Pfizer Inc.
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

14-Feb-2018

RE: Protocol Administrative Changes and Clarifications for Study B3741002 -- A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Dear Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the B3741002 protocol; version 13 Jul 2016. The edits described below are to clarify inconsistencies in the text of the protocol and provide administrative changes that do not impact the safety of subjects, the scope of the trial, or the scientific quality of the study, and therefore do not qualify as an amendment.

The specific exclusion criteria from the protocol listed below remain the same with no changes, as follows:

- Section 4.2, exclusion criterion #8 states "Use of a prescription or over the counter (OTC) drug with which administration of IBU, caffeine, or any other NSAID; codeine, tramadol or any other opioid is contraindicated and in the opinion of the Investigator will harm the subject to be included in the study (including: opioids, antipsychotics, antianxiety agents, or other central nervous system depressants [including alcohol])".
- Section 4.2, exclusion criterion #17 states "Patients who are currently taking any selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor or selective norepinephrine reuptake inhibitor (SNRI), or tricyclic antidepressant (TCA), and are not on a stable dose of this medication for at least 30 days prior to screening or will not maintain this dose throughout the study and their condition is judged by the Investigator to not be well controlled".

This PACL makes the following clarifications with regard to the above:

- To clarify the above two exclusion criteria (#8 and #17), only subjects who have been taking SSRIs/SNRIs/TCAs for more than 30 days on a stable dose are allowed to enroll in the study. All other subjects taking these drugs are not to be enrolled in the study.
- To clarify the above exclusion criterion (#8), if a subject has not used marijuana for one year or more from the date of screening, then it is okay to enroll the subject into the study. If the patient has used marijuana within the past one year of the date of screening, then the subject is not to be enrolled into the study.

In the event that this protocol requires substantial changes in the future, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/independent ethics committee of these changes, as required.

Sincerely,

PPD
PPD PharmD
Clinical Research Fellow
Pfizer Consumer Healthcare
One Giralda Farms, Madison, NJ 07940
cc: Trial Master File

Pfizer Inc
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

October 23, 2017

RE: Protocol Administrative Changes and Clarifications for Study B3741002 – A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Dear Investigator,

This Protocol Administrative Change Letter (PACL) is to notify you of the following administrative changes and clarifications to the B3741002 protocol; version 13 Jul 2016: The edits described below are to clarify inconsistencies in the text of the protocol and provide administrative changes that do not impact the safety of subjects, the scope of the trial, or the scientific quality of the study, and therefore do not qualify as an amendment.

This PACL makes the following changes:

- Page 8, under the Schedule of Activities, under section "e" – revise "staring" to "starting"
- Section 1.2, paragraph 3 – the statement beginning with "The results demonstrated the combination was 2.4 to 4.8 times more effective…" should actually state "The results demonstrated the combination was 2.4 to 2.8 times more effective…"
- Section 4.2, exclusion criteria #9 states: "Use of any type of systemic corticosteroid within the past 30 days or a history of current or previous use of anabolic steroids." To clarify, systemic corticosteroids refer to oral corticosteroids and are disallowed. However, topical and inhaled corticosteroids are not considered systemic and are allowed.

In the event that this protocol requires substantial changes in the future, the administrative changes described in this letter will be incorporated into the amended protocol.

Please inform your institutional review board/independent ethics committee of these changes, as required.

If you have any questions please feel free to contact me via email at PPD

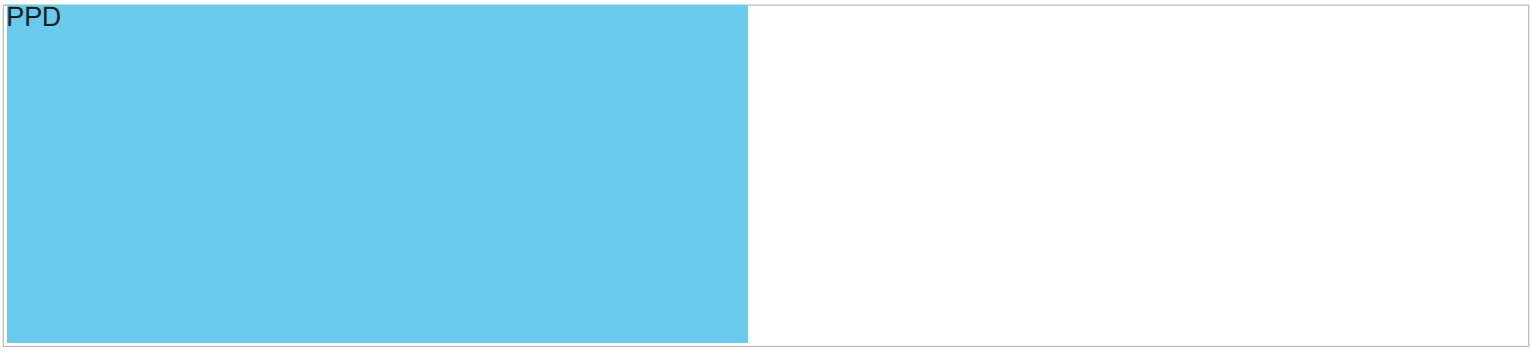
Sincerely,

PPD Ph.D.
PPD Global Clinical Research
Pfizer Consumer Healthcare
One Giralda Farms, Madison, NJ 07940

cc: Trial Master File

PPD

1



[redacted]

This page was added to the original document by the MySignatureBook Signature Validation Service (SVS) as part of the process to convert active signature block content into inactive text. A full validation report of each signature is generated and cross-referenced using a numeric footnote annotation.

Pfizer Inc
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

July 24, 2017

RE: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Dear Investigator,

This letter is to notify you of the following administrative changes and clarifications to the B3741002 protocol, version 13 Jul 2016:

- Introduction, Section 1.2, paragraph 3, sentence 1 the associated reference "3" should be corrected to reference "4."

- Table 1, Section 5 Study Treatments: the lot number for the Test and Placebo treatments were updated to WH-1769-0005-001 for the Test and WH-0689-0017-002 for the Placebo

- In Section 5.4.2, paragraph 4, sentence 5, the sentence should read: The dispenser will dispense the randomized investigational product (**1 liquid-filled gelatin capsule per dose**) from the appropriate bulk supply containers into an individual opaque plastic bottle."

- In Section 6.3, paragraph 5, sentence 1, the sentence should read: Upon completion of the baseline scales, eligible subjects will be randomized to receive a single oral dose of investigational product (consisting of 1 liquid-filled capsule) under double blind conditions.

- In Section 6.4, End of Study Assessments, the following procedure will only be completed in the event that a subject is Early Terminated from the study: "laboratory test." Currently the protocol indicates that the laboratory tests will be collected at the end of study however, this should be clarified and should only be done for early termination if possible.

The B3741002 protocol will be amended to reflect these administrative changes and clarifications if substantial changes that significantly affect the safety, scope, or scientific quality of the study are required in the future.

If you have any questions please feel free to contact me via email at PPD

Sincerely,

PPD

PPD PharmD

PPD Global Clinical Research

Pfizer Consumer Healthcare

One Giralda Farms, Madison, NJ 07940

cc: Trial Master File

Pfizer Inc
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

13 Jun, 2017

Re: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Dear Investigator,

This letter is to notify you of the following administrative changes and clarifications to the B3741002 protocol, version 13 Jul 2016:

- Introduction, Section 1.2, paragraph 3, sentence 1, the associated reference "3" should be corrected to reference "4."

- In Section 5.4.2, paragraph 4, sentence 5, the sentence should read: The dispenser will dispense the randomized investigational product (**1 liquid-filled gelatin capsule per dose**) from the appropriate bulk supply containers into an individual opaque plastic bottle."

- In Section 6.3, paragraph 5, sentence 1, the sentence should read: Upon completion of the baseline scales, eligible subjects will be randomized to receive a single oral dose of investigational product (consisting of 1 liquid-filled capsule) under double blind conditions.

- In Section 6.4, End of Study Assessments, the following procedure will only be completed in the event that a subject is Early Terminated from the study: "laboratory test." Currently the protocol indicates that the laboratory tests will be collected at the end of study however, this should be clarified and should only be done for early termination if possible.

The B3741002 protocol will be amended to reflect these administrative changes and clarifications if substantial changes that significantly affect the safety, scope, or scientific quality of the study are required in the future.

If you have any questions please feel free to contact me via email at PPD

Sincerely,

PPD

PPD PharmD
PPD Global Clinical Research
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

cc: Trial Master File

Pfizer Inc
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

12 Oct, 2016

Re: A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Dear Investigator,

This letter is to notify you of the following administrative changes and clarifications to the B3741002 protocol, version 13 Jul 2016:

- Schedule of Activities, Column 15 from the left titled "8.0/Early Termination" will be revised to read, "8.0/ End of Study/ Early Termination."

- In Section 6.3, in the second paragraph, the statement beginning with "Subjects who do not reach a qualifying baseline pain threshold (at least 6 or greater on NPSR..." should actually state "...(at least 5 or greater on NPSR confirmed by a score of at least 50 mm on the VAS PSR)..."

- Section 5.9: "Subjects taking rescue medication within one hour after dosing will be considered discontinued and must be replaced," will be revised to remove "...and must be replaced." Subjects are not replaced in this study.

- The following text in Section 6.4 will be removed: "after the last efficacy assessment is collected and assuming there are no outstanding AEs of concern." This sentence will be revised to read as follows, "At the 8-hour assessment for the study, ie, the End of Study, the subject will undergo the following study assessments:"

The B3741002 protocol will be amended to reflect these administrative changes and clarifications if substantial changes that significantly affect the safety, scope, or scientific quality of the study are required in the future.

If you have any questions please feel free to contact me via email at PPD

PPD

PPD PharmD
PPD Global Clinical Research
Pfizer Consumer Healthcare
One Giralda Farms
Madison, NJ 07940

cc: Trial Master File

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY COMPARING THE ANALGESIC EFFICACY AND SAFETY OF A SINGLE ORAL DOSE OF A NOVEL FIXED-DOSE COMBINATION OF IBUPROFEN 400 MG WITH CAFFEINE 100 MG TO IBUPROFEN 400 MG AND TO PLACEBO IN THE TREATMENT OF POST-SURGICAL DENTAL PAIN IN OTHERWISE HEALTHY SUBJECTS

Investigational Product Number:	PF-06359262
Investigational Product Name:	Caffeine with Ibuprofen
United States (US) Investigational New Drug (IND) Number:	125,736
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	B3741002
Phase:	3

[redacted]

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	13 Jul 2016	Not applicable (N/A)

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

APPENDICES

SCHEDULE OF ACTIVITIES

The schedule of activities (SOA) 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 table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

			Time relative to dose (hrs.)											
	Screening[a]	Surgery	0	0.25	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0 / Early Termination	Day 14 (+3 days)
Informed Consent	x														
Review Inclusion & Exclusion Criteria	x	x													
Demographic Information	x														
Medical History	x														
Prior Medications	x														
History of drug and alcohol use	x														
Laboratory Test[b]	x													x	
Pregnancy Test[c]	x	x													
Serum FSH (post-menopausal females only)	x														
Contraception Check[d]	x													x	x
Surgical Procedure		x													
Surgical Trauma Scale		x													
Vital Signs (eg, HR, BP, T, RR)	x		x											x	
Randomization			x												
Dosing			x												
Pain Evaluations:															
0-100 mm VAS Pain Severity Rating (PSR)[e]			x												
11-point Numerical Pain Severity Rating Scale (NPSR)[k]			x	x	x	x	x	x	x	x	x	x	x	x	
5-point Categorical Pain Relief Rating[f]				x	x	x	x	x	x	x	x	x	x	x	

[redacted]

	Screening[a]	Surgery	Time relative to dose (hrs.) 0	0.25	0.5	1.0	1.5	2.0	3.0	4.0	5.0	6.0	7.0	8.0 / Early Termination	Day 14 (+3 days)
Time to 'First Perceptible' Relief[g]				→	→	→	→	→	→	→	→	→	→	→	
Time to 'Meaningful' Relief[h]				→	→	→	→	→	→	→	→	→	→	→	
6-Point Categorical Patient Global Evaluation[i]														x	
Subjects taking a rescue medication during this time will be considered:			Discontinued	Treatment Failure											
Concomitant Medications		x	x	x	x	x	x	x	x	x	x	x	x	x	
AE	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
SAE[j]	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

a. Screening must be within 30 days of surgery.
b. Screening laboratory tests include hematology, blood chemistry, urinalysis, coagulation, serum pregnancy test, and serum FSH as described in the protocol. In addition, females of child bearing potential will be given a serum pregnancy test at screening. If Early Termination, repeat safety labs.
c. Pregnancy test will be serum based at screening and urine based thereafter, provided the test has a sensitivity of at least 25 mIU/mL Females of CBP (child-bearing potential) must be given a urine pregnancy test on the morning of (but before) the surgery.
d. Contraception will be checked at Screening, Early Termination, and Follow-up. For subjects, this is the opportunity to assess any shift to or from childbearing to non-childbearing potential and address appropriately. In addition, the investigator or his/her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected.
e. 100 mm VAS Pain Severity Rating Scale: none=0 to severe=100.
f. 5-point Categorical Pain Relief Rating Scale: none=0, a little=1, some=2, a lot=3, and complete=4. Completed at each time point staring at 15 minutes post-dose and immediately before rescue medication use (if it occurs before hour 8).
g. Subject is instructed to stop the first stopwatch "when you first begin to feel any pain relieving effect whatsoever of the drug".
h. Subject is instructed to stop the second stopwatch "when you have meaningful relief, that is, when the relief from the pain is meaningful to you".
i. 6-point categorical Global Evaluation score: very poor=0, poor=1, fair=2, good=3, very good=4, excellent=5. Completed at the 8-hour time point or immediately before taking rescue medication.
j. SAE/AE active reporting period starts from when subject signs the ICD through 14 calendar days after the last administration of the investigational product. A qualified site staff member will conduct a post-study follow up via telephone 14 (or up to 17) days after the last dose of investigational product and inquire about any new SAE/AE. Assess immediately before administering rescue medication.
k. The 11-point Numerical Pain Severity Rating (NPSR) will evaluate pain intensity with 0= no pain and 10=worst possible pain. Completed at each time point and immediately before rescue medication use (if it occurs before hour 8). Subject must have a baseline pain score ≥5 on the 11-point NPSR confirmed by ≥50 on theVAS to be randomized to receive study medication.

Abbreviations & symbols: → = ongoing/continuous event; CBP= child bearing potential; FSH= follicle stimulating hormone; HR = heart rate; BP = blood pressure; NPSR= Numerical Pain Severity Rating; T = temperature; RR = respiration rate; PRR= Pain Relief Rating Scale; VAS = Visual Analogue Scale; PSR= Pain Severity Rating; AE= adverse event; SAE= serious adverse event;

[redacted]

1. INTRODUCTION

1.1. Mechanism of Action/Indication

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]

Caffeine, a methylxanthine, behaves as a competitive adenosine receptor antagonist at the A1 and A2 receptors, when plasma concentrations are between 10-100 μM, which has directly been implicated in action of caffeine in humans including the blockage of hyperalgesic effects of adenosine.[2]

1.2. Background and Rationale

Ibuprofen (IBU) is one of the most widely used nonprescription analgesic/antipyretic agents available. Serum concentrations of IBU have demonstrated a linear relationship to the level of analgesia.[4] The 400 mg strength of IBU is considered to be the most efficacious over-the-counter (OTC) dose of IBU in terms of efficacy and safety when compared to other available OTC NSAIDs.[7,8]

Caffeine, a methylxanthine, exerts a variety of pharmacological actions both peripherally and centrally in the body.[9] Generally, when caffeine is consumed in foods and drinks, the intake of caffeine can be classified into three broad categories: low (<100 mg per day), moderate (100-400 mg per day), and high intake (>400 mg per day), with a majority of individuals falling into the moderate consumption category.[5,6] Caffeine is also available as an oral pharmacologic agent at doses of 100-200 mg every 3-4 hours as needed for somnolence.[2]

Clinical studies have demonstrated that the combination of NSAIDs with caffeine is more effective than the NSAID alone in postpartum, headache, and postsurgical (dental) pain states.[3] Forbes et al, intended to quantify the relative incremental efficacy of the addition of caffeine 100 mg with IBU 100 mg and 200 mg using the postsurgical dental pain model. The results demonstrated the combination was 2.4 to 4.8 times more effective than IBU alone, and that the combination provides more rapid onset and longer duration of analgesic effect than IBU alone.[4] Subsequent studies of the combination of IBU with caffeine have shown that it may provide similar enhancement of analgesic effect versus the IBU alone and placebo in dental pain, post-episiotomy pain, tension headache, migraine headache, and dysmenorrhea pain.[10,11,12,13]

Pfizer Consumer Healthcare (PCH) has developed a novel fixed-dose liquid-filled gelatin capsule (subsequently referred to as liquid capsule) formulation consisting of 400 mg IBU with 100 mg of caffeine. The aim of this clinical study is to evaluate the relative analgesic efficacy of this novel formulation of IBU 400 mg with 100 mg of caffeine in a liquid capsule compared to IBU liquid capsule alone, providing consumers with a novel more effective formulation of IBU 400 mg for extra-strength pain relief.

PCH has not conducted any previous efficacy or safety studies using the IBU with caffeine combination. However, recently Boehringer Ingelheim has completed a study that has shown positive results with the combination of IBU and caffeine. However, a full publication is not yet available. Their preliminary data in abstract form suggest that the combination of IBU 400 mg and caffeine 100 mg provides 30-50% greater reduction in pain over 0-8 hours and 0-2 hours versus IBU alone.[14]

IBU and caffeine individually have safety and efficacy information that is available in the literature. Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's Brochure (IB) for the combination of IBU with caffeine. The SRSD for the comparator is the IB for Ibuprofen as a single agent.

1.2.1. Design Rationale

The dental pain model was chosen for this trial because the surgical procedure is elective, relatively consistent, and has a proven record of assay sensitivity, ie, separating active drugs from one another as well as from placebo. This acute pain model is accepted by the Agencies of interest for the proposed application and is the most widely used model to evaluate the efficacy of NSAID-type analgesics. The results from dental pain studies have been widely extrapolated to other general pain conditions including the most common non-prescription pain indications. The design of this study was presented and agreed to by the Agencies of interest, Health Canada and ANVISA (Agência Nacional de Vigilância Sanitária; Brazilian Health Surveillance Agency), with the intent of obtaining market approval for the same indication and dosing schedule as the currently marketed IBU liquid capsule formulation.

The patient-reported outcomes (PROs) and design elements of this study have been described in further detail and are recommended in the Food & Drug Administration (FDA) Draft Guidance for Industry Analgesic Indications: Developing Drug and Biological Products.[15]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of this study is to assess analgesic efficacy of a single oral dose of IBU 400 mg plus caffeine 100 mg, versus IBU 400 mg alone, and placebo, in subjects undergoing dental surgery for third molar extraction.

The secondary objective of the study is to assess the safety and tolerability of IBU 400 mg with caffeine 100 mg, IBU 400 mg, and placebo.

2.2. Endpoints

2.2.1. Primary Endpoint

- Time-weighted sum of pain relief rating (PRR) and pain intensity difference (PID) from 0 to 8 hours (SPRID0-8) for IBU 400 mg with caffeine 100 mg versus IBU 400 mg.

2.2.2. Secondary Endpoints

- Time-weighted sum of pain relief rating (PRR) and pain intensity difference (PID) scores over 2 hours (SPRID0-2), over 4 hours (SPRID0-4), over 6 hours (SPRID0-6) and over 8 hours (SPRID0-8, for IBU 400 mg with caffeine 100 mg versus placebo comparison) post dose;

- Time-weighted sum of pain intensity difference (PID) scores over 2 hours (SPID0-2), over 4 hours (SPID0-4), over 6 hours (SPID0-6), and over 8 hours (SPID0-8) post dose;

- Time-weighted sum of pain relief rating (PRR) over 2 hours (TOTPAR0-2), over 4 hours (TOTPAR0-4), over 6 hours (TOTPAR0-6), and over 8 hours (TOTPAR0-8) post dose;

- The sum of pain relief rating and pain intensity difference scores (PRID) at 0.25, 0.5, 1, 1.5, 2, 3, 4 5, 6, 7, and 8 hours post dose;

- Pain Relief Rating (PRR): scored on the 5-point Categorical Pain Relief Rating Scale (0=No relief to 4=Complete relief) at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post dose;

- Pain Intensity Difference (PID): calculated as the baseline 11-point Numerical Pain Severity Rating (NPSR) minus the post-dose NPSR at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post dose;

- Time to onset of "meaningful" relief;

- Time to onset of "first perceptible" relief, confirmed by "meaningful" relief;

- Duration of relief, as measured by the time to treatment failure (ie, time to first dose of rescue medication or discontinuation due to lack of efficacy).

CCI

[redacted]

- CCI [redacted]

[redacted]

CCI [redacted]

3. STUDY DESIGN

This will be a 3-arm, randomized, double-blind, placebo-controlled, parallel group, single-center, 8-hour inpatient study. Approximately 385 adolescent and adult subjects will be enrolled to ensure 346 complete the study.

Subjects will be healthy males and females aged 16-40 years, inclusive, who are experiencing post-operative pain following surgical extraction of 3 or more third molars, of which at least 2 must be a partial or complete bony mandibular impaction. Following extraction, subjects will rest quietly at the study center until they experience post-surgical pain severity of ≥5 on the 0-10 point numeric pain severity rating (NPSR) scale measuring pain severity, confirmed by a Visual Analog Pain Severity Rating Scale (VAS PSR) of at least 50 mm on a 100 mm VAS PSR scale. Upon completion of the baseline scales, eligible subjects will be randomized to receive a single oral dose of study medication under double-blind conditions and will be evaluated on-site for 8 hours following administration of study medication.

Subjects will be randomized to receive one of the following treatments in a 3:3:1 ratio:

- IBU 400 mg with caffeine 100 mg fixed-dose combination liquid-filled gelatin capsule;
- Advil® Extra Strength Liqui-Gels®, IBU 400 mg liquid-filled gelatin capsule (currently marketed product in Canada);
- Placebo (unprinted liquid filled gelatin capsule).

Once subjects have received the investigational product, they will complete post-baseline assessments described in Section 6.3. Subjects will evaluate the time to first perceptible relief and time to meaningful relief using a double stopwatch method up to 8 hours post-dose or until the time of first rescue medication use, whichever is sooner. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post-dose, subjects will provide ratings of pain severity using the 11-point NPSR and a rating of PR at each time point using a 5-point categorical Pain Relief Rating (PRR) scale. At 8 hours, subjects will also complete an overall assessment using the 6-point categorical Global Evaluation of the study medication. Adverse events will be assessed during the course of the study. All efficacy assessments are further described in Section 7.

[redacted]

4. SUBJECT ELIGIBILITY CRITERIA

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.

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

4.1. Inclusion Criteria

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

1. Males and females 16 years to 40 years of age (inclusive).

2. Female subjects of nonchildbearing potential must meet at least 1 of the following criteria:

   - Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

   - Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   - Have medically confirmed ovarian failure.

   All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

3. In good general health, and have no contraindications to any of the investigational products, rescue medications, or anesthetic drugs.

4. Evidence of a personally signed and dated informed consent document indicating that the subject [or a legally acceptable representative/parent(s)/legal guardian] has been informed of all pertinent aspects of the study. Subjects requiring a parent or legal guardian to sign the informed consent form will also be required to sign an assent document.

5. Subjects who have undergone outpatient surgical extraction of 3 or more third molars, of which at least 2 must be a partial or complete bony mandibular impaction within 30 days of Screening and have met baseline pain criteria as described in this protocol. (Note: dosing of study medication must occur within approximately 5 hours (ie, less than or equal to 5 hours, 15 minutes) after surgery is complete).

6. Subjects who are medically eligible to use only the following pre-operative medication(s)/anesthetic(s): topical benzocaine, a short acting parenteral (local) anesthetic (mepivacaine or lidocaine) with or without vasoconstrictor and/or nitrous oxide.

7. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

8. Reliable, cooperative, and of adequate intelligence to record the requested information on the analgesic questionnaire form.

9. Subjects who are willing and able to comply with the Lifestyle Guidelines listed in Section 4.4.

10. Examined by the attending dentist or physician and medically cleared to participate in the study.

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 hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurologic, metabolic or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing) determined by the Investigator to place the subject at increased risk including the presence or history within 2 years of screening of the following medical conditions/disorders:

    - Bleeding disorder;
    - Gastrointestinal ulcer or gastrointestinal bleeding;
    - Paralytic ileus or other gastrointestinal obstructive disorders.

2. Other severe acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior 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.

3. Subjects at risk for excessive bleeding, eg, those on anticoagulant therapy, etc.

4. Acute localized dental alveolar infection at the time of surgery that could confound the post-surgical evaluation.

[redacted]

5. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects of childbearing potential 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 14 days after the last dose of investigational product.

6. Hypersensitivity to ibuprofen, naproxen, aspirin, or any other NSAID, caffeine, or other component of the product.

7. History of asthma, urticaria, or other allergic-type reaction following aspirin or other NSAID or caffeine administration.

8. Use of a prescription or over the counter (OTC) drug with which administration of IBU, caffeine, or any other NSAID; codeine, tramadol or any other opioid is contraindicated and in the opinion of the Investigator will harm the subject to be included in the study (including: opioids, antipsychotics, antianxiety agents, or other central nervous system depressants [including alcohol]).

9. Use of any type of systemic corticosteroid within the past 30 days or a history of current or previous use of anabolic steroids.

10. Use of prescription or OTC antihistamines within 24 hours prior to taking study medication. (Note exceptions: loratadine [Claritin®], desloratadine [Clarinex®], cetirizine [Zyrtec®], levocetirizine [Allegra®], and azelastine [intranasal, Astelin®]).

11. Habituation to analgesic medications or caffeine (ie routine use of oral analgesics 5 or more times per week or ingestion of 4 or more caffeine-containing drinks daily); consumption of caffeine-containing "high energy" drinks (eg, Red Bull, Monster, etc.) more than once per week.

12. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated two more times and the average of the three BP values, which are taken approximately 5 minutes apart, should be used to determine the subject's eligibility.

13. Subjects who have ingested any caffeine-containing beverages, chocolate or alcohol, within 48 hours prior to taking study medication.

14. Inability or unwillingness to comply with the requirements of the protocol as judged by the Investigator.

15. Use of a bisphosphonate (eg, pamidronate [Aredia®], risedronate [Actonel®], alendronate [Fosamax®], or ibandronate [Boniva®]) within the past 5 years.

16. Prior use of any type of analgesic or NSAID within five half-lives of that drug or less before taking the first dose of study medication, except for pre-anesthetic medication and anesthesia required for the surgical procedure.

17. Currently taking a monoamine oxidase inhibitor (MAOI), antipsychotic, or any other neuroleptic or has taken:

    - A MAOI within 2 months of screening (Note: subjects may not discontinue taking an MAOI solely for the purpose of qualifying for the study);

    - An antipsychotic or other neuroleptic within 14 days of surgery (Note: subjects may not discontinue taking these medications solely for the purpose of qualifying for the study).

    - Patients who are currently taking any selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor or selective norepinephrine reuptake inhibitor (SNRI), or tricyclic antidepressant (TCA), and are not on a stable dose of this medication for at least 30 days prior to screening or will not maintain this dose throughout the study and their condition is judged by the Investigator to not be well controlled (Note: subjects may not discontinue taking these medications solely for the purpose of qualifying for the study).

18. History of regular alcohol consumption exceeding 7 drinks/week for females or 14 drinks/week for males (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. Patients who are taking St. John's Wort, or any other nutritional supplement known to have psychotropic effects may be enrolled if they have been on stable doses of medication for at least 2 months prior to screening will maintain this dose throughout the study, and their condition is judged by the Investigator to be well-controlled.

19. Clinically significant abnormalities on the screening laboratory tests determined by the Investigator or designee that would place the subject at increased risk, or subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat, if deemed necessary:

    - Aspartate aminotransferase (AST)/ serum glutamic oxaloacetic transaminase (SGOT) or alanine aminotransferase (ALT)/ serum glutamic pyruvic transaminase (SGPT) ≥3 × upper limit of normal (ULN);

    - Total bilirubin (Tbili) ≥1.5 × ULN; subjects with a history of Gilbert's syndrome may have a direct bilirubin measured and would be eligible for this study provided the direct bilirubin is less than or equal to ULN;

    - Hemotologic abnormality that is judged by the Investigator to be clinically significant, as evidenced by screening hematology assessment.

20. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

[redacted]

21. 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, including their family members, directly involved in the conduct of the study.

4.3. Randomization Criteria

Subjects must have at least a pain severity score of ≥5 on the 0-10 NPSR, confirmed by ≥50 mm on the 100 mm VAS-PSR scale within approximately 5 hours (ie, less than or equal to 5 hours, 15 minutes) after surgery to be eligible for randomization.

4.4. Lifestyle Requirements

4.4.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential as applicable to the study who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 14 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 from the permitted list of contraception methods (see below) and will confirm that the subject has been instructed in its consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use highly effective contraception consistently and correctly and document the conversation and the subject's affirmation in the subject's chart (subjects needs to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or 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 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. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (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.

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the investigational products) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

4.4.2. Dietary Restrictions

Subjects will report to the study center on the morning of their surgery in a fasted state (ie, they should not ingest food or drink after midnight of the preceding evening). At the surgeon's discretion, clear liquids or gelatin may be provided to the subject prior to surgery. Subjects may not ingest any caffeine containing beverages, chocolate, or alcohol within 48 hours prior to taking study medication or during the entire 8 hour evaluation period.

No food will be allowed following surgery through 2 hours after the ingestion of study medication. Low fat (≤20% of calorie intake from total fat)[10] xanthine free beverages, soups, or soft foods suitable for consumption by a post-surgical dental patient will be available to the subject at all other times provided that no food is consumed within 30 minutes before a pain assessment time point. The times of food consumption will be recorded in the source document.

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 supporting study documentation.

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 product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator 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 investigator 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 investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. 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 investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator 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).

For this study, the investigational product(s) are:

Table 1. Investigational Product Description

	Strength and Product Identification	**Dosage Form and Package Size**	**Route of administration**
Test	Ibuprofen 400 mg + caffeine 100 mg Advil Migraine Liqui-Gels (International, Unprinted) (WH-1769-0002-001)	Liquid filled gelatin capsule unprinted (72-count bottle)	Oral
Active Comparator	Ibuprofen 400 mg Advil Extra Strength LiquiGels (Canada) (WH-1121-0004-001)	Liquid filled gelatin capsule printed (80-count bottle)	Oral
Placebo	Placebo capsule Placebo for Advil Migraine Liqui-Gels II (Unprinted) (WH-0689-0017-001))	Liquid filled gelatin capsule unprinted (identical to Test product; 72-count bottle)	Oral

5.1. Allocation to Treatment

Treatment assignments will be determined by a computer generated randomization schedule and will be maintained by Pfizer Global Randomization Operations team. In order to maintain the double-blind integrity of the study at the investigator and subject levels, only a third party person(nel) at the investigational site (ie, not involved in any other aspect of the trial) assigned to prepare and administer the study medication will have access to the randomization schedule and dispensing records during the study period.

Subjects will be stratified by gender and baseline pain severity (moderate or severe, where a score of 5 to 7 on the 11-point NPSR will be classified as "moderate" and a score of 8 to 10 will be classified as "severe"), and be randomized to receive one of the following study medications in a 3:3:1 ratio:

- Test: IBU 400 mg with caffeine 100 mg liquid capsule;
- Active Comparator: Advil Extra Strength LiquiGels® 400 mg liquid capsule;
- Placebo (administered as a liquid capsule).

Randomization numbers will be assigned in consecutive ascending order within each stratum as shown in Table 2. The site will be provided with sufficient study medication to allow for the enrollment of approximately 385 subjects.

Table 2. Study Number Assignment Sequence

Gender	Baseline Pain	Randomization Number Series (allocation system)
Male	Moderate	Ascending 10000 series (eg, 10001, 10002, 10003, …)
Male	Severe	Ascending 20000 series (eg, 20001, 20002, 20003, …)
Female	Moderate	Ascending 30000 series (eg, 30001, 30002, 30003, …)
Female	Severe	Ascending 40000 series (eg, 40001, 40002, 40003, …)

Note: Subjects will also be assigned an 8-digit enrollment ID number at Screening.

5.2. Breaking the Blind

The study will be investigator- and subject-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 should consult 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 in the case report form (CRF).

In the event of a medical emergency that necessitates breaking the code, the third party person(nel) will be permitted to inform the Investigator what investigational product the subject was given. This disclosure will only be broken by the Investigator 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 Sponsor's Clinician in advance.

When the blind is broken, the Investigator will notify the Sponsor's Clinician 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 be recorded in the CRF and in the source document. Any AE or serious adverse events (SAE) associated with breaking the blind must be recorded and reported as specified in this protocol.

5.3. Subject Compliance

All doses of investigational product will be administered by the appropriately designated study staff at the investigator site.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

The Sponsor will provide the investigational products described above in bulk and will send prepared labels for the corresponding medication to the site.

Rescue medications, tramadol and codeine, will be supplied by the site.

5.4.2. Preparation and Dispensing

The Sponsor, PCH Clinical Supplies will provide instructions on how to prepare the investigational product for administration. Investigational product (ie, study medication and placebo) and rescue medication 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 and state laws, and institutional guidance.

On the day of surgery, each subject entered into the study will be given one dose (1 liquid filled capsule) of the randomly assigned investigational product with approximately 6-8 ounces of room temperature water when they are experiencing post-surgical pain of at least moderate severity. From the time that study medication is taken, the duration of evaluation will be 8 hours.

The Sponsor will supply the investigational products in bulk and in an unblinded fashion. PCH Consumer Study Supplies will provide randomization codes generated by the Pfizer Global Randomization Operations directly to the individual identified by the study site. A documentation packet consisting of the investigational product dispensing record that will contain the randomization codes and 2-part double-blind labels will be provided to the assigned third party person(nel) only. Opaque plastic bottles and caps will be supplied separately from the labels to the third party person(nel) as well.

The third party dispenser will prepare study medication for each subject in a designated dispensing room. Baseline pain assessments and drug administration will be completed in the subject's room. Investigational product will be dispensed at the time the subject's pain level is determined by verbal assessment by the appropriately qualified site staff member, just prior to the completion of the baseline NPSR for pain severity and VAS PSR. The study coordinator will communicate the subject's pain severity to the dispenser. If qualified for randomization, the dispenser will assign the next available randomization number. The dispenser will dispense the randomized investigational product (2 liquid-filled gelatin capsules per dose) from the appropriate bulk supply containers into an individual opaque plastic bottle. The double-blind label with the same randomization number will be affixed to the bottle and the identification tab will be affixed to the investigational product dispensing record. The investigational product dispensing record will remain in a secure locked area with access limited to the dispenser and the alternate(s). A second individual with no other study involvement will witness the preparation and dispensing process. No other study personnel will be present in the designated dispensing room at the time of investigational product dispensing. No other individuals will be able to see the investigational product in the bottle once the bottle cap is closed.

The third party dispenser will inform the study coordinator once the investigational product is dispensed and is ready to be administered to the subject. The dispenser will deliver the investigational product from the designated dispensing room to the subject's room.

5.5. Administration

Investigational product will be administered to the subject within 7 minutes of the completion of the qualifying baseline pain assessments by the third party dispenser. To maintain blinding to study treatments, no other study personnel should be present at the time of dosing.

After the subject has been blindfolded, while the subject is sitting up, the dispenser will give the capsule to the subject with approximately 6-8 ounces of room temperature water (Time=0). Subjects will swallow the study medication whole, and will not manipulate or chew the medication prior to swallowing.

5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products, including comparator and/or marketed products, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the IB will be superseded by the storage conditions stated on the product label.

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 evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the

temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.7. Investigational Product Accountability

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

Upon receipt at the study site, the carton containing the investigational product will be stored unopened in the study treatment storage room. The Principal Investigator or an appropriate designee, and a representative of PCH will conduct an inventory and complete the study treatment inventory record, preferably at study initiation, but prior to first subject first visit (FSFV). Any interim shipments will be inventoried by the Principal Investigator or his/her designee, and if possible, a representative of PCH. For all interim shipments, a study treatment inventory record will be completed.

The Principal Investigator or an appropriate designee, upon dispensing the investigational product, must record the information in an investigational product dispensing/return log. For accounting purposes and assessing subject compliance, a representative of PCH will review the investigational product dispensing/return log, inventory the investigational product, 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.

5.7.1. Destruction of Investigational Product Supplies

All investigational products shipped for this clinical trial will be returned to the Sponsor upon conclusion or termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of PCH will inventory all used and unused investigational product. PCH will retain the original shipment documentation and inventory record, and the Investigator will retain a copy for his/her files. All used investigational product (empty containers), as well as all unused investigational product will then be returned to:

Pfizer Consumer Healthcare
Consumer Study Supplies
1211 Sherwood Avenue
Richmond, VA 23220
Attention: Returned Study Supplies
Protocol No. B3741002
(804) 257-2905

[redacted]

5.8. Concomitant Treatment(s)

Rescue medication as defined in Rescue Medication, will be allowed during the course of the study. Ice packs may only be applied once the subject has completed the 2-hour pain assessment, and they may not be applied within 30 minutes prior to any other pain assessment.

Except for the above treatments, no other treatments expected to confound the evaluation of the investigational product. All concomitant medications used during the study will be recorded in the case report form. Antibiotics are permitted at the discretion of the Investigator.

5.9. Rescue Medication

Rescue medications should be dispensed and administered by an appropriately qualified member of the site in accordance with state and local laws, and institutional guidance.

Subjects not experiencing adequate relief after the one-hour time point evaluation may be given tramadol hydrochloride (immediate release tablets) 50 to 100 mg orally, based on the discretion of the Investigator, as rescue medication. If needed, subjects may receive up to 2 additional doses of rescue medication (ie, tramadol 50 to 100 mg orally every 4 to 6 hours as needed [prn] based on the discretion of the Investigator) at the study center (ie, within 8 hours after dosing with study medication). The total maximum dose of tramadol, which may be taken at the study center, is 300 mg (total daily dose should not exceed 400 mg).

Alternatively, any subject not experiencing adequate relief after the one-hour time point evaluation may be given codeine sulfate (immediate release tablets) 15 to 60 mg orally, based on the discretion of the Investigator, as rescue medication. If needed, subjects may receive up to 2 additional doses of rescue medication (ie, codeine sulfate 15 to 60 mg orally every 4 hours as needed (prn) [based on the discretion of the Investigator]) at the study center (ie, within 8 hours after dosing with study medication). The total maximum dose of codeine sulfate, which may be taken at the study center, is 180 mg (total daily dose should not exceed 360 mg).

Subjects may not take any study rescue medication home with them.

Subjects who take rescue medication during the course of the evaluation period will remain in the study for the full 8-hour duration and continue to perform their efficacy assessments.

Subjects taking rescue medication within one hour after dosing will be considered discontinued and must be replaced. They will remain in the study for the full 8-hour duration and continue to perform their efficacy assessments.

The use of rescue medication will be recorded in the appropriate section of the CRF. The date, time, name of rescue medication taken, and reasons for use will be recorded.

6. STUDY PROCEDURES

6.1. Screening

During the screening period (for this protocol, defined as the time period from the screening visit until start of surgery), the Investigator or his/her designee will examine each subject in order to determine the subject's eligibility. Screening procedures include:

- Informed consent/assent;
- Review Inclusion and Exclusion criteria;
- Demographic information;
- Medical history including history of drug and alcohol use;
- Prior medications;
- Vital signs, including sitting blood pressure (BP), heart rate (HR), respiratory rate (RR), temperature (T);
- Contraception check;
- Assess for spontaneous reporting of adverse events and/or serious adverse events (AEs/SAEs) by asking the subjects to respond to a non-leading question such as "How do you feel?
- Laboratory testing (See Laboratory Tests for further details); Following at least a 4-hour fast, collect blood and urine specimens for the following:
  - Hematology;
  - Blood chemistry (complete metabolic panel);
  - Urinalysis;
  - Coagulation tests;
  - Serum pregnancy test (females of CBP only);
  - Serum FSH (post-menopausal women only).

Screening procedures must be completed within 30 days of the surgery. Subjects will be screened only once and are assigned a screening number. Subjects may undergo screening procedures again only if the surgery cannot be scheduled within 30 days. The Investigator or his/her designee will enter the pertinent historical information (including any medication taken recently) and clinical findings in the appropriate section(s) of the source documents. A Subject Screening and Enrollment Record (provided by PCH) will be maintained to

document all subjects screened for entry into the study. All subjects/parent(s)/legal guardian/legally acceptable representative will provide written informed consent before participating in the study. Subjects are required to read, comprehend, and sign the informed consent/assent.

6.2. Day of Surgery

Surgery will be scheduled within 30 days of the screening visit.

Subjects will not be allowed to wear a watch during the study, and they may not have access to a clock, including mobile electronic devices that display time. Furthermore, stopwatches used in the study will have the time display covered when in use by the subject.

Day of Surgery procedures that should be completed prior to surgery include:

- Review Inclusion and Exclusion criteria;
- Check for concomitant medications (assessed through hour 8);
- Assess for any AEs or SAEs (assessed through hour 8): An assessment of symptoms should be completed for spontaneous reporting of adverse events by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Females of child-bearing potential (CBP) must be given a urine pregnancy test on the morning of, but before the surgery.

Upon surgery, the following will be noted and recorded on the CRF:

- Date of surgery and the times surgery was initiated and completed (for this protocol, surgery initiation and completion are defined as the time of first incision and as the time of last suture completion, respectively);
- Surgical status of each extracted tooth (ie, erupted, soft tissue impacted, partial bony impacted, full bony impacted);
- The identifying number of each tooth extracted (this may not exceed four third molars; a single additional supernumerary tooth may be extracted if necessary), and
- The surgical trauma rating scale;
- The time of the last meal prior to surgery will be noted in the source document only.

6.3. Study Period

Post-operatively, no ice packs may be applied to the patient until completion of the 2-hour pain assessment, and they may not be applied within 30 minutes prior to any other pain assessment.

Subjects will be asked to rest quietly at the study center until they experience post-surgical pain at a level that meets the entry criteria for randomization (See Randomization Criteria). At that time, subjects will be asked to complete the baseline 11-point Numerical Rating Scale and the 100 mm VAS PSR scale.

- 11-point Numerical Pain Severity Rating (NPSR);
    - A minimum score of 5 out of 10 must be indicated before the subject can enter the trial. The NPSR will be assigned a whole number value where 0= none and 10= worst possible pain.
- VAS Pain Severity Rating Scale (VAS PSR);
    - A minimum score of 50 mm on the VAS PSR is required to confirm that the subject has at least moderate pain at baseline in order to be randomized. Subjects with scores <50 mm by approximately 5 hours (ie, less than or equal to 5 hours, 15 minutes) after surgery will not be randomized.

Subjects who do not reach a qualifying baseline pain threshold (at least 6 or greater on NPSR confirmed by a score of at least 50 mm on the VAS PSR) within approximately 5 hours (ie, less than or equal to 5 hours, 15 minutes) of completion of surgery will not be randomized to receive investigational product.

Baseline vital signs (HR, BP, RR, and T) will also be measured and recorded and should be complete within approximately 15 minutes prior to dosing.

Upon completion of the baseline scales, eligible subjects will be randomized to receive a single oral dose of investigational product (consisting of 2 liquid-filled capsules) under double blind conditions. Investigational product must be administered within approximately 7 minutes of baseline measurements. The time of dosing "time 0" is recorded in the source and CRF.

When the subject is administered study medication at time 0, the Study Coordinator will start two stopwatches (see Time to First Perceptible Relief and Time to Meaningful Relief for further details).

Throughout the study period, an assessment of symptoms should be completed for reporting of adverse events by asking the subjects to respond to a non-leading question such as "How do you feel?"

6.3.1. Post-baseline Assessment

The following assessments will be conducted at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post-dose:

- 11-point NPSR;

- 5-point Categorical PRR Scale.

Subjects will also evaluate the time to "First Perceptible" Relief by depressing a stopwatch at the moment they first begin to experience "perceptible" relief as well as the time to "Meaningful" Relief by depressing a second stopwatch at the moment they first begin to experience "meaningful" relief (see Time to First Perceptible Relief and Time to Meaningful Relief for further details). These elapsed times will be recorded up to 8 hours after dosing, or until the time of (first) rescue medication use, whichever is sooner.

6.4. End of Study Assessments

At the 8-hour assessment for the study, ie, after the last efficacy assessment is collected and assuming there are no outstanding AEs of concern, the subject will undergo the following study assessments.

At this time, the following procedures will be completed:

- 6-point Categorical Global Evaluation of the study medication;
- Assess vital signs (ie, HR, BP, RR, and T) within 15 minutes of last collection of efficacy assessments;
- Review of any reported AE/SAEs;
- Assess for concomitant treatments;
- Laboratory test;
- Contraception check;
- Discharge from clinical research unit (CRU).

For any subject with outstanding AEs, the end of study procedures are performed after the Principal Investigator is satisfied that all AEs are resolved. In the event that the subject is unwilling to complete end of study assessments, every effort should be made to contact the subject and document outcome appropriately.

6.4.1. Follow-up Contact

Follow-up contact will be completed at least 14 calendar days, and up to 17 calendar days after the last administration of the investigational product to capture any potential adverse events (see the Time Period for Collecting AE/SAE Information section) and to confirm appropriate contraception usage (see the Contraception section). Contact with the subject will be done via a phone call.

6.5. Rescue Medication Assessments

The following assessments will be conducted immediately before (within 5 minutes) the first use of rescue medication or at the time of withdrawal (if applicable):

- 11-point NPSR;
- 5-point categorical PRR Scale;
- 6-point categorical Global Evaluation of the study medication;
- Assess for AE/SAEs;
- Vital signs (ie, HR, BP, T, and RR) will be measured and recorded within 15 minutes of administration of the rescue medication.

6.6. Subject Withdrawal/ Early Termination

Subjects will be withdrawn from the study at any time under the following circumstances:

- Any subject who violates any condition of the entrance criteria after having been entered into the study;
- Any subject who reports inadequate relief and requires rescue medication prior to one hour after taking the study medication;
- Any subject who develops a confounding concomitant illness (discontinuation as deemed necessary by the subject, research coordinator or investigator), serious AE, or a hypersensitivity to the investigational product;
- Any subject who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study;
- Any subject who requires any concomitant medication (other than rescue medication) during the course of the study that could confound the study results;
- Any subject who vomits within 1 hour following dosing.

The following assessments will be conducted at the time of withdrawal/Early Termination, if possible:

- 11-point NPSR;
- 5-point categorical PRR Scale;
- 6-point categorical Global Evaluation of the study medication;
- Assess vital signs (ie, HR, BP, T, and RR);

- Contraception Check;
- Review of any reported AE/SAEs;
- Assess for concomitant treatments;
- Discharge from clinical research unit (CRU).

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved. The early termination visit only applies to subjects who are randomized and then are prematurely withdrawn from the study.

Withdrawal of consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

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 (see also the Withdrawal From the Study Due to Adverse Events section) 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 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's 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) or serious adverse events (SAEs).

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.

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

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 manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Baseline Efficacy Assessments

7.1.1. 11-Point Numerical Pain Severity Rating (NPSR)

The 11-point NPSR for pain severity will be completed at all of the times specified in the Schedule of Activities, and immediately before rescue medication is taken (if necessary) or at the time of withdrawal, to evaluate pain intensity in response to the question:

"How much pain do you have at this time?"

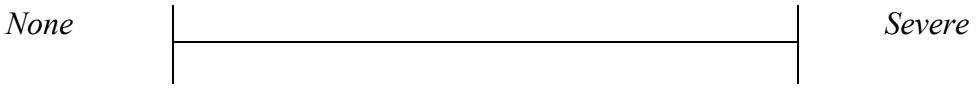
None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible Pain

Subjects will be instructed to circle the number that best matches their pain severity. A score of 5 or above must be indicated to confirm subject entry into the trial. Subjects with a score of 5 to 7 are considered to be moderate pain and a score of 8 to 10 will be considered to be severe pain.

7.1.2. VAS Pain Severity Rating Scale (VAS PSR)

The 100 mm VAS PSR is administered after the NPSRand will also be used to rate the severity of baseline pain. Subjects will be instructed to:

"Draw a single vertical line on the scale that shows how much pain you have at this time."



(Figure not to scale)

Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left (none=0 to severe=100). A minimum score of 50 mm is required to confirm that the subject has reached an appropriate level of pain measured by the 11-point NPSR baseline. Subjects with scores <50 mm by approximately 5 hours (ie, less than or equal to 5 hours, 15 minutes) after surgery will not be randomized.

7.2. Post-Baseline Efficacy Assessments

7.2.1. Numerical Pain Severity Rating (NPSR)

The 11-point NPSR for pain severity will be completed at all of the times specified in the Schedule of Activities, and immediately before rescue medication is taken (if necessary) or at the time of withdrawal, to evaluate pain intensity in response to the question:

"How much pain do you have at this time?"

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible Pain

Subjects will be instructed to circle the number that best matches their pain severity.

7.2.2. Categorical Pain Relief Rating (PRR) Scale

The 5-point Categorical Pain Relief Rating (PRR) Scale will be completed at the times specified in the Schedule of Activities, and immediately before rescue medication is taken (for the first time, as necessary) or at the time of withdrawal, to evaluate pain relief in response to the question:

"How much relief do you have from your starting pain?"

None A Little Some A Lot Complete

Each category on this scale will be assigned a whole number value of 0 (none), 1 (a little), 2 (some), 3 (a lot), or 4 (complete) and the corresponding number will be recorded in the CRF.

7.2.3. Time to First Perceptible Relief

When the subject is administered study medication at time 0 hours, the Study Coordinator will start two stopwatches. Each stopwatch will have its face covered; one will be labeled "first perceptible relief" and the other "meaningful relief." In an effort to determine the exact moment that the subject begins to obtain noticeable pain relief, the subjects will be given the stopwatch labeled "first perceptible relief" and will be instructed as follows:

> *"Stop the stopwatch when you first begin to feel any pain relieving effect whatsoever of the drug. That is, when you first feel a little relief. This does not necessarily mean that you feel completely better, although you might, but when you first feel any difference in the pain that you have now."*

The elapsed time of this stopwatch will be recorded in the CRF. The stopwatch will remain active for 8 hours, until stopped by the subject, or until rescue medication is administered.

7.2.4. Time to Meaningful Relief

In an effort to determine the exact moment that the subject begins to obtain meaningful pain relief, the subjects will be given the stopwatch labeled "meaningful relief" and instructed as follows:

> *"Stop this stopwatch when you have meaningful relief, that is, when the relief from the pain is meaningful to you."*

The elapsed time of this stopwatch will be recorded in the CRF. The stopwatch will remain active for 8 hours, until stopped by the subject, or until rescue medication is administered.

7.2.5. Global Evaluation

At the time points specified in the Schedule of Activities (at the 8-hour time-point), or immediately before taking rescue medication (for the first time, as necessary), a Global Evaluation of the study medication will be performed. The Global Evaluation, on a 6-point categorical scale, will be performed in response to the following question:

"How would you rate this medication as a pain reliever?"

Very Poor Poor Fair Good Very Good Excellent

Responses on this categorical scale will be assigned values of 0 (Very Poor), 1 (poor), 2 (fair), 3 (good), 4 (very good) or 5 (Excellent) and the corresponding number will be recorded in the CRF.

7.3. Laboratory Tests

The following safety laboratory tests will be performed at screening. 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. All laboratory data will be collected in the source documentation.

Table 3. Laboratory Tests

Hematology	**Blood Chemistry**	**Urinalysis**	**Other**
Hemoglobin	BUN/urea and creatinine	pH	FSH[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	β-hCG[c]
RBC count	Calcium	Protein (qual)	
MCV	Sodium	RBC	
MCH	Potassium	WBC	
MCHC	Chloride	Ketones	
Platelet count	Total CO_2 (bicarbonate)	Nitrites	
WBC count	AST, ALT	Leukocyte esterase	
Total neutrophils (Abs)	Total bilirubin	Urobilinogen	
Eosinophils (Abs)	Alkaline phosphatase	Urine bilirubin	
Monocytes (Abs)	Uric acid	Hyaline Casts	
Basophils (Abs)	Albumin	Granular Casts	
Lymphocytes (Abs)	Total protein	Epithelium	
		Bacteria	
		Crystals	
		Mucous Threads	
		Microscopy[a]	
	Coagulation		
	PT		
	PTT		
	INR		

a. Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b. At Screening only, in female subjects who are amenorrheic for at least 12 consecutive months.
c. Serum β-hCG at screening, and urine β-hCG pregnancy test at all other listed time points for females of childbearing potential.

RBC = red blood cell; MCV = mean corpuscular volume; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; WBC = white blood cell; Abs = absolute; BUN = blood urea nitrogen; AST = aspartate transaminase; ALT = alanine transaminase; pH= potential of Hydrogen; PT = prothrombin time; PTT= partial thromboplastin time; INR = international normalized ratio; qual = qualitative; FSH = follicle-stimulating hormone; β-hCG = beta human chorionic gonadotropin

7.3.1. Temperature

Oral temperature will be measured at times specified in the STUDY PROCEDURES section and recorded in the source document and CRF to the nearest 0.1° Fahrenheit. No eating, drinking or smoking is allowed for 15 minutes prior to the measurement (with the exception of baseline measurement following dosing). Additional collection times, or changes to collection times will be permitted, as necessary, to ensure appropriate collection of safety data.

[redacted]

7.3.2. Blood Pressure and Heart Rate

BP and HR 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.

Sitting BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after at least approximately 5 minutes of rest. Repeated measures should be taken after 5 minutes of rest as well. When possible the same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated blood pressure cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and HR should be obtained prior to the nominal time of the blood collection and recorded to the nearest mm Hg in the source and CRF.

7.3.3. Respiratory Rate

Respiratory rate (RR) will be measured after approximately 5 minutes rest in sitting position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When BP is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before BP measurement. Measurements will be recorded to the nearest breaths per minute in the source and CRF.

7.4. Pregnancy Testing

For female subjects of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at screening and a urine pregnancy test of the same sensitivity will be performed at admission before investigational product administration at the baseline visit to confirm the subject has not become pregnant during the study.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

7.5. Contraception Check

Subjects need to affirm that they meet adequate methods of contraception as outlined in the protocol. 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 (SOA) and document such conversation in the source document. In addition, the investigator or his/her designee will instruct the subject to call immediately if a selected contraception method is discontinued or if pregnancy is known or suspected.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and 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 Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see Also the Subject Withdrawal Section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject /parent(s)/legal guardian/legally acceptable representative provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 14(+3) calendar days after the last administration of the investigational product. At Day 14 (or up to Day 17) following the last administration of study medication (final telephone contact), the subject /parent(s)/legal guardian/legally acceptable representative will be contacted by telephone to inquire about SAEs, including hospitalizations and newly diagnosed chronic medical conditions since the day of the surgery when the last study medication was administered.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety 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 must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

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.

8.1.5. 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 on the CRF, 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. 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, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. 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.

[redacted]

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study 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 signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

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

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- 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 (outside of any protocol-specified dose adjustments) 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 recording as an AE.

8.2.3. 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.

Or that is considered to be:

- An important medical event.

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.

8.2.4. 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 is 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 a 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 SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, 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.

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between the investigational product and an event specified below, these events should not be reported to Pfizer Safety by the investigator as SAEs. These events are anticipated to occur commonly in a population requiring surgical extraction. However, these events should still be recorded as AEs on the CRF.

Protocol-specified SAEs that will not normally be reported to Pfizer Safety in an expedited manner:

- Paresthesia;
- Fracture of the mandible;
- Fracture of the maxilla;
- Oroantral communication.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal standard operating procedures.

[redacted]

8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator 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 and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.3.1. Exposure During Pregnancy

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

- 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).

- 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 subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT 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) to Pfizer Safety 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 Safety 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 to Pfizer Safety 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 sponsor. 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 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.

8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.3.3. 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 Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.4.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- 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.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is 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 of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

One hundred forty-eight (148) subjects in each of the IBU with caffeine and IBU treatment groups will assure at least 85% power to detect a difference of 10.5 units in SPRID 0-8 using a two-sided t-test at the 0.05 significance level. This calculation was based on a root mean square error of 30, which was observed in an earlier study.[14] Additionally, a sample size of 50 subjects in the placebo group will provide at least 85% power to detect a difference of 14.83 units in SPRID 0-8 between each active treatment and placebo at the 5% significance level (two-sided).

Thus, a total of 346 (148 for each active treatment and 50 for the placebo) subjects are required to complete the study per protocol. To allow for 10% drop-outs, a total of approximately 385 (165 for each active treatment group and 55 for the placebo) subjects will be enrolled.

9.2. Efficacy Analysis

9.2.1. Analysis Populations

9.2.1.1. Primary Analysis Set

The full analysis set (FAS) will be the primary analysis population and it is defined as all randomized subjects who dosed with the study medication and provided a baseline assessment.

9.2.1.2. 'Per Protocol' Analysis Set

The 'per-protocol' analysis set will include all subjects who completed the study per protocol (evaluable subjects). Thus, this analysis set will exclude any subjects who were discontinued from the study, or had a significant protocol violation. The subjects who will be excluded from the 'per-protocol' analysis set will be documented prior to breaking of the study blind. If the per protocol population consists of 90% or more of the FAS subject population, a per protocol analysis will not be performed.

9.2.2. Analysis of the Primary Endpoint

- The primary endpoint SPRID 0-8 will be analyzed using an analysis of covariance (ANCOVA) model with treatment, gender, and baseline pain severity terms in the model. Ninety five percent (95%) confidence limits for the treatment difference will be reported.

9.2.3. Analysis of Secondary Endpoints

- The summary scores of SPID, TOTPAR and SPRID from 0-2, 0-4, 0-6 and 0-8 hours, as well as PRR, PID and PRID scores at each post-dosing time point will be analyzed using ANCOVA with treatment, gender, and baseline numerical pain severity terms in the model. Ninety five percent (95%) confidence limits for the treatment difference will be reported.

- Time to onset of meaningful relief will be analyzed using the Gehan-Wilcoxon test to compare treatments, stratifying by gender and baseline pain severity (moderate or severe) factors. It will also be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals for the median will be reported by treatment.

- Time to onset of first perceptible relief, confirmed by meaningful pain relief, and duration of relief as measured by the time to rescue medication, will be analyzed using the Gehan-Wilcoxon test to compare treatments, stratifying by gender and baseline pain severity (moderate or severe) factors. They will also be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals for the median will be reported by treatment.

9.2.4. Adjustment for Multiple Comparisons

No multiple comparisons are planned for primary endpoint.

9.2.5. Derivation of Endpoints

- PID: based on the 11-point NPSR scale ranging from 0 (”no pain”) to 10 (”worst possible pain”), will be derived by subtracting the score at each post-dosing time point from the baseline score, so that a higher positive value is indicative of greater improvement.

- PRID: will be calculated by summing the PID and PRR at each post-dosing time point.

- SPIDt: time-weighted sum (weighted by the time since the prior scheduled assessment) of PID scores from time 0 to t (where t=2, 4, 6 and 8).
- TOTPARt: time-weighted sum of pain relief rating from time 0 to t (where t=2, 4, 6 and 8).
- SPRIDt, time-weighted sum of PRID scores from time 0 to t (where t=2, 4, 6 and 8).

9.2.6. Data Conventions/ Handling of Missing Data

Efficacy assessments are scheduled to be completed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, and 8 hours post-dose and the analyses will be done corresponding to these time points. Because some subjects may complete their assessments at times differing from the scheduled time points, each such score will be adjusted so as to reflect more accurately the score that would have been observed had it been recorded at the scheduled time point. For each analysis time point, time windows will be created, using a width of ±5 minutes for time points which are less than one hour apart, and a width of ±10 minutes for time points which are one hour or more apart. All pain relief and pain severity scores for each subject will be assigned to analyzed time points according to these windows. The assignment rules will be as follows:

- All assessments completed more than a minute after a subject takes the first dose of rescue medication will be ignored. Remaining efficacy scores subsequent to the time of rescue medication will be extrapolated (see below for method of extrapolation).
- If an assessment is performed within a time point window, the corresponding value will be assigned to that time point (eg, an assessment performed anywhere between 115 and 125 minutes, regardless of when it was scheduled, will be assigned to the 2-hour time point). If more than one value falls within a window (this may include assessments completed at the time of rescue medication), a simple average of the values will be used.
- If a particular time point has no value within its window, then a value will be assigned by either interpolation or extrapolation. If an assessment is available before and after the time point window, then a value will be interpolated by calculating the weighted average of the values immediately preceding and subsequent to the time point window, with weights inversely proportional to the duration between the analyzed time point and the actual time.
- If a window is empty and no subsequent scores are available, a value will be assigned to the empty window via extrapolation. The extrapolated value will depend on whether rescue medication was taken or whether the subject dropped out due to lack of efficacy during or before the particular time point's window. If so, the worse of the preceding score (this may be the assessment completed at the time of rescue medication) and the baseline score will be assigned as the pain severity scores, and a score of 0 (no relief) as the pain relief score. If the missing data are not due to subject taking rescue medication, or discontinuation due to lack of efficacy, then the last observation will be carried forward for the pain severity scores and the pain relief scores.

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

9.4. Safety Analysis

The safety analysis set will include all subjects who received at least one dose of the investigational product.

Adverse event (AE) analyses will include all events which initially occurred, or worsened following treatment. Adverse events will be summarized by the MedDRA system organ class (SOC) and preferred term and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to investigational 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 investigational product, the AE will be classified according to the worst relationship.

9.5. Interim Analysis

No interim analysis is planned.

9.6. 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 investigator site may be subject to review by the IRB/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 investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. 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 or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/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/assent 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/assent 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 the protocol, legal and regulatory requirements, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

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 numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator 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/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

At the conclusion of the study treatment period, subjects must return all products to the site. No products should be given to the subjects or legal guardian or parents to take home.

12.4. 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 regulatory 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

The end of trial is defined as the last subject last visit (LSLV).

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 the fixed- dose combination of ibuprofen with caffeine at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 15 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 (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD 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 prespecified 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 PCD for studies in adult populations or within 6 months of the PCD 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 the principal investigator (PI) of the results of the study based on information collected or generated by the PI, 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 it is 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 investigator sites, and that any subsequent publications by the PI 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.

[redacted]

16. REFERENCES

1. Ibuprofen. In: DRUGDEX System (Micromedex Pharmaceutical Knowledge). Greenwood Village, CO: Truven Health Analytics; c1974-2016. http://www.micromedexsolutions.com.proxy1.athensams.net. Accessed 31 May 2016.

2. Caffeine. In: DRUGDEX System (Micromedex Pharmaceutical Knowledge). Greenwood Village, CO: Truven Health Analytics; c1974-2016. http://www.micromedexsolutions.com.proxy1.athensams.net. Accessed 31 May 2016.

3. Laska EM, Sunshine A, Marrero I, et al. The correlation between blood levels of ibuprofen and clinical analgesic response. Clin Pharmacol Ther. 1986; 40:1–7.

4. Forbes JA, Beaver WT, Jones KF, et al. Effect of caffeine on ibuprofen analgesia in postoperative oral surgery pain. Clin Pharmacol Ther 1991;49:674-84.

5. Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. Cochrane Database Systematic Review 2014;12:CD009281.

6. Drewnowski, A.; Rehm, C.D. Sources of Caffeine in Diets of US Children and Adults: Trends by Beverage Type and Purchase Location. *Nutrients* (2016), *8*, 154.

7. Black P, Max MB, Desjardin P, et al. A Randomized Double-Blind Placebo-Controlled Comparison of the Analgesic Efficacy, Onset of Action, and Tolerability of Ibuprofen Arginate and Ibuprofen in Postoperative Dental Pain. Clinical Therapeutics 2002; 24 (7): 1072-1089.

8. Sachs CJ. Oral analgesics for acute non-specific pain. *Am Fam Physician.* 2005*;* 71 (5): 913-18.

9. Sawynok J and Yaksh TL. Caffeine as an Analgesic Adjuvant: A Review of Pharmacology and Mechanisms of Action. Pharmacological Review; 45 (1): 43-85.

10. Diamond S, Balm TK, Frederick GF. Ibuprofen plus caffeine in the treatment of tension-type headache. Clin Pharmacol Ther 2000;68:312-19.

11. Bloomfield SS, et al. Ibuprofen/caffeine for dysmenorrhea. International Congress and Symposium Series 218; Advances in the Management of Acute Pain. 1996: 93-104.

12. Lipton RB, Stewart WF, Ryan RE, et al. Efficacy and safety of acetaminophen, aspirin, and caffeine in alleviating migraine headache pain – Three double-blind, randomized, placebo-controlled trials. Arch Neurol 1998;55:210-17.

13. Akin MD, VanOsdell DJ, Balm TK. Multiple dose study evaluating the analgesic efficacy of ibuprofen plus caffeine compared to ibuprofen and placebo in women with primary dysmenorrhea. Clin Pharmacol Ther 1996;59(2):131.

14. Weiser T, Hegewisch A, Richter E, et al. Ibuprofen/caffeine is a superior analgesic compared to ibuprofen caffeine and placebo: a randomized, placebo-controlled trial in patients with postoperative dental pain. (Abstract EFIC5-0289) Presented at the 9th Congress of the European Pain Federation EFIC, 2015, Vienna, Austria.

15. FDA Arthritis Advisory Committee. Discussion of revisions to FDA's guideline for the clinical evaluation of analgesic drugs. Bethesda, MD; July 29-30, 2002.

16. FDA Arthritis Advisory Committee. Pain claim structure for chronic and acute pain and onset of pain relief for Rx and OTC oral analgesics. Gaithersburg, MD; March 25, 1998.

17. Lichtenstein, AH, Appel LJ, Brands M, et al. Diet and Lifestyle Recommendations Revision 2006: A Scientific Statement from the American Heart Association Nutrition Committee. Circulation 2006 Jul 4; 114 (1):82 96.

[redacted]

Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	Analysis of covariance
ANVISA	Agência Nacional de Vigilância Sanitária (Brazilian Health Surveillance Agency)
AST	aspartate aminotransferase
BP	blood pressure
CBP	child-bearing potential
CMH	Cochrane Mantel-Hanzel
CK	creatine kinase
CRF	case report form
CRU	clinical research unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
DILI	drug-induced liver injury
EC	ethics committee
EDP	exposure during pregnancy
EMA	European Medicines Agency
FDA	Food & Drug Administration
FSFV	first subject first visit
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
IB	Investigator's Brochure
IBU	ibuprofen
ICH	International Conference on Harmonisation
ID	identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
LFT	liver function test
LSLV	last subject last visit
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
N/A	not applicable

Abbreviation	Term
NPSR	Numerical Pain Severity Rating Scale
NSAID	non-steroidal anti-inflammatory drug
OTC	Over the counter
PCH	Pfizer Consumer Healthcare
PCD	Primary completion date
PI	principal investigator
PRID	Sum of pain relief rating and pain intensity difference score
PRR	Pain relief rating
PSR	Pain severity rating
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SNRI	selective norepinephrine reuptake inhibitor
SOA	schedule of activities
SOC	System Organ Class
SOP	standard operating procedure
SPID	Time-weighted sum of pain intensity difference
SPRID	Time-weighted sum of pain relief and pain intensity difference
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
t	time
TBili	total bilirubin
TCA	tricyclic antidepressant
ULN	upper limit of normal
US	United States
VAS	Visual analog scale
VAS-PSR	Visual analog scale- pain severity rating