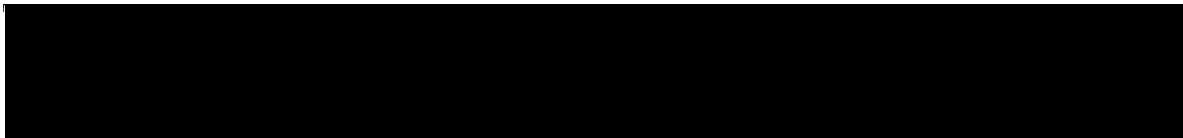




A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, FULL FACTORIAL, SAFETY AND EFFICACY STUDY COMPARING THE ANTIPIRETIC EFFECTS OF A SINGLE ORAL DOSE OF IBUPROFEN (IBU) 250 MG/ ACETAMINOPHEN (APAP) 500 MG CAPLETS TO IBU 250 MG AND APAP 500 MG CAPLETS IN HEALTHY MALE VOLUNTEERS WITH FEVER INDUCED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

Compound:	PF-06438867
Compound Name:	Ibuprofen/Acetaminophen (IBU/APAP)
United States (US) Investigational New Drug (IND) Number:	112,538
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	B5061002
Phase:	3



Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 6	21 September 2017	<p>The following changes were made:</p> <ul style="list-style-type: none">• The primary analysis set will be modified intent to treat (mITT) population. This population will exclude all randomized subjects prior to amendment 4. The study was initiated with higher doses of endotoxin which were then lowered under amendment 4.• Revised per protocol analysis set to include subjects in mITT population• CCI [REDACTED]• 20 additional subjects were added to ensure a total of 270 subjects in the mITT analysis set.• Added, as a covariate, time from the first RSE full dose to randomization in the analysis model.
Amendment 5	04 April 2017	<p>The following change was made following FDA communication received on 31 March 2017 recommending the use of IV acetaminophen instead of IV ketorolac as rescue medication</p> <ul style="list-style-type: none">• Rescue medication changed from IV ketorolac to IV acetaminophen (500 mg dose) and added the option for investigator or qualified individual to institute appropriate medical interventions at the discretion of the investigator including administration of IV ibuprofen (up to 400 mg dose) to subjects whose temperature continues to rise after administration of rescue IV acetaminophen.• Minor revisions and clarifications to ensure consistency in different sections were made.

<p>Amendment 4</p>	<p>28 March 2017</p>	<p>The following changes were made to the dosing algorithm of endotoxin</p> <p>Figure 1. Determination of RSE Full Dose;</p> <ul style="list-style-type: none"> • Test dose of RSE changed from 1 ng/kg to 0.5 ng/kg • Full dose of RSE changed from 2ng/kg and 1ng/kg to 1.5 ng/kg, 1ng/kg and 0.5 ng/kg based on subject fever response and presentation of systemic symptoms after administration of RSE test dose <p>Administration of ondansetron changed from approximately 30 minutes after test dose to approximately 45-60 minutes after RSE test dose administration;</p> <p>At any time after administration of endotoxin before randomization, subject will not be randomized if he develops two or more systemic RSE-related adverse events where both are rated as severe;</p> <p>Temporary hold on randomization included as example of when subject can be allowed to rescreen</p> <p>Minor revisions and clarifications to ensure consistency in different sections were made.</p>
<p>Amendment 3</p>	<p>30 January 2017</p>	<p>Use of CorTemp® Wireless Ingestible Temperature Sensor discontinued. The following changes to the study protocol were therefore effected.</p> <ul style="list-style-type: none"> • Subject temperature will be monitored via the standardized electronic digital thermometer. • Removed verification of non-interference with CorTemp® sensor. • Removed 48 hour phone call to subjects. • Removed exclusion criteria 13 (subjects who may undergo MRI). <p>The following changes were made to dosing algorithm of RSE:</p>

		<ul style="list-style-type: none">• Full dose of RSE changed from 3ng/kg and 2ng/kg to 2ng/kg and 1ng/kg plus an additional 1ng/kg for subjects who do not respond to full dose after 60-90 minutes of monitoring at the discretion of the investigator.• Added 100 minute and 110 minute time points for temperature recordings.• Administration of prophylactic antiemetic changed from 30 minutes before RSE test dose by mouth to approximately 30 minutes after RSE test dose intravenously to maximize efficacy.• Figure 1 revised to reflect above changes for RSE dosing. <p>The following 3 changes were made to the Rescue Medication section:</p> <ul style="list-style-type: none">• Subject temperature for rescue changed from 103.5 core temperature to ≥ 102.5 oral temperature.• Added consideration of subjects overall clinical presentation to conditions for administering rescue medication.• Added the option for investigator or qualified individual to institute appropriate medical interventions at the discretion of the investigator including administration of IV acetaminophen (up to 500 mg/dose) to subjects whose temperature continues to rise after administration of rescue ketorolac.• Removed time window for temperature time points that are one hour apart. Maximum time points are 30 minutes apart.• Removed statement that one vial of RSE will be reconstituted for each subject• Typographical and grammatical error changes clarifications were made throughout the document
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		<ul style="list-style-type: none"> Minor revisions and clarifications to ensure consistency in different sections were made
Amendment #2	26 October 2016	<ul style="list-style-type: none"> Subject temperature for randomization changed from $\geq 99.5^{\circ}\text{F}$ (oral), $\geq 100.5^{\circ}\text{F}$ (core) to 100.5°F (oral) 101.5°F (core) as per FDA advice/information letter dated 26 Aug 2016. Deleted the following statement; ‘Post treatment vital signs and its change from baseline will be summarized by treatment groups’ from section 9.4 due to duplication. Typographical and grammatical error changes clarifications were made throughout the document. Minor revisions and clarifications to ensure consistency in different sections were made. <p>The following changes were made based on statistical and operational reconsiderations:</p> <ul style="list-style-type: none"> Removed statement estimating study duration; Sample size for randomized subjects increased from 230 to 270; Added weighted sum of temperature differences from baseline to 2 hours (WSTD0-2) and to 4 hours (WSTD0-4) as secondary efficacy endpoints; The primary analysis set definition revised to include all randomized subjects who were dosed with study medication and had a baseline assessment; CCI [REDACTED] Added New reference #14; CCI [REDACTED]

Amendment #1	26 May 2016	<p>The following changes were made based on comments and recommendations before, during and after the Site Initiation Visit (10-May 2016):</p> <ul style="list-style-type: none">• Subjects screening window changed from 14 to 28 days prior to administration of study medication;• The study duration changed from approximately 7 to 10 months;• 24 hour safety phone call revised to include question asking subjects if they have had a bowel movement;• Study site will conduct a follow-up phone call to applicable subjects 48 hours after the 24 hour phone call to ascertain whether they have had a bowel movement since the previous call;• Ingestion of CorTemp thermometer sensor changed from with breakfast to approximately 1 hour prior to breakfast;• Clarification in Inclusion criteria 2: Where applicable an average of the 3 consecutive temperatures will be used to determine eligibility for subjects with temperatures that fall outside protocol requirements;• Inclusion criteria 3: BMI changed from 32 to 37;• Contraception requirements revised to exclude female partner requirement;• Third party unblinded staff will be allowed to administer RSE to subjects;• Breakfast Lunch and Dinner will be provided to subjects on Day 0;• Site will be required to use, whenever possible, the same qualified individual to conduct the physical examination for any one subject;
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		<ul style="list-style-type: none"> • Site will be allowed to use the same type of blood pressure cuff; • Clarification that QTcF is used for assessing QTc Interval for Database; • Revision to indicate that the source data from the CorTemp thermometer may be requested by Pfizer and used for a separate exploratory analysis; • Revision to remove Protocol Specified Adverse Event of Fever. All SAEs will be reported by the Investigator as described in Section 8; • The title of Section 8.6.1. was revised from Protocol-Specified Adverse Events to Protocol Specified Serious Adverse Events; • CCI [REDACTED] • Typographical and grammatical error changes clarifications were made throughout the document; • Minor revisions and clarifications to ensure consistency in different sections were made; • Figure 1 revised to include a question which instructs site to withdraw subjects who whose temperature is $\geq 99.5^{\circ}\text{F}$ after RSE test dose and before the full dose.
Original Protocol	18 March 2016	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

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PROTOCOL SUMMARY

BACKGROUND/RATIONALE

Ibuprofen (IBU) and acetaminophen (APAP) are the two most widely used non-prescription over-the-counter (OTC) analgesic/ antipyretic drugs both in the United States and globally. The objective of this currently proposed program is to develop a fixed-dose combination (FDC) of IBU plus APAP with efficacy superior to either agent alone, without increasing the risk of side effects. Combining two different antipyretic agents with different mechanisms of action, such as IBU and APAP, may provide superior efficacy and may also lower the total amount of each independent agent, thus lowering the risk of side effects associated with higher doses when taken as a single medication.

OBJECTIVES AND ENDPOINTS

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

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.

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

STATISTICAL METHODS

The sample size calculation was partly based on the data from a previous induced fever study (Whitehall-Robins Protocol ED-93-03). In that study, subjects with normal body temperature took study medication 30 minutes prior to receiving Endotoxin. The estimated variability (root mean square error RMSE) of the weighted sum of temperatures difference over 0-8 hours was 3.372, and treatment difference between APAP and Placebo was 3.57. Literature review and simulations were additionally conducted to assess the treatment effect and variability.¹⁴

In this study, we assume a treatment difference of 1.77 and 1.88 units in WSTD0-8 (weighted sum of temperature differences) for APAP/IBU vs IBU and APAP/IBU vs. APAP, respectively, and a variability (RMSE) of 3.406. A sample of 78 subjects per active treatment group will be required to provide about 85% joint power to achieve statistical significance at two-sided 0.05 level. Furthermore, this sample size for each active group and 26 subjects in placebo group (3:3:3:1 allocation ratio) will provide about 85% power to detect a treatment difference of 2.35 units in WSTD0-8 for the comparison of each active treatment to placebo.

Therefore, a total of approximately 270 subjects are to be randomized into the study after adjusting for additional 3.7% subjects who are randomized but not dosed or with no post-baseline data for analysis.

Additional 20 subjects (two randomization blocks) will be randomized for a total of 290 subjects. This addition ensures a total of approximately 270 subjects in the modified intent to treat (mITT) analysis population which will include only subjects randomized after protocol amendment 4. Seventeen subjects (replaced by the added 20 subjects) not included in the mITT were dosed with a different RSE dosing algorithm than the RSE current dosing algorithm before amendment 4. These subjects were dosed with much higher test and full doses of endotoxin.

All statistical tests will be performed at a two-sided 0.05 level of significance.

The primary efficacy endpoint, the weighted sum of temperature difference from baseline over 0-8 hours (WSTD0-8) will be analyzed using an analysis of covariance (ANCOVA) model with treatment group term and covariates baseline temperature and time from the first RSE full dose to randomization using mITT. Additional analyses will be conducted based on the intent to treat (ITT) analysis set.

Time from the first RSE full dose to randomization is added to the model as subjects demonstrated significant variations in time from RSE first full dose to randomization (ie, reaching threshold temperature of 100.5).

All measures relating to weighted sum of temperature difference from baseline, or temperature difference from baseline at individual post-dose time point will be analyzed by ANCOVA model with treatment group term and covariates baseline temperature and time from the first RSE full dose to randomization.

Time to rescue medication will be analyzed using a proportional hazards model with treatment group term in the model.

The time to return to “normal temperature” (time until fever clearance) will be analyzed using interval-censored survival analysis approach, since the exact time to fever clearance will not be observed.

Safety (adverse events [AE]/serious adverse events [SAE]) data will be summarized by treatment groups. Post treatment vital signs and change from baseline values will be summarized by treatment groups. Number and percent of subjects with abnormal electrocardiogram (ECG) exam at end of study will be summarized by treatment groups.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier	1	2																							Within 24 hrs of Discharge	Early Termination	14 Calendar Days After Last Dose(+3days)										
	Visit Window	RSE Period			Study Treatment Period																																
		Screening: Day -28 to Day 0	Day 0	Prior to RSE Test Dose Day 1	RSE Test Dose Administration	60 - 90 min after RSE Test Dose	RSE Full Dose Administration *	0 hrs	10, 20, 30, 40, & 50 min	60 min	70 min	80 min	90 min	100 min	110 min	2 hrs	2.5 hrs	3 hrs	3.5 hrs	4 hrs	4.5 hrs	5 hrs	5.5 hrs	6 hrs				6.5 hrs	7 hrs	7.5 hrs	8 hrs						
Informed Consent	X																																				
Inclusion/Exclusion criteria	X	X																																			
Demographics	X																																				
Medical History	X	X																																			
Prior Treatments ^a	→	→	→	→	→	→																															
Concomitant Treatments(s) ^a							→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Physical Examination ^b	X	X																																		X	
Safety Laboratory Tests ^c	X	X																																			
History of Drug, Alcohol, & Nicotine Use	X																																				

Visit Identifier Visit Window	1			2																				Within 24 hrs of Discharge	Early Termination	14 Calendar Days After Last Dose(+3days)						
	Screening: Day -28 to Day 0	Day 0	Prior to RSE Test Dose Day 1	RSE Period																	Study Treatment Period											
				RSE Test Dose Administration	60 - 90 min after RSE Test Dose	RSE Full Dose Administration *	0 hrs	10, 20, 30, 40, & 50 min	60 min	70 min	80 min	90 min	100 min	110 min	2 hrs	2.5 hrs	3 hrs	3.5 hrs	4 hrs	4.5 hrs		5 hrs	5.5 hrs				6 hrs	6.5 hrs	7 hrs	7.5 hrs	8 hrs	
Temperature Recording ^d	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Admit to Study Unit		X																														
Blood Pressure & Pulse Rate ^e	X	X	X		X			X						X		X		X		X		X		X		X		X		X		
Single, 12-lead ECG ^f	X		X																									X		X		
Respiratory Rate ^g								X						X		X		X		X		X		X		X		X				
Contraception Check	X	X																														
Dinner		X																														
Lunch		X																	X													
Breakfast		X	X																													
Antiemetic dose administered ^h					X																											
Endotoxin Test Dose				X																												
Monitor for Allergy / Systemic Response ⁱ				→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	

Visit Identifier Visit Window	1			2																				Within 24 hrs of Discharge	Early Termination	14 Calendar Days After Last Dose(+3days)												
	Screening: Day -28 to Day 0	Day 0	Prior to RSE Test Dose Day 1	RSE Period																																		
				Study Treatment Period																																		
				RSE Test Dose Administration	60 - 90 min after RSE Test Dose	RSE Full Dose Administration *	0 hrs	10, 20, 30, 40, & 50 min	60 min	70 min	80 min	90 min	100 min	110 min	2 hrs	2.5 hrs	3 hrs	3.5 hrs	4 hrs	4.5 hrs	5 hrs	5.5 hrs	6 hrs				6.5 hrs	7 hrs	7.5 hrs	8 hrs								
Endotoxin Full Dose						X																																
Randomization/ Treatment Administration							X																															
Lunch ^l																																						
Global Evaluation ^k																																				X	X	
Adverse Event Monitoring ^l	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Discharge from Study Unit ^m																																				X		
Follow up-call ^{n, o}																																			X	X		

Abbreviations: RSE= Reference Standard Endotoxin; ECG= electrocardiogram; IV= intravenous; hrs= hours; min= minutes; AE= Adverse Events; SAE= Serious Adverse Events

a. Treatments taken within 28 days before the first dose of study treatment will be documented as prior treatments and will be assessed at Screening and Day 0. Treatments taken after the first dose of study treatments will be documented as concomitant treatments and will be assessed after dosing on Day 1.

b. Full physical exam will be performed at Screening and on Day 0. Brief physical exam will be performed at early termination.

c. Safety Laboratory Tests will be performed at Screening and on Day 0 according to [Section 7.5](#) of the protocol. Test results will need to be available prior to RSE test dose administration to ensure subjects are free of occult infection and eligible to partake in the study.

- d. During Screening and on Day 0, an oral temperature will be taken to verify that the subject is afebrile. Prior to the test dose of RSE administration, subject's oral temperature will be recorded as their '**normal**' temperature. Subject's temperature will also be recorded 60 and 90 minutes (90 minutes if 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](#) 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).

1. INTRODUCTION

IBU and APAP are the two most widely used non-prescription OTC analgesic/ antipyretic drugs both in the United States and globally. The objective of this currently proposed program is to develop a FDC of IBU plus APAP with efficacy superior to either agent alone, without increasing the risk of side effects. Combining two different antipyretic agents with different mechanisms of action, such as IBU and APAP, may provide superior efficacy and may also lower the total amount of each independent agent, thus lowering the risk of side effects associated with higher doses when taken as a single medication. Both drugs have been extensively studied, and their efficacy and safety profiles in humans are well-established.

1.1. Mechanism of Action/Indication

FDC IBU/APAP is an analgesic/antipyretic formulation that is being developed for OTC use. The FDC is intended to have the same indications as each individual medication: the relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, the common cold, muscular aches, minor pain of arthritis and the temporary reduction of fever.

Ibuprofen, a “traditional” non-steroidal anti-inflammatory drug (NSAID), decreases the synthesis of pain- and inflammation-promoting prostaglandins via non-selective inhibition of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2).¹ The mechanism of action of APAP, which has no significant anti-inflammatory activity, is not clear. However, it may involve COX inhibition in the central nervous system and activation of central serotonergic pathways.^{2,3} IBU and APAP do not share metabolic pathways, which diminishes the likelihood of drug-drug interactions. Pharmacokinetic studies have demonstrated that there are no alterations in drug levels when the two analgesics are administered together, which is consistent with a lack of drug-drug interactions.^{4,5}

1.2. Background and Rationale

1.2.1. Study Rationale

For the majority of subjects who do not achieve fever reduction with lower doses of currently-marketed OTC antipyretic medications, or are intolerant to higher doses, no single antipyretic agent can completely reduce fever. Combining two different antipyretic agents with different mechanisms of action, such as IBU and APAP, may provide superior efficacy and may also lower the total amount of each independent agent, thus lowering the risk of side effects associated with higher doses when taken as a single medication. In addition, a combination antipyretic with superior efficacy may reduce the need for additional doses of other antipyretics, thereby reducing the total amount of antipyretic consumed and leading to improved consumer safety.

The current study is therefore designed to evaluate the efficacy of a fixed dose combination of IBU and APAP in reducing fever induced with RSE.

1.2.2. Rationale for Endotoxin Induced Fever Model

An induced fever model was selected for this study. Fever is known to be associated with chronic and acute infections and inflammation in which antibiotics, amongst other medications, are generally required. Use of antibiotics and other medications in addition to the study treatment could affect study results as they would likely decrease the pain or fever associated with the infection. Using only an antipyretic/analgesic to treat the infection, and not an antibiotic, would also not be appropriate as it would not treat the underlying cause of the infection. Therefore, a traditional fever study is not appropriate for evaluating the antipyretic efficacy of an antipyretic/analgesic combination treatment.

Gram negative bacterial lipopolysaccharide (typically from *E. coli*), endotoxin is known to trigger inflammation and various other responses including fever. The immune response to endotoxin is predictable and reproducible which offers an opportunity to evaluate therapeutic agents. Endotoxin results in a well characterized, transient acute fever response. The model has been widely used for decades as a system to study new therapeutic agents for fever and inflammation. Worldwide, thousands of subjects have received controlled endotoxin doses and serious adverse events have been rarely observed. A monophasic rise in core body temperatures starts by 1 hour post-RSE dose, peaks at approximately 4 hours, with increases of 2-4°F above baseline, and returns to baseline by 8-12 hours post-RSE dose. The endotoxin is cleared rapidly from blood.⁶

Endotoxin induced fever was therefore selected as the best approach to evaluate the antipyretic efficacy of the FDC.

1.2.3. Safety Data

IBU and APAP have demonstrated antipyretic efficacy and are nonprescription medications widely used for the reduction of fever. The main safety concern with IBU use, primarily at higher prescription doses over extended periods of time, is gastrointestinal toxicity.⁷ APAP over-dosage may cause potentially fatal hepatic failure.⁸ Based on safety concerns related to APAP, the Food and Drug Administration (FDA) has recommended reducing the maximum single adult dose of APAP in OTC products from 1,000 mg to 650 mg, and lowering the current maximum total daily dose APAP from 4,000 mg to 3,250 mg.⁹ However, since there is no overlap in metabolic pathways with IBU and APAP, and the dose in this study will be less than the recommended maximum single adult dose for each product, there is no anticipated increase in the risk of adverse events.

IBU/APAP combinations at OTC levels have been studied in humans, including single and multiple dose pharmacokinetic studies, single and multiple dose oral surgery studies, and a multiple dose knee pain study. These studies show that the adverse event (AE) profile of an IBU/APAP combination product at the doses proposed in this document is not materially different than the AE profile of the individual mono-components at their maximum dose level.¹⁰⁻¹³

1.2.4. Dose Rationale

The dose to be evaluated in this study is a single oral dose of FDC IBU 250 mg/APAP 500 mg (administered as two caplets of IBU 125 mg/APAP 250 mg). The anticipated dosing interval for the FDC is three times per day, which will provide a maximum daily dose of 750 mg IBU/1500 mg APAP. This is well below the current allowed OTC maximum dose of IBU 1200 mg and APAP 4000 mg, respectively, as well as the FDA's Analgesics Advisory Committee recommendation of reducing the maximum single adult dose of APAP in OTC products from 1,000 mg to 650 mg, and lowering the current maximum total daily dose APAP from 4,000 mg.⁹

Since there is no overlap in metabolic pathways in the two mono-components, and the dose of each drug will be lower than current OTC dose or anticipated future prescription dose limits, there is no anticipated increase in the risk of adverse events in this fixed dose combination product in comparison to that of each individual ingredient.

Complete information for this FDC IBU/APAP compound may be found in the single reference safety document (SRSD), which for this study is the Investigator Brochure (IB). The SRSD for the active comparator agents are the IBU (Advil[®]) IB and the APAP (Tylenol[®]) OTC Drug Facts Label.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. 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 RSE.

2.2. Endpoints

In the following, baseline is defined as the time of dosing with study medication.

Primary Endpoints:

- Weighted sum of temperature differences from baseline (the time of dosing with study medication) to 8 hours (WSTD0-8), weights being equal to the time elapsed between each two consecutive time points.

Secondary Endpoints:

- 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 during the last two hours of observation (6-8 hours) (WSTD6-8).

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- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]

- Safety evaluated by AE monitoring.

3. STUDY DESIGN

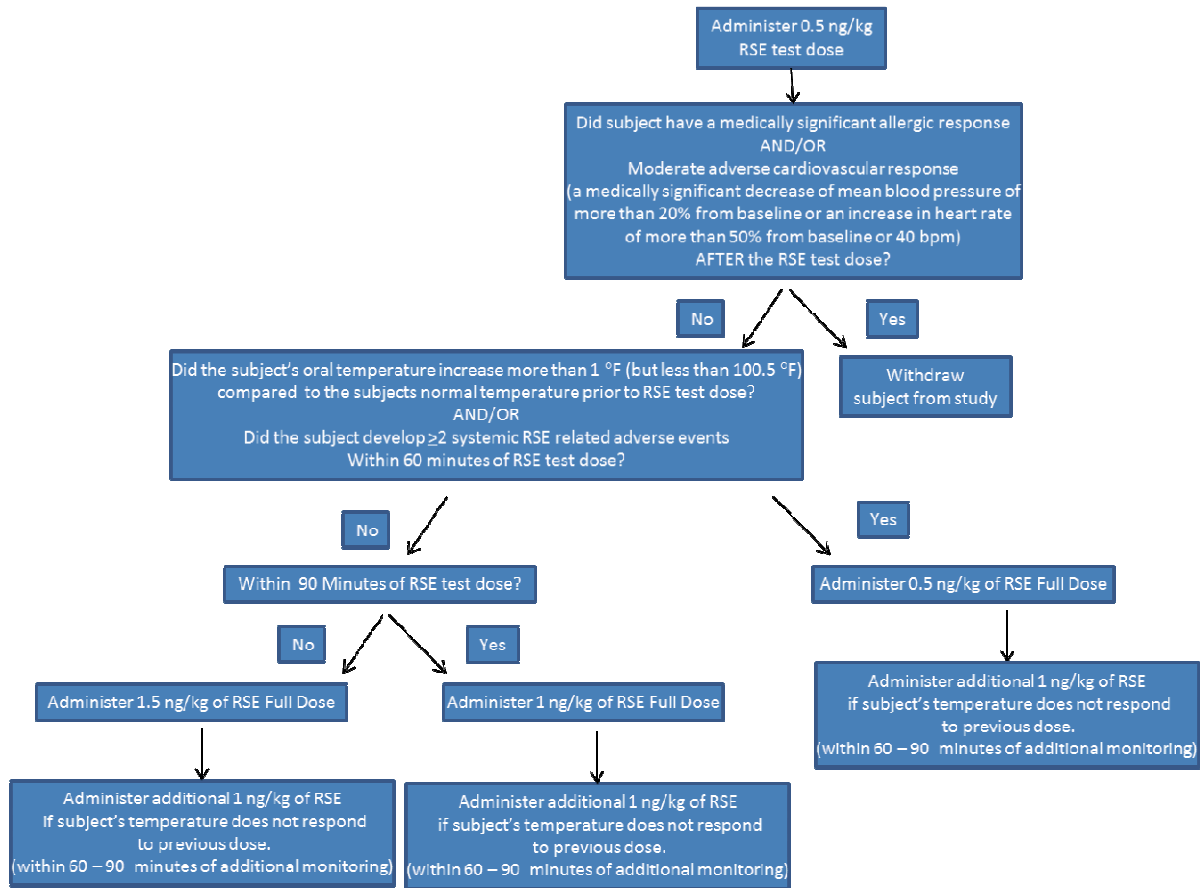
This study is a single-center, 8-hours, single-dose, inpatient, double-blind, randomized, placebo-controlled, full-factorial, parallel arm, safety and efficacy study in healthy male subjects 18 to 55 years of age (inclusive). Approximately 290 subjects will be enrolled in this study.

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. Site personnel will also conduct a follow-up call 14 calendar days after the last dose of study medication to ascertain if any SAEs have occurred.

The night prior to dosing on Day 0, subjects will report to the study site to complete several study procedures and will undergo urine and blood testing to ensure they are afebrile, free of occult infection and healthy. Afebrile is defined as a mean oral temperature between 97.4°F and 98.8°F that does not vary by more than 0.4 F° from the lowest to highest on three repeated assessments during a 30 minute period.

On Day 1, 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 and recorded in the source document. All endpoints for this study will be based on oral temperature measurements using a standardized electronic, digital thermometer.

Figure 1. Determination of RSE Full Dose



At any time after administration of endotoxin before randomization, subject will not be randomized if he develops two or more systemic RSE-related adverse events where both are rated as severe.

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

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 treatment 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.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Healthy male subjects who, at the time of screening, are between 18 and 55 years of age, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG and clinical laboratory tests.
2. The subject must have a normal, stable body temperature at Screening and on Day 0. If the subject's oral temperature is not between 97.4°F and 98.8°F, then 2 additional oral temperature readings will be obtained within a 30 minute period and averaged. The average of these 3 consecutive temperature readings must be between 97.4°F and 98.8°F, with the highest value within 0.4 F° of the lowest temperature value.
3. Body Mass Index (BMI) of 17.5 to 37.0 kg/m²; and a total body weight ≥50 kg (110 lbs) at Screening.
4. The subject has demonstrably adequate veins, by visual inspection, for intravenous (IV) catheter insertion.
5. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
6. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.
7. Male subjects able to father children must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Evidence or history of clinically significant laboratory abnormality, hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease (excluding untreated, asymptomatic, seasonal allergies at the time of dosing) within the last 5 years that may increase the risk associated with study participation.
2. Subjects with any gastrointestinal disorders (eg, gastrectomy, tracheostomy, esophageal surgeries, short gut syndrome, peptic ulcer disease, known or suspected obstructive disease, previous gastrointestinal surgery, felinization of the esophagus, hypomotility of the gastrointestinal track) that could affect the absorption, metabolism, or excretion of the study medication.
3. Subjects at risk for excessive bleeding.
4. Subjects with a history of nasal polyps, angioedema, or significant or actively treated bronchospastic disease.
5. Screening supine blood pressure ≤ 90 or ≥ 140 mm Hg (systolic) or ≤ 50 or ≥ 90 mm Hg (diastolic), following at least 5 minutes of supine rest. If blood pressure (BP) is ≤ 90 or ≥ 140 mm Hg (systolic) or ≤ 50 or ≥ 90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three consecutive BP values should be used to determine the subject's eligibility.
6. Screening supine 12-lead ECG demonstrating QTc > 450 msec or a QRS interval > 120 msec at Screening and on Day 1 prior to RSE administration. If QTc exceeds 450 msec, or QRS exceeds 120 msec, the ECG should be repeated two more times and the average of the three consecutive QTc or QRS values should be used to determine the subject's eligibility.
7. The subject has a history of recurrent or acute or chronic infections of any type or any findings suggestive of occult infection, such as tuberculosis, sinusitis, urinary tract infection, respiratory tract or dental (abscess) infection, etc., or those with a positive QuantiFERON Tuberculosis, Hepatitis B surface antigen, Hepatitis C antibody, and/or Human immunodeficiency virus (HIV) test at Screening. Also excluded are subjects with frequent (more than 3 outbreaks per year), recurrent oral or genital herpes, recurrent herpes zoster, or any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study.

8. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
9. Subjects who have experienced cold/flu symptoms (ie, runny nose, cough, and/or fever) within 2 weeks prior to the first administration of study treatments.
10. The subject has a history of an allergic-type reaction or known hypersensitivity to NSAIDS including ibuprofen, ondansetron, cyclooxygenase inhibitors, sulfonamides, APAP, endotoxins, lactose, tetanus vaccine, or other vaccines.
11. Subjects unable to swallow large capsules without gagging/choking.
12. Subjects with a cardiac pacemaker or other implanted device.
13. A positive urine drug screen or alcohol breath test during Screening or on Day 0.
14. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
15. Subject is unwilling to abstain from tobacco or nicotine-containing product use during the treatment evaluation period.
16. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study medication (whichever is longer) or administration of endotoxin within 3 months of receiving study medication.
17. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication.
18. History of sensitivity to heparin or heparin-induced thrombocytopenia.
19. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.
20. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.
21. Male subjects able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
22. Subjects who have previously been enrolled in this study.

23. Subjects with a reduction in heart rate to ≤ 50 beats per minute or deemed to be at high risk of syncope and/or hypotension per the clinical judgment of the investigator following a carotid sinus massage procedure.

4.3. Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject eligibility criteria.

All subjects must reach an oral temperature ≥ 100.5 °F within approximately 3 hours of receiving the full (or additional) IV bolus dose of endotoxin in order to be randomized to study treatment.

4.4. Lifestyle Guidelines

Any severe fluctuations in site temperature or humidity should be reported to study monitor.

4.4.1. Contraception

All subjects who are able to father children and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his partner(s) from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the [schedule of activities](#) and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.
2. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

4.4.2. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any laboratory evaluations.

- On Day 0, breakfast, lunch and dinner will be provided in accordance to all study procedures.
- On Day 1, subjects will receive a standardized light, low-fat breakfast (in order to minimize the chances of subjects vomiting following RSE administration) of plain toast and approximately 8.0 oz. of apple juice, or another non acidic juice, prior to receiving RSE. Dairy products, carbonated drinks and juices with high acid content will be eliminated from the breakfast.
- During the rest of the study period, subjects can sip plain, room temperature water.
- Subjects will not be allowed to drink water within 2 minutes of an oral temperature measurement.
- Approximately 4 hours after dosing and after the 4 hour temperature reading, lunch may be served at the investigator's discretion and will consist of room temperature food (ie, sandwiches) and room temperature water.

4.4.3. Alcohol, Tobacco and Caffeine

- Subjects will abstain from alcohol for 48 hours prior to admission to the Clinical Research Unit (CRU) and will continue to abstain from alcohol until after the final study evaluation is complete. Subjects will be required to have negative alcohol breath test at Screening and Day 0.
- Subjects will abstain from caffeine for 24 hours prior to the start of dosing until after the final evaluation on Day 1.
- Subjects must abstain from nicotine-containing products and smoking cessation products from Day 0 until after the final study evaluation on Day 1.

4.4.4. Activity

- No strenuous activity will be allowed while the subjects are in the clinical research unit (CRU). Only walking, sitting, and lying down will be allowed.
- After RSE administration, subjects will remain in their beds at a 45° angle (unless study procedures require otherwise) until permitted to get out of bed with the Investigator's permission. If subjects need to void or briefly ambulate, they will need to notify site staff and will be assisted as needed.
- Subjects will not be allowed to assume a supine position during the first 4 hours following administration of randomized study treatment, unless study procedures require otherwise.

4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the trial master file (TMF).

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

5.1. Allocation to Treatment

The investigator will assign subject numbers sequentially as subjects are screened for the study. Subjects will be randomized after they have been administered endotoxin and reached an oral temperature of $\geq 100.5^{\circ}\text{F}$. Treatment assignments will be determined by a computer generated randomization schedule, generated and maintained by Pfizer and provided to the site. Pfizer will provide a randomization schedule to the third party person(nel) assigned to prepare and administer the study medication. Only the third party person(nel) assigned to prepare and administer the study medication will have access to the randomization schedule and dispensing records during the study period.

The randomization numbers, which are 5-digits, PPD, etc. will be used.

In accordance with the randomization numbers, subjects will randomly receive one of the study medications listed in [Table 1](#) below, in a 3:3:3:1 ratio.

Study treatments will include single doses of the following medications taken orally:

Table 1. Study Treatments

Treatment Group	Treatment Arm	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

Study medication will be prepared for dosing by a third party who is otherwise not involved in the study, and subjects will be blindfolded with a sleep mask or similar object when taking their assigned study medication.

5.2. Breaking the Blind

The study will be subject- and investigator-blinded. At the initiation of the study, the study site will be instructed on the method for breaking the blind. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form.

In the event of a medical emergency that necessitates breaking the code, the third party personnel will consult the Study Treatment Dispensing Record to confirm which study treatment the subject received and will then report it to the Investigator. This disclosure will only be broken in the event of an emergency for which knowledge of the subject's double-blind investigational product will have a direct impact on treatment decisions. Every effort will be made to discuss the decision to break the blind with the Pfizer Consumer Healthcare (PCH) monitor in advance.

When the blind is broken, the Investigator will notify the Sponsor's Clinician and Medical Monitor within 24 hours after determining that it is necessary to unblind the treatment assignment and document the reason and date of the unblinding. The event will also be recorded on the Case Report Form (CRF) and in the source document. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

5.3. Subject Compliance

RSE will be administered by a qualified investigative site person(nel). Study treatment will be administered by a third party person(nel) and the oral cavity of each subject will be examined following dosing to assure the study medication was swallowed.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

IBU 250 mg/ 500 mg caplets, IBU 125 caplets, APAP 500 mg caplets, and placebo caplets for oral administration will be supplied by PCH (Richmond, VA). Study product will be supplied in bulk along with individual, opaque, plastic dosing containers for unit dosing. Dosage form and packaging related to RSE can be found in [Appendix 2](#). Rescue medications, ondansetron, and supplies will be provided by the study site.

5.4.2. Preparation and Dispensing

Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

The Sponsor will supply study treatment in bulk and in an un-blinded fashion. To maintain the double-blind status of the study treatments, the following dispensing and dosing procedures will be followed. The site will identify a qualified third party and alternate(s) who are otherwise not involved in the study and will be responsible for dispensing and administering the study medication and/or RSE. PCH (Richmond, VA) will provide randomization codes generated by Pfizer directly to the individual identified by the study site. A documentation packet consisting of a Study Treatment Dispensing Record and 2-part double-blind labels will be provided to the assigned third party person(nel) only. The codes will be kept in a secured area with access limited to only the assigned third party dispenser. Opaque plastic bottles and caps will also be supplied to the third party person(nel).

The third party dispenser will prepare study medication for each subject in a designated dispensing room. The study coordinator or designee will notify the third party dispenser once the subject has reached an oral temperature ≥ 100.5 °F. The third party dispenser will assign the next available randomization number to the subject and will dispense the appropriate 2 caplets of study medication from the bulk supply container into an individual opaque plastic bottle according to the randomization schedule. The appropriate double-blind label, with the same randomization number, will be affixed to the bottle and the identification tab will be attached to the Study Treatment Dispensing Record, which will then be fully completed. The Study Treatment Dispensing Record will remain in a secure locked area with access limited to the dispenser and the designated alternate(s). A second qualified individual with no other study involvement will witness the preparation and dispensing process. No other study person(nel) will be present in the designated dispensing room at the time of study drug dispensing. No other individuals will be able to see the study drug in the bottle once the bottle cap is closed. The third party dispenser will inform the study coordinator or designee once the study drug is dispensed and is ready to be administered to the subject.

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5.5. Administration

The investigational product will be administered to the subject within 10 minutes of the subject reaching an oral temperature of ≥ 100.5 °F. Immediately prior to administration of study medication, the subject's oral temperature will be recorded by site person(nel) and the subject will be blindfolded. The third party person(nel) will then enter the room and all other blinded study person(nel) will leave.

The third party person(nel) will then give the appropriate study medication to the blindfolded subject with approximately 8 ounces of room temperature water (time=0) while they are sitting up. Subjects will swallow the study medication whole, and will not manipulate or chew the investigational product prior to swallowing. No blinded study person(nel) will be present at the time of dosing. The time of dosing will be documented by the third party person(nel).

Investigational product administration details will be recorded on the case report form (CRF).

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5.6. Investigational Product Storage

The third party person(nel) will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Other site person(nel) will ensure that rescue medication, antiemetic, and RSE are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Storage conditions stated in the single reference safety document (SRSD) (eg, investigator's brochure [IB] and OTC Drug Facts Label) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions will be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

All materials for this study must be stored in an area free from environmental extremes and with restricted access. A PCH representative will inspect the study product storage area and discuss the study product accountability system with the Principal Investigator before any agreements are concluded between the Principal Investigator and PCH.

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5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

The designated third party person(nel), upon dispensing the study treatment, must record the information on a study treatment dispensing/return log. For accounting purposes and assessing subject compliance, a representative of PCH (unblinded monitor) will review the study treatment dispensing/return log, inventory the study treatment, and inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of the study. The Principal Investigator must account for any significant discrepancy and/or deficiency.

All investigational study treatments shipped for this clinical trial will be returned to the Sponsor at the termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of PCH (unblinded monitor) will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed.

All used investigational product (empty containers), as well as all unused study product will then be returned to:

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5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

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5.9. Concomitant Treatment(s)

Ondansetron (8 mg IV) will be provided by the study site and stored in accordance to the product's current approved product label.

Except for rescue medications as defined in [Section 5.10](#), ondansetron antiemetic, and the treatment of adverse events, no other medications or fever reducing treatments such as cold compress will be allowed during the course of the study. Treatments taken within 28 days

before the first dose of study treatment will be documented as a prior treatments and will be assessed at screening and Day 0. Treatments taken after the first dose of study treatment will be documented as concomitant treatments and will be assessed after dosing on Day 1. Concomitant medications for fever reduction administered after 8 hours post dosing of study product or after early termination will not be considered as rescue medication. All concomitant medications used during the study will be recorded with indication, daily dose, and start and stop dates of administration in the case report form.

5.10. Rescue Medication

Medical supportive care per established clinical practice will be provided to manage AEs associated with the use of RSE at the discretion of the investigator in addition to the administration of rescue medication.

IV acetaminophen and IV ibuprofen will be provided by the study site and stored in accordance to the product's current approved product label.

At the investigator's discretion, the investigator or other qualified staff member may administer a single 500 mg dose, of IV acetaminophen. The IV catheter will then be flushed with 0.9% normal saline (NS). The following conditions for rescue medication administration may be considered:

- A subject requests rescue medication at any time during the study;
- A subject's oral temperature reaches 102.5 °F;
- Subject's overall clinical presentation such as but not limited to, the presence of chills, nausea and/or vomiting.

A temperature of 102.5 °F should not be used by itself and in isolation of the clinical condition of the subject to decide whether or not to administer IV acetaminophen. The subject's oral temperature will be taken and recorded prior to administration of rescue medication and recorded in the source document. The use of rescue medication will be recorded in the appropriate page of the CRF with the date, time, dose, and reason for use. Subjects taking rescue medication during the course of the evaluation period will remain in the study for the full 8 hour duration and continue to be monitored for a decrease in temperature. All subjects who were given rescue medication within 1 hour of dosing with investigational product will be considered discontinued.

In addition, should a subject's oral temperature continue to rise after administration of rescue acetaminophen, and/or other clinically significant symptoms develop, appropriate medical interventions may be instituted at the discretion of the investigator (eg, administration of IV ibuprofen not to exceed a 400 mg/dose, frequent vital sign recordings, pulse oximetry, etc) These and other safety measurements may be conducted more frequently, if clinically indicated, or at the discretion of the investigator

Subjects will be released from the study center at the investigator's discretion.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 28 days prior to administration of the study medication to confirm that they meet the subject selection criteria for the study. Serious adverse events will be reported starting at Screening after informed consent has been signed and serious and non-serious adverse events will be recorded starting on Day 1 after dosing with study treatment. AEs and SAEs related to endotoxin will be collected on Day 1 after administration of endotoxin.

If the time between Screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment, scheduling problems, temporary hold on randomization), then subjects will be allowed to rescreen once.

The following procedures will be completed during screening:

- Informed consent will be obtained from each subject in accordance with the procedures described in [Section 12.3 on Subject Information and Consent](#). This will be recorded on the CRF;
- Review Inclusion and Exclusion criteria. This will be recorded on the CRF;
- Complete demographic information. This will be recorded on the CRF;
- Review medical history within the past 5 years. This will be recorded on the CRF;
- Review complete history of all prescription or nonprescription drugs, and dietary and herbal supplements (ie, vitamins, minerals, herbs or other botanicals and amino acids) taken within 28 days prior to the first dose. This will be recorded on the CRF;
- Inform subjects of contraception requirement described in [Section 4.4.1](#). This will be documented in the source document;
- Obtain an oral temperature using a standardized electronic, digital thermometer to verify that the subject is afebrile. If the subject's oral temperature is not between 97.4°F and 98.8°F, then obtain 2 additional oral temperature readings within a 30 minute period. The subject will only be eligible if the highest value is within 0.4°F of the lowest temperature value. The temperature or average of the three temperatures (if three are taken) will be recorded on the CRF;
- Conduct full physical examination including weight and BMI. This will be recorded on the CRF;
- Obtain history of drug, alcohol and nicotine use, which will be recorded in the source document;

- Obtain supine blood pressure [BP] and pulse rate [PR]. This will be recorded on the CRF;
- Conduct single, standard supine 12-lead electrocardiogram (ECG). This will be recorded on the CRF;
- Conduct a carotid sinus massage to evaluate subject's risk of syncope and/or hypotension. This will be recorded in the source document;
- Following at least a 4-hour fast, collect blood and urine specimens for safety laboratory tests (chemistry, hematology and urinalysis, urine drug test, alcohol breath test, QuantiFERON tuberculosis test, hepatitis B surface antigen test, hepatitis C antibody test, Human Immunodeficiency Virus (HIV) test, and some additional tests as listed in [Table 2](#). See [Section 7.5](#) for a table of laboratory tests.

To prepare for study participation, subjects will be instructed on the use of the [Lifestyle Guidelines](#) and [Concomitant Treatment\(s\)](#) sections of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to:

- Oral temperature should be taken first, followed by respiratory rate, vitals [BP and pulse], and then a single, 12 lead ECG.

SAEs will be assessed after completion of informed consent and AEs will be assessed after dosing with study medication. AEs and SAEs related to endotoxin will be collected on Day 1 after administration of endotoxin.

6.2.1. Day 0

Subjects will be admitted to the study site on Day 0 and will stay overnight. The following procedures will be completed after admission to the study site:

- Obtain an oral temperature using a standardized electronic, digital thermometer to verify that the subject is afebrile. If the subject's oral temperature is not between 97.4°F and 98.8°F, then obtain 2 additional oral temperature readings within a 30 minute period. The subject will only be eligible if the highest value is within 0.4°F of the lowest temperature value. The temperature or average of the three temperatures (if three are taken) will be recorded on the CRF.
- Review changes to [Inclusion Criteria](#) and [Exclusion Criteria](#) since Screening. This will be recorded on the CRF;
- Review changes in subject's medical history since Screening. This will be collected on the CRF;

- Review any new prescription and nonprescription drugs, and dietary and herbal supplements taken since Screening. This will be recorded on the CRF;
- Inform subjects of contraception requirement described in [Section 4.4.1](#). This will be documented in the source document;
- Blood and urine specimens will be collected for safety laboratory tests and to ensure the subjects are free of occult infection. The results to these laboratory tests need to be available prior to RSE test dose administration and must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed and eligible to partake in the study. See [Section 7.5](#) for a table of laboratory tests for more information. All lab test results will be recorded in source document;
- Conduct a full physical examination including weight to calculate RSE dose. This will be recorded on the CRF;
- Obtain supine blood pressure [BP] and pulse rate [PR]. This will be recorded on the CRF;
- Breakfast, lunch and dinner will be provided in accordance to study procedures.

6.2.2. Day 1

Prior to RSE administration, the following procedures will be completed:

- Record changes to prior treatments since Day 0. This will be recorded on the CRF;
- Obtain supine blood pressure [BP] and pulse rate [PR]. This will be recorded on the CRF;
- Conduct single, standard supine 12-lead electrocardiogram (ECG). This will be recorded on the CRF.
- Subjects will then be given a standardized low-fat light breakfast of plain toast and 8.0 oz. of apple juice, or another non acidic juice. Dairy products, carbonated drinks and juices with high acid content will be eliminated from the breakfast. During the rest of the study period, subjects can sip plain, room temperature water;
- Oral temperatures will be recorded (using a standardized electronic, digital thermometer) immediately prior to administration of RSE test dose. This temperature will be recorded as the subjects “**normal**” temperature in the CRF.

During RSE administration, the following procedures will be completed:

- AEs and SAEs related to endotoxin will be collected on Day 1 after administration of endotoxin;

- Subjects will be administered a test dose of endotoxin (0.5ng/kg body weight). The IV catheter used for RSE administration will be flushed with NS after RSE administration is complete. The dose and time of administration will be recorded on the CRF;
- Site staff will continuously monitor subjects for approximately 60 – 90 minutes (90 minutes if increase in temperature is <1 °F and subject experiences <2 systemic symptoms) (Refer to [Figure 1](#) and [Table 3](#) to determine the subject's full RSE dose) to verify the absence of a medically significant allergic or exaggerated systemic response to the endotoxin (as described in [Section 7.6](#)). Subjects must remain in a semi-recumbent position (45° angle from supine unless procedures require otherwise). Any medically significant allergic or exaggerated systemic responses will be recorded on the CRF.
- Subject's oral temperature (using a standardized electronic, digital thermometer) will be documented at 60 or 90 minutes (90 minutes if increase in temperature is <1 °F and subject experiences <2 systemic symptoms) after receiving the test dose of endotoxin to determine the subject's full dose of RSE. Refer to [Figure 1](#) and [Table 3](#) to determine the subject's full RSE dose. This will be recorded on the CRF;
- Subjects will be given a prophylactic dose of antiemetic (IV ondansetron 8 mg) after approximately 45 – 60 min of administering the test dose of RSE;
- Subject's vitals will be taken and recorded immediately prior to receiving the full dose of RSE to ensure they do not have more than a moderate cardiovascular response to the test dose. 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. This will be recorded on the CRF;
- Subjects who tolerate the endotoxin test dose with no more than a moderate cardiovascular response will receive the full dose of endotoxin. See [Figure 1](#) and [Section 7.6](#) for more detail on determining the full dose of RSE. The IV catheter used for full RSE administration will be flushed with NS after RSE administration is complete. RSE dose and time administered will be recorded on the CRF;
- Subjects will be monitored or given additional dose of RSE until their body temperature reaches an oral temperature of ≥ 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 and recorded in the source document until the subject reaches this temperature or is given an additional dose of RSE.

- Subjects whose oral temperature does not reach ≥ 100.5 °F (after approximately 60 – 90 minutes of vital signs monitoring) after administration of the full bolus dose of endotoxin may be administered an additional 1 ng/kg bolus dose of endotoxin at the discretion of the investigator (Subject's vitals will be taken and recorded immediately prior to receiving the additional dose of RSE). Subject's temperature will then be monitored every 5 minutes until their oral temperature reaches ≥ 100.5 °F within approximately 3 hours;
- Subjects will continue to be monitored to verify the absence of a medically significant allergic or exaggerated systemic response. At any time after administration of endotoxin before randomization, subject will not be randomized if he develops two or more systemic RSE-related adverse event where both are rated as severe.

During randomization and dosing with study medication, the following procedures will be completed:

- Once an oral temperature of ≥ 100.5 °F is reached, subjects will be randomized to receive treatment as described in [Section 5.1](#). The time between the subject reaching an oral temperature of ≥ 100.5 °F and being dosed should not exceed 10 minutes. This will be recorded on the CRF;
- Following randomization and immediately prior to study medication dosing an oral temperature will be recorded. This will be referred to as the “baseline” temperature. The time of dose administration will be documented. This will be recorded on the CRF.

After dosing with study medication, the following procedures will be completed:

- SAEs will be assessed after completion of informed consent and AEs will be assessed after dosing with study medication. AEs and SAEs related to endotoxin will be collected on Day 1 after administration of endotoxin;
- Oral temperatures will be obtained using a standardized electronic, digital thermometer and will 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. Subjects will remain in bed during the times of body temperature measurements. See [Section 9.3](#) for allowable windows to capture temperature. This will be recorded on the CRF;
- Respiratory rate and vital signs [BP and pulse] will be collected every hour after dosing up until 8 hours after dosing. This will be recorded on the CRF;
- Subjects will continue to be monitored to verify the absence of a medically significant allergic or exaggerated systemic response to the endotoxin (as described in [Section 7.6](#));

- The investigator or delegated site staff members will continuously monitor the subject's temperature using an oral standardized electronic, digital thermometer. If the subject's temperature exceeds 102.5°F, subjects may receive rescue medication as described in [Section 5.10](#). Prior to administration of rescue medication, the subject's oral temperature will be taken and recorded in the source document and CRF;
- If a subject vomits within 2 hours of taking the study medication, he will be considered discontinued from the treatment period and this will be recorded as an AE. Once the subject is stable, in the opinion of the investigator, he may be discharged;
- Lunch may be served at the investigator's discretion, approximately 4 hours after dosing with study medication, after the temperature measurement. Lunch will consist of low-fat, room temperature food (ie, sandwiches) and room temperature water;
- Review concomitant treatments. This will be recorded on the CRF;
- At the end of the 8-hour monitoring or at the time of rescue medication (within 5 minutes), subjects will complete a Global Evaluation of study medication using a 6-point categorical rating scale where applicable. This will be recorded on the CRF;
- At the end of 8-hour monitoring, a single, 12-lead ECG will be taken. This will be recorded on the CRF;
- Subjects will be discharged at the investigator's discretion once all study procedures are complete.

6.3. Post-study Subject Interview and Follow-Up

- Study site personnel will conduct a safety follow-up within 24 hours of discharge via a telephone call to the subject asking an open-ended question such as "How do you feel?" Any AEs from this follow-up call will be collected on the AE page of the CRF.
- The investigator (or an appropriate designee at the investigator site) will contact the subject via telephone, 14 calendar (+3 days) days after the last dose of the study medication to ascertain if any SAEs have occurred. Reporting of SAEs discovered during this process must be completed as outlined in [Section 8.1](#) in the protocol.
- Every effort (three telephone contact attempts) should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented.

6.4. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort (three telephone contact attempts followed by a certified letter) should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs). Early Termination procedures, at the investigator's discretion, will include:

- Oral temperature;
- Brief physical examination;
- Single supine blood pressure and pulse rate measurements;
- Single 12-lead ECG measurement;
- Global Evaluation (if applicable; within 5 minutes of rescue).

Subjects must be withdrawn from the study under the following circumstances:

- The subject develops a concomitant illness (discontinuation as deemed necessary by the Investigator), SAE, or hypersensitivity to the study product;
- The subject requires any concomitant treatment, other than the rescue medication, during the course of the study that could confound the study results;
- The subject becomes uncooperative or refuses to complete the study according to the study conditions outlines in this protocol;
- If the subject vomits within 2 hours of taking study treatment;
- If the subject requires rescue medication within 1 hour of dosing with study treatment;
- If the subject's temperature does not reach the threshold temperature;
- If the subject does not tolerate endotoxin as described in [Section 7.6](#).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the

investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation, times specified in [STUDY PROCEDURES](#) section of this protocol. Whenever possible, the same qualified individual should conduct the physical examinations for any subject. A full physical examination will include general appearance of the subject, head, ears, eyes, nose, mouth, throat, neck, skin, heart and lung examinations, lymph nodes, abdomen, musculoskeletal, and neurological systems. Weight and BMI will be recorded in the CRF. Height will be recorded in the source document. The brief physical examination will focus on general appearance, the respiratory and cardiovascular systems, and subject reported symptoms.

Any untoward findings identified on physical exams conducted after the administration of the first dose of study medication will be captured as an adverse event, if those findings meet the definition of an adverse event.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight. This information will be collected in the CRF.

7.2. Vital Sign Measurements

Blood pressure and pulse rate will be measured at times specified in [STUDY PROCEDURES](#) section of this protocol. Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mmHg after at least 5 minutes of rest. Whenever possible, the same arm (preferably the dominant arm) should be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff or type, will be used to measure blood pressure each time. The use of automated devices for measuring BP and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds and multiplied by two. This information will be collected in the CRF.

7.3. Respiratory Rate

Respiratory Rate will be measured at times specified in [STUDY PROCEDURES](#) section of this protocol. Respiratory rate will be measured after approximately 5 minutes of rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2.

When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

7.4. Electrocardiogram (ECG)

Single, 12-lead ECGs should be collected at times specified in [STUDY PROCEDURES](#) section of this protocol, as well as any additional times the investigator feels necessary. All scheduled ECGs should be performed in a supine position and after the subject has rested quietly for at least 10 minutes in a supine position. For purposes of this study, the QTcF correction should be used for QTc assessments.

To ensure safety of the subjects, a qualified individual at the investigator site will make comparisons to baseline measurement collected on Day 1 prior to RSE administration. If the QTc interval is increased by ≥ 45 msec from the baseline, or an absolute QTc value is ≥ 500 msec for any scheduled ECG, then 2 additional ECGs will be collected, approximately 2-4 minutes apart, to confirm the original measurement. If either of the QTc values from these repeated ECGs remains above the threshold value (≥ 45 msec from the baseline; or is ≥ 500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥ 500 msec (or ≥ 45 msec from the baseline) for greater than 4 hours (or sooner at the discretion of the investigator); or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to < 45 msec above the baseline) after 8 hours of monitoring (or sooner at the discretion of the investigator).

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified physician's interpretation determines that the QTc values are in the acceptable range.

7.5. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [STUDY PROCEDURES](#) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Table 2. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and Creatinine	pH	Urine drug screening
Hematocrit	Glucose (fasting)	Glucose (qual)	Alcohol breath test
RBC count	Calcium	Protein (qual)	HIV testing ^b
MCV	Sodium	Blood (qual)	Hepatitis B surface antigen ^b
MCH	Potassium	Ketones	Hepatitis C antibody ^b
MCHC	Chloride	Nitrites	QuantIFERON tuberculosis ^b
Platelet count	Total CO ₂ (Bicarbonate)	Leukocyte esterase	
WBC count	AST, ALT	Urobilinogen	
Total neutrophils (Abs)	Total Bilirubin	Urine bilirubin	
Eosinophils (Abs)	Alkaline phosphatase	Microscopy ^a	
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total protein		
	Additional Tests (Needed for Hy's law)		
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	Alkaline phosphatase (repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	Creatine kinase		
	GGT		
	PT/INR		

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

b Only during screening.

- Minimum requirement for drug screening includes: cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines.
- Subjects may undergo random urine drug screening at the discretion of the investigator. Drug screening conducted prior to dosing must be negative for subjects to receive study medication.
- Any remaining serum/plasma from samples collected for clinical safety labs at baseline and at all times post-dosing may be retained and stored for the duration of the study. Upon completion of the study, retained safety samples may be used for the assessment of exploratory safety biomarkers; samples to be used for this purpose will be packaged and shipped to Pfizer's Biobank for storage. These data will not be included in the clinical study report. Samples will be retained in Pfizer's Biobank for 1 year following completion of the study.

7.6. Endotoxin Administration and Monitoring

Subjects will be administered a test dose of endotoxin (0.5 ng/kg body weight) by a qualified individual and will then be monitored for approximately 60 – 90 (90 minutes if increase in temperature is $<1^{\circ}\text{F}$ and subject experiences <2 systemic symptoms) minutes to verify the absence of a medically significant allergic or exaggerated systemic response to the endotoxin. 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.

Subjects will then be administered a full dose of RSE at a dose of 1.5 ng/kg, 1 ng/kg or 0.5 ng/kg as an IV bolus over 30-45 seconds into a forearm vein via an indwelling catheter. Subjects will receive 0.5 ng/kg endotoxin full dose if the subject shows more than a 1°F oral temperature increase (but less than 100.5°F) and/or experiences two or more adverse events within approximately 60 minutes of receiving test dose. Subjects who do not show more than a 1°F oral temperature increase and/or do not experience two or more adverse events within approximately 60 minutes of receiving test dose will be monitored for an additional 30 minutes. After the additional 30 minutes of monitoring (90 minutes in total) subjects will be administered a 1 ng/kg of full dose endotoxin if they show more than a 1°F increase in oral temperature (but less than 100.5°F) and/or experience two or more adverse events. Subjects who do not show a more than a 1°F oral temperature increase and/or do not experience two or more adverse events within approximately 90 minutes of receiving endotoxin test dose will be administered a 1.5 ng/kg dose of endotoxin. (See [Figure 1](#) for an algorithm on determining the full dose of RSE). At any time after administration of endotoxin before randomization, subject will not be randomized if he develops two or more systemic RSE-related adverse events where both are rated as severe.

Subjects whose oral temperature does not reach $\geq 100.5^{\circ}\text{F}$ (after 60 – 90 minutes of additional monitoring) after administration of the full endotoxin dose may be administered an additional 1 ng/kg bolus dose of endotoxin at the discretion of the investigator (Subject's vitals will be taken and recorded immediately prior to receiving the additional dose of RSE). Subject's temperature will then be monitored approximately every 5 minutes and documented in the source document until their oral temperature reaches $\geq 100.5^{\circ}\text{F}$ within approximately 3 hours.

Refer to [Figure 1](#) to help determine the full dose of RSE for each subject.

Site staff will continuously monitor subjects to verify the absence of a medically significant allergic or exaggerated systemic response to the endotoxin and observe for signs and symptoms of endotoxemia (ie, chills, fever, headache, body aches, hypotension, etc.). The onset of these symptoms will generally occur approximately 1-2 hours after RSE administration and usually begins with transient chills, followed shortly thereafter by fever and other associated flu-like symptoms over the next 4-6 hours.

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7.7. Temperature Recording/Monitoring

During Screening and on Day 0, an oral temperature will be obtained from each subject (using a standardized electronic, digital thermometer) to ensure they are afebrile. Afebrile is defined as a mean temperature between 97.4°F and 98.8°F that does not vary more than 0.4 F° from the lowest to highest on three repeated assessments within a 30 minute period.

On Day 1, 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. At the discretion of the investigator, additional oral temperatures will be taken more frequently to monitor the subject's oral temperature. If the subject's temperature exceeds 102.5°F subjects may receive rescue medication. All endpoints for this study will be based on oral temperature measurements via 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 $\leq 1^\circ\text{F}$ and subject experiences < 2 systemic symptoms) after the test dose of RSE in order to determine what full dose of RSE the subject will receive (see [Section 7.6](#) above for RSE dosing). After approximately 60 or 90 min (90 min if increase in temperature $\leq 1^\circ\text{F}$ 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 $\geq 100.5^\circ\text{F}$. 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 approximately every 5 minutes and recorded in the source document 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. 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, ± 5 minutes for time points that are 30 minutes apart.

- 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.

Subjects will remain in bed during the times of temperature measurements. The investigator or delegated site staff members will continuously monitor the subject's oral temperature using a standardized, digital thermometer. If this temperature exceeds 102.5°F subjects may receive rescue medication as described in [Section 5.10](#). An oral temperature will be taken and recorded in the source document and CRF prior to rescue medication is administered.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

All AEs believed by the investigator to be related to endotoxin will be marked as of “other” causality in the AE page of the CRF. Investigators are advised to enter that the AE is due to endotoxin in the causality description of “other”.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject’s participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 14 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the subject’s last visit. AEs and SAEs related to endotoxin should be reported on the CRF from the time the subject has been administered the test dose of endotoxin.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;

- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE CRF page. If there are errors related to endotoxin, they will be captured as a protocol deviation.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on [Serious Adverse Event Reporting Requirements](#)).

Endotoxin-related adverse events will be recorded in the AE section of the CRF as of “other” causality and that the AE is due to endotoxin in the causality description of “other”.

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥ 3 times the upper limit of normal (\times ULN) concurrent with a total bilirubin value $\geq 2 \times$ ULN with no evidence of hemolysis and an alkaline phosphatase value $\leq 2 \times$ ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:
 - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values and $\geq 3 \times$ ULN, or $\geq 8 \times$ ULN (whichever is smaller).

Concurrent with

- For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least $1 \times$ ULN **or** if the value reaches $\geq 3 \times$ ULN (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for Liver Function Test (LFT) abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on [Subject Withdrawal](#))

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

As noted in the [Protocol-Specified Serious Adverse Events](#) section, should an investigator judge one of the identified protocol-specified SAEs to have a causal relationship with the investigational product, the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for the summary and statistical analyses of the data collected in this study are outlined here and further detailed in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications to the primary endpoint definitions and/or their analyses will also be reflected in a protocol amendment.

Pfizer Consumer Healthcare will perform statistical analyses of data. 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.

9.1. Sample Size Determination

The sample size calculation was based on the data from a previous induced fever study (Whitehall-Robins Protocol Number ED-93-03). In that study, subjects with normal body temperature took study medication 30 minutes prior to receiving Endotoxin. The estimated variability (root mean square error RMSE) of the weighted sum of temperatures difference over 0-8 hours was 3.372, and treatment difference between APAP and Placebo was 3.57. Literature review and simulations were additionally conducted to assess the treatment effect and variability for sample size.

In this study, we assume a treatment difference of 1.77 and 1.88 units in WSTD0-8 for APAP/IBU vs IBU and APAP/IBU vs. APAP, respectively, and a variability (RMSE) of 3.406. A sample of 78 subjects per active treatment group will be required to provide about 85% joint power to achieve statistical significance at two-sided 0.05 level. Furthermore, this sample size for each active group and 26 subjects in placebo group (3:3:3:1 allocation ratio) will provide about 85% power to detect a treatment difference of 2.35 units in WSTD0-8 for the comparison of each active treatment to placebo.

Thus, after adjusting for additional 3.7% who are randomized but not dosed or with no post-baseline data, a total of approximately 270 subjects are to be randomized into the study. All statistical tests will be performed at a two-sided 0.05 level of significance.

Additional 20 subjects (two randomization blocks) will be randomized. This addition ensures a total of approximately 270 subjects in the modified Intent to treat (mITT) analyses population which will include only subjects randomized after protocol amendment 4. Seventeen subjects (replaced by the added 20 subjects) not included in the mITT were dosed with a different RSE dosing algorithm than the RSE current dosing algorithm before amendment 4. These subjects were dosed with much higher test and full doses of endotoxin.

9.2. Efficacy Analysis

The statistical analysis methods will be detailed in the SAP, and are briefly summarized below. Subjects will be assigned to the randomized treatment group for efficacy summary and analysis regardless of the treatment received.

9.2.1. 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.

CCI

9.2.4. Analysis of the Primary Endpoint

The primary efficacy endpoint, the weighted sum of temperature difference from baseline over 0-8 hours (WSTD0-8) will be analyzed using an ANCOVA model with treatment group term and covariates baseline temperature and time from the first RSE full dose to randomization using mITT. Additional analyses will be conducted based on the ITT analysis set.

Time from the first RSE full dose to randomization is added to the model as subjects demonstrated significant variations in time from RSE first full dose to randomization (ie, reaching threshold temperature of 100.5).

9.2.4.1. Protection for Multiple Comparisons

In order for the study to be deemed successful, the combination product should be significantly better than both active comparators 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.
 1. A comparison will not be eligible for being declared significant unless the one preceding it is also significant.
 2. All pairwise comparisons will be presented for the sake of clinical completeness even if they are not technically eligible for being declared significant.

9.2.5. Analysis of Secondary Endpoints

All measures relating to weighted sum of temperature difference from baseline, temperature difference from baseline at individual post-dose time point will be analyzed by ANCOVA model with treatment group term and covariates baseline temperature and time from the first RSE full dose to randomization. Additional analyses may be conducted based on the ITT analysis set.

Time to rescue medication will be analyzed using a proportional hazards model with treatment group term in the model.

The time to return to “normal temperature” (time until fever clearance) will be analyzed using interval-censored survival analysis approach, since the exact time to fever clearance will not be observed.

CCI [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

9.4. Safety Analysis

The safety analysis set comprises all subjects who dosed with study medication. Subjects will be analyzed according to the treatment they received, regardless of the randomized treatment assigned.

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment. 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.

Safety (adverse events [AE]/serious adverse events [SAE]) data will be summarized by treatment groups.

Non- treatment emergent AEs will be summarized.

Post-treatment vital signs and their change from baseline values will be summarized by treatment groups. Number and percent of subjects with an abnormal ECG exam at the end of the study will be summarized by treatment groups.

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the Hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in United States

End of trial is defined as last subject last visit (LSLV), which is the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of PF-06438867 at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies conducted in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

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Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
APAP	acetaminophen
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CDS	core data sheet
COX	cyclo-oxygenase
CRF	case report form
CRU	clinical research unit
CSA	Clinical study agreement
EC	ethics committee
ECG	electrocardiogram
<i>E.coli</i>	<i>Escherichia coli</i>
EDP	Exposure of partner during pregnancy
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDC	Fixed-dose combination
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
IB	investigator's brochure
IBU	ibuprofen
ICH	International Conference on Harmonization
ID	identification
IND	investigational new drug application
INR	International normalized ratio
IRB	institutional review board
CCI	
IUS	intrauterine system
IV	intravenous
LFT	liver function test
LPD	local product document
LSLV	last subject last visit
MedDRA	medical dictionary for regulatory affairs
MITT	modified intent to treat
MRI	magnetic resonance imaging
N/A	not applicable
NMR	nuclear magnetic resonance
NS	normal saline 0.9%

Abbreviation	Term
NSAID	non-steroidal anti-inflammatory drug
OTC	over-the-counter
PCH	Pfizer Consumer Healthcare
PR	pulse rate
PT	prothrombin time
RMSE	root mean square error
RSE	reference standard endotoxin
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOP	standard operating procedure
SRSD	single reference safety document
THC	tetrahydrocannabinol
TMF	trial master file
ULN	upper limit of normal
US	United States
WSTD	weighted sum of temperature differences

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