Figure 14.6	[redacted]	All Randomized Subjects
Figure 14.7	[redacted]	All Randomized 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	[redacted]	All Randomized
16.2.5.2	[redacted]	All Randomized
16.2.5.3	[redacted]	All Randomized
16.2.5.4	[redacted]	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

APPENDIX 3: DATA PATTERN AND CENSORING

Pattern	TCPR (Primary analysis)	TCPR (Sensitivity analysis 1)	TCPR (Sensitivity analysis 2)	[redacted]
1. AB	A	A	A	
2. ABR	A	A	A	
3. ABD	A	A	A	
4. A	*12hr	*12hrs	*A	
5. AR	*12hr	*R	*A	
6. AD	*12hr	*D	*A	
7. R (or BR)	*12hr	*R	*12hr	
8. D (or BD)	*12hr	*D	*D	
9. None	*12hr	*12hr	*12hr	

Notation: Time of Stopwatch 1-A ;Time of Stopwatch 2- B ;Time to Rescue - R ;Time to Discontinue: D (last observed time point)
*censored