A PHASE 3, DOUBLE-BLIND, RANDOMIZED SAFETY AND EFFICACY STUDY COMPARING MULTIPLE ADMINISTRATIONS OF IBU 250 MG/APAP 500 MG (ADMINISTERED AS TWO TABLETS OF IBU/APAP 125 MG/250 MG) TO PLACEBO IN THE TREATMENT OF POST SURGICAL DENTAL PAIN IN ADULT SUBJECTS

Compound:	PF-06438867
Compound Name:	Not Applicable
United States (US) Investigational New Drug (IND) Number:	112538
European Clinical Trials Database (EudraCT) Number:	Not Applicable
Protocol Number:	B5061004
Phase:	3

Document History

Document	Version Date	Summary of Changes
Original Protocol	13 May 2016	Not Applicable (N/A)
Original final protocol	15-Dec-2015	Not Applicable (N/A)
Revised final protocol	12-Jan-2016	Addition of 28-day post final dose call visit added to schedule of activities and Section 6.3 modified to describe this call. Modification of the rescue medication from codeine phosphate to codeine sulfate.
Revised final protocol	2-Feb-2016	Modification of Section 1.2.2, so that first sentence of the 4th paragraph now reads: IBU/APAP combinations at OTC levels have been studied in humans, including single and multiple dose pharmacokinetics, single and multiple dose oral surgery studies, and a multiple dose knee pain study. Modification of Section 4.1 so that inclusion criterion 8 now reads: Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment. Modification of Section 4.4, so that the first sentence of the first paragraph now reads: All male subjects who are able to father children and female subjects who are of childbearing potential and are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. Modification of Section 5.2, 2nd paragraph, first sentence which now reads: 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 study drug the subject was given. Section 5.4.1, second sentence inserted: Rescue medication, tramadol and codeine sulfate, and supplies will be provided by the study site. Modification of Section 5.5, first sentence, which now reads: Investigational product will be administered to the subject within 7 minutes of the completion of the baseline pain assessments and, thereafter, every 8 hours by the third party dispenser. Modification of Section 5.7, first paragraph, second sentence which now reads: Study product will be sent to the third party dosing person(nel). Confirmation of receipt of study product by the third party dosing person(nel) must be documented. Modification of Section 6.2, so that the last sentence now reads: Each subject's vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded at baseline, prior to other assessments being performed.
Revised final protocol	13-May-2016	Section 4.1 Inclusion Criteria. Inclusion Criterion add was modified and now reads: 1. Male subjects able to father children and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment. Section 4.4 Lifestyle Guidelines was modified to allow the investigator to allow sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with study treatments) to obviate

		the need for contraception ONLY if this is the preferred and usual lifestyle of the subject. Section 5.1. Allocation to Treatment was modified and now reads: Treatment assignments will be determined by a computer generated randomization schedule generated and maintained by Pfizer Randomization Administration. Section 5.4.2 Preparation and Dispensing. Investigational Product preparation was modified to allow for preparation up to 48 (forty-eight) hours in advance of actual dispensing. 5.6. Investigational Product Storage was modified to clarify storage conditions for IP prepared up to 48 hours in advance of actual dispensing. 5.9 Rescue Medication. The text was modified to indicate that rescue medication should be administered within 5 minutes of rescue assessments being performed. 6.1 Screening & Day of Surgery. Section was modified to include information and instructions relating to the day of surgery. Add Section 9.2.1. which now reads: 9.2.1.1 Primary Analysis Set: The full analysis set (primary population) is the intent to treat (ITT) subject population, defined as all randomized subjects who dosed with the study medication and provided a baseline assessment. CCI [redacted]

		CCI 9.2.1.3. Safety Analysis Set The safety analysis set will include all subjects who received at least once dose of the study product. Section 9.2.2. Modified ANCOVA model and now reads: Analysis of Primary Endpoint. Primary efficacy endpoint SPID[11] 0 24 will be analyzed by an analysis of covariance model (ANCOVA) with treatment, categorical baseline PSR, baseline numerical PSR, and gender terms. CCI Section 9.2.3 Modified using log-rank(Gehan-Wilcoxon) test for time to event endpoints to using Gehan-Wilcoxon test for time to event endpoints.
Amendment 1	09 Feb 2017	CCI Throughout the protocol gender was changed to sex.

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

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PROTOCOL SUMMARY

Background and Rationale

Ibuprofen (IBU) and acetaminophen (APAP) are the two most widely used non-prescription analgesic/ antipyretic drugs both in the United States and globally. 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] Both drugs have been extensively studied, and their efficacy and safety profiles in humans are well-established. IBU and APAP do not share metabolic pathways, which diminishes the likelihood of drug-drug interactions.[4] Pharmacokinetic studies[5,6] have demonstrated that there are no alterations in drug levels when the two analgesics are administered together, which is consistent with a lack of drug-drug interactions.

Pfizer Consumer Healthcare (PCH) conducted a proof-of-concept (POC) dental pain study (B5061001) to determine the minimum dose of IBU and APAP fixed-dose combination that was superior to IBU 400 mg. Three IBU/APAP fixed dose combinations (FDCs) were evaluated for overall analgesic efficacy: 200 mg/500 mg, 250 mg/500 mg, and 300 mg/500 mg, provided as two tablets, compared to IBU 400 mg and placebo in the third molar extraction model of dental pain. The results indicated that all active treatments were significantly better than placebo for all endpoints. Furthermore, the 200 mg/500 mg FDC formulation was numerically better compared to IBU 400 mg for the primary and most of the secondary endpoints. As anticipated, the overall incidence of adverse events (AEs) was comparable across all treatment groups with no meaningful differences observed in any system organ class (SOC). There were no safety concerns observed and all treatments were well tolerated.

Previous-published studies[7,8] have also shown that FDC IBU 200 mg/APAP 500 mg was statistically superior to APAP 1000 mg and nearly significantly superior to IBU 400 mg, suggesting a synergistic analgesic effect. This potential synergistic analgesic effect would suggest lower doses of each medication can be used in combination to provide superior analgesia compared to maximum amounts of either medication alone.

Based on these results, PCH proposes to continue the development of a non-prescription IBU/APAP 250 mg/500 mg FDC (administered as two tablets of 125 mg/250 mg IBU/APAP) to support the over the counter (OTC) approval of an FDC of IBU and APAP tablet that would provide superior analgesia and antipyresis compared to the maximum single OTC dose of either monocomponent alone.

Objectives and Endpoints

The objective of the study is to compare the analgesic efficacy and safety of FDC IBU/APAP 250 mg/500 mg dosed every 8 hours compared to placebo in a 48-hour period following extraction of ≥3 third molar teeth.

Primary Efficacy Endpoint

- SPID [11] (sum of pain intensity difference scores) from 0-24 hours (time-weighted sum of PID[11] scores based on the 11-point numerical Pain Severity Rating [PSR] scale).

Secondary Endpoints

- SPID [11] (time-weighted sum of Pain Intensity Difference scores PID[11] based on the 11-point Numerical PSR scale) from 0-8, 6-8, 8-16, 0-16, and 0-48 hours;
- Duration of relief after first dose, as measured by the time from first dose to rescue medication or second dose whichever occurs first;
- Time to onset of "meaningful" relief for the first dose.

Other Endpoints

- CCI [redacted]
- CCI [redacted];
- CCI [redacted];
- CCI [redacted]
- CCI [redacted]
- CCI [redacted];
- CCI [redacted];
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted];
- CCI [redacted]
- CCI [redacted]

Study Design

This will be a Phase 3, 48-hour, single-center, in-patient, multiple-dose, fixed dosing interval, randomized, placebo-controlled, sex and baseline pain severity-stratified, double-blind, parallel group trial. Subjects will be adult males and females (18 to 40 years of age, inclusive) who are experiencing post-operative pain following surgical extraction of 3 or more third molar teeth. Following extraction of 3 or more third molar teeth, subjects will rest quietly at the study center until they experience post-surgical pain of at least moderate severity. At that time, subjects will be asked to assess their pain intensity and severity using categorical, numerical, and/or visual scales. Subjects with a qualifying baseline pain threshold within approximately 5 hours of completion of surgery will be entered into the study. Upon completion of the baseline scales, eligible subjects will receive an oral dose of investigational product at 0 hours (baseline) and at 8, 16, 24, 32, and 40 hours post-baseline under randomized, double-blind conditions. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 32, 40, and 48 hours post-baseline, subjects will provide self-ratings of pain severity using the categorical and numerical PSRs. Subjects will also provide a self-rating of pain relief at each time point (except at baseline) using a categorical CCI [redacted] scale. At 24 and 48 hours, or at the first rescue medication administration on the respective day, subjects will also complete a CCI [redacted] of the investigational product. Additionally, subjects will also evaluate the time to CCI [redacted] and time to meaningful relief using a double stopwatch method up to 8 hours post-baseline (ie, up to the second dose administration), or until the time of first rescue medication use, whichever is sooner. A review of any reported adverse events will also be completed.

Study Treatments

Study treatments will be: A) FDC IBU/APAP 250 mg/500 mg and B) Placebo.

Statistical Methods

A detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the plans outlined in the protocol; however, any major modifications to the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

All statistical tests will be performed at a two-sided 0.05 level of significance. The primary end point, SPID[11]0-24 hours (based on numerical pain scale), will be analyzed by an analysis of covariance (ANCOVA) model with treatment, sex, baseline categorical PSR, and baseline numerical PSR terms in the model.

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

Sample Size: Using root mean square of error (RMSE) data for SPID[11] over 2, 8 and 12 hours from Study B5061001, a single dose dental pain study, it was estimated that the RMSE for SPID[11] over 0-24 will be approximately 52 units. Based on this assumption, a sample size of 68 subjects for IBU/APAP 250 mg/500 mg group and 34 for placebo group (a ratio of 2:1) will provide 85% power (at 5% level of significance, two sided) to detect a treatment difference of at least 33 units for SPID[11] 0-24.

Thus, a total of 102 subjects are required to complete the study (evaluable subjects). Assuming a 10% drop-outs rate, a total of approximately 112 subjects will be enrolled.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Schedule of Activities

Visit Identifier			Time (hours)													
	Screen[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	9.0, 10.0, 11.0, 12.0	16.0	24.0	32.0	40.0	48.0	28 Calendar Days after Last Dose
Informed Consent	x															
Inclusion & Exclusion Criteria	x	x														
Demographic Information	x															
Medical History	x															
Physical Examination	x															
Screening Laboratory Tests[b]	x															
Hematology	x															
Blood Chemistry	x															
Urinalysis	x															
Coagulation	x															
Serum Pregnancy Test	x															
Urine Pregnancy Test[c]		x														
Surgical Procedure		x														
Surgical Trauma Scale		x														
Vital Signs (HR, BP, T, RR)[d]	x		x						x						x	
Randomization[e]			x													
Dosing			x						x		x	x	x	x		
Pain Evaluations																
VAS Pain Severity Rating[f]			x													
Categorical Pain Severity Rating[g]			x	x	x	x	x	x	x	x	x	x	x	x	x	
Numerical Pain Severity Rating[h]			x	x	x	x	x	x	x	x	x	x	x	x	x	
CCI				x	x	x	x	x	x	x	x	x	x	x	x	
CCI [j]				→												
Time to 'Meaningful' Relief[k]				→												
CCI													x		x	
Subjects taking a rescue medication during this time will be considered:			Discontinued					Treatment Failure								
Prior/Concomitant Medications			→													
Adverse Events			Recorded at any time during the study as they occur.													x[m]
Follow-Up Call[m]																x

a. Screening must be within 30 days of surgery; it may occur on the morning of surgery.
b. Screening laboratory tests include complete blood count (CBC) with differential count, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), chemistry panel including liver function tests, and urinalysis. In addition, females of child bearing potential will be given a serum pregnancy test at screening.
c. Females of child bearing potential must be given a urine pregnancy test on the morning of surgery.
d. Vital signs also done at time of rescue if applicable.
e. Those subjects meeting all inclusion/exclusion criteria, including at least moderate baseline pain on the Categorical PSR Scale confirmed by a score of at least 50 mm on a 100 mm Visual Analog PSR Scale.
f. 100 mm Visual Analog PSR Scale: none=0 to severe=100.
g. CCI : none=0, mild=1, moderate=2, and severe=3. Completed at each post-baseline time point and immediately before rescue medication use.
h. 11 point Numerical PSR Scale: none=0 to 10 = Worst Possible Pain. Completed at each time point and immediately before rescue medication use.
i. CCI : none=0, a little=1, some=2, a lot=3, and complete=4. Completed at each time point and immediately before rescue medication use.
j. Subject is instructed to stop the first stopwatch "when you first begin to feel any pain relieving effect whatsoever of the drug." Stopwatches should only be maintained for the first 8 hours.
k. 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".
l. CCI : very poor=0, poor=1, fair=2, good=3, very good=4, excellent=5. Completed at the designated time points or immediately before taking rescue medication on each day.
m. Study site personnel will conduct a safety follow-up 28 calendar days after last dose via a telephone call to the subject to ascertain if any SAEs have occurred.

End of Study procedures will include the assessment/reporting of vital signs and a review of AEs.
Abbreviations: → = ongoing/continuous event; BP = blood pressure; HR = heart rate; multiple-admin. = multiple administrations; RR = respiration rate; T = temperature.

1. INTRODUCTION

Ibuprofen (IBU) and acetaminophen (APAP) are the two most widely used non-prescription analgesic/ antipyretic drugs both in the United States and globally. Ibuprofen, a "traditional" non-steroidal anti-inflammatory drug (NSAID), decreases the synthesis of pain- and inflammation-promoting prostaglandins via non-selective inhibition of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2).[1] The mechanism of action of APAP, which has no significant anti-inflammatory activity, is not clear. However, it may involve COX inhibition in the central nervous system (CNS) and activation of central serotonergic pathways.[2,3] Both drugs have been extensively studied, and their efficacy and safety profiles in humans are well-established. IBU and APAP do not share metabolic pathways, which diminishes the likelihood of drug-drug interactions.[4] Pharmacokinetic studies[5,6] have demonstrated that there are no alterations in drug levels when the two analgesics are administered together, which is consistent with a lack of drug-drug interactions.

The main safety concern with IBU use, primarily at higher prescription doses over extended periods of time, is gastrointestinal toxicity. In contrast, APAP over dosage may cause potentially fatal hepatic failure. Based on safety concerns related to APAP, in June 2009 an FDA Analgesics Advisory Committee recommended reducing the maximum single adult dose of APAP in OTC products (from 1000 mg to 650 mg), and lowering the current maximum total daily dose APAP (from 4000 mg to 3250 mg) (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM174697.pdf).

This study will compare the efficacy and safety of a fixed-dose combination (FDC) of IBU/APAP 250 mg/500 mg (administered as two tablets of IBU/APAP 125 mg/250 mg) administered every 8 hours compared to placebo over a 48-hour period in subjects with at least moderate dental pain after extraction of ≥3 third molar teeth.

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] The mechanism of action of APAP, which has no significant anti-inflammatory activity, is not clear. However, it may involve COX inhibition in the CNS and activation of central serotonergic pathways.[2,3]

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

1.2. Background and Rationale

IBU and APAP are among the most widely used non-prescription medications, both in the United States and globally, and have well established efficacy and safety profiles. For many of those who use currently marketed OTC pain relievers, no single analgesic agent can completely relieve moderate to severe acute pain. A ceiling effect is obtained with

non-opioid analgesics such as IBU and APAP, in which increasing doses produce little or no analgesic benefit but increase the risk of adverse effects. Therefore, there is an unmet consumer need for a superior non-prescription analgesic with a favorable safety profile. Combining two different analgesics with different mechanisms of action, such as IBU and APAP, may provide superior efficacy to either agent alone without increasing the risk of side effects. In addition, an analgesic with superior efficacy may reduce the need for additional doses of other analgesics, thereby reducing the total amount of analgesics consumed and leading to improved consumer safety.

1.2.1. Study Rationale

Two published studies[7,8] demonstrated that a combination of IBU 400 mg plus APAP 1000 mg provided analgesic efficacy superior to either analgesic alone in post-surgical dental pain, without increasing the occurrence of side effects. Furthermore, the same combination, at a dose of IBU/APAP 200 mg/500 mg, was statistically superior to APAP 1000 mg and nearly significantly superior to IBU 400 mg. The finding that IBU 200 mg/APAP 500 mg is nearly statistically superior to IBU 400 mg suggests that slightly higher doses of IBU in the combination may be significantly superior to IBU 400 mg.

The modern version of the dental pain model, developed in the mid-1970s, has been used in hundreds of clinical trials conducted by many different investigators.[9] One of the most widely utilized of all acute pain models, the surgical procedure is extremely standardized, and the surgery requires either minimal or no use of CNS depressant anesthetics. While the methodology is similar to that utilized in other acute pain models, the assay sensitivity is very good due to the homogeneity of the study population, the predictable level and appropriate intensity of the postsurgical pain, and the minimization of variability by using only a small number of study centers. The dental impaction pain model has been used to evaluate NSAIDs, opioids, and combination analgesics, as well as some investigational drugs with unique mechanisms of action. The model is particularly useful for proof of concept studies that require dose ranging and profiling the time effect curve for efficacy including onset, peak effect, and duration of analgesic activity.

1.2.2. Safety Data

Ibuprofen and APAP each have an extensive literature evaluation in nonclinical studies. Most studies have been performed in rodents which are more sensitive to IBU and APAP, particularly to gastrointestinal (GI) toxicity associated with IBU. IBU has been linked to vomiting, gastric irritation and ulceration in dogs, with additional duodenal and jejunal ulceration in rats, mice, and monkeys. There are significant interspecies differences in the severity and location of GI toxicity and the differences are thought to be associated with levels of COX 1 and COX 2 and the ratio of COX 1 to COX 2 in the GI tract. Both COX 1 expression and relative COX 1/COX 2 expression are highest in the rat and dog compared to humans. Of the species tested, rats are the most sensitive to GI toxicity, showing effects at doses that are therapeutic in humans (Radi and Khan, 2006).[10] Therefore, quantitative dose comparisons between animals and humans regarding gastrointestinal toxicity are not useful.

Two year rodent assays have shown that neither IBU (up to 180 mg/kg, lowered at week 55 to 60 mg/kg due to gastric lesions) nor APAP (up to 320 mg/kg) present a risk for human carcinogenicity, despite some mixed findings in genotoxicity assays. Neither compound is teratogenic, with APAP, however, having some potential effect on fertility.

Two studies[11,12] have been conducted in rats to investigate the toxicity of an IBU and APAP combination. The doses of APAP and IBU used were very high, up to 100 mg/kg and 200 mg/kg, respectively. Both studies reported an increase in the number and severity of lesions in the stomach of rats when the drugs were administered in combination. Neither study, however, tested a range of doses nor identified a no observed adverse effect level (NOAEL), so it is not possible to calculate a safety factor based on data from these studies.

IBU/APAP combinations at OTC levels have been studied in humans, including single and multiple dose pharmacokinetics, single and multiple dose oral surgery studies, and a multiple dose knee pain study. These studies show that the adverse event (AE) profile of an IBU/APAP combination product at the doses proposed in this document is not materially different than the AE profile of the individual components at their maximum dose level.[6,7,8,13]

In a more recent Pfizer Consumer Health (PCH)-sponsored proof of concept study, the safety of three IBU/APAP FDCs (200 mg/500 mg, 250 mg/500 mg, and 300 mg/500 mg administered as two tablets) was compared to IBU 400 mg and placebo in the third molar extraction model of dental pain. The overall incidence of adverse events (AEs) was comparable among all treatment groups with no meaningful differences observed in any SOC. There were no safety concerns observed and all treatments were well tolerated. (Data on file).

In summary, IBU and APAP have good safety profiles at OTC doses. In combination, at very high doses, increased frequency and severity of stomach lesions were observed in rats. However, these data are of limited relevance to human use for three reasons. First, rats are more sensitive than humans to GI toxicity and a NOEL was not identified. Second, the doses of APAP and IBU used, up to 100 mg/kg and 200 mg/kg, respectively, are many fold higher than the proposed maximum single human doses. Third, increased gastrointestinal toxicity has not been observed with IBU and APAP combination products in human studies at the dose levels proposed for this program.

1.2.3. Dose Rationale

The dose to be evaluated in this study is a multiple oral dose of FDC IBU/APAP 250 mg/500 mg (administered as two tablets of IBU/APAP 125 mg/250 mg). Based on once per day dosing, the proposed maximum daily dose of the IBU/APAP combination will be 250 mg/500 mg, which is well below the current daily OTC maxima of 1200 mg and 4000 mg, respectively and is in line with the FDA's Analgesics Advisory Committee recommendation of lowering the current maximum total daily dose APAP (from 4000 mg to 3250 mg).
(http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM174697.pdf).

In the PCH-sponsored proof of concept study (B5061001), the efficacy of three IBU/APAP FDCs (200 mg/500 mg, 250 mg/500 mg, and 300 mg/500 mg administered as two tablets) was compared to IBU 400 mg and placebo in the third molar extraction model of dental pain. The results indicated that all active treatments were significantly better than placebo for all endpoints. (Data on file).

1.2.4. Single Reference Safety Document

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The objective of the study is to compare the analgesic efficacy and safety of FDC IBU/APAP 250 mg/500 mg (administered as two tablets of IBU/APAP 125 mg/250 mg) every 8 hours compared to placebo in a 48-hour period following extraction of ≥3 third molar teeth.

2.2. Endpoints

This protocol will not use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using pre-defined endpoint criteria.

2.2.1. Primary Efficacy Endpoint

- SPID[11] (sum of pain intensity difference scores) from 0-24 hours (time-weighted sum of PID[11] scores based on the 11-point Numerical PSR scale).

2.2.2. Secondary Endpoints

- SPID[11] (time-weighted sum of Pain Intensity Difference scores PID[11] based on the 11-point Numerical PSR scale) from 0-8, 6-8, 0-16, 8-16, and 0-48 hours;
- Duration of relief after first dose, as measured by the time from first dose to rescue medication or second dose whichever occurs first;
- Time to onset of "meaningful" relief for the first dose.

2.2.3. Other Endpoints

- CCI [redacted]
- CCI [redacted];

- CCI [redacted];
- CCI [redacted]
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted];
- CCI [redacted]

3. STUDY DESIGN

This will be a Phase 3, 48-hour, single-center, in-patient, multiple-dose, fixed dosing interval, randomized, placebo-controlled, sex- and baseline pain severity-stratified, double-blind, parallel group trial in approximately 102 subjects (68 subjects for IBU/APAP 250 mg/500 mg group and 34 for placebo group [a ratio of 2:1]). Subjects will be adult males and females (18 to 40 years of age, inclusive) who are experiencing post-operative pain following surgical extraction of 3 or more third molar teeth.

Following extraction of 3 or more third molar teeth, subjects will rest quietly at the study center until they experience post-surgical pain of at least moderate severity. At that time, subjects will be asked to assess their pain intensity and severity using categorical, numerical, and/or visual scales. Subjects with a qualifying baseline pain threshold within approximately 5 hours of completion of surgery will be entered into the study.

Upon completion of the baseline scales, eligible subjects will receive an oral dose of investigational product at 0 hours (baseline) and at 8, 16, 24, 32, and 40 hours post-baseline under randomized, double-blind conditions. At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 32, 40, and 48 hours post-baseline, subjects will provide self-ratings of pain severity using the categorical and numerical PSRs. Subjects will also provide a self-rating of pain relief at each time point (except at baseline) using a categorical CCI [redacted] scale. At 24 and 48 hours, or at the time of first rescue medication on each respective day, subjects will also complete a CCI [redacted] of the investigational product. Additionally, subjects will also evaluate the time to CCI [redacted] and time to meaningful relief using a double stopwatch method up to 8 hours post-baseline (ie, up to the second dose administration) or until the time of first rescue medication use, whichever is sooner. A review of any reported adverse events will also be completed.

4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Males and females 18 years to 40 years of age (inclusive).

2. Outpatients who have undergone surgical extraction of 3 or more third molars, of which at least 2 must be a partial or complete bony mandibular impaction.

3. Subject must have at least moderate pain on the 4-point categorical scale, confirmed by at least 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 is completed.

4. Use of 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.

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

6. In general good health and have no contraindications to the study or rescue medication.

7. Female subjects are not pregnant, as verified by a urine based pregnancy test, or breast feeding female subjects.

8. Male subjects able to father children and female subjects of childbearing potential who are, in the opinion of the investigator, sexually active at risk for pregnancy with their partner(s) must agree to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of assigned treatment.

9. 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.

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

4.2. Exclusion Criteria

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

1. Presence or history of any significant hepatic, renal, endocrine, cardiovascular, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorder 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:

    - Gastrointestinal ulcer or gastrointestinal bleeding;

    - Paralytic ileus or other gastrointestinal obstructive disorders;

    - Bleeding disorder.

2. Clinically significant abnormalities on the screening laboratory tests determined by the Investigator or designee that would place the subject at increased risk.

3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

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

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

6. Hypersensitivity to ibuprofen, naproxen, aspirin, or any other NSAID; or to APAP, tramadol, other opioids, or to their combinations.

7. Use of a prescription or OTC drug with which administration of ibuprofen or any other non-steroidal anti-inflammatory drug; acetaminophen; codeine, tramadol or any other opioid is contraindicated (including: opioids, antipsychotics, antianxiety agents, or other CNS depressants [including alcohol]).

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

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

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

11. 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).

    - Subjects 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).

12. 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, or currently abusing other mood altering drugs (eg, cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines and amphetamines, etc) within 6 months of screening. Subjects 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.

13. Habituation to analgesic medications (ie, routine use of oral analgesics 5 or more times per week).

14. Subjects who have ingested any caffeine-containing beverages, chocolate, or alcohol, within 4 hours prior to taking investigational product.

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

16. Subject has previously participated in this study.

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

18. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.

4.3. Randomization Criteria

Subject must have at least moderate pain on the 4-point categorical scale, confirmed by at least 50 mm on the 100 mm visual analog scale (VAS) PSR scale within approximately 5 hours after surgery to be eligible for randomization.

4.4. Lifestyle Guidelines

All male subjects who are able to father children and female subjects who are of childbearing potential and in the opinion of the investigator, are sexually active and at risk for pregnancy must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject and his or her partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to

use highly effective contraception consistently and correctly according to the Schedule of Activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of hormonal methods of contraception is associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal) provided the subject 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 post-vasectomy 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).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

Female subjects of non-childbearing potential must meet at least one of the following criteria:

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

- Have medically confirmed ovarian failure; or

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level confirming the post-menopausal state.

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

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

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose.

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 in the site master file.

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

5. STUDY TREATMENTS

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

5.1. Allocation to Treatment

Treatment assignments will be determined by a computer generated randomization schedule generated and maintained by Pfizer Randomization Administration. 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 investigational product (Section 5.4.2) will have access to the randomization schedule and dispensing records during the study period.

Subjects will be stratified by sex and baseline pain (moderate or severe pain as determined by their baseline categorical pain severity scores), and will randomly receive one of the following investigational products under randomized, double-blind conditions in a 2:1 ratio:

- IBU/APAP 250 mg/500 mg (administered as 2 tablets of IBU/APAP 125 mg/250 mg);
- Placebo (administered as 2 tablets).

CCI [redacted].

PPD [redacted]

5.2. Breaking the Blind

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

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 study drug 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 PCH monitor 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 also be recorded on the eCRF and in the source document. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

5.3. Subject Compliance

Study treatment will be administered under the supervision of qualified investigative site personnel.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

The Sponsor will supply investigational product and matched placebo in bulk (See Table 2) suitable for administration by a disinterested third party (ie, not involved in any other aspect of the trial). Rescue medication, tramadol and codeine sulfate, and supplies will be provided by the study site.

Table 2. B50610014 — Study Product

Investigational Product Description/ CCI	CCI
IBU/APAP 125/250 mg tablets CCI	CCI
Placebo CCI	CCI

A detailed description of each treatment (ie, the investigational product and placebo that each subject will receive) is shown in Table 3.

Table 3. Detailed Description of Each Treatment Group

Treatment Group	Strength Per Tablet	Strength Per Dose/Route
A: IBU/APAP 250/500 mg	IBU/APAP 125/ 250 mg per tablet	2 tablets (equivalent to IBU/APAP 250 mg/500 mg) Orally
B: Placebo	Not Applicable	2 tablets Orally

5.4.2. Preparation and Dispensing

On the day of surgery, each subject entered into the study will be given one dose (2 tablets) of the randomly assigned investigational product with approximately 6 to 8 ounces of room temperature water when they are experiencing post-surgical pain of at least moderate severity. Thereafter, subjects will receive investigational product in the same manner every 8 hours. From the time that investigational product is taken, the duration of evaluation will be 48 hours.

The Sponsor will supply investigational product in an unblinded fashion. To maintain the double blind status of the study, the following dispensing and dosing procedures will be followed. The site will identify a qualified third party and alternate(s) who will be responsible for dispensing and administering the investigational product. CCI [redacted] The 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 investigational product for each subject in a designated dispensing room. Investigational product may be prepared up to 48 (forty-eight) hours in advance of actual dispensing to enrolled subjects. 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, just prior to the completion of the baseline categorical pain severity scale and VAS PSR. The study coordinator will communicate the subject's pain severity to the dispenser. The dispenser will assign the next available randomization number. The dispenser will dispense the appropriate 2 tablets 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 tear off portion of the label will be attached to the investigational product dispensing record. The third party dispenser will affix the identification tab to the investigational product dispensing record and complete 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 baseline pain assessments and, thereafter, every 8 hours by the third party dispenser. No other study personnel will be present at the time of dosing.

After the subject has been blindfolded, while the subject is sitting up, the dispenser will give the 2 tablets to the blindfolded subject with 6 to 8 ounces of room temperature water (time=0). Subjects will swallow the investigational product 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 any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. A PCH representative will inspect the study product storage area and discuss the study product accountability system with the Principal Investigator before any agreements are concluded between the Principal Investigator and PCH.

Investigational product should be stored in its original container and in accordance with the label. Investigational product prepared in advance of actual dispensing to enrolled subjects must be stored under the same conditions, and along with, bulk containers from which the subject-specific product container was prepared. Storage conditions stated in the single reference safety document (SRSD) (eg, IB) will be superseded by the storage conditions stated in the labeling.

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

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

Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

Upon receipt at the study site, the carton containing the study product will be stored unopened in the study treatment storage room. Study product will be sent to the third party dosing person(nel). Confirmation of receipt of study product by the third party dosing person(nel) must be documented. At the study initiation, the Principal Investigator or an appropriate designee, and a representative of PCH will conduct an inventory and complete the study treatment inventory record. The original will be sent to PCH and the Principal Investigator will retain a copy. 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 original will be returned to PCH and the Principal Investigator will retain a copy.

The Principal Investigator or an appropriate designee, upon dispensing the study treatment, must record the information on a study treatment dispensing/return log. For accounting purposes and assessing subject compliance, a representative of PCH will review the study treatment dispensing/return log, inventory the study treatment, and inspect the storage facility at appropriate time intervals throughout the clinical investigation, depending on the length of

the study. The Principal Investigator must account for any significant discrepancy and/or deficiency.

5.7.1. Destruction of Investigational Product Supplies

All investigational study treatment shipped for this clinical trial will be returned to the Sponsor at the termination of the study. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of PCH will inventory all used and unused investigational study treatment. The study treatment inventory record for returned study treatment will then be completed. PCH will retain the original, and the Investigator will retain a copy for his/her files. All used investigational study treatment (empty containers), as well as all unused study treatment will then be returned to the sponsor (see Section 5.7).

Upon receipt at PCH Consumer Study Supplies, CCI [redacted], a letter acknowledging the receipt of returned materials and a copy of the packing slip will be sent to the Clinician.

5.8. Concomitant Treatment(s)

Except for rescue medication as defined in Section 5.9, no other medications expected to confound the evaluation of the study product will be allowed during the course of the study. All concomitant medications used during the study will be recorded in the eCRF. Antibiotics are permitted at the discretion of the Investigator (refer to Section 4.1).

5.9. Rescue Medication

Subjects not experiencing adequate relief after the one-hour time point evaluation may take tramadol (immediate release tablets) 50 to 100 mg orally, based on the discretion of the Investigator, as rescue medication. If needed, subjects may receive 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 48 hours after first dose of investigational product). The total maximum daily dose of rescue medication, tramadol hydrochloride, which may be taken at the study center, should not exceed 400 mg.

Alternatively, any subject not experiencing adequate relief after the one-hour time point evaluation may take 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 additional doses of rescue medication (ie, codeine sulfate 15 to 60 mg orally every 4 hours prn [based on the discretion of the Investigator]) at the study center (ie, within 8 hours after

dosing with investigational product). The total maximum daily dose of rescue medication, codeine sulfate, which may be taken at the study center should not exceed 360 mg.

Subjects may not take any rescue medication home with them. Subjects who take rescue medication during the course of the evaluation period will remain in the study continue to perform their efficacy assessments.

Rescue medication should be administered within 5 minutes of rescue assessments being performed. Subjects taking rescue medication within one hour after dosing will be considered discontinued and must be replaced. The use of rescue medication will be recorded in the appropriate section of the case report form. The date, time, name of rescue medication taken, and reasons for use will be recorded.

6. STUDY PROCEDURES

6.1. Screening & Day of Surgery

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 and complete a checklist of the inclusion and exclusion criteria (see Section 4.1 and Section 4.2) in order to determine the subject's eligibility. Screening procedures include:

- Medical history;
- Prior/Concomitant medication review;
- Brief physical examination, including blood pressure, heart rate, respiratory rate, temperature;
- Laboratory testing (See Section 7.5);
  - Hematology;
  - Coagulation tests;
  - Serum chemistry (complete metabolic panel);
  - Urinalysis;
  - Serum pregnancy test (females only).

Screening procedures may be performed on the morning of surgery, but if a separate screening visit is conducted, it must be completed within 30 days of the surgery. 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 Record (provided by PCH) will be maintained to document all subjects screened for entry into the study. Subjects will be screened only once. All subjects will provide written informed consent before participating in the study. Subjects **are**

required to read, comprehend, and sign the informed consent. Appropriate screening information for eligible subjects who are assigned a subject number and receive investigational product will be transcribed onto the corresponding sections of the eCRF.

AEs and concomitant medications will be collected throughout the study.

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

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, liquids or Jell-O® may be provided to the subject prior to surgery. Subjects may not ingest any caffeine containing beverages, chocolate, or alcohol within 4 hours prior to taking study medication or during the entire 48 hour evaluation period.

No food will be allowed from 1 hour before to 2 hours after the scheduled ingestion times of all doses of study medication. Low fat (≤20% of calorie intake from total fat) 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 time point assessment. The times of food consumption will be recorded in the source document.

On the morning of surgery, females with reproductive potential will have a urine based pregnancy test. At surgery, the following will be noted and recorded on the eCRF:

- 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);
- Any medications that have been administered, including pre-operative medications and anesthetics: name, dose, and time;
- 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;
- The time of the last meal prior to surgery will be noted in the source document only.

6.2. Study Period

Subjects will not be allowed to wear a watch during the study, and they may not have access to a clock or any electronic device with a time function (including iPods, iPads, Nooks, Kindles).

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.

Post-operatively, subjects will be asked to rest quietly at the study center until they experience post-surgical pain of at least moderate severity. At that time, subjects will be asked to complete pain rating scales in the following order: baseline 4-point categorical PSR scale, 100 mm VAS PSR scale followed by the 11-point numerical pain rating scale.

- Categorical PSR Scale:
  - A score of at least moderate must be indicated before the subject can enter the trial. Each category on this scale will be assigned a whole number value from 0 (none) to 3 (severe);
  - Numerical PSR Scale.
- VAS PSR Scale (VAS PSR):
  - A minimum score of 50 mm is required to verify that the subject has at least moderate pain at 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.

Subjects who do not reach a qualifying baseline pain threshold (at least moderate pain indicated by a score of 2 or greater on the categorical scale, 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 entered into the study.

Upon completion of the baseline scales, eligible subjects will receive an oral dose of investigational products at 0 hours (baseline) and at 8, 16, 24, 32, and 40 hours post-baseline under randomized, double blind conditions. Subjects will be stratified by sex and baseline pain (moderate or severe pain as determined by their baseline categorical pain severity scores).

Each subject's vital signs (heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded at baseline, prior to other assessments being performed.

6.2.1. Post-Baseline Assessments

The following assessments will be conducted at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 32, 40, and 48 hours:

- CCI [redacted];
- 11 point Numerical PSR Scale;

- CCI [redacted];
- A review of any reported adverse events and concomitant medications will also be completed.

The following additional assessments will be conducted at 8 hours post-Baseline:

- Vital signs (ie, heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded.
- A review of any reported adverse events and concomitant medications will also be completed.

The following additional assessment will be conducted at 24 and 48 hours post-Baseline (or at the time of first rescue medication dosing on each day):

- CCI [redacted];
- Vital signs (ie, heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded (hour 48 only).

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

- CCI [redacted];
- 11 point Numerical PSR Scale;
- CCI [redacted];
- CCI [redacted];
- Vital signs (ie, heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded.

Subjects will also evaluate the time to CCI [redacted] Relief by depressing a stopwatch at the moment they first begin to experience "perceptible" relief and the time to "Meaningful" Relief by depressing a second stopwatch at the moment they first begin to experience "meaningful" relief (see Section 7.3.4 for further details). These times will be recorded up to 8 hours after dosing (ie up to the time the subjects are administered the second dose) or until the time of (first) rescue medication use, whichever is sooner.

6.2.2. End of Study

The following assessments will be conducted at the end of the study:

- Vital signs (ie, heart rate, blood pressure, temperature, and respiratory rate) will be measured and recorded;

- A review of any reported adverse events will also be completed.

6.3. Follow-up Visit

The investigator (or an appropriate designee at the investigator site) will contact the subject via telephone, 28 calendar days after the last dose of the study medication to ascertain if any SAEs have occurred. Reporting of SAEs discovered during this process must be completed as outlined in Section 8.1 in the protocol. Every effort (three telephone contact attempts) should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented.

6.4. Subject Withdrawal

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

1. Any subject who violates any condition of the entrance criteria after having been entered into the study.

2. Any subject who reports inadequate relief and requires rescue medication prior to one hour after taking the investigational product.

3. 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 study product.

4. Any subject who becomes uncooperative, does not adhere to the requirements of the study protocol, or refuses to complete the study.

5. Any subject who requires any concomitant medication (other than rescue medication) during the course of the study that could confound the study results.

6. Any subject who vomits within 1 hour following dosing.

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

If a subject does not return for a scheduled visit, every effort 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 the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved Adverse Events (AEs).

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.

Additional coded study product will be provided to the study site for replacement subjects. Should a subject discontinue, he/she will be replaced by the next available subject number. Subjects who discontinue due to an AE will not be replaced {except subjects who vomit the study product within 1 hour of dosing, if applicable}. The reason(s) why a subject has been discontinued from the study should be recorded in the appropriate section of the eCRF.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. 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. On the day of surgery, before investigational product administration at the baseline visit, a urine pregnancy test will be administered. A negative pregnancy result is required before the subject may receive the investigational product. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

In the case of a positive confirmed pregnancy see Section 8.10.

7.2. Baseline Efficacy Assessments

7.2.1. Categorical Pain Severity Rating Scale

The following 4 point Categorical PSR Scale will be used to rate the severity of baseline pain in response to the query:

"My starting pain is:"

None Mild Moderate Severe

A score of at least moderate must be indicated before the subject can enter the trial. Each category on this scale will be assigned a whole number value from 0 (none) to 3 (severe).

7.2.2. VAS Pain Severity Rating Scale (VAS PSR)

The 100 mm VAS PSR will be used to rate the severity of baseline pain. Subjects will be asked to:

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

None |——————————————————————| Severe

Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left. A minimum score of 50 mm is required to verify that the subject has at least moderate pain at 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.

7.2.3. Numerical Pain Severity Rating Scale

The following 11 point Numerical PSR Scale will be used to rate the severity of baseline pain in response to the query:

"My starting pain is:"

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.

Upon completion of the baseline scales, eligible subjects will receive a single oral dose of investigational product under randomized, double blind conditions.

7.3. Post-Baseline Efficacy Assessments

CCI [redacted]

CCI

[redacted]

7.3.3. Numerical Pain Severity Rating Scale

The 11 point Numerical PSR Scale will be completed at 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.

7.3.4. Time to Relief

When the subject is administered investigational product at time 0, the Study Coordinator/ Designee will start two stopwatches. Each stopwatch will have its face covered; one will be labeled "first perceptible relief" (Section 7.3.4.1) and the other "meaningful relief" (Section 7.3.4.2).

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7.3.4.2. Time to Meaningful Relief for the First Dose

In an effort to determine the exact moment that the subject begins to obtain meaningful relief for the first dose, the subject will be 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 will be recorded in the case report form. The stopwatch will remain active for 8 hours or until stopped by the subject, or until second dose or a rescue medication whichever is administered first.

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7.4. Safety Assessments

Adverse events will be recorded as they occur or reported. During surgery and the pain assessment period, subjects will be closely monitored for any AE. The Principal Investigator or designated Investigator will decide if any treatment is necessary. All AEs, whether serious or not, will be recorded on source documents. All AEs and SAEs for subjects who are not screen failures will be recorded in the eCRFs. The recording period for a non-serious AE starts at the time the subject takes the first dose of the study product. For SAEs, the reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. This includes events that emerge during screening. Any SAE occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected. For non-serious AEs, the reporting period starts at the time of first administration of study product. The reporting period is 28 days after the subject's last administration of study product, regardless of the relationship to the study product or protocol.

Each subject's vital signs (ie, pulse, heart rate, blood pressure, respiratory rate and temperature) will be measured at baseline (prior to dosing), at 8 hours and again at the end of study or at the time of rescue medication (if needed). A review of any reported AEs will be completed at the end of the study, and collected at the time of subject withdrawal from the study.

Note: Details about any recorded AE will be obtained from the subject at the end of an in house study. The Principal Investigator or study coordinator will review the start and stop dates and times, severity, action taken, present at end of study, and whether present pre-treatment for each AE. Only the Principal Investigator will determine the relationship to study product for each AE. The information will be recorded on the appropriate eCRF.

7.5. Laboratory Assessments

Laboratory assessments will be performed at Screening only.

7.5.1. Hematology

Hematology assessments will include:

- White blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red blood cell distribution width, platelets, differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).

- Mean platelet volume will not be assessed as part of the hematology assessment.

7.5.2. Coagulation

Coagulation assessments will include:

- Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR);

- Serum chemistry (complete metabolic panel):

    - Sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, total protein, albumin, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose.

7.5.3. Urinalysis

Urinalysis assessments will include:

- Appearance, color, specific gravity, pH, glucose, ketones, blood, protein, bilirubin, urobilinogen, nitrites, leukocyte esterase, red blood cells, white blood cells, hyaline casts, granular casts, epithelium, bacteria, crystals, mucous threads.

7.6. Assessment of Suicide

This blinded, controlled trial is for non-CNS indications. The FDC IBU/APAP formulations have no known effects on mood. There are no concerns about the mechanism of action, and neither the subject population nor disease under study is associated with a substantial risk of suicidality. Therefore, additional information on spontaneously reported suicidality adverse events may be collected at the time the event is reported using the suicidality narrative guide. No additional screening or detection methods are recommended at this time.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

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

As part of ongoing safety reviews conducted by the sponsor, any nonserious 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.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

For non-serious AEs, the reporting period starts at the time of first administration of study product. The reporting period is 28 calendar days after the subject's last administration of study product, regardless of the relationship to the study product or protocol.

AEs (serious and nonserious) should be recorded on the Case Report Form (eCRF) from the time the subject has taken at least 1 dose of investigational product through the subject's last visit.

8.3. Definition of an Adverse Event

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

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

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

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

8.4. Medication Errors

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

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

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

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the AE page and, if applicable, any associated AE(s) are captured on an AE eCRF page.

8.5. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

8.6. Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

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

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

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between investigational product and an event specified below, these events should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section on this protocol. These events are anticipated to occur commonly in a population with undergoing surgical extraction of third molars. However, these events should still be captured as AEs in the eCRF.

Protocol-specified events that will not normally be reported in an expedited manner:

- Paresthesia; Fracture of the mandible or maxilla;

- Oro antral communication.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, 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 analysis of safety data will be performed on a regular basis per internal standard operating procedures (CCI [redacted]).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to run LFTs because of clinical sign/symptom presentation in a subject, such LFT results should be handled and followed up as described below.

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

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

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X the upper limit of normal [ULN]) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).

    Concurrent with

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

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

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

results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

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

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

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

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

8.10. Exposure During Pregnancy

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

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

2. 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).

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

8.11. Occupational Exposure

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

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

8.12. Withdrawal Due to Adverse Events (See Also Section 6.4 on Subject Withdrawal)

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

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

8.13. Eliciting Adverse Event Information

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

8.14. Reporting Requirements

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

8.14.1. Serious Adverse Event Reporting Requirements

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

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

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

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

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

8.14.2. Nonserious Adverse Event Reporting Requirements

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

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications to the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

Pfizer Consumer Healthcare will perform statistical analyses of data. All computations will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC). Statistically significant treatment differences will be declared if the probability of random occurrence among or between treatments, p, is ≤0.05 (two-sided). Treatment differences will be considered marginally significant if $0.05<p\leq0.10$.

9.1. Sample Size Determination

Using RMSE data for SPID[11] over 2, 8 and 12 hours from Study B5061001, a single dose dental pain study, it was estimated that the RMSE for SPID[11] over 0-24 will be approximately 52 units. Based on this assumption, a sample size of 68 subjects for IBU/APAP 250 mg/500 mg group and 34 for placebo group (a ratio of 2:1) will provide 85% power (at 5% level of significance, two sided) to detect a treatment difference of at least 33 units for SPID[11] 0-24.

Thus, a total of 102 evaluable subjects are required to complete the study. Assuming a 10% drop-out rate, a total of approximately 112 subjects will be enrolled.

9.2. Efficacy Analysis

The statistical analysis methods will be detailed in the SAP, and are briefly summarized below.

9.2.1. Analysis Populations

9.2.1.1. Primary Analysis Set

The full analysis set (primary population) is the intent to treat (ITT) subject population, defined as all randomized subjects who dosed with the study medication and provided a baseline assessment.

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9.2.1.3. Safety Analysis Set

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

9.2.2. Analysis of Primary Endpoint

Primary efficacy endpoint SPID[11] 0-24 will be analyzed by an analysis of covariance model (ANCOVA) with treatment, categorical baseline PSR, baseline numerical PSR, and sex terms.

9.2.3. Analysis of Secondary Endpoints

- Secondary efficacy endpoints of SPID[11] over 0-8, 6-8, 0-16, 8-16, and 0-48 hours will be analyzed by ANCOVA model with treatment, categorical baseline PSR, baseline numerical PSR and sex terms.

- Time to onset of "meaningful" relief, and duration of relief as measured by the time to treatment failure will be analyzed using the Gehan-Wilcoxon test to compare treatments, adjusting for sex, and baseline categorical PSR terms.

9.2.4. Analysis of Other Endpoints

- Other efficacy endpoints of PID (both scales), PRR CCI at each time point, the corresponding summary measures SPID, CCI , will be analyzed by ANCOVA CCI models with treatment, CCI , baseline numerical PSR (CCI) and sex terms.

- CCI .

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9.4. Safety Analysis

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

9.5. Data Monitoring Committee

This study will not use a data monitoring committee.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on eCRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion. During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term eCRF 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.

An eCRF is required and should be completed for each included subject. The completed original eCRFs 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 eCRFs 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 eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

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

11.2. Record Retention

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

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

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

12. ETHICS

12.1. Institutional Review Board /Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

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

12.3. Subject Information and Consent

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

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

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

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

The investigator must ensure that each study subject, 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.

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, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

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

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in All Participating Countries

The end of the trial is defined as the last visit by the last subject.

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 investigational product at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 15 days. As directed by Pfizer, all study materials must be collected and all eCRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is further discussed in the CSA.

15.1. Communication of Results by Pfizer

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

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

www.clinicaltrials.gov

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

Primary completion date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the 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 primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

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Appendix 1. Abbreviations

This is a list of abbreviations used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
APAP	acetaminophen
AST	aminotransferase
CMH	Cochran Mantel Haenszel
COX-2	cyclooxygenase 2
eCRF	electronic case report form
EDP	exposure during pregnancy
CSA	clinical study agreement
DMC	data monitoring committee
EC	ethics committee
FDA	Food and Drug Administration (United States)
FDC	fixed dose combination
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
THC	tetrahydrocannabinol
IBU	ibuprofen
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
LFT	liver function tests
MAOI	monoamine oxidase inhibitor
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
OTC	over the counter
PCH	Pfizer Consumer Health
CCI	CCI
POC	proof-of-concept
CCI	CCI
PT	prothrombin time
PTT	partial thromboplastin time
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	norepinephrine reuptake inhibitor

SOA	schedule of activities
SOC	system organ class
SPID	sum of pain intensity difference scores
CCI [redacted]	CCI [redacted]
SRSD	single reference safety document
SSRI	serotonin reuptake inhibitor
TCA	tricyclic antidepressant
CCI [redacted]	CCI [redacted]
ULN	upper limit of normal
US	United States
USPI	United States package insert
UTN	Universal Trial Number