



Protocol B5061002

A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, FULL FACTORIAL, SAFETY AND EFFICACY STUDY COMPARING THE ANTIPYRETIC EFFECTS OF A SINGLE ORAL DOSE OF IBUPROFEN (IBU) 250 MG/ ACETAMINOPHEN (APAP) 500 MG CAPLETS TO IBU 250 MG AND APAP 500 MG CAPLETS IN HEALTHY MALE VOLUNTEERS WITH FEVER INDUCED BY AN ENDOTOXIN

**Statistical Analysis Plan
(SAP)**

Version: 2.0

Date: 01-Nov-2017

DMB02-GSOP-RF02 3.0 STATISTICAL ANALYSIS PLAN TEMPLATE 30-Jun-2015

TABLE OF CONTENTS

LIST OF TABLES4

1. VERSION HISTORY5

2. INTRODUCTION5

 2.1. Study Objectives5

 2.2. Study Design6

 2.2.1. Study Treatments7

 2.2.2. Schedule of Activities7

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS 12

 3.1. Primary Endpoint12

 3.2. Secondary Endpoints13

CCI [REDACTED]

 3.4. Baseline Variables15

 3.4.1. Demographic Data15

 3.4.2. Endotoxin Administration Data15

 3.4.3. Baseline Temperature, Vital Signs and ECG16

 3.4.4. Prior Medical Conditions and Medical History16

 3.4.5. Concomitant Medications/Non-Drug Treatments (except Rescue Medication)16

 3.4.6. Rescue Medication17

 3.5. Safety Endpoints17

 3.5.1. Adverse Events17

 3.5.2. Laboratory Data18

 3.5.3. Vital Signs18

 3.5.4. Electrocardiogram19

 3.5.5. Physical Examination21

4. ANALYSIS SETS21

 4.1. Primary Analysis Set21

CCI [REDACTED]

 4.3. Safety Analysis Set21

CCI [REDACTED]

CCI [Redacted]

5. GENERAL METHODOLOGY AND CONVENTIONS.....22

5.1. Hypotheses and Decision Rules22

5.2. General Methods23

5.2.1. Analyses for Continuous Data23

5.2.2. Analyses for Time to Event Data.....23

5.2.3. Analysis of Interval-Censored Time to Event Data.....23

5.2.4. Analyses of Ordinal Categorical Data24

CCI [Redacted]

6. ANALYSES AND SUMMARIES25

6.1. Primary Endpoint25

6.1.1. Weighted Sum of Temperature Difference From Baseline Over 0-8 Hours (WSTD0-8) – Primary Efficacy Endpoint25

6.1.2. Sensitivity Analysis of Primary Efficacy Endpoint.....26

6.2. Secondary Endpoints.....26

6.2.1. Weighted Sum of Temperature Difference From Baseline to 2, 4, and 6 Hours and from 6-8 Hours (WSTD0-2, WSTD0-4, WSTD0-6, and WSTD6-8) – Secondary Endpoints in Continue Data Format26

6.2.2. Time To Return To “Normal Temperature” - Secondary Endpoints in Interval-Censored Time-to-Event Data Format27

6.2.3. Time to Rescue Medication - Secondary Endpoints in Time-to-Event Data Format27

CCI [Redacted]

6.4. Subset Analyses.....29

6.5. Baseline and Other Summaries and Analyses29

6.5.1. Baseline Summaries.....29

6.5.1.1. Demographics.....29

6.5.1.2. Baseline Temperature.....29

6.5.1.3. Baseline Vital Signs and Baseline QTcF Interval (msec)29

6.5.1.4. Prior Medical Conditions and Medical History29

6.5.2. Study Conduct and Subject Disposition29

6.5.2.1. All Subjects Dosed with Endotoxin29

6.5.2.2. Subject Randomized to Study Medication Treatment.....30

6.5.3. Study Medication Exposure.....30

6.5.4. Concomitant Medications and Non-Drug Treatments.....30

6.5.5. Rescue Medication.....30

6.6. Safety Summaries and Analyses30

6.6.1. Adverse Events31

6.6.2. Laboratory Data32

6.6.3. Vital Signs32

6.6.4. Electrocardiogram.....32

6.6.5. Physical Examination32

7. INTERIM ANALYSES33

8. REFERENCES33

CCI

[Redacted]

[Redacted]

[Redacted]

LIST OF TABLES

Table 1 Summary of Major Changes in the SAP Amendment.....5

1. VERSION HISTORY

The initial version of the statistical analysis plan (SAP) dated on 23-Mar-2016 for study B5061002 is being amended. This SAP amendment is based on all the amendments made to the protocol up to Protocol Amendment 6 dated on 21-Sep-2017. Summary of major changes are presented below.

Table 1 Summary of Major Changes in the SAP Amendment

SAP Version	Version Date	Summary of Major Changes and Rationale
1	23-Mar-2016	Not applicable
2	01-Nov-2017	<p>Changes made based on amendments to protocol:</p> <ul style="list-style-type: none"> • Additional efficacy endpoints of WSTD0-2, WSTD0-4, and WSTD0-6 were added (per Protocol Amendment 2); • Methods for reporting Endotoxin dosing data during Endotoxin administration period (per Protocol Amendments 3 and 4); • Change of the primary analysis set from ITT to modified intent-to-treat (mITT) analysis set (per Protocol Amendment 6); • Add time from RSE first full dose to randomization as a covariate in the ANCOVA model (per Protocol Amendment 6); • Various clarifications and minor revisions are made on, for example, baseline variables and safety summaries.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study B5061002. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

Note: in this document any text taken directly from the protocol is *italicized*.

2.1. Study Objectives

The objective of this study is to evaluate the safety and antipyretic efficacy of single, oral doses of IBU/APAP 250 mg/500 mg caplets versus APAP 500 mg caplets, IBU 250 mg caplets, and placebo in subjects in whom pyrexia has been induced by the intravenous administration of a Reference Standard Endotoxin (RSE).

2.2. Study Design

This study is a single-center, 8-hours, single-dose, inpatient, double-blind, randomized, placebo-controlled, full-factorial, parallel arm, safety and efficacy study in healthy male subjects 18 to 55 years of age (inclusive). Approximately 290 subjects will be enrolled in this study.

The study is comprised of a screening visit and a study treatment period. The screening visit will occur within 28 days prior to the study treatment period. Subjects will remain at the research center during the study treatment period for approximately 36 hours over 2 days. Subjects will enter the study center on Day 0 and will remain in-house until after the completion of all study procedures on Day 1, at the investigator's discretion. Site personnel will conduct a safety follow up within 24 hours of discharge via a telephone call to the subject and again 14 calendar days after the last dose of study medication to ascertain if any Serious Adverse Events (SAEs) have occurred.

Fever will be induced in healthy male volunteers using RSE and temperature measurements will be taken throughout the study to monitor the subject's fever. Once subjects have received a dose of RSE, their oral temperature will continue to be monitored at the discretion of the investigator approximately every 5 minutes using an oral standardized electronic, digital thermometer. Subject temperatures from test dose till randomization will be recorded in the source document.

All endpoints for this study will be based on oral temperature measurements using a standardized electronic, digital thermometer. Oral temperatures will be recorded at the following times:

- *At screening and Day 0 to ensure the subjects are afebrile and eligible to participate in the study;*
- *Prior to administration of the test dose of RSE. This will be referred to as the “normal” temperature;*
- *Approximately 60 and 90 minutes (90 minutes if increase in temperature is $\leq 1^{\circ}\text{F}$ and subject experiences < 2 systemic symptoms) after the test dose of RSE in order to determine the full dose of RSE that the subject will receive. After approximately 60 or 90 min (90 min if increase in temperature is $\leq 1^{\circ}\text{F}$ and subject experiences < 2 systemic symptoms) of receiving the test dose of RSE, subjects who tolerate the test dose of RSE will receive a full dose of RSE;*
- *After the full dose of RSE when the subject has reached an oral temperature of $\geq 100.5^{\circ}\text{F}$. The subject's oral temperature will need to be $\geq 100.5^{\circ}\text{F}$ in order to be randomized to study medication. If the subject's oral temperature is not $\geq 100.5^{\circ}\text{F}$, additional oral temperature measurements will be taken and recorded in the source document approximately every 5 minutes until the subject reaches this temperature or is given an additional dose of RSE. The time between the subject reaching an oral temperature of $\geq 100.5^{\circ}\text{F}$ and being dosed should not exceed 10 minutes;*

- *Immediately prior to study medication dosing after the subject has reached an oral temperature of $\geq 100.5^{\circ}\text{F}$ and has been randomized. This will be referred to as the “**baseline**” temperature;*
- *At 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 and 110 minutes post dose and at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 and 8 hours post dose;*
- *At the discretion of the investigator, additional oral temperatures may be taken by the investigator or delegated site staff members more frequently to monitor the subject’s oral temperature. If the subject’s temperature exceeds 102.5°F , subjects may receive rescue medication. An oral temperature will be taken and recorded prior to rescue medication administration.*

Safety evaluations including adverse event (AE) monitoring, vital signs (blood pressure and pulse rate), and respiratory rate will be monitored throughout the study. At the end of the 8-hour post dose period or at the time of rescue medication (within 5 minutes) subjects will complete a global evaluation of study medication using a categorical rating scale where applicable, and then will be discharged from the study site.

2.2.1. Study Treatments

The study will consist of the following blinded treatments:

Study Treatments

Treatment Group	Treatment	Treatment Description
A	IBU 250 mg/ APAP 500 mg	2 IBU 125 mg/ APAP 250 mg caplets
B	APAP 500 mg	1 APAP 500 mg caplet + 1 placebo caplet
C	IBU 250 mg	2 IBU 125 mg caplets
D	Placebo	2 placebo caplets

2.2.2. Schedule of Activities

The schedule of baseline, efficacy, safety, and treatment activities across the study visits are listed in the following tables. For details of schedule visit activities, refer to protocol sections including “Schedule of Activities”.

increase in temperature is <1 °F and subject experiences <2 systemic symptoms) after the test dose of endotoxin in order to determine their full dose of endotoxin. After administration of a full dose of RSE, subjects will be monitored using the standardized, electronic digital thermometer until their oral temperature reaches 100.5°F. The subject's oral temperature will need to be ≥ 100.5 °F in order to be randomized to study medication. If the subject's oral temperature is not

≥ 100.5 °F, additional oral temperature measurements will be taken every 5 minutes until the subject reaches this temperature or is given an additional dose of RSE. Within 10 minutes of reaching this temperature, subjects will be randomized and their oral temperature will be recorded immediately prior to dosing with study medication (this will be known as their 'baseline' temperature). Oral temperatures will also be recorded at 10, 20, 30, 40, 50, 60, 70, 80, 90,

100 and 110 minutes after dosing and at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 and 8 hours after dosing. The following time windows will be allowed for each of the time points; the widths of ± 3 minutes for time points that are 10 minutes apart and ± 5 minutes for time points that are 30 minutes apart. An oral temperature will be taken and recorded in the CRF prior to subjects receiving rescue medication.

- e. Vital signs (Supine blood pressure and pulse rate) will be collected at Screening, Day 0, Day 1 prior to test dose of RSE, Day 1 prior to the full dose of RSE, Day 1 prior to additional 1 ng/kg dose of RSE if applicable and then every hour after dosing up until 8 hours after dosing and/or at early termination.
- f. Single, 12-lead ECGs will be collected at Screening, Day 1 prior to test dose of RSE administration, at the end of the 8-hour monitoring period and/or early termination.
- g. Respiratory Rate will be collected every hour after dosing up until 8 hours after dosing.
- h. A prophylactic dose of antiemetic (ondansetron 8 mg IV) will be given approximately 45 - 60 min after test dose of RSE administration.
- i. After the 0.5 ng/kg test dose administration of RSE, subjects will be monitored for approximately 60 - 90 minutes (90 minutes if increase in temperature is <1 °F and subject experiences <2 systemic symptoms) to verify the absence of a medically significant allergic or exaggerated systemic response. Subjects who tolerate the test dose will receive a full dose of RSE (see [Figure 1 of protocol](#) for RSE full dose details) and will be monitored or given additional dose of RSE until their body reaches an oral temperature of ≥ 100.5 °F on an oral thermometer. Subjects will continue to be monitored to verify the absence of a medically significant allergic or exaggerated systemic response.
- j. Lunch will be served at the investigator's discretion, approximately 4 hours after dosing. Lunch will consist of low-fat, room temperature food (ie, sandwiches) and room temperature water.
- k. Global Evaluation will be completed at 8-hours post-dose, at the time of rescue medication administration (within 5 minutes) or at the time of subject withdrawal (if applicable).
- l. Serious adverse events will be reported starting at screening after informed consent has been signed and non-serious adverse events will be recorded starting on Day 1 after dosing. AEs and SAEs related to endotoxin will be collected after endotoxin administration on Day 1.
- m. Subjects will be discharged from study unit at the investigator's discretion after all study procedures are complete.
- n. Study site personnel will conduct a safety follow-up within 24 hours of discharge via a telephone call to the subject to ascertain if any AEs or SAEs have occurred.
- o. Study site personnel will conduct a safety follow-up 14 calendar days after last dose via a telephone call to the subject to ascertain if any SAEs have occurred.
- * Subjects may be administered an additional 1 ng/kg bolus dose of endotoxin at the discretion of the investigator if applicable (Subject's vitals will be taken and recorded immediately prior to receiving the additional dose of RSE)

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

The following definitions and conventions will be used in the derivation of endpoints described in Section 3:

- Baseline temperature (and time) will be defined as the highest oral temperature assessment between randomization time and study medication dose time.
- The time of administration of study medication will be considered time 0.
- Temperature difference from baseline (at each assessment time point) is defined as the baseline temperature minus the post baseline temperature so that a higher positive value is indicative of a greater improvement.
- The time-weighted sum of temperature difference (or deduction) from baseline over time interval $t_0 - t_T$ will be derived as $\sum_1^T (t_i - t_{i-1}) * x_i$, where t_0 is the time of baseline assessment and x_1, x_2, \dots, x_n are the temperature differences (or deduction) from baseline at scheduled post-treatment assessments time t_1, t_2, \dots, t_n .
- ‘Normal temperature’ is defined as the last non-missing oral temperature measurement prior to or at the time the subject takes the first RSE test dose.
- The time of end of the study for a subject who is not discontinued is defined as the last time the subject performed the global assessment of study medication or last temperature assessment time whichever occurs last.
- The time of end of the study for a subject with early withdrawal due to adverse events is defined as the onset time for the adverse event(s) that lead to the subject’s discontinuation.
- The time of end of the study for a subject with early withdrawal due to other reasons (i.e. not adverse events) is defined as the time the subject performed the global assessment of study medication at discontinuation.
- Subjects are allowed to receive rescue medication(s) at any time during the study for the treatment of fever. The rescue medication is defined as medication(s) received for the treatment of fever during the time period from the administration of study medication to the time of end of the study.

3.1. Primary Endpoint

The primary endpoint for this study is the weighted sum of temperature difference from baseline to 8 hours (WSTD0-8), weights being equal to the time elapsed between each two consecutive time points.

Weighted sum of temperature difference (or deduction) from baseline over 0-8 hours (WSTD0-8) will be derived using the temperature difference from baseline at each post study treatment assessment time point over 8 hours (i.e., baseline temperature minus analysis value of temperature derived per method of [Section 5.3](#) at 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 and 110 minutes, and at 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 and 8 hours post-treatment scheduled time points).

The primary efficacy endpoint will be analyzed by the method specified in [Section 5.2.1](#) and summarized as described in [Section 6.1.1](#).

3.2. Secondary Endpoints

The secondary efficacy endpoints are:

- *Weighted sum of temperature differences from baseline to 2 hours (WSTD0-2);*
- *Weighted sum of temperature differences from baseline to 4 hours (WSTD0-4);*
- *Weighted sum of temperature differences from baseline to 6 hours (WSTD0-6);*
- *Time to return to “normal temperature” (time until fever clearance);*
- *Time to rescue medication;*
- *Weighted sum of temperature differences from baseline during the last two hours of observation (6-8 hours) (WSTD6-8).*

Weighted sum of temperature difference WSTD0-2, WSTD0-4, WSTD0-6 and WSTD6-8 will be derived as sum of temperature difference (or deduction) from baseline over time intervals of 0-2 hours, 0-4 hours, 0-6 hours, and over 6-8 hours, respectively.

These secondary efficacy endpoints will be analyzed by the method specified in [Section 5.2.1](#) and summarized as described in [Section 6.2.1](#).

Time to Rescue Medication: Subjects can receive medication at any time during the study for the treatment of fever. The rescue medication is defined as medication received for the treatment of fever during the time period from the administration of study medication to the time of end of the study (as noted at the beginning of this section). The time to rescue medication will be computed as the minutes from the time of dosing study medication to the time a subject first takes a rescue medication (censoring is No), or to the end of the study time for subjects that do not take any rescue medication prior to the end of the study (censoring is Yes).

This secondary efficacy endpoint will be analyzed by the method specified in [Section 5.2.2](#) and summarized as described in [Section 6.2.3](#).

Time to Return to Normal Temperature (Interval-Censored): The last temperature assessed prior to or on the time of RSE test dose is defined as “normal temperature” (as noted at the beginning of this section). For analysis purpose, return to normal temperature would be counted only if it occurs after the subject’s post-treatment temperature has already peaked. Interval censored time to return to “normal temperature” endpoint will be computed at discrete scheduled time points (T_j) of 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, and 480 minutes after dosing of study medication (time 0). For each subject, this endpoint will have two values of L_{time} and R_{time} defined as follows:

- If T_j is the first scheduled time point (post-treatment) when the temperature first reaches a value less than or equal to the “normal temperature”, after the subject’s post-treatment temperature has already peaked, and the subject does not take rescue medication prior to this time point, then the value of L_{time} and R_{time} for the subject will be the actual temperature assessment time at the scheduled time points T_{j-1} and T_j , respectively. If multiple temperatures are assessed at the scheduled time point T_j , the actual time of a temperature when it first returns to “normal temperature” will be used for R_{time} . If multiple temperature are assessed at the scheduled time point T_{j-1} , the actual time of a temperature assessed mostly close to R_{time} will be used for L_{time} ;
- If the temperature for the subject is always higher than the “normal temperature” by T_{resc} , time when the subject takes a rescue medication (at or prior to taking rescue medication, temperature will be recorded at time T_{resc}), then the value of L_{time} and R_{time} will be T_{resc} and *missing*, respectively;
- If the temperature for the subject is always higher than the “normal temperature” by T_{disc} (time associated with the last observed temperature at or prior to early withdrawal) when the subject discontinues from study, then the value of L_{time} and R_{time} will be T_{disc} and *missing*, respectively;
- If the subject does not use any rescue medication, and does not discontinue from the study, and the temperature is higher than the “normal temperature” through all the 8 hours post-treatment, the value of L_{time} and R_{time} will be the time associated with the last observed temperature at the end of study and *missing*, respectively.

This endpoint will be analyzed by the method specified in [Section 5.2.3](#) and summarized as described in [Section 6.2.2](#).

CCI [Redacted]

- [Redacted]
- [Redacted]
- [Redacted]

[Redacted]

[Redacted]

[Redacted]

CCI




3.4. Baseline Variables

All baseline assessments, with the exception of baseline temperature (see [Section 3](#)), and baseline vital signs and ECG (see [Section 3.4.3](#)), are defined as the last assessment taken prior to the administration of study medication. This can occur at screening or between Endotoxin and study medication administration.

3.4.1. Demographic Data

Demographic data such as sex, race, ethnicity and age will be collected at screening. Body weight will be collected at screening and on Day 0. These variables will be summarized as described in [Section 6.5.1.1](#). The corresponding listings will be also produced.

3.4.2. Endotoxin Administration Data

The administration time and dosage of Endotoxin (RSE) test dose, and RSE first full dose and RSE second full dose will be collected on Day 1 before randomization. Variables of interest will be discussed as follow:

- Time duration from RSE first (test dose), second (first full) and third (second full) doses to study randomization will be derived as:
 - time from first RSE dose (RSE test dose) to time of study randomization,
 - time from second RSE dose (RSE first full dose) to time of study randomization,
 - time from third RSE dose (RSE second full dose, if applicable) to time of study randomization.
- Time from RSE first full dose to randomization (i.e. reaching the threshold temperature of 100.5 °F) varies among subjects and is indicative of induced fever individual profile over time. It will be added as a covariate for continuous efficacy endpoint analyses. This

covariate may also be categorized and adjusted for in other efficacy endpoint analyses where deemed appropriate.

- Dosage (*ng*) of Endotoxin test dose, first full dose, and second full dose will be derived as dosage (in unit of *ng*) of first RSE dose (RSE test dose), the second RSE dose (RSE first full dose), and possible the third RES dose (RSE second full dose) took by subjects prior to randomization.

Total dosage of Endotoxin will be derived as the sum of all Endotoxin dosages administered prior to randomization per subject.

- Number of subjects administered with RSE test dose, and first and second RSE full doses will be derived as number of subjects who take the first RSE dose (RSE test dose), the second RSE dose (RSE first full dose), and the third RSE dose (RSE second full dose) prior to randomization. And the corresponding 3 groups of subjects (i.e. taking only one, two, or all three doses) may be used, additionally, in Exposure to Endotoxin summaries.

These Endotoxin administration relevant variables will be summarized as described in [Section 6.5.2.1](#) The corresponding listings will be also produced.

3.4.3. Baseline Temperature, Vital Signs and ECG

Baseline temperature and normal temperature (see [Section 3](#)) will be summarized as described in [Section 6.5.1.2](#). The corresponding listings will be also produced.

Baseline vital signs and baseline ECG will be those that will be assessed prior to the Endotoxin test dose, and will be summarized as described in [Section 6.5.1.3](#).

3.4.4. Prior Medical Conditions and Medical History

Prior medical conditions and medical history are those occurred prior to the administration of the Endotoxin test dose. These data will be summarized as described in [Section 6.5.1.4](#).

3.4.5. Concomitant Medications/Non-Drug Treatments (except Rescue Medication)

All concomitant medications and/or non-drug treatments used/taken at any time post the administration of the Endotoxin test dose will be collected throughout the study. The following will be considered as concomitant medications and/or nondrug treatments:

- Concomitant medications and/or non-drug treatments used during the study treatment period (except rescue medication) are these medications and/or non-drug treatments that were administered not for fever reduction at any time point from the administration of study medication up to the time of end of study ([Section 3](#)).
- Concomitant medications and/or non-drug treatments used post the study are these medications and/or non-drug treatments that were administered after the time of end of study.

- Concomitant medications and/or non-drug treatments used during the Endotoxin administration period are these medications and/or non-drug treatments that were administered at any time point from the first administration of Endotoxin up to study medication dose.

Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant non-drug treatments will be coded using MedDRA preferred term. Concomitant medications and/or non-drug treatments will be summarized as described in [Section 6.5.4](#).

3.4.6. Rescue Medication

Rescue medication will be the medications that are administered for fever reduction such as acetaminophen and ibuprofen at any time point from the administration of study medication to the end of study ([Section 3](#)). Rescue medication will be summarized as described in [Section 6.5.5](#).

3.5. Safety Endpoints

3.5.1. Adverse Events

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment (i.e., treatment-emergent). Adverse events will be summarized by the medical dictionary for regulatory affairs (MedDRA) system organ class (SOC) and preferred term and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the worst relationship.

In the study, adverse events (including serious adverse events [SAE] if any) will be collected after dosing of Endotoxin. Subjects will be contacted 14 (± 3) calendar days post end of the study to ascertain if any SAEs have occurred after end of the study.

An AE is considered treatment emergent relative to the treatment (i.e., the study medication or Endotoxin, respectively) if:

- the event occurs for the first time during the effective duration of the treatment and was not seen prior to the start of the treatment, or
- the event was seen prior to the start of the treatment but increased in severity during treatment.

Adverse events will be classified as study medication treatment-emergent, and Endotoxin treatment-emergent, respectively, according to their corresponding onset time. Adverse events will also be classified according to their causality with the relevant treatment, i.e. whether it is due to Endotoxin, study medication, or other reasons, based on the study case report form.

No tier-1 events (pre-specified events of clinical importance) have been identified in the Safety Review Plan (SRP) for this product. However, for this study AEs include in the Targeted Medical Event (TME) list of the SRP [REDACTED] will be summarized in a similar manner as Tier-1 events if any are identified. Therefore, a 3-tier approach will be used to summarize these types of AEs. Under this approach, AEs are classified into 1 of 3 tiers.

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's SRP [REDACTED]

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA preferred term (PT) is defined as a tier-2 event if there are at least 2% in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events. Tier-3 events will not be summarized separately from all adverse events.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

All adverse events will be summarized as described in [Section 6.6.1](#).

3.5.2. Laboratory Data

Laboratory data collected at Screening and Day 0 prior to RSE administration are considered source data and will not be included in the study database.

3.5.3. Vital Signs

Vital signs of blood pressures, pulse rate, and respiratory rate will be collected prior to dosing of RSE test dose and RSE full dose (except respiratory rate), and at every hour up to 8 hours post-treatment as scheduled, or up to time for early termination. Unscheduled blood pressures and pulse rates will be collected as necessary.

Baseline vital signs will be the one assessed prior to RSE test dose, unless otherwise noted.

During the Endotoxin dosing period, subjects who tolerate the endotoxin test dose with no more than a moderate cardiovascular response will receive a full dose of endotoxin. Moderate response is defined as a medically significant decrease of mean blood pressure of more than 20% from baseline or an increase in heart rate of more than 50% from baseline or 40 bpm, whichever is less.

After the administration of study medication till the end of study, vital signs will be considered as out of normal range per the following criteria (Protocol Appendix 3):

Pulse Rate	Supine/Sitting: <40 or >120 bpm; Standing: <40 or >140 bpm
Systolic Blood Pressure:	≥ 30 mmHg for change from baseline in same posture; or <90 mmHg
Diastolic Blood Pressure:	≥ 20 mmHg for change from baseline in same posture; or <50 mmHg
Respiratory Rate:	<12 bmp or >25 bpm

Refer to Protocol Appendix 3.

Changes from baseline in vital signs will be calculated at each post-baseline scheduled hour till the end of study, and at mostly prior to RSE full dose time, as post baseline value minus baseline value based on non-missing data of both baseline and post-baseline.

Post-treatment vital signs and their change from baseline values will be summarized by treatment groups.

Vital signs will be taken at the following scheduled time points: 1, 2, 3, 4, 5, 6, 7, and 8 hours post study treatment, at unscheduled time points, and prior to the Endotoxin full dose administration. For all these, if vital signs assessment is performed within ± 25 minutes around a schedule post-treatment hour, the corresponding value will be assigned to that hour, regardless of the specific scheduled time. If more than one value falls within the ± 25 minutes window, a simple average of the values will be used. For the summary of vital signs that are assessed at unscheduled time points within 1 hour post study treatment such as 6 minutes post study treatment, a ± 5 minutes time window may be applied. Vital signs assessed at early termination will be included in a scheduled time window according to the vital sign assessment time. Any missing vital sign measurements will be kept as missing.

All these vital signs variables will be summarized as described in [Section 6.6.3](#). Any abnormal vital signs will be presented in data listings .

3.5.4. Electrocardiogram

Electrocardiogram (ECG) will be measured at screening, prior to Endotoxin test dose (baseline), at 8 hours post administration of study medication or early termination, or at any unscheduled additional times the investigator feels necessary (such as unscheduled taken prior to RSE full dose, prior to or after dose of study medication, etc.). The general abnormality of ECG will be assessed by Investigator and collected into study database as 'Normal', 'Abnormal, Not Clinically Significant', 'Abnormal, Clinically Significant', and 'Not Evaluable'. The ECG component of QTcF interval (msec) assessed at each of these time points will be collected into study database.

As noted above, baseline QTcF Interval (msec) will be the one assessed prior to the Endotoxin test dose. However, if this QTcF interval data is missing, then the QTcF interval assessed at screening period will be used.

Per Protocol, it will be considered as 'abnormal' if the QTc interval is increased by ≥ 45 msec from the baseline, or an absolute QTc value is ≥ 500 msec. Therefore:

- If baseline QTcF Interval ≥ 500 msec, then the QTcF interval of the subject at baseline will be counted as 'Abnormal'. Otherwise it will be counted as 'Normal';
- If a subject has at least one QTcF Interval ≥ 500 msec at any time after study medication dose, or has a value of ≥ 45 msec increase from the baseline, then the QTcF interval of the subject during the study treatment period will be counted as 'Abnormal'. Otherwise it will be counted as 'Normal'.

Number and percent of subjects with an abnormal ECG exam at the end of the study will be summarized by treatment groups. Specifically:

- The number and percent of subjects with abnormal QTcF Interval (msec) at end of the study (as defined above) will be summarized by treatment groups as described in [Section 6.6.4](#).
- The number and percent of subject with ECG exam of 'Normal', 'Abnormal, Not Clinically Significant', 'Abnormal, Clinically Significant', and "Not Evaluable" at end of the study will be summarized by treatment groups as described in [Section 6.6.4](#).

QTcF Interval (msec) at end of study will be the QTcF Interval assessed at schedule time of 8 hours post study treatment if subject completes the study, or at time close to the time of early termination (see [Section 3](#)) for early terminated subjects.

Unscheduled QTcF Interval (msec) includes:

- QTcF interval (msec) taken prior to RSE first full dose;
- QTcF interval (msec) taken after RSE first full dose and prior to study medication;
- QTcF interval (msec) taken post study treatment but not at scheduled 8 hours.

Change from baseline QTcF Interval will be calculated as post baseline value minus baseline value based on non-missing data of both baseline and post-baseline values.

If QTcF Interval (msec) assessment is performed within ± 25 minutes around schedule 8 hours post-treatment time point, the corresponding value will be assigned to that time point. If more than one value falls within ± 25 minutes window, a simple average of the values will be used. Any missing post-baseline QTcF Interval (msec) measurements will be kept as missing.

3.5.5. Physical Examination

Full physical exam will be performed at screening for all randomized subjects, and brief physical exam will be performed at early termination only for early terminated subjects.

Full physical exam data collected at screening for all randomized subjects and brief physical exam collected for early terminated subjects, will be presented in data listings. Subjects with data out of normal ranges will be flagged, and the investigator's assessment whether the abnormal physical exam is clinically significant will be provided.

Physical exam data will be summarized as described in [Section 6.6.5](#).

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis populations prior to unblinding and releasing the database, and classifications will be documented per standard operating procedures.

4.1. Primary Analysis Set

The primary analysis set is the modified intent to treat (mITT) subject population, defined as all randomized subjects who were dosed with the study medication and RSE per procedures specified in protocol post amendment 4 and had a baseline assessment.

In the primary analysis set, subjects will be assigned to the randomized treatment regardless of what treatment they actually received.

CCI



4.3. Safety Analysis Set

The safety analysis sets comprises all subjects who dosed with study medication. Subjects will be analyzed according to the treatment they received, regardless of the randomized treatment assigned. A randomized but not treated subject will be excluded from the safety analyses.

CCI







5. GENERAL METHODOLOGY AND CONVENTIONS

All analyses will be performed upon the database lock following completion of the study.

5.1. Hypotheses and Decision Rules

For the analyses of efficacy endpoints, the statistical hypotheses to be tested are that (1) IBU/APAP is significantly better than Placebo, (2) IBU/APAP is significantly better than both IBU and APAP, (3) IBU is significantly better than Placebo, (4) APAP is significantly better than Placebo, and (5) IBU is significantly better than APAP.

In order for the study to be deemed successful, the combination product should be significantly better than both active treatments for the primary endpoint. The type 1 error for the primary endpoint will be preserved by testing each hypothesis at 0.05 level of significance (two-sided) in the following order:

- (1) IBU/APAP vs placebo,*
- (2) IBU/APAP vs IBU and IBU/APAP vs APAP*
- (3) IBU vs placebo*
- (4) APAP vs placebo*
- (5) IBU vs APAP*

A comparison will not be eligible for being declared significant unless the one preceding it is also significant. All pairwise comparisons will be presented for the sake of clinical completeness even if they are not technically eligible for being declared significant..

Protections for multiple comparisons will only be applied to the primary endpoint.

5.2. General Methods

All computations will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC). Statistically significant treatment differences will be declared if the probability of random occurrence among or between treatments, p , is ≤ 0.05 (two-sided). Treatment differences will be considered marginally significant if $0.05 < p \leq 0.10$. All tests will be two sided.

5.2.1. Analyses for Continuous Data

All analyses of efficacy endpoints with continuous data will use analysis of covariance (ANCOVA) model with treatment group term and covariates time from the first RSE full dose to randomization and baseline temperature. Pairwise treatment differences will be tested using least-squares means (LSM) estimated from the ANCOVA models. Difference between least squares means for each pair of comparison, its standard error, and two-sided 95% confidence interval will be presented.

5.2.2. Analyses for Time to Event Data

Time to event endpoints such as *time to rescue medication* will be analyzed using a *proportional hazards model with treatment group term in the model*. Pairwise treatment differences will be estimated by the hazard ratio (HR), associated two-sided 95% confidence interval for HR, and p-value derived from the proportional hazard model using SAS software procedure PROC PHREG. Time when at least 25% subjects (25% quartile) reach the event by each treatment group, and its 95% confidence interval may be obtained from estimated survival function based on LIFETEST procedure.

In addition, time to event endpoints will be displayed graphically by treatment using the survival curves (with estimated probability of zero representing no event) based on the Kaplan-Meier estimates.

5.2.3. Analysis of Interval-Censored Time to Event Data

Time to interval-censored event endpoint will be analyzed using *interval-censored survival analysis approach* by the nonparametric survival method of Peto (1973) and Turnbull (1976). The SAS software procedure PROC ICLIFETEST (C. Guo, Y. So, and G. Johnston) which implements the method of Peto and Turnbull will be used to obtain p-values for the generalized log-rank tests on the interval-censored data (Section 3.2), testing the overall treatment effect and the difference between each pair of treatments. The time when at least 25% subjects (25% quartile) first return to “normal temperature” by each treatment group, and its 95% confidence interval will be obtained from estimated survival function using the ICLIFETEST procedure. A stratification variable defined by number of RSE full doses taken or by categorized time from first RSE full dose to randomization may be considered.

In addition, Interval-Censored Time to Event data will be displayed graphically by treatment groups using the step-function curve estimated by the ICLIFETEST procedure.

5.2.4. Analyses of Ordinal Categorical Data

Patient global evaluation of investigational product at 8 hours post dose of the study medication will be analyzed using a chi-square test, and where deemed appropriate, based on an ANCOVA model, treating it as a continuous outcome, with treatment term and baseline covariates. Frequency counts (n, %) by treatment will be presented for each evaluation categories. Mean, standard deviation, median, minimum and maximum values for the overall categories by treatment will be presented as well.

CCI [Redacted]

■ [Redacted]

■ [Redacted]

■ [Redacted]

■ [Redacted]

CCI


6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint

6.1.1. Weighted Sum of Temperature Difference From Baseline Over 0-8 Hours (WSTD0-8) – Primary Efficacy Endpoint

The primary efficacy endpoint WSTD0-8 will be analyzed based on the primary analysis set (mITT, [Section 4.1](#)) using the ANCOVA model described in [Section 5.2.1](#). The primary efficacy endpoint will also be analyzed based on the ITT analysis set ([Section 4.4.1](#)) using the ANCOVA model described in [Section 5.2.1](#).

If the ANCOVA model as described in [Section 5.2.1](#) does not converge, an analysis using ANCOVA model with the treatment term and either covariate baseline temperature or time from RSE first full dose to randomization may be conducted.

Reporting of Results:

Tables:

The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm as well as the LSM and standard error based on the ANCOVA models. The root mean square of error (RMSE) and overall p-value based on the ANCOVA models will be also presented. Similarly, for each pair-wise comparison of treatment difference (in terms of the LSM, in the order specified in [Section 5.1](#)), and the corresponding two-sided 95% confidence intervals and p-values will be presented.

Figures:

- Vertical bar chart showing the LSM for each treatments of WSTD0-8 plus the corresponding standard errors on the y-axis showing any statistical significant differences based on the ANCOVA models will be presented .
- A forest plot showing the treatment differences in terms of LSM, its 95% CIs and p-values based on the ANCOVA models will be presented .

CCI



6.2. Secondary Endpoints

6.2.1. Weighted Sum of Temperature Difference From Baseline to 2, 4, and 6 Hours and from 6-8 Hours (WSTD0-2, WSTD0-4, WSTD0-6, and WSTD6-8) – Secondary Endpoints in Continue Data Format

These secondary endpoints WSTD0-2, WSTD0-4, WSTD0-6, and WSTD6-8 will be analyzed based on the primary analysis set (mITT, [Section 4.1](#)) and ITT ([Section 4.4.1](#)) using the model described in [Section 5.2.1](#), respectively.

Reporting of Results:

Tables:

The sample size, mean, standard deviation, median, minimum and maximum will be presented for each treatment arm as well as the LSM and standard error based on the ANCOVA models. The RMSE and overall p-value based on the ANCOVA models will be also presented. Similarly, for each pair-wise comparison of treatment difference (in terms of the LSM, with the order specified in [Section 5.1](#)), and the corresponding two-sided 95% confidence interval and p-value will be presented.

Figures:

For each secondary endpoint and by treatment, vertical bar charts showing the LSM plus the corresponding standard errors on the y-axis showing any statistical significant differences based on the ANCOVA models will be presented.

6.2.2. Time To Return To “Normal Temperature” - Secondary Endpoints in Interval-Censored Time-to-Event Data Format

Time to return to “normal temperature” interval censored data (Section 3.2) will be analyzed based on the primary analysis set (mITT) using the analysis methods for interval-censored time to event endpoint described in Section 5.2.3.

Reporting of Results:

Tables:

The sample size, numbers of subjects with event, and number of censored subjects, estimated 95% confidence interval of the time when at least 25% subjects (25% quartile, see Section 5.2.3) reach the event (temperature return to normal) will be tabulated by treatment group. For each pair of treatment groups, p-value of the generalized log-rank test per procedure specified in Section 5.2.3 will be presented.

Figures:

The survival functions of Time to “Normal Temperature” estimated using by the PROC ICLIFETEST procedure (similar to Kaplan-Meier plot) will be plotted by treatment groups.

6.2.3. Time to Rescue Medication - Secondary Endpoints in Time-to-Event Data Format

Time to first use of rescue medication will be analyzed based on the primary analysis set (mITT) using the proportional hazard model described in Section 5.2.2.

Reporting of Results:

Tables:

The sample size, numbers of subjects with event, and number of censored subjects, estimated 95% confidence interval of the time when at least 25% subjects (25% quartile, see Section 5.2.2) reach the event (temperature return to normal) will be tabulated by treatment group. For each pair of pairwise comparison of treatments difference, the hazard ratios and the corresponding 95% confidence interval estimated from the proportional hazard model (Section 5.2.2) will be presented.

Figures:

Kaplan-Meier plot of Time to Rescue Medication for each treatment group will be presented.

CCI



CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

6.4. Subset Analyses

No subset analyses are planned.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

6.5.1.1. Demographics

Demographic data of race, ethnicity and age will be summarized by treatment group and overall for the mITT, and for the safety analysis sets.

Continuous demographic variables of age and body weight will be summarized using sample size, mean, median, standard deviation, and range by treatment groups and overall. Categorical demographic variables of sex, race, and ethnicity will be summarized using frequencies and percentages. No statistical tests will be conducted.

6.5.1.2. Baseline Temperature

Baseline temperature will be summarized by treatment groups and overall for both mITT and ITT analysis sets.

Continuous baseline temperature will be summarized using sample size, mean, median, standard deviation, and range by treatment group and overall.

6.5.1.3. Baseline Vital Signs and Baseline QTcF Interval (msec)

Baseline vital signs and baseline QTcF interval (msec) will be summarized by treatment group and overall for safety and the exposure to Endotoxin analysis sets ([Section 4.4.2](#)).

These continuous baseline variables will be summarized using sample size, mean, median, standard deviation, and range by treatment group and overall.

6.5.1.4. Prior Medical Conditions and Medical History

Frequency and percentage of subjects with prior medical conditions and medical history will be tabulated by treatment group and overall for the safety set based on the MedDRA preferred term.

6.5.2. Study Conduct and Subject Disposition

6.5.2.1. All Subjects Dosed with Endotoxin

Endotoxin administration data ([Section 3.4.2](#)) will be summarized by treatment group and overall for the mITT and for the safety analysis sets. Similar summary will be done for the subject exposure to Endotoxin analysis set ([Section 4.4.2](#)), in which subjects who dosed with Endotoxin but not randomized will be summarized in the “non-randomized” group.

Continuous Endotoxin administration variables: total dosages, and time from Endotoxin first full dose and second full dose to randomization will be summarized using sample size, mean, median, standard deviation, and range by treatment group and overall.

Categorical Endotoxin administration variables (number of subjects taking Endotoxin test dose, first full dose and second full dose prior to randomization) will be summarized using frequencies and percentages. For the mITT and the safety analysis sets, the number and percentage of subjects will be summarized by treatment group, stratified by the following two categories:

- (1) subjects who have taken RSE test dose and RSE first full dose only, and
- (2) subjects who have taken RSE test dose, RSE first and second full doses.

6.5.2.2. Subject Randomized to Study Medication Treatment

The number and percentage of subjects who are randomized to study medication, dosed with study medication, complete the study, or withdraw from the study after randomization will be summarized by treatment group and overall for each analysis sets of mITT, CCI safety, and CCI [REDACTED] respectively. Reasons for discontinuation or early withdrawal will be also summarized within each analysis population.

6.5.3. Study Medication Exposure

Study medication administration data will be presented in a data listing but will not be summarized into a table.

6.5.4. Concomitant Medications and Non-Drug Treatments

Frequency and percentage of subjects taking concomitant medications during the study treatment period, after the end of study (see [Section 3](#)), and during the Endotoxin exposure period ([Section 3.4.5](#)) will be tabulated by treatment group and overall for the safety analysis set based on the WHO Drug dictionary terms. No statistical test will be conducted.

6.5.5. Rescue Medication

Frequency and percentage of subjects taking at least one rescue medication during the study treatment period ([Section 3.4.6](#)) will be tabulated by treatment group and overall for safety analysis set based on the WHO Drug dictionary terms. No statistical test will be conducted.

6.6. Safety Summaries and Analyses

Safety analyses will be performed using the safety analysis set ([Section 4.3](#)).

6.6.1. Adverse Events

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment (i.e., treatment-emergent). Adverse events will be summarized by the MedDRA system organ class (SOC) and preferred term and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE will be classified according to the worst reported severity of the AE. Similarly, for the summary by relationship to the study product, the AE will be classified according to the worst relationship.

Treatment emergent adverse events will be presented by overall incidence of at least one event, incidence within system organ class (SOC) only, and incidence by SOC and preferred term (PT).

Treatment emergent adverse events will be summarized as follows:

- Study Period Treatment-Emergent Adverse Events which occurred only after subjects received a study medication or occurred before but got worse will be summarized by incidence within SOC and preferred term, and tabulated by study treatment, and selectively, by Endotoxin exposure subgroups using the safety analysis set. These AEs will also be included in Tier-1 and Tier-2 events (see [Section 3.5.1](#)) summaries. Summary tables will be presented mainly by causality categories.
- Endotoxin Period Treatment-Emergent Adverse Events which occurred after subjects received at least one dose of Endotoxin but before they took the study medication, or occurred before receiving an Endotoxin dose but got worse during the Endotoxin period will be summarized by incidence within SOC and preferred term, and tabulated by study treatment groups and the additional group of non-randomized subjects, using the exposure to endotoxin analysis set. These AEs will also be summarized by study treatment and causality using the safety analysis set. Additional summaries may be conducted by the endotoxin exposure subgroups, using the Exposure to Endotoxin analysis set. In any of the scenarios discussed here, all events will be listed. However, only a smaller set of summaries (selected from a standard set of AE tables) will be performed and presented.

Serious adverse events (SAE) occurred within 24 hours after dosing of study medication will be listed as in study treatment period. SAE reported after 24 hours till 14 calendar days post-treatment via follow up telephone call will be listed as in study follow up period if applicable.

Non-treatment emergent AEs (i.e., adverse events occurred before subject took any dose of study medication or Endotoxin) will be summarized by incidence within SOC and preferred term and tabulated by study treatment.

All adverse events data will be listed for subjects who were enrolled into the study and received at least one dose of Endotoxin.

6.6.2. Laboratory Data

Laboratory data as stated in [Section 3.5.2](#) is considered source data and will not be entered into the study database. Therefore these data will not be analyzed unless otherwise noted.

6.6.3. Vital Signs

All vital signs data will be summarized by treatment group and overall for the safety analysis set. No statistical tests will be conducted. The following will be produced ([Section 3.5.3](#)):

- Baseline (i.e. assessed prior to the Endotoxin test dose) and post baseline (i.e., prior to full dose of Endotoxin, and at each schedule hour from 1 hour till 8 hours post-treatment) vital signs for systolic and diastolic blood pressures, pulse rate and respiratory rate will be summarized using sample size, mean, median, standard deviation, and range by treatment group and overall, and data will be tabulated and presented graphically over time.

All vital sign data will be listed for subjects who were enrolled into the study and received at least one dose of Endotoxin.

6.6.4. Electrocardiogram

The end of study QTcF interval (msec) and change from baseline values ([Section 3.5.4](#)) will be summarized by treatment group and overall for the safety analysis set. No statistical test will be performed.

Number and percent of subjects with abnormal (clinically significant or not) ECG at the end of study (and at baseline) will be summarized by treatment groups and overall for the safety analysis set. No statistical test will be conducted.

Number and percent of subjects with normal/abnormal QTcF interval (msec) at the end of study ([Section 3.5.4](#)) will be summarized by treatment groups and overall for the safety analysis set. No statistical test will be conducted. Baseline and at the end of study QTcF interval (msec) ([Section 3.5.4](#)) will be summarized using sample size, mean, median, standard deviation, and range by treatment group and overall. No statistical test will be conducted.

All ECG data will be listed for subjects who were enrolled into the study and received at least one dose of Endotoxin.

6.6.5. Physical Examination

All physical exam data will be listed for subjects who were enrolled into the study and received at least one dose of Endotoxin.

7. INTERIM ANALYSES

No interim analysis is planned.

8. REFERENCES

Peto, R. (1973), “Experimental Survival Curves for Interval-Censored Data,” *Applied Statistics*, 22, 86–91.

Turnbull, B. W. (1976), “The Empirical Distribution Function with Arbitrarily Grouped, Censored and Truncated Data,” *Journal of the Royal Statistical Society, Series B*, 38, 290–295.

Guo C., So Y., Johnston G. (2014), “Analyzing Interval-Censored Data with the ICLIFETEST Procedure,” Paper SAS279-2014, Cary, NC: SAS Institute Inc.

SAS Institute Inc. (2013), “SAS/STAT® 13.1 User’s Guide: The ICLIFETEST Procedure,” Cary, NC: SAS Institute Inc.

SAS Institute Inc. (2008), “SAS/STAT® 9.2 User’s Guide: The PHREG Procedure,” Cary, NC: SAS Institute Inc.

SAS Institute Inc. (2012), “SAS/STAT® 12.1 User’s Guide: The LIFETEST Procedure,” Cary, NC: SAS Institute Inc.

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]

[Redacted]

CCI [Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]
[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]								
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]

[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]