

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211733Orig1s000**

**CLINICAL REVIEW(S)**

## Decisional Memorandum

New Drug Application 211733

Advil Dual Action with Acetaminophen® (Ibuprofen 125 mg plus Acetaminophen 250 mg) Tablets

Karen Murry Mahoney, MD, FACE

Acting Deputy Director, Office of Nonprescription Drugs

Acting Deputy Director, Division of Nonprescription Drugs I

February 28, 2020

### Approval Decision:

Approval is appropriate for Advil Dual Action with Acetaminophen® (ibuprofen 125 mg plus acetaminophen 250 mg) tablets, hereafter referred to as Advil Dual Action, for the following Uses:

“temporarily relieves minor aches and pains due to:

- headache
- toothache
- backache
- menstrual cramps
- muscular aches
- minor pain of arthritis”

The population is limited to adults and children 12 years of age and older.

### Discussion:

Please refer to Dr. Jody Green’s Cross-Discipline Team Leader (CDTL) Memorandum (DARRTS November 14, 2019). I have little to add to Dr. Green’s analyses, and concur with her recommendation for approval. Dr. Green’s memorandum also includes the names of the review team members, from a wide array of disciplines, who contributed to the review and basis for decision; all of these reviewers are to be commended for their thoughtful, collaborative, and scientifically sound reviews.

As noted in Dr. Green’s CDTL memo, the applicant (Pfizer, Inc.) provided adequate data to support the efficacy and safety of Advil Dual Action for the temporary relief of pain for the Uses detailed above. The applicant also provided adequate data to meet the requirements of the fixed-dose combination (FDC) drug product rule, i.e. the applicant demonstrated that both individual active ingredient components of the FDC contributed to the claimed effect for pain. The applicant also provided adequate consumer behavior and label comprehension data to demonstrate that consumers are likely to understand how to use this product safely and effectively, and importantly, that consumers appear likely to understand that this product contains an NSAID and acetaminophen, and that the FDC should not be used in combination with other products that contain acetaminophen or an NSAID.

The individual components (ibuprofen and acetaminophen) of the FDC each have an indication (or Use as termed in nonprescription labeling) (b) (4). However, the data provided by the applicant from an (b) (4) study did not meet the requirements of the FDC drug product rule, i.e., the combination of the ingredients was not more effective (b) (4)

either of the individual components. (b) (4)

Please refer to Dr. Green's CDTL memo, and to the clinical review (DARRTS October 17, 2019) by Dr. Timothy Jiang of the Division of Anesthesia, Analgesia, and Pain, for complete discussion of the analyses of the data (b) (4).

During the review cycle, after the determination was made that (b) (4) could not be granted, it appeared that a Complete Response (CR) action would need to be taken. This was because the product labeling that had been tested for consumer comprehension included (b) (4)

Per Dr. Charles Ganley, Director of ODE IV at that time, it was deemed important for the labeling regarding (b) (4) and to know that consumers are likely to understand that the product is indicated only for pain. During discussions of the probable need for a CR, Ms. Amanda Pike-McCrudden (Social Science Analyst) proposed a novel and flexible approach, of allowing the applicant to perform a limited label comprehension study of the revised labeling that does not include (b) (4) information. The applicant was offered this option, and the option of submitting that study report before the original PDUFA goal date, so that the study report would be a major amendment, and would just extend the PDUFA clock by three months, rather than the division having to take a CR action. The applicant accepted these options, and the study data support that consumers are likely to understand that this FDC product is only for pain. Ms. Pike-McCrudden, and our colleagues in Biometrics and the Division of Medication Error Prevention and Analysis, deserve special mention for their collaborative, rapid turnaround review work that made this action (a major amendment with an approval, rather than a Complete Response) possible. (b) (4)

As determined by FDA's Pediatric Review Committee, this application has several required postmarketing studies under the Pediatric Research Equity Act. The required studies and associated completion dates are specified in the approval letter. Briefly, the requirements include:

- a pediatric pharmacokinetic and tolerability study in children 2 years to < 12 years of age with acute pain suitable for treatment with an OTC analgesic
- a pediatric pharmacokinetic, efficacy, and safety study in children 6 months to < 2 years of age with acute pain suitable for treatment with an OTC analgesic
- a pediatric targeted Label Comprehension Study for caregivers of children from birth to < 12 years of age
- a pediatric Self-Selection Study, and
- a pediatric Actual Use Study.

#### **Summary:**

Overall, approval is appropriate, although some residual concern exists regarding whether consumers, under the broad availability of nonprescription marketing (and outside the structure of a consumer behavior study) will avoid concomitant use of other products containing acetaminophen or an NSAID. The applicant has provided appropriate data to address this risk, and it appears that the labeling of the product is adequate in this regard. As with all nonprescription products, the applicant will be required to

report to FDA all serious postmarketing adverse events associated with use of the product, and FDA's pharmacovigilance staff will be conducting systematic surveillance.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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KAREN M MAHONEY  
02/28/2020 01:43:24 PM

## Cross-Discipline Team Leader Review

|  |  |
|--|--|
| <b>Date</b>  | Stamped Date   |
| <b>From</b>  | Jody E. Green, M.D.  |
| <b>Subject</b>   | Cross-Discipline Team Leader Review  |
| <b>NDA/BLA # and Supplement#</b>                               | NDA 211733   |
| <b>Applicant</b>   | Pfizer, Inc.   |
| <b>Date of Submission</b>                                      | January 31, 2019   |
| <b>PDUFA Goal Date</b>   | November 22, 2019  |
| <b>Proprietary Name</b>  | Advil Dual Action with Acetaminophen                                       |
| <b>Established or Proper Name</b>                              | Ibuprofen and Acetaminophen  |
| <b>Dosage Form(s)</b>  | Tablet   |
| <b>Applicant Proposed Indication(s)/Population(s)</b>          | Pain Reliever  |
| <b>Applicant Proposed Dosing Regimen(s)</b>                    | Take two tablets every 8 hours as needed for minor aches and pains (b) (4) |
| <b>Recommendation on Regulatory Action</b>                     | <i>Complete Response</i>   |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b> | <i>Temporary Relief of Minor Aches and Pains</i>                           |
| <b>Recommended Dosing Regimen(s) (if applicable)</b>           | <i>2 tablets every 8 hours as needed</i>                                   |

|   |  |
|---|--|
| Material Reviewed/Consulted   | Name of discipline reviewers                           |
| DNDP Medical Officer Review   | Shila Azodi, MD  |
| DAAAP Medical Officer Review  | Timothy Jiang, MD<br>Joshua Lloyd, MD, Deputy Director |
| DAAAP Efficacy Statistical Review                                     | Feng Li, PhD. David Petullo, MS                        |
| DNDP Pharmacology Toxicology Review                                   | Jenny White, PhD Jane Sohn, PhD                        |
| DNDP Social Scientist/Behavioral Science Statistics Integrated Review | Amanda Pike-McCruden, MS<br>Jody Green MD Team Leader  |

Cross Discipline Team Leader Review

|  |   |
|--|---|
|  | Elande Baro PhD<br>Yong Ma, PhD Team Leader<br>Mat Soukup, PhD Deputy Director  |
| DNDP Labeling Review                       | Robert Bahde, PhD<br>Kevin Lorick, PhD Team Leader  |
| DNDP Pharmacology/Toxicology Review        | Jennie White, MPH, PhD<br>Jane Sohn, PhD Team Leader  |
| OPQ/ONDP/DNP/II/NPBVI Review               | Swapan De, PhD Technical Lead   |
| Environmental Assessment and Labeling      | Elise Luong, PhD  |
| Drug Substance                             | Ramshran Mittal, PhD  |
| Process and Facilities                     | Yoon Oh, Ph.D.  |
| Biopharm                                   | Hansong Chen PhD  |
| Clinical Pharmacology Review               | Deep Kwatra, PhD<br>Xu Yun, PhD Team Leader   |
| OSE/DMEPA Review                           | Grace Jones, PharmD, BCPS<br>Chi-Ming Tu, PharmD, DBPS Team Leader<br>Danielle Harris, PharmD, BCPS Deputy Director   |
| DPMH Review                                | Elizabeth Durmowicz, MD<br>Mona Khurana, MD, Team Leader  |
| Division of Pharmacovigilance (DPV) Review | Regina Lee, PharmD<br>Allison Lardieri, PharmD, BCPPS<br>Jessica Weintraub, PharmD, BCPS<br>Linda McCulley PharmD, MPH, MS, BCPS<br>Christopher Jones, Pharm D, MPH, MS |
| OSI Review                                 | Susan Liebenhaut, MD<br>Susan Thompson, MD Team Leader<br>Kassa Ayalew MD, MPH Branch Chief   |

Abbreviations: DAAAP, Division of Anesthesiology, Addiction Medicine, and Pain Medicine Products; DMEPA, Division of Medication Error Prevention and Analysis; DNDP, Division of Nonprescription Drug Product; DPMH, Division of Pediatric and Maternal Health; DPV, Division of Pharmacovigilance II; OPQ/ONDP/DNDP/II/NPBVI, Office of Pharmaceutical Quality/Office of New Drug Products/Division of Nonprescription Drug Products-II/New Products Branch VI; OSI, Office of Scientific Investigations

# 1. Benefit-Risk Assessment

## Benefit-Risk Assessment Framework

### Benefit-Risk Integrated Assessment

I recommend a Complete Response for this application. The Applicant has proposed Advil Dual Action with acetaminophen (ibuprofen 125 mg/acetaminophen 250 mg fixed dose combination tablet) for the temporary relief of pain (b) (4). The dose of the product is two tablets (IBU 250 mg/APAP 500 mg) every eight hours to be used no more than 10 days for the acute remediation of symptoms. The drug is intended for those ages 12 and above. The application provides adequate support for pain relief lasting eight hours (b) (4).

As a result, I recommend that the purpose and use of the product be restricted to the temporary relief of pain (b) (4). Further consumer testing will need to be performed to ensure that consumers understand the proper use of the product and how it differs from its components, ibuprofen (IBU) and acetaminophen (APAP). Since there is a lengthy history of IBU and APAP being marketed (b) (4), it is important that labeling adequately convey proper use of this product and how its use is different than its components.

There are currently no fixed dose combination (FDC) ibuprofen (IBU) and acetaminophen (APAP) products marketed in the United States, although there are many other FDCs used worldwide with good safety records. A combined tablet dosed every eight hours will be more convenient for consumers to use when their pain is poorly controlled with a single currently marketed over-the-counter (OTC) product. The FDC when taken every eight hours for a full day contains 1500 mg/day of APAP and 750 mg/day of IBU. The therapeutic doses of the longest acting monocomponents when taken as scheduled over a 24-hour period are APAP ER 3900 mg (1300 mg four times a day) and IBU 800-2400 mg (200-400 mg every 4-6 hours).

It was thought that by combining two analgesics with different mechanisms of action that the FDC would achieve faster, longer, and better pain relief than either component individually, and this was the case. The full factorial single dose trial used to support the approval for pain reduction showed that the FDC worked significantly better than the placebo, 250 mg IBU, and 500 mg APAP over eight hours (SPID8). Additionally, at end of the dosing interval, the SPID6-8 showed significantly better pain reduction with the FDC than with the placebo or APAP and it was numerically better than with IBU. A second confirmatory pain study was performed and after six doses, there was statistically significant analgesic efficacy for the FDC sustained over 24 hours (SPID24) compared with the placebo. In summary, the combination rule was fulfilled for sustained pain relief at eight hours with the FDC.

The study with and without food in the peri-dosing period demonstrated a fast onset of meaningful pain relief in less than 60 minutes which is important for an acute analgesic. Although the clinical pharmacology study demonstrated that food decreased the  $C_{max}$  by about 1/3 and

delayed Tmax for each individual component, food did not affect the bioavailability of the product (ACU). Although there was a delay in the onset of action of the FDC in the fed state compared to the unfed state, the Applicant was able to provide evidence from the literature that a food effect is seen for many OTC analgesics including the monocomponent products and is not unique to this product. Hence, there was no need to label the product any differently than other OTC analgesics with regard to food intake.

(b) (4)

In the United States there are many different formulations, brands, and generic choices of IBU and APAP that have been marketed for many years. The adverse event (AE) profiles have been well established. The most prominent safety issue with APAP is hepatotoxicity. The approved dose of APAP as described in the AAA Tentative Final Monograph is up to 4000 mg per day, but this is extremely close to the safety margin and doses  $\leq 2600$  mg are recommended for NDA combination products. Use of the FDC with its lower dose of APAP than the other longer acting product, Tylenol ER 650 mg, should reduce the risk of hepatotoxicity. Although the IBU component carries the typical nonsteroidal anti-inflammatory (NSAID) warnings of risk for gastrointestinal bleeding and cardiovascular events, the daily dose is lower than other OTC IBU products. This is a desirable feature, as although risk can occur from only a single dose of a NSAID, in general, risk is dose and duration dependent.

In the small clinical trial database performed under this NDA, the adverse events (AEs) that occurred were minimal and no greater on drug than on placebo. Examination of the WHO Vigibase as well as the 120-day Safety update and the published literature revealed no new safety signals. Special attention was given to all the known major AEs related to the monocomponents including cardiovascular thromboembolic events, gastrointestinal, hepatobiliary, renal, skin and subcutaneous disorders, immune system disorders including hypersensitivity, anaphylaxis, and asthma, injury, and there were no areas of concern.

Results of the Label Comprehension Study indicated that consumers understood well ( $> 90\%$  performance threshold) the most important communication message which was to not use the product with additional drugs that contain acetaminophen. They also understood that a dose was two tablets (lower bound point estimate of 88.9%). Subjects understood that severe liver injury could occur if the product was taken with other products that contained APAP and might cause severe stomach bleeding, especially if combined with other NSAIDs. Unfortunately, subjects did have some difficulty identifying other products that contained acetaminophen, but did understand the concept to avoid

acetaminophen when using this product. (b) (4)

**Benefit-Risk Dimensions**

| Dimension                               | Evidence and Uncertainties   | Conclusions and Reasons   |
|---|--|---|
| <p><b>Analysis of Condition</b></p>     | <ul style="list-style-type: none"> <li>Minor aches and pains (headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, and arthritis) (b) (4) are often self-limited common occurrences and amenable to symptomatic treatment with OTC products.</li> <li>Acute pain episodes can be single events or recurrent, and can be related to trauma, surgical procedures, infection, inflammation, menstruation, or other conditions.</li> <li>Clinical symptoms of acute pain often include increased heart rate, blood pressure changes in respirations, agitation or restlessness, facial grimaces, and splinting.</li> <li>Acute pain can be associated with autonomic, endocrine-metabolic, physiological, and behavioral responses.</li> <li>(b) (4)</li> <li>(b) (4)</li> </ul> | <ul style="list-style-type: none"> <li>Acute pain conditions (b) (4) are straightforward to self-diagnose and can potentially be managed with OTC pain medication.</li> <li>Inadequate treatment of pain can lead to impaired sleep, reduced ability to conduct activities of daily life, psychological distress, depression and anxiety.</li> <li>(b) (4)</li> </ul> |
| <p><b>Current Treatment Options</b></p> | <ul style="list-style-type: none"> <li>Current pharmacological treatments for acute pain include both prescription (Rx) and OTC medication including APAP, aspirin, and NSAIDs such as naproxen sodium and IBU for mild to moderate symptoms and opioids for more severe symptoms.</li> <li>IBU and APAP as single components have been marketed for decades as pain relievers (b) (4). Typically, they require dosing every</li> </ul>  | <ul style="list-style-type: none"> <li>Consumers rely on available safe and effective OTC options for symptomatic treatment of pain (b) (4).</li> <li>Current OTC treatment options are limited especially for moderate pain.</li> <li>A combination of analgesics with different</li> </ul>  |

| Dimension                       | Evidence and Uncertainties   | Conclusions and Reasons  |
|---------------------------------|--|--|
|                                 | <p>4-6 hours, although APAP ER is dosed every eight hours.</p> <ul style="list-style-type: none"> <li>The safety profile for ibuprofen and acetaminophen as single components are well characterized.</li> </ul>   | <p>mechanisms of action and different safety profiles has the potential to provide greater relief than either agent alone.</p>   |
| <b>Benefit</b>                  | <ul style="list-style-type: none"> <li>As an acute analgesic, both studies with food and without food demonstrated a fast onset of action with meaningful pain relief at 48 minutes (Study 5061003) and 59 minutes in Studies 5061004.</li> <li>In the multi-dose Study B5061004 without food, the primary endpoint (SPID24) was met with the FDC achieving statistically significant pain relief compared to placebo. In the single dose trial, the FDC achieved statistically significant pain relief using the SPID8 over placebo and numerically better than IBU 250 mg and APAP 650 mg.</li> <li>As dosed every 8 hours, both Studies 5061003 and 5061004 demonstrated that the tendency for the product to last the proposed dosing interval based on the key secondary endpoint of duration of pain relief measured by time to treatment failure.</li> <li>The current OTC daily limit for ibuprofen is 1200 mg and in an NDA application, FDA recommends manufacturers limit daily acetaminophen to 2600 mg. When used as directed, the fixed dose combination provides ibuprofen 750 mg and acetaminophen 1500 mg daily.</li> </ul> | <ul style="list-style-type: none"> <li>Each component in the FDC contributes to pain relief with a lower total daily dose of ibuprofen and acetaminophen, faster onset of action, and longer duration of pain relief.</li> <li>Eight-hour dosing may enable consumers with pain to sleep through the night.</li> <li>The anticipated doses of IBU and APAP in the FDC are less than when the monocomponents are taken separately.</li> </ul> |
| <b>Risk and Risk Management</b> | <ul style="list-style-type: none"> <li>Consumers need to be informed about the use of this product since it is different than the components, APAP and IBU.</li> <li>(b) (4)</li> <li>Although food decreased <math>C_{max}</math> by about 1/3 and delayed <math>T_{max}</math> for each individual component, food did not affect the bioavailability (ACU). The food effects on PK profile suggests that food has a potential to delay the onset of action of the product.</li> </ul>   | <ul style="list-style-type: none"> <li>Further consumer testing will be needed to ensure that consumers understand the correct use of the product.</li> <li>(b) (4)</li> <li>Consumer testing demonstrated that consumers understood the risks of the product including the risk of liver toxicity</li> </ul>  |

| Dimension | Evidence and Uncertainties   | Conclusions and Reasons   |
|-----------|--|---|
|           | <ul style="list-style-type: none"> <li>• Serious adverse reactions related to the fixed dose combination could include those seen with ibuprofen and acetaminophen (hypersensitivity, gastrointestinal bleeding, liver toxicity, and skin reactions).</li> <li>• Consumers should not combine this product with other products containing APAP due to the possibility of liver toxicity.</li> <li>• Consumers should be cautioned about combining this medication with more NSAIDs due to increasing the risk of adverse reactions.</li> <li>• The limited clinical trial data and postmarket data do not demonstrate a new safety signal for the FDC compared to the single components.</li> <li>• The added risk of taking a product with two components can be justified, if both active ingredients contribute to the effect of the drug. This is the case for the temporary relief of pain (b) (4)</li> </ul> | <p>when consumed with other APAP products, allergies, skin reactions, and other warnings for NSAIDs.</p> <ul style="list-style-type: none"> <li>• There is extensive postmarketing data for the OTC single components IBU and APAP.</li> <li>• Food effect is common for all OTC analgesics.</li> <li>• The product will only be approved for pain (b) (4)</li> </ul> |

## 2. Background

### 2.1 Introduction

Pfizer, Inc, referred to here as the Applicant, has submitted a New Drug Application for a novel formulation of a fixed dose combination (FDC) product composed of ibuprofen (IBU) and acetaminophen (APAP). The FDC will be referred to as IBU 250 mg + APAP 500 mg in this application or as FDC. The FDC is proposed by the Applicant for the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, and minor pain of arthritis (b) (4)

(b) (4) The Applicant requests labeling of their product for those ages 12 and older. They propose that two caplets of the FDC be used every eight hours, not to exceed six caplets in 24 hours, unless directed by a medical provider.

The Applicant has proposed the proprietary name “Advil Dual Action with Acetaminophen” for their product. If granted an approval, this will be the first such combination product marketed in the United States, although there are many similar combination products marketed internationally. Combinations of analgesics have been used for years. Most combinations are formulated to enhance analgesia while reducing the adverse effects by combining two analgesics with different mechanisms of action. The Applicant contends that this formulation will deliver IBU and APAP in doses less than the maximal doses of the individual products and achieve plasma concentrations adequate to provide eight hours of analgesic (b) (4) efficacy. The proposed product, IBU 125 + APAP 250 mg is taken as two tablets every 8 hrs and delivers 750 mg of IBU and 1500 mg APAP in 24 hours. The monocomponents, when taken as their highest daily OTC dose, deliver 1200 mg of IBU and 4000 mg of APAP in 24 hours. The product is an immediate release product whose onset of action is faster than the extended release APAP ER 650 mg product, while delivering better pain control with less acetaminophen. The Applicant anticipates that the lower dose of the FDC components compared with the marketed monocomponents will lead to increased safety with a lower risk of gastrointestinal, cardiovascular, renal and hepatic AEs in addition to having increased pain efficacy.

This application is based on the following 3 pivotal efficacy studies.

- B5061003 (pain single dose)
- B5061004 (pain multiple dose)

(b) (4)

Four other clinical trials were also submitted to support this application.

- B5061001: Proof of concept phase 2 single-dose, dose-ranging dental pain stud
- B5061005: Relative bioavailability and food effects study.

- B5061006: Formulation effects and drug-drug interactions study
- B5061008: PK in adolescents 12 to <18 years of age

### 2.3 Disease Condition

The Applicant has proposed that the FDC receive an indication typical of most OTC analgesic medications governed by the Internal Analgesic, Antipyretic, Antirheumatic Drug Products (IAAA) monograph, the temporary relief of minor aches and pains due to headache, toothache, backache, menstrual cramps, (b) (4) muscular aches, minor pain of arthritis (b) (4) in those ages 12 and above. Both monocomponents already have this use.

#### Pain

Pain can be a transient condition and can come on acutely. Acute pain is an unpleasant sensory and emotional experience usually arising from actual or potential tissue damage. When it is short-lived it may last for minutes, hours, days or several months. Pain is considered chronic when it lasts longer than six months. Often the pain is sharp and intense and is triggered by a specific physiologic process such as trauma, surgery, burns or cuts, labor and childbirth. When acute pain resolves without complication it resolves completely. Although some acute pain may be treated by a medical provider, such as postsurgical pain, when pain is mild to moderate it is often amendable to self-diagnosis and treatment and is a common occurrence in everyday life. It is generally the intensity and longevity of the pain that typically drives the patient to receive medical assistance for further pain control. As pain is a physiological response and disruption of homeostasis, it can be accompanied by increased heart rate, blood pressure, changes in respiratory rate and deepness of breath, agitation, restlessness, facial grimacing and splinting. (b) (4)

(b) (4)

(b) (4)

(b) (4)

## 2.4 Available Therapies

The following table lists NDA and monograph OTC oral drug products available for the temporary relief of pain (b) (4). As is evident from Table 1, the only products that are dosed  $\geq 8$  hrs are Tylenol ER and naproxen sodium, the others are dosed every 4-6 hrs.

(b) (4)

**Table 1 OTC pain (b) (4) preparations used as needed, not to exceed 10 days for pain (b) (4)**

| Product Name     | Dosage form   | Dosing Instructions  | NDA or Monograph Product; date |
|------------------|---------------|--|--------------------------------|
| Acetaminophen    | 325 mg tablet | 2 tablets every 4-6 hrs not to exceed 8 tablets in 24 hrs                                | Monograph 1959                 |
| Acetaminophen    | 500 mg tablet | 2 tablets every 4-6 hrs not to exceed 8 tablets in 24 hrs                                | NDA 1960 + Monograph           |
| Acetaminophen ER | 650 mg tablet | 2 tablets every 8 hrs not to exceed 6 tablets in 24 hrs                                  | NDA 1994                       |
| Ibuprofen        | 200 mg tablet | 1-2 tablets every 4-6 hrs not to exceed 6 tablets in 24 hrs                              | NDA 1984                       |
| Naproxen sodium  | 220 mg        | 1 tablet every 8-12 hr. while symptoms last, do not exceed 3 tablets in a 24-hour period | NDA 1994                       |
| Aspirin          | 325 mg        | 1-2 tablets every 4 hrs, do not exceed 12 tablets in 24 hours                            | Monograph                      |

Source: Orange Book

Advil (Ibuprofen 200 mg), the Applicant’s product, was first approved as an OTC NDA analgesic/antipyretic in 1984 under NDA 18989. It is available in a 200 mg tablet that can be dosed as 1-2 tablets every 4-6 hr not to exceed 6 tablets in 24 hr with a daily limit of 1200 mg. As an OTC product the drug is to be used for acute pain for no more than 10 days and for fever for no more than 3 days without consulting a physician. The drug is also approved as a prescription (Rx) product where the maximal daily dose is 800 mg every 8 hrs for a total of up to 2400 mg over 24 hrs. Ibuprofen works as a non-selective inhibitor of both COX-1 and COX-2 receptors helping to decrease the synthesis of pain- and inflammation-promoting prostaglandins conferring benefits for both pain and fever as well as a general anti-inflammatory. Ibuprofen is known to be a superior pain reliever than acetaminophen. For example, ibuprofen 400 mg is superior to both aspirin 325 mg and acetaminophen 650 mg in a dental pain model. Ibuprofen prepared in a solubilized formulation (gel cap) can work even faster than the nonsolubilized formulation.<sup>7</sup>

IBU is a nonsteroidal anti-inflammatory drug (NSAID) and as such has class warnings in the label. It was proposed as a monograph ingredient in 2002, but this proposal was withdrawn in 2018 because of the known safety issues associated with NSAIDs according to Dr. Azodi. Several Advisory Committee meetings have convened to discuss the class effects of the NSAIDs. At the February 2005 joint meeting of the FDA Arthritis Advisory Committee and Drug Safety and Risk Management Advisory Committee the risk of

<sup>7</sup> Beaver, WT Review of the analgesic efficacy of ibuprofen Int J Clin Pract Suppl 2003 Apr; (135): 13-7.

thromboembolic events was discussed and class labeling was established to include both cardiovascular and gastrointestinal warnings. The warnings were further updated after a second advisory meeting in February 2014. The risk of serious injury increases with duration and dose. The warnings for IBU include the following:

- Serious skin reactions including Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis, which can be fatal
- Hypersensitivity reactions with anaphylaxis (respiratory distress, facial swelling, urticaria, rash, pruritis), particularly in those with asthma
- Occurrence or worsening of kidney injury, particularly when combined with other potentially nephrotoxic agents such as diuretics or angiotensin converting enzyme inhibitors
- Increased risk of adverse cardiovascular thromboembolic events including myocardial infarction and stroke. This risk varies based on the NSAID chosen, the dose used, the duration of use, and an individual's baseline CV risk factors
- Attenuation of aspirin's anti-thrombotic effects on platelets if administered before aspirin
- Hepatic AEs, but these are less common
- Non-specific GI symptoms (heartburn, nausea, dyspepsia, emesis, abdominal pain)
- Endoscopically visualized asymptomatic mucosal lesions<sup>8</sup>
- Serious GI complications (perforated ulcers, bleeding requiring hospitalization)

APAP (Acetaminophen) has been available for OTC use since 1955 as a monograph product, when a 325 mg immediate release tablet was approved for OTC use for the minor aches and pains and reduction of fever. Because of the known risk of hepatotoxicity with the product, prescription medication is limited to 325 mg of APAP per dosage unit, although this requirement does not apply to OTC products, although similar safety concerns exist. The Tentative Final Monograph (TFM) for APAP as an analgesic instructs that no more than 4000 mg can be used in 24 hours which is very close to the safety margin for liver failure (approximately 5400 mg in 24 hr.). Hence, the dose of APAP in NDA products is limited to 2600 mg in 24 hr. but varies by the dosing unit which may be immediate release or extended release.

All products with APAP carry a label warning for severe hepatotoxicity based on a final rule for the IAAA monograph from 1998 (21CFR 201.322). All APAP also carry an alcohol warning which was a further enhancement of the label in 2009 (based on 21CFR

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<sup>8</sup> Sostres C, Gargallo CJ, Lanás A. Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage. *Arthritis Res Ther.* 2013;15 Suppl 3(Suppl 3):S3. doi:10.1186/ar4175

201.326). This warning states that all acetaminophen-containing products when ingested with three or more alcoholic beverages or other drugs that contain acetaminophen have an increased risk of hepatotoxicity. Although the risk of liver injury can potentially be mitigated against, there are other serious injuries that can be related to acetaminophen. These include:

- Serious skin reactions including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis
- Hypersensitivity reactions with anaphylaxis (respiratory distress, facial swelling, urticaria, rash, pruritis)

APAP is approved OTC as a 325 mg product, 500 mg product and as a 650 mg extended release product. APAP is a frequent component of both OTC and Rx products. It can be combined with other ingredients such as in Excedrin Migraine and Anacin to treat migraine. It can be combined with narcotics such as Percocet and Vicodin. Often patients and consumers are unaware that the product that they are using contains APAP, and hence this product’s label is designed to emphasize this warning.

The mechanism of action of APAP is unknown and it may cause COX inhibition in the central nervous system and activation of central serotonergic pathways. APAP does not inhibit prostaglandin synthesis. Since IBU and APAP do not share metabolic pathways, they have little likelihood of drug-drug interactions and this was confirmed when the two drugs were administered together.

## 2.5 Regulatory History

NDA 221733 was supported by clinical studies conducted by Pfizer Pharmaceuticals under IND 112538 for the oral fixed dose combination product of IBU and APAP. (b) (4)

**Table 2 Regulatory History**

| 9/20/2011 | PreIND meeting   |
|-----------|--|
|           | <p>The Applicant was advised of the following:</p> <ul style="list-style-type: none"> <li>○ <span style="background-color: #cccccc; display: inline-block; width: 150px; height: 1em;"></span> (b) (4) analgesic effect must be studied using adequate models. <span style="float: right;">(b) (4)</span></li> <li>○ To demonstrate efficacy the Combination Rule must be met. Each active ingredient must contribute to the claimed effect and the combination must not decrease the safety or effectiveness of any of the individual active ingredients as described in 21CFR 330.10 (a)(4)(iv)</li> <li>○ In general, it would be unlikely that the FDC would be approved <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 1em;"></span> (b) (4) due to the extensive history of Advil and other monograph products approved <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 1em;"></span> (b) (4).</li> </ul> |

|                  |  |
|------------------|--|
|                  | <ul style="list-style-type: none"> <li>○ If the option of a 1 or 2 tablet dosing regimen is desired, then both doses would need to be assessed for efficacy.</li> <li>○ To fulfill 505 (b)(2) related bioavailability requirements, bioavailability needs to be evaluated with the FDC and a proper reference product. The effect of food on PK must also be studied of the FDC and the dosage form proportionality of the product as it is used in multiples (2x single tablet).</li> <li>○ PK studies need to be done to evaluate the interactions between IBU and APAP.</li> <li>○ The reference product for APAP was discussed. To rely on the safety and effectiveness of acetaminophen the Applicant must not rely upon the tentative final IAAA monograph for APAP. The reference product must rely on the safety and effectiveness found in an NDA product found in the Orange Book.</li> <li>○ Since the dose of IBU is considered “non-standard,” where C<sub>max</sub> is likely to be different that the chosen reference drug, the FDA will not require bioequivalence to the reference drug but will require a relative exposure to form a scientific bridge (such as safety data if the proposed product has a higher exposure and efficacy data if the proposed product has a lower exposure).</li> <li>○ The proprietary name with Advil must be modified with APAP to differentiate it from existing Advil products.</li> <li>○ PREA will be triggered by this FDC and the Applicant was advised to submit an iPSP with proposed studies in pediatric patients ≤ 17 years of age who are either symptomatic or at risk for the condition being treated.</li> </ul> |
| <b>1/30/2012</b> | <b>New IND submitted</b>   |
|                  | IND opened with study B5061001 a dose finding proof of concept (POC) study in post-surgical dental pain.   |
| <b>5/15/2014</b> | <b>End of Phase 2 Meeting</b>  |
|                  | <p>The results of the POC study were discussed as was further drug development. The Applicant chose IBU 250 mg + APAP 500 mg as the FDC. The agency advised:</p> <ul style="list-style-type: none"> <li>○ For the pain model, two dental pain studies could suffice if one had a full-factorial design and one had a one-factorial design with multiple-doses over at least 48 hours. In the later study the SPID24 could suffice as the primary endpoint.</li> <li>○ Both studies should evaluate the efficacy of the FDC over the last two hours of the dosing interval as well as time to rescue medication to support the longer dosing interval of every eight hours.</li> <li>○ <span style="background-color: #cccccc; display: inline-block; width: 500px; height: 1em;"></span> (b) (4)</li> <li>○ <span style="background-color: #cccccc; display: inline-block; width: 500px; height: 1em;"></span></li> <li>○ <span style="background-color: #cccccc; display: inline-block; width: 500px; height: 1em;"></span></li> <li>○ The choice of comparator for the IBU component could be either NDA 019012 Motrin IB (ibuprofen 200 mg) or NDA 018989 Advil (ibuprofen 200 mg).</li> </ul>  |

|                  |  |
|------------------|--|
|                  | <ul style="list-style-type: none"> <li>○ The submitted label comprehension study (LCS) did not evaluate the safety concern regarding potential duplication and overdose with acetaminophen, so additional label comprehension studies would be needed.</li> <li>○ The risk of liver toxicity and the risk for GI bleeding need to be explored.</li> <li>○ At a minimum the Applicant is required to study PK and safety in children ages 2-12 years with pain; efficacy could be extrapolated from adults</li> </ul>   |
| (b) (4)          |  |
| <b>4/3/2017</b>  | <b>Type C meeting primarily discussing the Label Comprehension Study</b>   |
|                  | <ul style="list-style-type: none"> <li>○ Applicant advised to add a subgroup of adolescents and 30% low literacy to the study population</li> <li>○ Questions should be added that test consumer’s understanding of the correct dose (number of tablets) as well as the correct timing (every 8 hours rather than every 4-6 hours)</li> <li>○ Consumers should be advised that the maximal daily dose of APAP is 2600 mg.</li> <li>○ The name Advil Dual Action with Acetaminophen was found to be a conditionally acceptable proprietary name.</li> <li>○ <span style="background-color: #cccccc; display: inline-block; width: 600px; height: 1.2em; vertical-align: middle;"></span> (b) (4)</li> </ul>   |
| <b>3/19/2018</b> | <b>PreNDA meeting the following agreements were made.</b>  |
|                  | <ul style="list-style-type: none"> <li>○ The Applicant asked if the agency would consider labeling the product for the pain indication <span style="background-color: #cccccc; display: inline-block; width: 100px; height: 1.2em; vertical-align: middle;"></span> (b) (4). The division responded that this would be a review issue.</li> <li>○ The Statement of Identity (SOI) on the principal display panel and DFL must contain acetaminophen 250 mg and ibuprofen 125 mg.</li> <li>○ Efficacy analysis needs to address the generalizability of the clinical trial data to a broad population and include the following analyses:             <ol style="list-style-type: none"> <li>1. time-to-onset of first perceptible pain relief using the double stopwatch method</li> <li>2. time-to-onset of first meaningful pain relief using the double stopwatch method</li> </ol> </li> </ul> |

|                         |   |
|-------------------------|---|
|                         | <ol style="list-style-type: none"> <li>3. time-to-rescue medication</li> <li>4. time to request a second dose of study medication</li> <li>5. duration of effect/adequacy of the dosing interval</li> <li>6. analgesic efficacy over multiple doses</li> <li>7. an analysis that evaluates summed pain intensity differences (SPIDs) over hours 6-8</li> <li>8. an analysis of pain intensity and pain intensity difference over time curves for each of the treatments and evaluation of rescue medication during the latter part of the dosing interval</li> </ol> <ul style="list-style-type: none"> <li>○ Post-hoc analyses may be requested for SPID4-6 and SPID4-8.</li> <li>○ Postmarketing literature and WHO Vigibase should include a demographic subgroup analysis of those over age 64.</li> <li>○ International data of combination use of ibuprofen and acetaminophen should be provided that included package size, if drug has been withdrawn for safety reasons, if behind-the-counter, or OTC, relevance of AE to the US population.</li> <li>○ Safety data should be analyzed by dose-response, age, gender, time-to-onset, accidental or intentional overdose, dose and duration, misuse and abuse.</li> <li>○ The following special safety topics should be included: cardiac disorders, gastrointestinal disorders, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, nervous system disorders, renal and urinary disorders, respiratory disorders, skin and subcutaneous disorders, vascular disorders.</li> </ul> |
| <p><b>5/19/2018</b></p> | <p><b>Type C WRO meeting The Label Comprehension Study was further discussed and Advice Letter sent 6/5/2018</b></p>  |
|                         | <ul style="list-style-type: none"> <li>○ Applicant was advised to avoid leading, branching or duplicative questions. Several suggestions were made regarding scoring responses and mitigations. Applicant advised to send in the LCS protocol and data collection instrument (DCI) for further review.</li> <li>○ Subjects were to be asked why the product is “Dual Action”. They were to be given a list of products and asked to check off if they recognized which products contained acetaminophen and which contained an NSAID.</li> </ul>  |

**2.6 Issues Raised by Advil Dual Action with Acetaminophen Development Program**

Products for OTC development containing two or more ingredients or drug products need to follow the Combination Rule for OTC products. The Combination Rule as found in 21 CFR 330.10 (a)(4) (iv) states the following:

“A drug may combine two or more safe and effective active ingredients and may generally be recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the

safety or effectiveness of any of the active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides a rational concurrent therapy for a significant proportion of the target population.”

According to Dr. Azodi, the 2015 Proposed Rule for Fixed-Combination and Co-Packaged Drugs advises that Applicants are to state the intended use of each active ingredient in the combination drug product and to submit sufficient evidence to demonstrate that the combination meets the stated requirements. The data can include data from adequate and well controlled clinical trials, clinical pharmacology data, in vitro and animal model data, or other relevant information such as a basis for concluding there is a plausible pharmacologic rationale for the combination.



## 2.7 Foreign Labels

FDC products containing APAP + IBU are marketed throughout the world in various combinations. Below is a table summarizing what is known about such products. It is noted that several of the products are indicated for pain alone such as products in Ireland, Russia, the United Kingdom. From what is known about the products, none are dosed less frequently than every six hours. Some of the products emphasize in the label that they are suitable for pain conditions where stronger analgesia is needed than the monocomponents, such as in products marketed in Russia and the United Kingdom.

**Table 4 Sample of Fixed Dose Combination Products Marketed Worldwide**

| Country   | Product          | Dose (IBU/APAP)                               | Indication  |
|-----------|------------------|---|---|
| Australia | Amcal            | 200/500 tablet                                | Temporary relief of acute pain and inflammation associated with migraine, tension headache, sinus pain, toothache, dental procedures, backache, muscular aches and pains, period pain, sore throat, tennis elbow, rheumatic pain and arthritis, and the aches and pains associated with colds and flu. Reduces fever. |
|           | Chemist's Own    | 200/500 tablet                                | Temporary relief of acute pain and inflammation.  |
| Ireland   | Easolief Dup/18+ | 150/500 tablet<br>2 tablets q6 hr. (6/24 hr.) | Short term symptomatic treatment of mild to moderate pain   |
| Russia    | Brustan          | 100/125 in 5 ml solution                      | Mild or moderate pain syndrome, including headache and toothache, migraine, neuralgia, ear and throat pain, pain from strains, and other types of pain. The drug product is intended for  |

|                |               |   |  |
|----------------|---------------|---|--|
|                |               |   | symptomatic therapy, relief of pain and inflammation at the time of use, does not impact disease progression.  |
|                | Next/12+      | 400/200<br>Adults 1 tablet tid                                  | Migraine and tension headache, toothache, dysmenorrhea, neuralgia; myalgia, back pain, joint pains, pain syndrome with inflammatory and degenerative diseases of the locomotive system, pain associated with bruises, sprains, dislocations, Fractures, post-traumatic and post-operative pain syndrome, fevers including with flu or cold<br>For symptomatic relief, does not impact disease progression. |
|                | Nurufen/12+   | 200/500<br>Adults 2 tablets q 6 hr.<br>Maximal 6 tablets/24 hr. | Backache, joint pain, muscle and rheumatic pain, neuralgia, migraine and tension headache, toothache, painful menstruation, throat ache, fever, cold and flu symptoms. For symptomatic relief of pain that requires a more robust analgesic effect than the monocomponents.  |
| United Kingdom | Novogesic/18+ | 150/500<br>2 tablets q 6 hr.<br>Maximal 6 tablets/24 hr.        | Short-term symptomatic treatment of mild to moderate pain  |
|                | Nuromol/18+   | 200/500<br>1-2 tablets tid or qid<br>maximal 6 tablets/24 hr.   | For the temporary relief of mild to moderate pain and fever associated with migraine and tension headache, backache, period pain, dental pain, rheumatic and muscular pain, pain of non-serious arthritis, cold and flu symptoms, sore throat and fever. This product is especially suitable for pain which requires stronger analgesia than monocomponents.   |

### 3. Product Quality

The Integrated Quality Assessment was completed by Swapan De, PhD from ONDP, DNDP-II, Branch VI. Dr. De recommends approval from the CMC perspective and I agree. Please see the integrated review for more complete details on quality issues. Some key elements are summarized here. IBU is manufactured by (b) (4). Review of the drug’s DMF status is adequate for (b) (4) DMF # (b) (4). APAP is manufactured by (b) (4) and tested at (b) (4). Review of the drug’s DMF status is adequate for DMF # (b) (4). All facilities making each component have been inspected by the FDA and comply with cGMP. The Nomenclature, Structure and Properties Information, synthetic description, control of materials, process validation, manufacture process, elucidation and characterization data support the proposed structure of drug substances. The identification and characterization of actual and potential impurities is considered satisfactory. The assay for stability was acceptable and impurities were

adequately monitored. The content of the product was uniform and controlled with specifications as was dissolution, and the microbial limits. Based on the stability data generated, (b) (4) recommends that a retest at (b) (4) be applied for both components. IBU and APAP are reported at BCS class II and III respectively and the biopharmaceuticals reviewer concurs to this classification.

The product is manufactured using (b) (4)

(b) (4) The excipients in the product include the following: Carnauba wax, Colloidal silicon dioxide, Croscarmellose sodium, Ferric oxides, glyceryl dibehenate, Hypromellose (b) (4) Polydextrose, Polyethylene Glycol, Pregelatinized starch (b) (4), Titanium oxide, (b) (4)

The commercial product will be packed in 3 types of container closure systems:

- (1) White, opaque high-density polyethylene (HDPE) bottles with (b) (4) caps with induction seal liners

The product will be available in bottles of (b) (4) 18 ct, 36 ct, 72 ct, 90 ct, 144 ct, (b) (4) 162 ct, 180 ct, (b) (4) 288 ct

- (2) 8 count (b) (4) vial with (b) (4) cap

- (3) 2 count low-density polyethylene (LDPE), (b) (4) foil laminate pouch.

All HDPE bottles (b) (4) The physician samples (b) (4) vial with (b) (4) cap) and the blister packs (b) (4)  
(b) (4) The Container Closure System is considered adequate.

The shelf-life of the product when stored at (b) (4) -25 C or 68-77 F) is 36 months. The Ibuprofen 125 mg/Acetaminophen 250 mg Tablet is an immediate release yellow, film-coated, capsule-shaped tablet printed on one side in black ink. The tablet is not scored.

## 4. Nonclinical Pharmacology/Toxicology

Jennie White, MPH, PhD recommended an approval from the nonclinical pharmacology/toxicology perspective and I agree. No new nonclinical data was submitted to support the NDA. The active ingredients are well characterized and in numerous OTC products. The review was limited to a safety assessment of the excipients and impurities of the FDC product. All proposed impurity and

excipient levels are deemed acceptable. There were no novel excipients, all are found in other approved drugs or are listed in Title 21 of the Code of Federal Regulations (21 CFR) sections 73, 172, or 184 as food additives or substances generally recognized as safe for direct human consumption.

## 5. Clinical Pharmacology

The clinical pharmacology review was conducted by Deep Kwatra, PhD, and the secondary reviewer was Xu Yun, PhD. Please see Dr. Kwatra's review for full details which are summarized here. The product was considered approvable from the clinical pharmacology perspective, and I agree. There are no outstanding clinical pharmacology issues. No population pharmacokinetic (PK) studies were done to evaluate intrinsic factors that may have an effect on IBU or APAP pharmacokinetics such as age, gender, race, body weight renal or hepatic impairment. Three PK studies were performed including one in adolescents. Extrinsic factors such as food-drug interaction and drug-drug interaction between the monocomponents were assessed. Based on their review the clinical pharmacology team had no labeling recommendations for the product.

### Mechanism of Action of the FDC

The FDC is composed of IBU and APAP. IBU is a nonselective NSAID that inhibits both cyclooxygenase 1 and 2. Cyclooxygenase 1 inhibition is largely responsible for unwanted AEs in the gastrointestinal tract. Cyclooxygenase 2 inhibition is thought to mediate the therapeutic actions of ibuprofen. Cyclooxygenase inhibitors decrease prostaglandin production and reduce inflammation.

APAP has a less well-defined mechanism and may activate central serotonin pathways and inhibit prostaglandin synthesis. APAP has limited anti-inflammatory activity.

### Absorption

- IBU is lipophilic, rapidly absorbed in intestine with a time to peak plasma concentration between 1.4 to 1.9 hours
- APAP is rapidly absorbed in small intestine, has a relative bioavailability of 85% to 98%. The peak concentration occurs in < 1 hour.

Absorption of the FDC in this study revealed a decrease of the  $C_{max}$  of 36% for IBU and 37% for APAP with food. The  $T_{max}$  also increased for each component in the fed state. In the fed state, absorption was delayed for both IBU and APAP. For IBU when fed the median (range) of the  $T_{max}$  was 3.00 (0.33-10.0) hours compared to 1.38 (0.50-4.00) hours when fasted. Similarly, under fed conditions, absorption was delayed with a median (range)  $T_{max}$  of 2.49 (0.333-6.0) hours for APAP compared to 0.58 (0.167-2.00)

hours under fasted conditions. Administration of the FDC, each component separately, and each component taken at the same time were all absorbed similarly as seen in the DDI study.

### **Distribution**

- APAP is 10-25% protein bound. It crosses the blood-brain barrier.

### **Metabolism**

- IBU is extensively metabolized in the liver mediated by CYP2C9 and CYP2C8. Only a small portion of the drug is directly conjugated. The metabolites are inactive. The drug does not induce CYP enzymes.
- APAP is metabolized in the liver directly by glucuronidation and sulfation as well as some oxidation by CYP. NAPQI is formed by oxidative metabolism, which when it builds up is responsible for drug induced liver injury. When levels are lower it is detoxified by conjugation with glutathione. There are two other catechol metabolites. None of the metabolites have analgesic activity. The drug does not induce CYP enzymes.
- Since the two drugs have different metabolic pathways and absorption sites there is little potential for drug-drug interactions.

### **Excretion**

Both IBU and APAP are excreted in the urine.

The studies performed included the following:

B5061005: Relative bioavailability and food effects study

B5061006: Formulation effects and drug-drug interactions study

B5061008: PK in adolescents 12 to <18 years of age

### **B5061005: Relative bioavailability and food effects study**

This study was an open-label, single oral dose 4-way crossover study in 35 healthy adult volunteers ages 18-55. In this study a comparison was made of the relative bioavailability and food effect of a single dose of the FDC to IBU 200 mg, and APAP 650 mg ER. The treatment arms were the following:

- Treatment A = FDC IBU 250 mg/APAP 500 mg, fasted
- Treatment B = IBU 200 mg (Advil), fasted
- Treatment C = APAP 650 mg extended release (Tylenol 8HR), fasted
- Treatment D = FDC IBU 250 mg/APAP 500 mg, fed

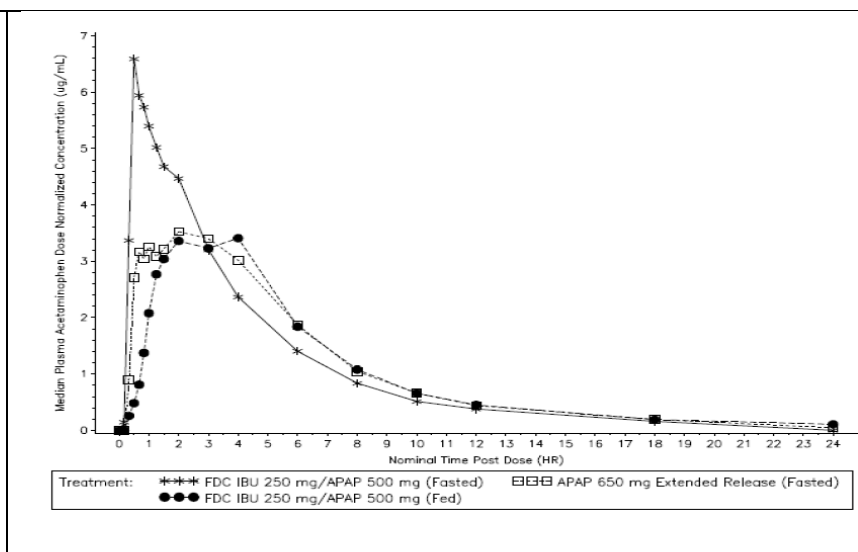
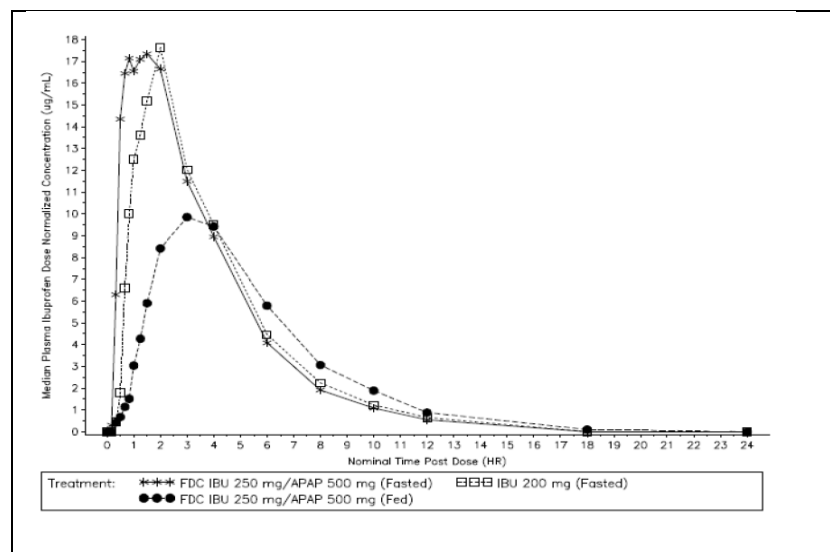
Subjects were assigned to one of four different treatment sequences. Between each dose there were two-day washout periods. The fed state was a high fat breakfast. The fasted state was after after fasting overnight for at least 10 hours. The study population was evenly distributed between males and females. The majority were black; there were also Caucasians or those that identified as other. The mean age 35.6 (range 18 to 52), mean weight 78.5 kg, and mean BMI 26.6 kg/m<sup>2</sup>.

Figure 1 show the relative bioavailability of the IBU in the FDC and as a 200 mg monocomponent in the fasted state as well as the bioavailability of the IBU in the FDC in the fed state after a single dose. In the fasted state the median T<sub>max</sub> for the FDC treatment was 1.38 hours and 2 hours for the IBU 200 mg treatment. In the fasted state the IBU component of the FDC showed a comparable peak plasma IBU level (C<sub>max</sub>) with IBU 200 mg, but in the fed state the T<sub>max</sub> was delayed and the C<sub>max</sub> was decreased.

As seen in Figure 2 in the fasted state the APAP component of the FDC showed a higher peak plasma APAP level (C<sub>max</sub>) compared with APAP 650 mg ER or the fed state after a single dose. The T<sub>max</sub> was delayed when taken with food and the C<sub>max</sub> was decreased. The C<sub>max</sub> was decreased approximately 37% compared to the fasted state. The T<sub>max</sub> was delayed to 1.5 hours in the fed state compared with 0.58 in the fasted state for the APAP component.

Figure 1 Median Plasma IBU level in fed and fasted state B5061005

Figure 2 Median Plasma APAP level in fed and fasted state B5061005



Applicant's CSR B5061005 Figure 2 p 48

Applicant's CSR B5061005 Figure 4 p 54

This study demonstrated that under fasted conditions the exposure of APAP and APAP administered as the FDC was bioequivalent to the dose normalized exposure of IBU 200 mg and APAP 650 mg administered as monocomponents. This study also demonstrated that the plasma concentrations of the FDC were not affected by food.

The FDC was bioequivalent to the dose normalized exposure (AUC) of the long acting APAP 650 mg and the APAP  $C_{max}$  was approximately 78% higher for the FDC IBU 250 mg/APAP 500 mg treatment when compared to the APAP 650 mg  $C_{max}$  that was used in this study. According to Dr. Khwatra this increase in  $C_{max}$  for the FDC IBU 250 mg/APAP 500 mg immediate release treatment was not unexpected considering the extended release formulation was used for the APAP 650 mg treatment. There were no statistically meaningful effects of food on the IBU exposure (AUC) between the fed and fasted state.

As the food effect was of concern, several Information Requests were placed to the Applicant to see if similar delays had been observed for other OTC pain medication in the fed state. The Applicant provided sufficient justification that the food effect was common to analgesics and that AUC was well preserved even if the  $C_{max}$  and  $T_{max}$  were decreased. The Applicant stated that most analgesic studies are conducted on a high fat diet when in the fed state and this is not a typical meal, so it is not representative of how the drug is more typically affected by food. It represents a worst-case scenario. Dr. Kwatra reported that the Applicant undertook an extensive literature review and demonstrated that a food effect is well established for many NSAIDs and acetaminophen across studies but is not accounted for in labeling. A review paper by Moore et al., 2015<sup>9</sup> cited by Dr. Kwatra evaluated 38 publications that had information on the fed and fasted state with various analgesics. The papers were published between 1971- 2012. The metaanalysis demonstrated that taking ibuprofen with food does not affect the overall bioavailability as measured by the  $AUC_{inf}$ , however food delays absorption of IBU with a fasting  $T_{max}$  under 4 hours. Multiple examples were given of delayed  $T_{max}$  for IBU and APAP in these circumstances. Mean  $T_{max}$  for IBU in an analysis using 6 comparisons were from 1.34 to 1.96 hours and for APAP,  $T_{max}$  was delayed from 1.58 to 2.08 hours. Food also reduces  $C_{max}$  for all drugs with fasting  $T_{max}$  under 2 hours. In studies of APAP, food decreased the  $C_{max}$  by 38% when comparing the fed to fasted state. The presence of APAP may improve the onset of action of the FDC. Based on a model of the onset and offset of dental pain after extraction provided by Li et al.<sup>10</sup>, a comparison was made between IBU and placebo and the time to first perceptible pain relief and time to meaningful pain relief were calculated to be approximately 0.6 hr. and 1.5 hr. Since APAP would also be present, this suggests that there would be greater efficacy for the product in the fed state. According to Dr. Kwatra, based on a model provided by Divoli, et. al., a food effect was seen for APAP with a decrease of  $C_{max}$  by 38%. All justifications by the Applicant were based on pharmacodynamic studies for pain (b) (4).

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<sup>9</sup> Moore RA, Derr S, Wiffen PJ et al, Effects of food on Pharmacokinetics of Immediate Release Oral Formulations of aspirin, dipyrene, paracetamol, and NSAIDs- a systemic review, Br J Clin Pharmacol (2015) Sep 80 (3); 381-8.

<sup>10</sup> Li, H, Mandema, J, et. al, Modeling the Onset and Offset of Dental Pain Relief by Ibuprofen (2011) The Journal of Clinical Pharmacology 52: 89.

**B5061006: Formulation effects and drug-drug interactions study**

This was a randomized, open-label, single dose, 4-way crossover, PK study in 46 healthy adult volunteers to assess the formulation effects and drug-drug interactions (DDI) of a single dose of:

- FDC IBU 250 mg/APAP 500 mg (administered as 2 tablets of IBU 125 mg/APAP 250 mg) fasted
- IBU 250 mg (2 tablets of 125 mg) and APAP 500 mg under fasted conditions co-administered together
- IBU 250 mg administered separately under fasted conditions
- APAP 500 mg administered separately under fasted conditions

Following an overnight fast, all subjects received the study drug. Blood sampling was obtained over 12 hours. No formulation effects or DDI were observed when the FDC was compared to the monocomponents. There was no change in the C<sub>max</sub> and the AUC of IBU absorption in the FDC compared with the FDC and the reference IBU 250 mg alone. In both treatment comparisons, the 90% CIs of the adjusted geometric mean ratios (Test/Reference) for IBU plasma AUC<sub>inf</sub>, AUC<sub>last</sub>, and C<sub>max</sub> were within the acceptance range (80%, 125%) for bioequivalence. This is summarized in the tables that follows.

| Table 5 Statistical Summary of Treatment Comparisons for IBU |                              |   |                 | Table 6 Statistical Summary of Treatment Comparisons for APAP |                               |   |                      |
|--|------------------------------|---|-----------------|---|-------------------------------|---|----------------------|
| Parameter  | Adjusted Geometric Means     |   |                 | Parameter   | Adjusted Geometric Means      |   |                      |
|  | FDC IBU 250 mg + APAP 500 mg | IBU 250 mg+APAP 500 mg Monocomponents Co-administered | Ibuprofen 250mg |   | FDC IBU 250 mg + /APAP 500 mg | IBU 250 mg + APAP 500 mg Monocomponents Co-administered | Acetaminophen 500 mg |
| C <sub>max</sub> (ng/mL)                                     | 22.11                        | 19.67   | 19.74           | C <sub>max</sub> (ng/mL)                                      | 7.199                         | 7.633   | 7.083                |
| AUC <sub>0-∞</sub>   | 79.12                        | 77.17   | 77.01           | AUC <sub>0-∞</sub>  | 23.92                         | 23.97   | 23.00                |
| T <sub>max</sub> (hr.) *                                     | 1.25 (0.500-                 | 1.50 (0.333-4.00)                                     | 1.38 (0.500-    | T <sub>max</sub> (hr)*  | 0.67 (0.34-                   | 0.50 (0.34-2.05)  | 0.50 (0.34-3.03)     |
| T <sub>1/2</sub> (hr.)                                       | 2.07 ± 0.327                 | 2.10 ± 0.381  | 2.09 ± 0.328    | T <sub>1/2</sub> (hr)   | 2.71 ± 0.396                  | 2.74 ± 0.401  | 2.71 ± 0.386         |

Source: Deep Kwatra, PhD

**B5061008: PK in adolescents 12 to <18 years of age**

This PK study was performed to permit extrapolation for children age 12 to the adult data. This was a randomized open-label PK study in 21 adolescents ages 12 to 17, to assess the bioavailability of IBU and APAP from a single oral dose of FDC IBU 250

mg/APAP 500 mg under fasted conditions. This study showed that the exposure (AUC) of IBU and APAP was slightly higher in the younger age group (ages 12 – 14) compared with those older. The AUC was slightly lower in the older age group of 15-17 years as well as in adults. Those ages 15-17 also had a lower  $C_{max}$  than those ages 12-14. The median  $T_{max}$  of IBU was delayed in the older age group by 1.0 hour compared to the younger age group and by 0.5 hours for APAP. The mean  $t_{1/2}$ , were similar across all age groups. According to Dr. Khwatra, the slightly higher exposure in adolescents compared with adults may be due to the smaller body surface area and lower body weight of the younger subjects.

No new studies were conducted to assess the effect of renal and hepatic impairment on the PK of the FDC. No population PK studies were done to evaluate intrinsic factors that may have an effect on IBU or APAP PK such as age, gender, race, and body weight. The clinical pharmacology team had no labeling recommendations for the product.

## 6. Clinical Microbiology

Not applicable to this application.

## 7. Clinical/Statistical- Efficacy

The clinical team consisted of Timothy Jiang, MD and Joshua Lloyd, MD of DAAAP and biostatisticians Feng Li, PhD and David Petullo, MS who concluded that the Applicant provided sufficient evidence to support the efficacy of the IBU/APAP FDC for the pain indication based on the results of a single dose full factorial study and a multidose study. (b) (4)

(b) (4)  
The collaborating review division confirmed that efficacy was established for the pain indication (b) (4) and I agree. According to Dr. Jiang the data quality and integrity were deemed accurate and reliable.

Three pivotal phase 3, randomized trials (pain trials B5061003, B5061004 (b) (4) were provided to serve as the primary evidentiary support for the efficacy of Advil Dual Action with Acetaminophen for the temporary relief of minor aches and pains (b) (4). Additionally, data from a proof of concept phase 2 single-dose, dose-ranging dental pain study (B50610001) was provided. The FDC was administered as two tablets for a total of IBU 250 mg/APAP 500 mg in all four trials. Most of the trials were single dose, but in the sole multidose trial the medication was repeated every 8 hours. All trials were performed in the United

States and were performed in the fasted state. No meal was allowed for 1 hour before dosing and for 2 hours after dosing of study medication. Low fat liquids or soft foods could be consumed, but not within 30 minutes before dosing.

Trial B50610001 was a phase 2 dose-finding study. The study was a randomized, double-blind, parallel group, single oral dose evaluation of three different FDC IBU/APAP formulations compared to IBU 400 mg using a third molar dental extraction model to evaluate the analgesic effect. The study was performed in the fasted state. In this 12-hour single dose study male and female subjects ages 16-40 were randomized 1:3:3:3:3 to one of five treatment arms including:

- Placebo (Pb)
- IBU 200 mg + APAP 500 mg
- IBU 250 mg + APAP 500 mg
- IBU 300 mg + APAP 500 mg
- IBU 400 mg

The primary endpoint was to determine the analgesic efficacy of three different FDCs of IBU/APAP compared to IBU 400 mg and Pb using the SPID0-8 (Time weighted sum of pain intensity difference score [based on the 4-point Categorical Pain Severity, PID4] and pain relief scores from 0-8 hours after dosing). Secondary endpoints evaluated time to “meaningful” relief and several other time points.

The ITT population included the 568 randomized subjects. Most had four molar extractions and rated their pain as moderate. All three FDC appeared to have similar efficacy and were all significantly better than placebo. None were significantly better than IBU 400 mg.

**Table 7 Summary of the Primary Efficacy Endpoint Study B5061001- Intent to Treat Population (ITT)**

|                             | Placebo<br>(n=30)                       | IBU/APAP<br>200/500 mg<br>(n=90)        | IBU/APAP<br>250/500 mg<br>(n=93)        | IBU/APAP<br>300/500 mg<br>(n=89) | IBU<br>400 mg<br>(n=92)                |  |
|-----------------------------|---|---|---|----------------------------------|--|--|
| SPRID[4]0-8<br>Mean (SD)    | 5.0 (13.2)                              | 30.8 (12.7)                             | 29.6 (15.6)                             | 31.7 (14.6)                      | 28.8 (15.3)                            |  |
| <b>Pairwise Comparisons</b> |   |   |   |                                  |  |  |
|                             | IBU/APAP<br>200/500 mg<br>vs<br>Placebo | IBU/APAP<br>250/500 mg<br>vs<br>Placebo | IBU/APAP<br>300/500 mg<br>vs<br>Placebo | IBU<br>400 mg<br>vs<br>Placebo   | IBU/APAP<br>200/500 mg<br>vs<br>IBU400 | IBU/APAP<br>250/500 mg<br>vs<br>IBU400 |
| Treatment<br>Diff.^         | 26.3                                    | 24.4                                    | 27.5                                    | 24.9                             | 1.4                                    | -0.5                                   |
| p-value <sup>@</sup>        | <0.001*                                 | <0.001*                                 | <0.001*                                 | <0.001*                          | 0.501                                  | 0.817                                  |

Source: Sponsor’s CSR B5061001 Table S2 p

Other endpoints evaluated were the time to onset of meaningful pain relief (Table 8) and the time to treatment failure (Table 9). All the FDC were significantly better than Pb for time to meaningful pain relief. Only IBU 200 mg + APAP 500 mg was significantly better than IBU 400 mg for time to meaningful pain relief. For treatment failure, all FDC formulations and IBU 400 mg were significantly better than Pb. None of the FDC were better than IBU 400 mg for this endpoint.

**Table 8 Summary of Time to meaningful relief of pain Study B5061001 – ITT Population**

|                             | Placebo<br>(n=30)                       | IBU/APAP<br>200/500 mg<br>(n=90)        | IBU/APAP<br>250/500 mg<br>(n=93)        | IBU/APAP<br>300/500 mg<br>(n=89) | IBU<br>400 mg<br>(n=92)                |  |
|-----------------------------|---|---|---|----------------------------------|--|--|
| Median (minutes)            | >720                                    | 44.5                                    | 54.1                                    | 45.9                             | 56.2                                   |  |
| % with Event+               | 20.0                                    | 91.1                                    | 88.2                                    | 89.9                             | 85.9                                   |  |
| <b>Pairwise Comparisons</b> |   |   |   |                                  |  |  |
|                             | IBU/APAP<br>200/500 mg<br>vs<br>Placebo | IBU/APAP<br>250/500 mg<br>vs<br>Placebo | IBU/APAP<br>300/500 mg<br>vs<br>Placebo | IBU<br>400 mg<br>vs<br>Placebo   | IBU/APAP<br>200/500 mg<br>vs<br>IBU400 | IBU/APAP<br>250/500 mg<br>vs<br>IBU400 |
| Hazard<br>Ratio^            | 12.7                                    | 10.0                                    | 11.7                                    | 8.6                              | 1.5                                    | 1.2                                    |
| p-value <sup>@</sup>        | <0.001*                                 | <0.001*                                 | <0.001*                                 | <0.001*                          | 0.014*                                 | 0.332                                  |

Source: Sponsor’s CSR B5061001 Table S3 p8

**Table 9 Summary of Time to Treatment Failure – ITT Population**

|                           | Placebo<br>(n=30)                       | IBU/APAP<br>200/500 mg<br>(n=90)        | IBU/APAP<br>250/500 mg<br>(n=93)        | IBU/APAP<br>300/500 mg<br>(n=89) | IBU<br>400 mg<br>(n=92)                |  |  |
|---------------------------|---|---|---|----------------------------------|--|--|--|
| Median (hours)            | 1.6                                     | 9.7                                     | 10.1                                    | 11.1                             | 10.4                                   |  |  |
| % with Event +            | 80.0                                    | 64.4                                    | 57.0                                    | 50.6                             | 55.4                                   |  |  |
| Pairwise Comparisons      |   |   |   |                                  |  |  |  |
|                           | IBU/APAP<br>200/500 mg<br>vs<br>Placebo | IBU/APAP<br>250/500 mg<br>vs<br>Placebo | IBU/APAP<br>300/500 mg<br>vs<br>Placebo | IBU<br>400 mg<br>vs<br>Placebo   | IBU/APAP<br>200/500 mg<br>vs<br>IBU400 | IBU/APAP<br>250/500 mg<br>vs<br>IBU400 | IBU/APAP<br>300/500 mg<br>vs<br>IBU400 |
| Hazard Ratio <sup>^</sup> | 0.3                                     | 0.2                                     | 0.2                                     | 0.3                              | 1.1                                    | 1.0                                    | 0.9                                    |
| p-value <sup>@</sup>      | <0.001*                                 | <0.001*                                 | <0.001*                                 | <0.001*                          | 0.549                                  | 0.863                                  | 0.454                                  |

Source: Sponsor's CSR B5061001 Table S4 p12

### **CDTL's Comment**

*Although this was a dose-finding study there was no stated rationale as to the dose chosen. All three FDCs tested as well as IBU 400 mg were statistically significant over Pb for the primary endpoint. The Applicant chose the midrange dose of IBU 250mg + APAP 500 mg for their FDC.*

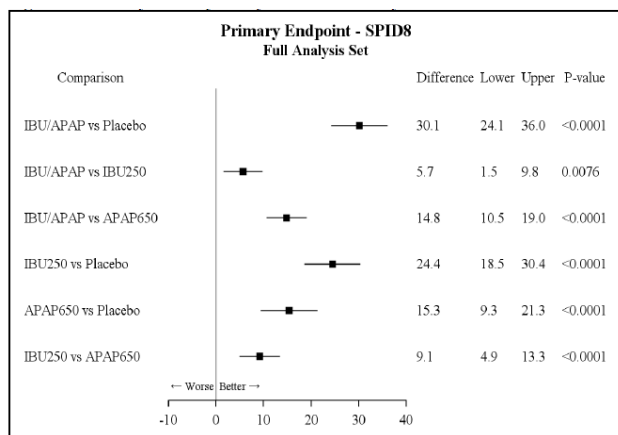
**Trial B50610003** was a full factorial phase 3, randomized, double-blind, parallel group trial of efficacy and safety comparing a single dose of the FDC to each active drug monocomponent and to Pb. Subjects were randomized 1:3:3:3. The four treatment arms included Pb, IBU 250 mg + APAP 500 mg, IBU 250 mg, and APAP 650 mg. In this 12-hour dental pain study male and female subjects who had an extraction of three or more molars and who experienced at least moderate intensity post-operative dental pain, were randomized and stratified by baseline pain and gender. After being given study medication, subjects were evaluated onsite for 12 hours with frequent monitoring. Pain was measured using a 4-point categorical scale confirmed by a Visual Analog Pain Severity Rating scale (VAS PSR) of at least 50 mm out of 100 mm. The baseline pain was rated on a 11-point numerical pain severity rating scale (PSR). The primary endpoint was the SPID0-8 (Time weighted sum of pain intensity difference score [based upon the numerical 11-point pain scale rating]) and pain relief scores from 0-8 hours after dosing). The measurement was obtained using the double stopwatch method. Key secondary endpoints evaluated time to meaningful relief (MR), pain relief rating (PRR), duration of relief (as measured by the time to treatment failure using time to rescue or dropout) and analysis of efficacy by gender and baseline pain. The primary efficacy endpoint was analyzed using an analysis of covariance model (ANCOVA), with treatment group, sex, baseline

categorical PSR as factors, and baseline numerical PSR as a continuous covariate. There were preplanned rules for imputation and censoring.

A total of 568 were enrolled and 560 completed the trial. Treatment arms were comparable for baseline pain level, sex, age, race and most were Caucasian (95%) and nonHispanic (87%). The mean age was 19.5. Only 1% discontinued, primarily due to AE. For the primary endpoint, SPID0-8 the FDC was statistically superior to comparisons including IBU 250 mg, APAP 650 mg, and Pb as seen in Figures 4 and 5 provided by the statistician. When the components were compared to Pb, the IBU 250 mg, offered more relief than the APAP component. The secondary endpoint duration of treatment effect also shows that pain relief lasted for approximately 78% of subjects at 8 hours with the FDC, 68% of those on APAP 650 mg and 50% of those on IBU 250 mg which demonstrates that the FDC has superior duration of effectiveness compared to the monocomponents. Several sensitivity analyses accounting for the effect on the results of rescue were performed by the statistician and were also confirmatory.

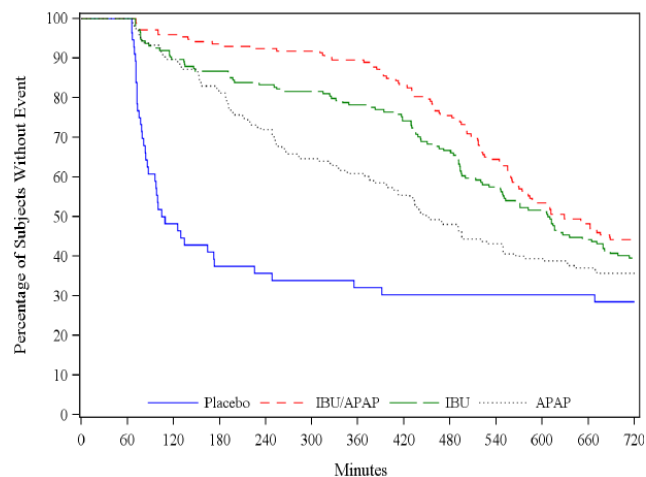
The median time to onset of meaningful pain relief was 47.9 minutes (95% CI 41.6, 57.4) for the FDC. This was statistically superior to IBU 250 mg at 65.9 minutes (95% CI 57.2, 81.6) and APAP 650 mg at 56.6 minutes (95% CI 50.5, 84.6), and to Pb. Additionally, the key secondary endpoint, the period from 6-8 hours was evaluated with the SPID6-8 as seen in Table 10 and the FDC was superior to Pb, APAP 650 mg, and IBU 250 mg during hours 6-8 which demonstrated the duration of effect.

**Figure 3 Primary Efficacy Analysis Result – Study B5061003**



Source: Statistician Review NDA 211733 Figure 4

**Figure 4 Duration of Relief Measured by Time to Treatment Failure**



Source: Statistician Review NDA 211733 Study B5061003 Figure 5

**Table 10 Time to onset of meaningful relief full analysis set****Table 11. Time to Onset of Meaningful Relief – Full Analysis Set**

|                                   | Placebo                          | FDC IBU<br>250 mg/APAP<br>500 mg | IBU<br>250 mg                    | APAP<br>650 mg                 | P-value <sup>a</sup>            |                                       |
|-----------------------------------|----------------------------------|----------------------------------|----------------------------------|--------------------------------|---------------------------------|---------------------------------------|
|                                   | N = 56                           | N = 172                          | N = 175                          | N = 165                        |                                 |                                       |
| Median (minutes) <sup>b</sup>     | N/A                              | 47.9                             | 65.9                             | 56.6                           | <0.001                          |                                       |
| 95% CI (median) <sup>b</sup>      | N/A                              | (41.6, 57.4)                     | (57.2, 81.6)                     | (50.5, 84.6)                   |                                 |                                       |
| Number(%) with event <sup>c</sup> | 16 (28.6%)                       | 147 (85.5%)                      | 139 (79.4%)                      | 118<br>(71.5%)                 |                                 |                                       |
| <b>Pairwise Comparisons</b>       |                                  |                                  |                                  |                                |                                 |                                       |
|                                   | FDC IBU<br>250 mg/APAP<br>500 mg | FDC IBU<br>250 mg/APAP<br>500 mg | FDC IBU<br>250 mg/APAP<br>500 mg | IBU<br>250 mg<br>vs<br>Placebo | APAP<br>650 mg<br>vs<br>Placebo | IBU<br>250 mg<br>vs<br>APAP<br>650 mg |
| P-value <sup>a</sup>              | <0.001 F                         | 0.003 F                          | 0.031 F                          | <0.001 F                       | <0.001 F                        | 0.631                                 |

Source: Sponsor's CSR B5061003 Study B5061003 Table 14.2.2.5.1

### ***CDTL's Comment***

*The FDC had superior efficacy as required on the SPID0-8 compared to IBU 250 mg and superior duration of effect compared to APAP 650 mg. Not only did the FDC work better than the comparators for the primary endpoint, but it also was superior to the comparators over the last 6-8 hour window of time showing sustained duration of effect. It is noted that the later measure was obtained without redosing the IBU 250 mg which is a short-acting medication typically lasting 4-6 hrs. Efficacy was further supported by other confirmatory endpoints such as time to onset of meaningful pain relief. The FDC had a median onset at 47.9 minutes (95% CI 41.6, 57.4) conforming to the expectation for OTC acute pain analgesics to work within an hour. The time to onset of first perceptible pain relief was considerably shorter at 21.3 minutes (95% CI 18.7, 24.2) compared to approximately 24 minutes for IBU 250 mg and APAP 650 mg. In summary, the combination rule was satisfied by the FDC over the monocomponents.*

**Trial B50610004** was a phase 3, randomized, double-blind, placebo-controlled, parallel group two-arm 6 dose efficacy and safety trial lasting 48-hours in subjects who experienced post-operative pain of at least moderate intensity after surgical extraction of three or more molar teeth. The treatment arms were the FDC compared to placebo. Subjects were randomized 1:2 and this included male and female subjects between the ages of 18-38. Pain was rated in a similar fashion to Trial B50610003 using the double stopwatch method. After an hour, if subjects had not had adequate relief of their pain they remained in the study but were permitted rescue medication, either tramadol or codeine.

The primary endpoint was to compare the analgesic efficacy of a single dose of the FDC to Pb using the SPID0-24 based on the 11-point numerical pain scale. The secondary endpoints were the SPID0-8, SPID6-8, SPID0-16, SPID8-16, SPID0-48, the duration of relief and time to onset of meaningful pain relief. The percentage of subjects requiring rescue medication by 2, 3, 4, 5, 6, 7 and 8-hour timepoints were evaluated. The primary efficacy endpoint was analyzed using an analysis of covariance model (ANCOVA), with treatment group, sex, baseline categorical PSR as factors, and baseline numerical PSR as a continuous covariate.

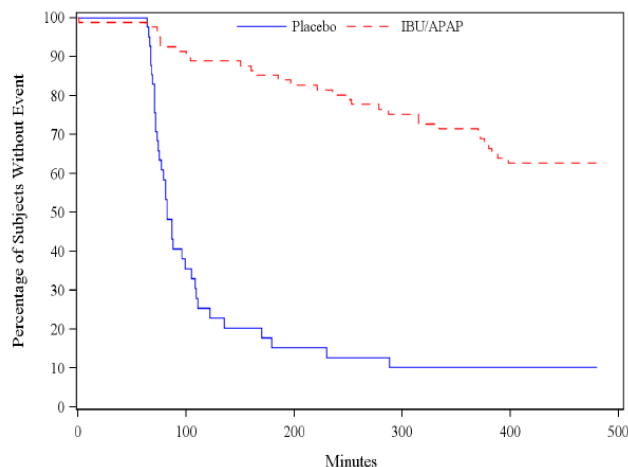
A total of 123 subjects were randomized and treated with either the FDC or Pb. In this 48-hour study 11(9%) discontinued, greater in the placebo arm 5 (12%), than in the FDC arm 6 (7%). Demographic and baseline characteristics were comparable between arms with a mean age of 21.8 years, approximately 55% female and 90% Caucasian. Mean baseline pain level on an 11-point scale was approximately 7.7. The primary endpoint showed that the SPID24 (time weighted sum of pain intensity difference score [based upon the numerical 11-point pain scale rating]) and pain relief scores from 0-24 hours after dosing) was statistically significant for the FDC compared with Pb ( $p < 0.001$  95% CI 50.1, 95.7). After the first dose the SPID6-8 also showed a statistically significant difference between FDC and Pb which reconfirms the findings in Trial B50610003 that there is a duration of treatment effect.

**Table 11 Primary analysis, SPID0-24 (full analysis se) – Study B5061004**

|                                       | Placebo             |                      | FDC IBU 250 mg/<br>APAP 500 mg  |                       |                   |
|---------------------------------------|---------------------|----------------------|---------------------------------|-----------------------|-------------------|
|                                       | N = 41              |                      | N = 82                          |                       |                   |
| Mean (SD)                             | -7.05 (54.525)      |                      | 64.58 (64.554)                  |                       |                   |
| Median                                | -16.00              |                      | 67.25                           |                       |                   |
| Range                                 | (-71.0, 161.8)      |                      | (-44.8, 206.0)                  |                       |                   |
| LSM (SE) <sup>a</sup>                 | -8.13 (9.426)       |                      | 64.76 (6.676)                   |                       |                   |
| FDC IBU 250 mg/APAP 500 mg vs Placebo |                     | P-value <sup>a</sup> | P-value<br>Trt*Sex <sup>d</sup> | Trt*Base <sup>e</sup> | RMSE <sup>b</sup> |
| Diff <sup>c</sup>                     | 95% CI <sup>c</sup> |                      |                                 |                       |                   |
| 72.89                                 | (50.075, 95.707)    | <0.001*              | 0.380                           | 0.444                 | 60.188            |

Source: Sponsor's CSR Study B5061004 Table S4 p 7As seen in Figure 5 the time to treatment failure at eight hours was approximately 37% on the FDC and approximately 88% on Pb. As seen in Table 12 the curves for the time to onset of meaningful pain relief separated at outset favoring the FDC (median 59.2 minutes; 95% CI 47.7, 74.5) over Pb (165.9 minutes; 95% CI 88.0, 170.0).

**Figure 5 Duration of Relief - Time to Treatment Failure**



Source: Statistician Review NDA 211733 Study B506100 Figure 6

**Table 12 Time to Onset of Meaningful Pain Relief**

|                                    | Placebo<br>N = 41 | FDC IBU 250 mg/<br>APAP 500 mg<br>N = 82 | FDC IBU 250 mg/<br>APAP 500 mg vs<br>Placebo<br>P-value <sup>a</sup> |
|------------------------------------|-------------------|--|--|
| Time to onset of meaningful relief |                   |  |  |
| Median (minutes) <sup>b</sup>      | 165.9             | 59.2                                     | <0.001*  |
| 95% CI (median) <sup>b</sup>       | (88.0, 170.0)     | (47.7, 74.5)                             |  |
| Number (%) with event <sup>c</sup> | 10 (24.4%)        | 72 (87.8%)                               |  |

Source: CSR NDA 211733 Study B5061004 Table S7 p 12.

**CDTL's Comment**

*This study confirmed analgesic efficacy of the FDC over the Pb in a multidose study. The FDC was faster than Pb, fewer failed treatment relief on the FDC and most importantly pain relief over the full treatment period of 0-24 hours was superior to Pb.*



(b) (4)

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## 8. Safety

The review of clinical trial safety and postmarketing safety was performed by Shila Azodi, MD. She concludes that no new safety signals emerged from the clinical trial data and postmarketing data and I agree. Due to some of Dr. Azodi's initial concerns about the postmarketing safety the Division of Pharmacovigilance was consulted, and they reviewed the findings as well. Please see their reviews for full details about the safety of the FDC. The clinical trial safety review including a total of four clinical trials and three pharmacokinetic trials. As the FDC is not marketed yet, but other FDCs are marketed worldwide, a review was done of the FAERS database, WHO Vigibase, as well as a literature review to explore the experience with other FDCs outside the United States.

The Applicant provided safety data from four clinical efficacy trials and three pharmacokinetic trials. There was no requirement for a prespecified safety database, presumably because of the many years of clinical experience with the use of IBU and APAP. The Applicant provided an integrated review of safety with data from all seven clinical studies. These included the following:

- Three PK studies including:
  - Single dose bioavailability study open label, single oral dose, 4-way crossover study, bioequivalence, volunteer male and females' volunteers (Study B5061005)
  - Single dose PK studies open-label, single oral dose, 4-way crossover, bioequivalence, healthy male and female volunteers, ages  $\geq 18$  years (B5061006)
  - Single dose PK studies open-label, single oral dose, bioavailability PK study in healthy male and female adolescent volunteers ages 12-17 (B5061008)
- Five clinical trials including:
  - A single dose, double-blind, placebo-controlled dose-finding dental pain study stratified by sex and baseline pain severity in healthy adults and adolescents ages  $\geq 16$  years of age (B5061001)

- Pivotal safety and efficacy study with multiple doses dental pain in a double-blind, placebo-controlled, study sex and baseline pain severity-stratified, in health make and female volunteers ages  $\geq 18$  years (B5061004)
- Pivotal safety and efficacy study with a single dose dental pain model in a double-blind, placebo-controlled, study sex and baseline pain severity-stratified, in health make and female volunteers ages  $> 18$  years (B5061003)
- (b) (4)

The Applicant was advised to provide an analysis of the safety data by dose-response, age, gender, time-to-onset, accidental or intentional overdose, dose and duration, misuse and abuse. They were additionally instructed to cover the following special safety topics: cardiac disorders, gastrointestinal disorders, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, nervous system disorders, renal and urinary disorders, respiratory disorders, skin and subcutaneous disorders, vascular disorders.

**Exposure**

A total of 1477 subjects were enrolled in trials. There were two treatment pools. The main treatment pool included those on FDCs from the clinical trials (both single and multidose trial data) for a total of 1375 subjects. The other pool was those in the pharmacokinetic trials which include a total of 102 subjects.

The main treatment pool included the following treatment arms:

| Treatment arm   |                               | Number subjects | Number of doses                                   |
|-----------------|-------------------------------|-----------------|---|
| <b>Placebo</b>  |                               | <b>156</b>      |   |
| <b>All IBU</b>  |                               | <b>432</b>      |   |
| <b>All APAP</b> |                               | <b>330</b>      |   |
| <b>All FDC</b>  |                               | <b>715</b>      |   |
|                 | <b>IBU 200 mg/APAP 500 mg</b> | <b>90</b>       | <b>All single dose</b>                            |
|                 | <b>IBU 250 mg/APAP 500 mg</b> | <b>454</b>      | <b>454 single dose</b><br><b>82 multiple dose</b> |
|                 | <b>IBU 300 mg/APAP 500 mg</b> | <b>89</b>       | <b>All single dose</b>                            |

In addition to the pooled clinical trials there was a pool for those in the pharmacokinetic trials with 102 subjects.

### **Demographics**

In the pharmacokinetic trials out of the 102 healthy subjects evaluated, the ages spanned 12-55. No older individuals were assessed. Both males and females were well represented. Approximately 50% of subjects were African American, and the remainder were Caucasian, Asian, or other. Weight ranged between 43.4 kg to 102.7 kg and BMI between 18.1 to 30.5.

In the pooled clinical trials there were 1375 subjects whose ages spanned 16-55 with a mean age of 22. No older individuals were assessed. Both male and female subjects were well represented. Caucasians were 91% of the population and the remainder were other. Compliance across the studies was excellent between 91.1% and 99.2% in these predominantly single dose studies.

### **Adverse Event Reporting**

During the trials there were no deaths and no serious AE. Less than 2% (25/1477) of subjects discontinued due to AEs. Of those, some had events most likely unrelated to the FDC, namely, vomiting after a dental extraction and symptoms typical of receiving endotoxin such as myalgias, headache. Treatment emergent AEs in the trials were typical of IBU and APAP and did not represent new safety concerns. AE reporting was higher in the placebo arm than in the treatment arms; there were 127 (18%) on IBU 250 mg/APAP 500 mg who had AE and 50 (32%) of those on placebo who had AE. The predominant AE that may have been related to the FDC were nausea, vomiting, dizziness, headache. Vital signs and electrocardiograms were stable. In summary, there were no unexpected findings during the clinical trials. This included an analysis by Dr. Azodi of cardiac disorders, gastrointestinal disorders, hepatobiliary disorders, immune system disorders, injury, poisoning and procedural complications, nervous system disorders, renal and urinary disorders, respiratory disorders, skin and subcutaneous disorders, vascular disorders. The trials included no more than two days of dosing. There were no accidental or intentional overdose, misuse or abuse. In the limited clinical trial data there was also no evidence of AEs related to a dose response. Subgroup analysis by sex, age, and race revealed no unexpected findings.

### **Postmarketing Assessments**

There was little postmarketing safety data available for review, as the product is not marketed yet in the United States. The following postmarketing safety databases from the literature and the rest of the world were reviewed including the following:

- World Health Organization (WHO) Vigibase search from January 1, 1995 to December 31, 2017
- Published medical literature review for safety issues associated with the combination of IBU and APAP
- 120-day Safety update of fixed dose combinations of IBU and APAP

Based on the known AE profiles of IBU and APAP the following special safety topics were identified for further assessment of postmarketing sources just they were analyzed in the clinical trials. These included the following:

- Cardiac disorders including increased risk of adverse cardiovascular thromboembolic events including myocardial infarction. This risk varies based on dose, duration, and an individual's baseline CV risk factors
- Gastrointestinal disorders including the risk of serious GI complications increases with increased duration of therapy and higher doses. These include non-specific GI symptoms such as heartburn, nausea, dyspepsia, emesis, abdominal pain, endoscopically visualized asymptomatic mucosal lesions and serious GI complications such as perforated ulcers, severe bleeding
- Hepatobiliary disorders including drug-induced liver injury (DILI) leading to transplantation and death
- Immune system disorders including hypersensitivity reactions with anaphylaxis (respiratory distress, facial swelling, urticaria, rash, pruritis), particularly in those with asthma
- Injury, poisoning and procedural complications including hepatotoxicity and suicide
- Nervous system disorders including stroke
- Renal and urinary disorders which can include occurrence or worsening of kidney injury, particularly when combined with other potentially nephrotoxic agents such as diuretics or angiotensin converting enzyme inhibitors
- Respiratory disorders including asthma
- Skin and subcutaneous disorders which can include Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), exfoliative dermatitis
- Vascular disorders including stroke, myocardial infarction

### **WHO Vigibase Database**

The WHO Vigibase is a database of clinical reports of AE to pharmaceutical products collected from national centers in participating countries. From January 1, 1995 through December 31, 2017 there were 1365 individual cases safety reports identified for IBU and APAP and of these, 1020 (74.7%) where this combination was thought to be the suspect drug. Of these only 243 (17.8%) AE reports were considered serious and five resulted in death. Of the deaths, only four are likely to be related to the product including skin reactions and allergy/sensitivity reactions. These included a case of anaphylactoid reaction, bronchospasm, Stevens Johnson Syndrome (SJS), and Toxic epidermal necrolysis (TEN). The 243 serious cases were predominantly skin and subcutaneous tissue disorder (141; 58%) and a variety of other conditions. Of the 28 serious cases of SJS, only 12 were thought to have a FDC as a suspect medication. Of the 14 cases of TEN, only 13 were thought to have the FDC as a suspect medication. Gastrointestinal disorders accounted for 49 AE reports which predominantly included vomiting, nausea, gastritis, and abdominal pain. For this entire database of 1365 cases, only seven were considered to have gastritis classified as serious. Injury, poisoning, and procedural complications only accounted for nine cases which were not well described, but which appeared unlikely to be related.

Of note, was that 1146 (84%) of the AEs were noted to come from Southeast Asia. As the Applicant could not provide an explanation for the disproportionate number of reports coming from this region, the Division of Pharmacovigilance (DPV) was asked to reassess the postmarketing data to see if they could determine an explanation for this finding. They reviewed both FAERS reports and the WHO Vigibase Database and were able to confirm the Applicant's findings. Although reports lacked detail, no new safety issues were raised according to Dr. Azodi.

### **Division of Pharmacovigilance (DPV) Consultation**

A consultation was placed with DPV because of concerns that 81% of postmarketing cases reported in the WHO Vigibase came from Southeast Asia. No exposure data was known regarding worldwide use of FDC products and it was thought that DPV had greater access to exposure data and would have some insight into why so many cases were from this region. DPV used the prescription product labels for Ofirmev (APAP injection) and Ibuprofen tablets 800 mg to determine the labeling status of the common AEs associated with the FDC product. They searched the FAERS database for all reports prior to May 13, 2019 using numerous product term names for the components of the FDC. They were able to specifically query cases identified outside of the US where FDC are marketed. They found 12 unique cases that reported serious outcomes. Out of the 12 cases 2 were  $\geq$  age 65, 2 were life-threatening, further details were not provided. Of the 20 most commonly reported MedDRA PTs there were only 6 cases of intentional overdose, 6 cases of hypotension, 2 cases of hepatitis and 2 of vomiting, and the rest were single cases. Most included PTs described in the label for either APAP or IBU. Eight cases reported unlabeled PTs but were confounded by other medication, the underlying disease, lack of temporal relationship, intentional overuse or inadequate information to determine causality.

DPV next searched Vigibase from December 31, 2017 through December 31, 2018. They retrieved 1217 unique reports. They were asked to analyze the reports by region and confirmed that 95.6% of the AE reporting came from Asia/Western Pacific Region. Further stratification showed that 68% were from India, 18% were from Thailand, 5.7% from Vietnam, 2.5% from Philippines, and 1.1% from Italy. The remaining countries contributed less than 1% a piece. All the top 20 PTs in the AE reports were from the IBU and APAP labels. Serious cutaneous adverse reactions were further assessed because the Applicant had assessed them previously. All have been reported before and include SJS, TEN, dermatitis bullous, erythema multiforme, acute generalized exanthematous pustulosis, dermatitis exfoliative, and cutaneous vasculitis. No new deaths other than those identified by the applicant were identified by DPV. The sole case that was not in the prior drug labels was a case of cystic fibrosis. Unfortunately, DPV had no access to exposure data worldwide and could not clarify why so many cases came from Southeast Asia. Anecdotal information suggests that, at least in India, predominantly combination products are available for sale, and IBU and APAP sold as single ingredients are less obtainable. DPV concluded that "the safety profile of FDC ibuprofen and acetaminophen products describes in the FAERS and VigiBase databases is consistent with the known safety profile of the individual acetaminophen and ibuprofen components.

### **120-Day Safety Update**

This report covered the period from January 1, 2018 through December 31, 2018. During this period the Applicant identified another 184 cases worldwide with AE reporting of which 48 were deemed serious. Cutaneous reactions and gastrointestinal disorders predominated. No new safety signals were identified.

### **Literature Review**

According to Dr. Azodi, the Applicant referenced 14 articles relevant to the evaluation of safety of various IBU/APAP combination products in clinical trials, and 4 review articles. The studies ranged from a single dose to a 13-week study where subjects took up to IBU 400 mg/ APAP 1000 mg three times a day. None of the reports raised any serious safety concerns according to Dr. Azodi. Most were in a dental pain model, but also included dysmenorrhea, knee pain, back pain, and postsurgical pain. According to Dr. Azodi, in the study where 892 subjects were placed on an FDC three times a day for 13 weeks, there was some elevated transaminase levels and some mild decline in hemoglobin levels as one might expect with chronic use of IBU and APAP.

Dr. Azodi did not describe any literature that reviewed the practice of alternating IBU and APAP or taking them together and any untoward AEs that consumers might experience even though this is a common practice among pediatric patients and dental patients. There was also very little literature that was reviewed that described any intentional abuse of FDCs even though it is known that APAP, one of the components of the FDC has been intentionally been used for suicide or unintentionally resulted drug induced liver injury, liver transplantation, and death. Unintentional injury can occur when consumers are unaware that they are using a combination product that contains acetaminophen such as Percocet or Excedrin and “double dip” or use two products containing APAP<sup>11</sup>.

### **CDTL's Comments**

*The safety review of the clinical trials revealed no new safety signals. This was anticipated, as both components of the FDC have a lengthy track record of use and are very well characterized. Additionally, the size of the small safety database and the duration of use ranging from the efficacy trials could not be expected to pick up a subtle safety signal. Additionally, no high-risk subjects were included in the patient population who were all healthy individuals with either induced (b) (4) pain from a dental extraction. The safety review of the postmarketing period also revealed no new safety signals. The only unexpected finding was that the predominant number of AEs came from Southeast Asia, predominantly India. It was not possible to determine from sources available to our DPV colleagues what the exposures were in India or throughout Southeast Asia compared with other locations. Based on some anecdotal information, FDC may be used very frequently in India rather than individual drug products or ingredients. Regardless of the findings, the AEs attributed to India were characteristic of the APAP and IBU components and did not reveal any new findings.*

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<sup>11</sup> Wolf, M.S., et al. Risk of Unintentional Overdose with Non-Prescription Acetaminophen Products. J Gen Int Med (2012) 27: 1587-1593.

*Although the applicant did not provide literature about DILI and the frequency expected with OTC products containing APAP, much is already known about this topic and the drug facts label (DFL) specifically includes the standard liver warning common to other OTC APAP products. We will attempt to strength this warning as described in the discussion of the consumer testing by relocating it above the allergy warning.*

*This concept is a difficult one for any consumer, but especially for those with less education and low literacy. Not only does the general public have little knowledge about the consequences of drug induced liver injury, this situation is compounded by the discrepancy between recommendations for safe dosing of APAP products that are regulated as NDA products and those that are regulated as Monograph products. Monograph product DFLs advise that doses up to 4000 mg can be used each day, whereas NDA APAP products use is restricted in DFLs to 2600 mg each day.*

*To protect consumers from liver injury the warning on the DFL will need to make clear than only six tablets of the FDC may be use in every 24-hour period which is no more than 1500 mg/day of AP. This is well below the commonly accepted safety margin of 2600 mg for NDA products. Even if consumers were to err and take one extra dose of APAP ER 650 mg in a 24-hour period, they would be below the 2600 mg upper limit for NDA products. As alcohol can increase liver toxicity when combined with APAP, consumers will be adequately warned in the label not to consumer alcohol with the product.*

## 9. Advisory Committee Meeting

Not applicable.

## 10. Pediatrics

This NDA triggers the Pediatric Research Equity Act (PREA) and as such a commitment to perform pediatric studies. During drug development there have been several meetings to discuss the development of this FDC for children. (b) (4)

The Applicant has provided an initial Pediatric Study Plan (iPSP) as well as several amendments to the iPSP. The Agreed Amended iPSP dated December 18, 2015 is currently in place as later amendments were not agreed to. In that document the agreement included the following:

- Applicant agrees to conduct an efficacy, PK, and tolerability study in children ages 6 months to < 2 years with **pain** if efficacy is demonstrated in adults.

Cross Discipline Team Leader Review

○

[Redacted]

(b) (4)

The following three studies are deferred according to the iPSP:

○

[Redacted]

(b) (4)

○ Pediatric efficacy, PK, and tolerability study in children with pain (6 months - <2 years)

○ Pediatric PK and tolerability study in children with [Redacted] acute pain (2 years - <12 years)

(b) (4)

[Redacted]

(b) (4)

## 11. Other Relevant Regulatory Issues

### Office of Scientific Investigations (OSI) Audits

Dr. Susan Leibenhaut completed an OSI review that described the audit to two clinical sites, each of which conducted a phase 3 trial as a single site. There were no significant regulatory findings or issues regarding data integrity and OSI found no issues that precluded approvability. I agree. Both sites were in the US. At the first site 568 subjects were enrolled and 42 subject records were reviewed. At the second site 123 subjects were enrolled and 45 subject records were reviewed. No significant deviations or discrepancies were noted, nor was there underreporting of AE or protocol deviations with one minor exception. In the second study there was a single source document which was discrepant with the derived line listing which was thought to be due to the investigator not obtaining the pain assessment prior to dosing.

## 12. Labeling

### 12.1 Proprietary Name

A review of the proprietary name was performed by Grace P Jones, PharmD, BCPS. Please see her review for full details. According to the DMEPA review, the applicant had previously been granted a conditionally acceptable name on October 28, 2016, namely Advil Dual Action with Acetaminophen. This name was formally resubmitted on February 5, 2019. DMEPA had no concerns related to the name or to misbranding. There were some concerns that consumers did not understand that the word “dual” might not refer to two drugs but to two mechanisms of action. Overall the name remained conditionally acceptable. If anything should change regarding the FDC such as proposed product characteristics, the name must be resubmitted for review.

### 12.2 Social Science Review of Consumer Label Comprehension Study

An Integrated review of the Label Comprehension Study was performed by Dr. Amanda Pike-McCrudden and Dr. Elande Baro. Please see their review and their addendum for full details. In summary they found that the application was not approvable without recommended changes to the label to make sure that consumers understand that this product is only to be used for the temporary relief of aches and pains (b) (4)

Additionally, some recommended changes to the label will help to reinforce the comprehension of the liver damage warning and the proper dosing interval and dose. This will require further label comprehension iterative testing. I agree with their recommendations.

A single consumer study, PF-06428867, was required for this application as the labeling of both IBU and APAP are well established. The study was required to test how well consumers understood key communication messages from the drug facts label (DFL) for

Advil Dual Action with Acetaminophen. A one-on-one interview was conducted to explore the DFL endpoints. There were specific questions for adults about their previous use of other individual pain medications and the meaning of “dual action”. There were specific questions for adolescents regarding their medication purchases and behavior regarding use of pain medication. The study population was to consist of males and females age 12 including 30% with low literacy. Subjects were recruited from a variety of sources including by telephone as well as direct contact at malls; interviews took place at malls. Adolescents targeted by phone were screened by questioning their parents to ensure that these adolescents were accompanied by a parent or legal guardian. Adolescents were tested with their guardians in the room. Subjects were given unlimited time to read the information on the drug packaging and could refer to it during the interview. Adult subjects were stratified for some of the questions to test out different presentations of the material. For example, for the question regarding “Dual Action” half the subjects were shown a list of OTC pain relievers and half the subjects were shown the package front image of other OTC pain relievers. Questions about the monocomponents of the FDC were alternated so that some consumers got questions about APAP first, and others got questions about IBU first. In scoring of the study, if the responses were not “correct” or “acceptable” then two trained reviewers and a supervisor mitigated the response so that it was resolved.

### **CDTL’s Comment**

*There was some concern that the randomization of the sample was compromised by the recruitment method of the adolescents. There was also some concern that adolescents were tested with their parents in the interview room. Despite these features, they did not disqualify the study and were not deemed highly significant by social scientist, Amanda Pike-McCruden.*

The study had two primary communication objectives that had a 90% pre-specified performance threshold (successful if the lower limit of the 95% confidence interval equals or exceeds 90%):

1. Do not use with any other drug containing acetaminophen
2. Take 2 tablets with each dose

Each question was followed by follow-up probes so that mitigations could potentially be performed to identify acceptable answers.

The study had two secondary communication objectives that had to an 80% prespecified performance threshold. These included:

1. Severe liver damage may occur if you take with other drugs containing APAP
2. May cause severe stomach bleeding. The chance is higher if you take other drugs containing Rx or OTC NSAIDs

Additional exploratory questions were performed to further explore:

1. Adult consumers’ understanding of the term “dual action”
2. Adult consumers’ understanding of the active ingredients in common OTC pain relievers

3. Take a dose every 8 hours
4. Take no more than 6 tablets in 24 hours

Post-hoc endpoints were added:

1. Adult consumers’ understanding if they have used a product in the past containing acetaminophen
2. Adolescent behavior regarding the purchase and use of OTC medication was also explored.

The statistical analysis of the study was descriptive for continuous variables such as subject disposition and demographics. Frequency distributions were provided for categorical variables. The sample size was based on an 88% power analysis assuming a 2-sided test with an  $\alpha = 0.05$ , an expected correct comprehension rate of 94% and a performance threshold of 90% of the primary endpoint. The performance threshold for the secondary endpoints was set at 80%. The adolescent data was handled descriptively, and the small sample size of the adolescents precluded being based on a power analysis. The lower literacy rate was set at 30%. The primary and secondary endpoints were reported with point estimates (PEs) and two-sided Wilson 95% confidence intervals (CIs). Various mitigations were allowed, some were prespecified and some were post-hoc. The social science and statistics reviewers did not agree with some of the mitigations which are described along with the results of the study. There were pre-specified rules for missing data. Data was to be reported for subgroups including those of low literacy and adolescents.

The trial was a multicenter, single-visit study in consumers ages 12 and above. A total of 563 subjects were enrolled and all save one completed at least one question. This included 482 adult subjects and 81 adolescent subjects. The target rate of 30% for enrollment of low literacy was almost met at 28.8%. The demographics of the population was representative of the adult United States population in terms of race, sex, and educational level. The results are summarized in Table 13 below.

**Table 13. LCS Communication Endpoints Results**

| Endpoints  | Result (Point Estimate) | Result (lower limit of 95% CI) | Low Literacy Result (lower limit of 95% CI) | Adolescents (lower limit of 95% CI) |
|--|-------------------------|--------------------------------|---|-------------------------------------|
| <b>Primary Endpoints</b>                                     |                         |                                |   |                                     |
| #1 – Do not use with any other drug containing acetaminophen | 95.4%                   | 93.2%                          | 83.7%                                       | 83.2%                               |
| #2 – Take 2 tablets (per dose)                               | 91.7%                   | 88.9%                          | 78.7%                                       | 74.5%                               |

| Secondary Endpoints  |       |       |       |       |
|--|-------|-------|-------|-------|
| Severe liver damage may occur if you take with APAP products                                     | 84.8% | 81.3% | 59.2% | 64.9% |
| May cause severe stomach bleeding. Chance increased with other drugs containing Rx or OTC NSAIDs | 92.1% | 89.3% | 79.5% | 81.7% |
| Other communication endpoints  |       |       |       |       |
| Take a dose every 8 hours  | 81.9% | 78.2% | 63%   | 73.1% |
| Take no more than 6 tablets in 24 hours  | 96%   | 93.9% | 87.2% | 89.7% |

Source: Shila Azodi, MD summary of Sponsor’s Pivotal LCS CSR (p 41,45,49, 54,57,59)

Testing of the primary endpoint #1 “do not use with other drugs containing acetaminophen” met the prespecified 90% target threshold with a lower bound of 93.2%. Even low literacy and adolescent subgroups scored above 80%. Regarding primary endpoint #2, the instructions to take two tablets/dose, the group nearly met the 90% performance threshold with a point estimate of 91.7% and a lower bound of 88.9% . Low literacy (lower bound 78.7%) and adolescents (74.5%) had some difficulty understanding proper dosing.

The Applicant did meet the 80% performance threshold for both of their secondary endpoints among the general population, but comprehension was poor for those of low literacy (lower bound 59.2%) and adolescents (64.9%) for understanding of the liver warning. It was noted that when the mitigations were looked at for “severe liver damage may occur if using the product with other products containing APAP” although consumers had satisfactory understanding that they should avoid other products with acetaminophen they had limited understanding why. Consumers attributed the cautions with acetaminophen products to an allergy alert rather than a liver warning alert. The group did reasonably well in understanding the severe stomach bleeding warning and its link to NSAID use. Ms. Pike-McCrudden suggested that to enhance the drug label, the liver warning should be placed above the allergy warning for greater prominence. Additionally, she recommended that the Directions of use could be enhanced with the use of a chart to make it easier for consumers to understand dosing.

**CDTL’s Comment**

*It is not a surprise to this reviewer that consumers, particularly those with low literacy had trouble understanding the significance of the liver warning. This is a difficult concept to convey on a label to those with low educational levels or poor English language skills. Ms. Pike-McCrudden suggested that to enhance comprehension of the liver warning it might be helpful to switch the order of the warnings and place the liver warning atop the allergy warning. As this suggestion is in compliance with regulation requirements for*

*boxed warnings, I agree with this suggestion. Additionally, as long as subjects know not to take extra APAP, even if they do not know the reason why, this will help guard against liver injury. Pertaining to some comprehension problems with dosing instructions, changing the format of the dosing instructions may prove helpful as is proposed in section 12.3.*

Regarding other warnings, 81.9% (CI 78.2, 85.1) of adult subjects were able to comprehend that they should take a dose every 8 hours. The most common incorrect answer, noted by Ms. Pike-McCruden, was that subjects recognized that they should take no more than 6 tablets in 24 hours which was independently well comprehended by 96% (CI 93.9, 97.5) of adult subjects. Regarding the “Dual Action” question, 85.4% gave a correct response that dual action meant that the product contained two ingredients or drugs. The most common incorrect response was that dual action referred to pain (b) (4) indications.

When subjects were tested to see if they understood the active ingredients in common OTC pain relievers so that they could make a correct decision about the use of the FDC product, subjects did better when presented with images of the other OTC medication packages (3.5-5.4% error rate) and worse when they received a laundry list of product names. Specifically, failure rate for recognizing names of various NSAIDS was between 2.9-10.5% and failure to recognize the name Bayer was 21.8%. For those who were questioned if they had used an OTC product in the past that contained APAP, 55.4% said that they had taken name brand Tylenol. When one considers all the other APAP-containing products on the market, it was thought that approximately 77.7% of subjects recognized that they had previously been on a product containing APAP. Approximately 10% of subjects were not able to know, remember or name such a product. According to Ms. Pike-McCruden, there were limited follow-up probes to be conclusive about the answer to this question, but since consumers did understand “do not use with any other drug containing APAP” this alleviate some of her concerns.

Regarding adolescent decision-making testing, all adolescents were asked to characterize how they select and use OTC medications. A total of 97.5% acknowledged that they had used OTC medication in the past. Most (97.4%) relied on their parents or caregivers for information about the purchase and use of these products. The frequency and quantity of medication was frequently also determined by parent or guardian (79.5%). When asked how often they themselves read the drug label 21.8% said all the time, 20.5% said most of the time, 23.1% said sometimes, and 21.8% said rarely. In terms of frequency of OTC product use, 51.3% said that they used an OTC product several times a month and 37.2% said that they used an OTC product several times a year.

The Applicant agreed to requested changes to the label of moving the location of the liver warning and enhancing the Directions section with a chart (b) (4). Ms. Pike-McCruden recommended further label comprehension testing to ascertain if consumers understood the use of the product properly.

### **CDTL's Comment**

*Subjects had adequate understanding of the dosing instructions to use no more than 2 tablets every 8 hours and no more than 6 tablets in 24 hours. Consumers understanding of the term “Dual Action” in the proprietary name was inadequate, as they thought that dual action meant (b) (4) pain rather than two products in one tablet, but that did not interfere with their ability to use the medication properly. They understood how to dose the medication and to avoid using the product with other products containing APAP. Since the product will continue to have two components but will only have one use, it becomes more important to confirm that consumers understand that this product is not for pain (b) (4). Consumers appear to understand that APAP is a component of the FDC and that it should be avoided when using the product. Although adolescents might have had less than optimal response to acknowledging that they read the drug label before they took the product, at least most claimed that they took advice from their parent or guardian regarding OTC drug use. As Ms. Pike-McCradden points out, it is possible that the response regarding where adolescents get their advice from might have been biased where adolescents responded to please their parents sitting close by in the testing room, on face, it appears that the product will be used appropriately by adolescents.*

### **12.3 Recommendations for Labeling**

An Interdisciplinary Science (IDS) Labeling review was conducted by Robert Bahde, PhD. (Team Leader Kevin Lorick, PhD.). For the full labeling recommendations and requests please see his review and addendum. Comments from other reviewers were taken into consideration when making these recommendations. A summary is provided below of clinically related recommendations, but it is noted that negotiations have not yet been completed.

1. Per 21 CFR 201.326(a)(1)(iii)(A), the liver damage warning, located on the Drug Facts Label (DFL), must be the first warning under the *Warnings* heading. Revise your labeling so that the liver damage warning is the first warning subheading, above the allergy alert warnings in the DFL and immediate container labeling that do not contain a DFL.
2. While the print size of the term “(NSAID)” in the statement of identity (SOI) on the loose vial principal display panel (PDP) is at least one-quarter the size of the most prominent printed matter, it is not at least as large as the size of the “Drug Facts” title, per 21 CFR 201.326(a)(2)(i). Increase the type size of the loose vial statement of identity so that “(NSAID)” is at least the size of the “Drug Facts” title.
3. Per 21 CFR 201.66(c)(2), change the DFL heading “*Active ingredient (in each caplet)*” to “*Active ingredients (in each caplet)*” because there are two active ingredients in each tablet.

4. Under **Purposes**, change [REDACTED] (b) (4) to “Pain reliever.”
5. Under **Uses**, remove [REDACTED] (b) (4)
6. Per 21 CFR 201.326(a)(2)(ii), change the format (i.e., move the asterisk) of the term “(NSAID)\*” in the statement “Ibuprofen 125 mg (NSAID)\*.... Pain reliever” under the Active ingredient section of the DFL to “(NSAID\*)”.
7. Change the statement of identity (SOI) to include the dosage form, “tablets,” move the term (NSAID) so that it immediately follows Ibuprofen and remove [REDACTED] (b) (4) Revise your labeling so that the SOI reads “**Acetaminophen 250 mg and Ibuprofen (NSAID) 125 mg Tablets Pain Reliever**.”
8. Provide annotated labeling for the 24-count (18-ct + 6-ct) immediate container (bottle).
9. The tamper evident statement located on the vial containers, “DO NOT USE IF SEAL AROUND CAP IS BROKEN OR MISSING. ADVIL SAFETY SEALED,” can only be viewed if the peel back label is peeled back. The goals of the tamper-evident statement would likely not be achieved if the statement only appears in a peel back or fold out label and is not clearly visible without peeling back or folding out the label. It is important that the consumer view the tamper-evident statement before purchase and use of the drug product so that he or she will be better aware of the tamper-evident features and any signs of tampering. Relocate the tamper evident statement so that it is prominently displayed, per § 211.132(c) and the guidance for industry *Labeling OTC Human Drug Products — Questions and Answers* (December 2008).
10. Immediate container labeling for bottles and vials without a full DFL separates statements using semi-colons instead of bullets. This format reduces clarity and ease of reading. Use bullets to separate statements under the “liver damage warning,” “stomach bleeding warning,” and “ask a doctor before use” warning. This revision is consistent with approved immediate container labeling for ibuprofen and acetaminophen drug products.
11. Only 82% of the study participants in the pivotal labeling comprehension study were able to identify that the dosing interval was 8 hours. The visibility of the directions can be improved by using a 2 x 2 table (four cells in total) for the Directions, “adults and children 12 years and over: take 2 caplets every 8 hours while symptoms persist” and “children under 12 years: ask a doctor.” Revise your labeling to include a table like the table provided below.

|                                       |  |
|---------------------------------------|--|
| adults and children 12 years and over | ▪ <b>take 2 caplets every 8 hours</b> while symptoms persist |
| children under 12 years               | ▪ ask a doctor   |

12. PDP labeling for bottles in cartons does not include the graphic image of two tablets marked with “Advil II.” This graphic image was added to reinforce the dosing regimen of two tablets every 8 hours and was included on the 5-panel carton tested in the pivotal labeling comprehension study. Revise your labeling so that the two-tablet graphic image is included on the PDP for all bottle immediate container labeling that has adequate spacing to accommodate the image.
13. Submit an actual tablet sample to allow for comparison to the graphic image on the PDP.
14. As currently presented, the format for the expiration date is not defined on the container label and carton labeling. Per United States Pharmacopoeia (USP) General Chapter <7> Labeling, “the expiration date shall be prominently displayed in high contrast to the background or it shall be sharply embossed, and easily understood (e.g., ‘EXP 6/13,’ ‘Exp. June 13,’ or ‘Expires 6/2013’).” To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.

### 13. Postmarketing Recommendations

There are no postmarketing requirements authorized by the Food and Drug Administration Amendments Act (FDAAA) for this product, as this product is intended for OTC use. There is a postmarketing requirement for pediatric studies as authorized by the Pediatric Research Equity Act (PREA) and this is discussed in section 10.

### 14. Recommended Comments to the Applicant

A Complete Response is recommended for your product. (b) (4)

[Redacted content]

### **Information Needed to Address Clinical Deficiencies**

To support nonprescription approval of Dual Action Advil with Acetaminophen you will need to 1) Modify the Drug Facts Label (DFL), 2) Modify the principle display panel (PDP) 3) Provide an updated Label Comprehension Protocol, 4) Provide an updated Data Collection Instrument (DCI), 5) Perform iterative testing of the modified DFL 6) submit adequate data to support the DFL and label comprehension. To accomplish this, we recommend the following:

1. Modify the proposed labeling and submit a revised Drug Facts Label (DFL). Under **Uses** (b) (4) and under **Purposes** change from (b) (4) to “pain reliever”.
2. Modify the PDP in a similar fashion to comply with new indication.
3. Remove the bullet (b) (4) from the list related to the temporary relief of pain (b) (4). Consider modifying the pain indication to a single statement that this product is for the temporary relief of minor aches and pains without modifications.
4. After changes that best communicate that this product is a pain reliever have been made, perform iterative label comprehension testing of the DFL to ensure that consumers understand these important changes.
5. The study protocol and Data Collection Instrument (DCI) will need to be changed. The study endpoints and corresponding success threshold of 85% for the primary endpoint are acceptable; however, changes will need to be made to the DCI for

confidence that the data collected support the endpoints. Each question must include a neutral follow-up probe such as “why do you say that,” which is asked of all subjects regardless of whether their initial answer is correct, incorrect, or acceptable, to provide a rationale for their response. The verbatim rationale is necessary to ascertain subject understanding.

6. Update the protocol with the net coding process showing how the initial response and follow-up response will be combined for a final determination of overall correct or incorrect for each question. The wording to the secondary endpoint will need to be updated after removal of (b) (4). Include the question “why do you think this product is called Dual Action” (b) (4) perception of the proprietary name, given that a significant number of responses to this question in the first comprehension study indicated subjects understood the name to mean “pain reliever (b) (4).” Also include an additional scenario question confirming the understanding of the product’s use as a pain reliever such as “Kevin has pain in his shoulder after playing tennis and is thinking about taking this product. Is it OK or not OK for him to use this product for his shoulder pain? Why do you say that?” We recommend that the study include approximately 30% of adults with low literacy and a representative adolescent population.
7. When the data is submitted include a data dictionary (or define file or reviewer guide). The data dictionary must include the name, label, type (e.g. text, integer, etc.), code list (e.g. each code value and associated text), and a column for comments for all the variables to be included in the datasets; an annotated screener/questionnaire. The annotated screener/questionnaire will indicate in the screener/questionnaire document what variable in the dataset will be used for each question and what code will be given for each response.

### **Additional Information Regarding Proprietary Name**

Your proprietary name Advil Dual Action with Acetaminophen was found acceptable. Although a change in proprietary name is not required, it might be helpful to assist consumers in understanding the use of your product. If you chose to change your proprietary name, a request for name change should be sent to the Agency so that this change can be reviewed.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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JODY E GREEN  
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Clinical Review  
 NDA 211733  
 Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

Table 10 Duration of Relief Measured by Time to Treatment Failure (Study B5061003)

|                                    | Placebo<br>N = 56                                 | FDC IBU<br>250 mg/APAP<br>500 mg<br>N = 172             | IBU<br>250 mg<br>N = 175                                 | APAP<br>650 mg<br>N = 165      | P-value <sup>a</sup>            |                                       |
|------------------------------------|---|---|--|--------------------------------|---------------------------------|---------------------------------------|
| Median (minutes) <sup>b</sup>      | 107.0   | 629.0   | 608.5  | 449.0                          | <0.001*                         |                                       |
| 95% CI (median) <sup>b</sup>       | (86.0, 173.0)                                     | (570.0, 720.0)  | (545.0, 671.0)   | (399.0, 547.0)                 |                                 |                                       |
| Number (%) with event <sup>c</sup> | 40 (71.4)   | 96 (55.8)   | 105 (60.0)   | 105 (63.6)                     |                                 |                                       |
| Pairwise Comparisons               |   |   |  |                                |                                 |                                       |
|                                    | FDC IBU<br>250 mg/APAP<br>500 mg<br>vs<br>Placebo | FDC IBU<br>250 mg/APAP<br>500 mg<br>vs<br>IBU<br>250 mg | FDC IBU<br>250 mg/APAP<br>500 mg<br>vs<br>APAP<br>650 mg | IBU<br>250 mg<br>vs<br>Placebo | APAP<br>650 mg<br>vs<br>Placebo | IBU<br>250 mg<br>vs<br>APAP<br>650 mg |
| P-value <sup>a</sup>               | <0.001 F  | 0.069   | <0.001 F   | <0.001 F                       | <0.001 F                        | 0.005 F                               |

Source: Table 14.2.2.4.1.

\* p ≤ 0.05 for treatment effect.

Abbreviations: APAP = acetaminophen; CI = confidence interval; FDC = fixed-dose combination; IBU = ibuprofen; mg = milligram; N = number of subjects; PSR = pain severity rating.

<sup>a</sup> P-values using the Gehan-Wilcoxon test, stratified by sex and baseline categorical PSR terms.

<sup>b</sup> Using the method of Simon and Lee, Cancer Treatment Report 66:37-42, 1982.

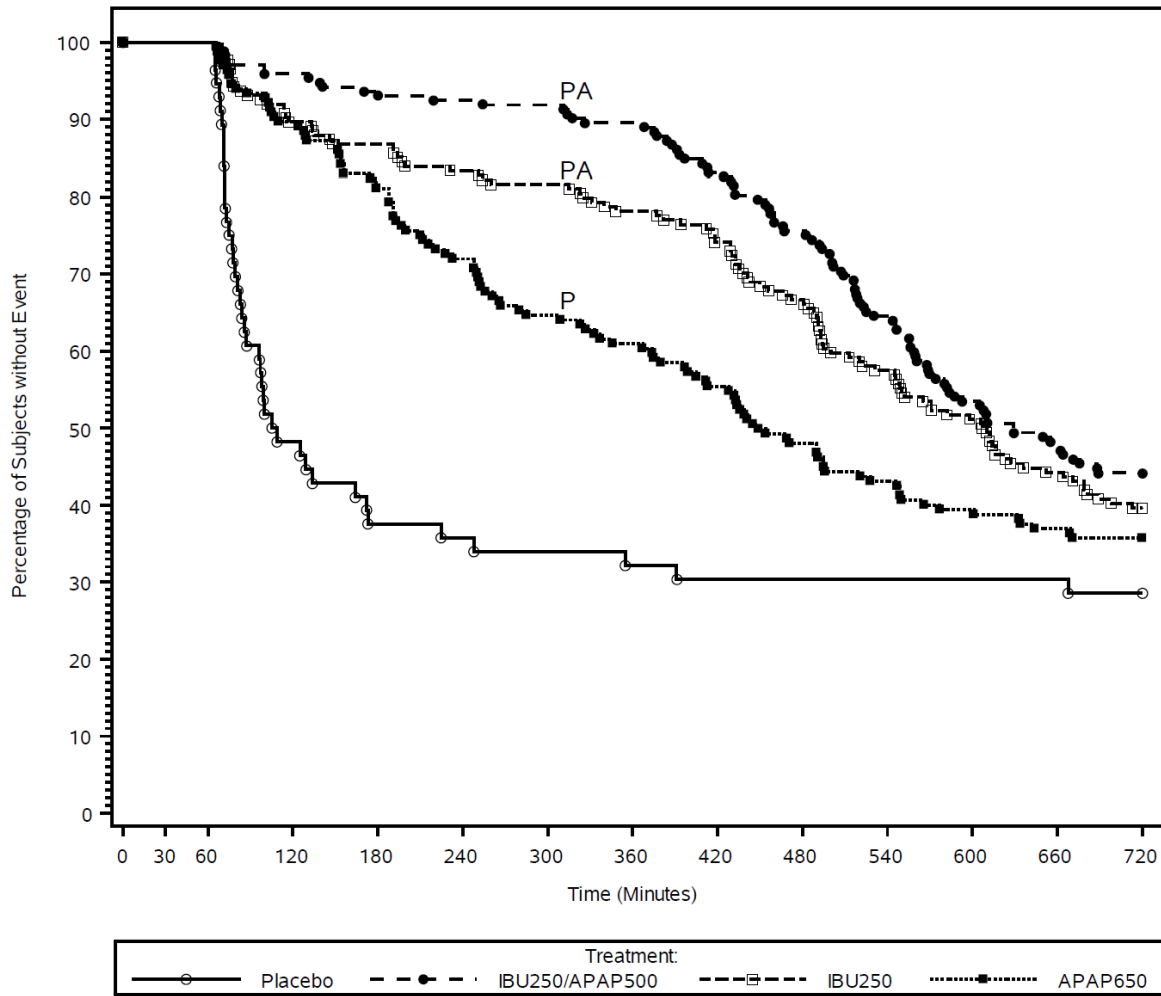
<sup>c</sup> Number (%) of subjects with treatment failure.

F: First treatment significantly better than second at 0.05 level. f: First treatment significantly better than second but technically ineligible.

S: Second treatment significantly better than first at 0.05 level. s: Second treatment significantly better than first but technically ineligible.

Applicant's Study Report (Page 59)

Figure 5 Time to First Rescue or Drop-out (Study B5061003)



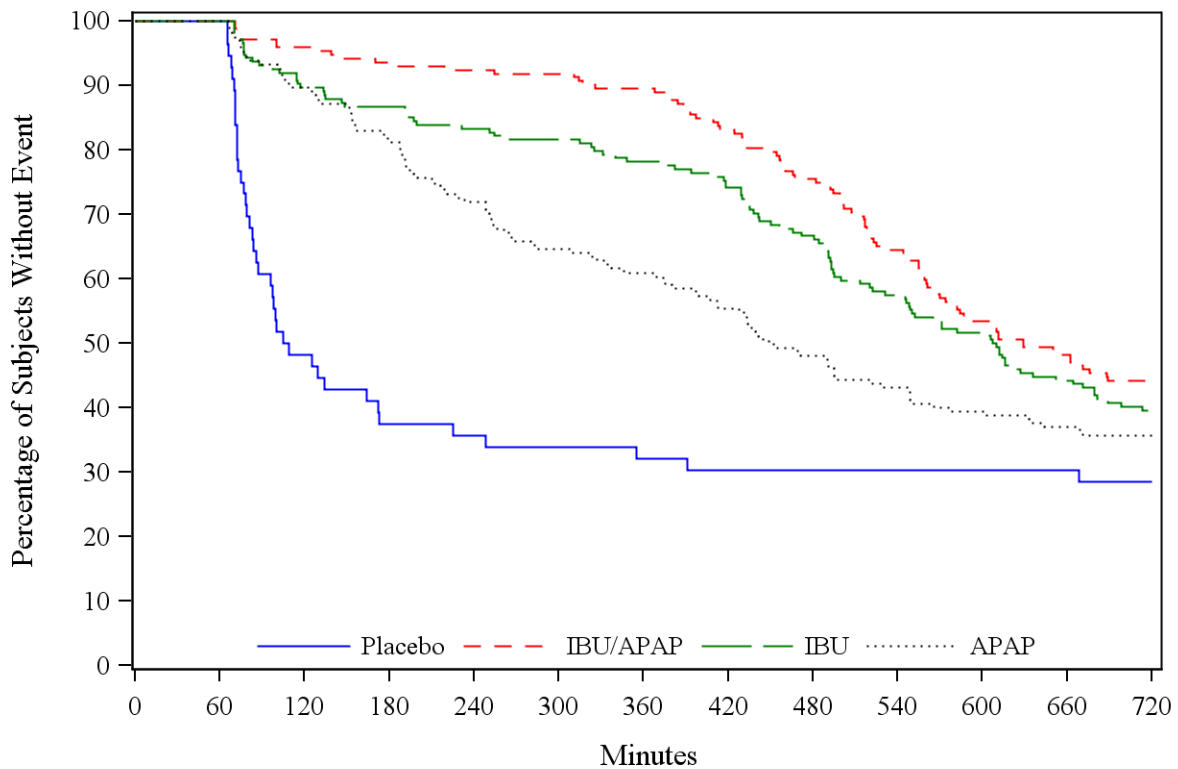
P: Significantly better than Placebo at the 0.05 level.  
 I: Significantly better than IBU 250 mg at the 0.05 level.  
 A: Significantly better than APAP 650 mg at the 0.05 level.  
 Abbreviations: APAP = acetaminophen; IBU = ibuprofen; mg = milligram.

Applicant’s Study Report (Page 60)

Time to first Rescue and Number of Subjects Requiring Rescue:

At the request of the clinical team, Dr. Li conducted the analysis of “pure” time to first rescue instead of the time to failure as defined as time to first rescue or drop-out as below.

Figure 6 Time to First Rescue (Study B5061003)



Source: Dr. Li

Table 11 Time to First Rescue (Study B5061003)

| Time to First Rescue |              |            |              |
|----------------------|--------------|------------|--------------|
| Planned Treatment    | N of subject | Mean (min) | Median (min) |
| Placebo              | 56           | 296        | 107          |
| IBU/APAP             | 172          | 572        | 629          |
| IBU                  | 175          | 522        | 607          |
| APAP                 | 165          | 447        | 445          |

Source: Dr. Li (modified)

The FDC treatment group time to first rescue (median: 629 minutes) was longer than APAP 650 mg (median: 445 minutes), but only slightly longer than IBU 250 mg alone (median: 607 minutes). As commented before, the duration of relief by time to treatment failures is defined

as the time from first dose of rescue or discontinuation due to AE or lack of efficacy. Since the discontinuation rate is about 1% for the single dose study, the plots of the duration of relief by time to treatment failures and of time to first rescue are, indeed, very similar (if not the same).

In addition, the number of subjects used rescue for each treatment group was analysis by Dr. Li at the clinical team's request. In this study, two rescues, codeine or tramadol, were used. It is noted that subjects used tramadol by far more than codeine. While subjects in the FDC treatment (55%) used far less rescue of tramadol than placebo (70%), the FDC treatment has a tend to use less than IBU (58%) and APAP (62%) as the table below.

Table 12 Number of Subjects Requiring Rescue (Study B5061003)

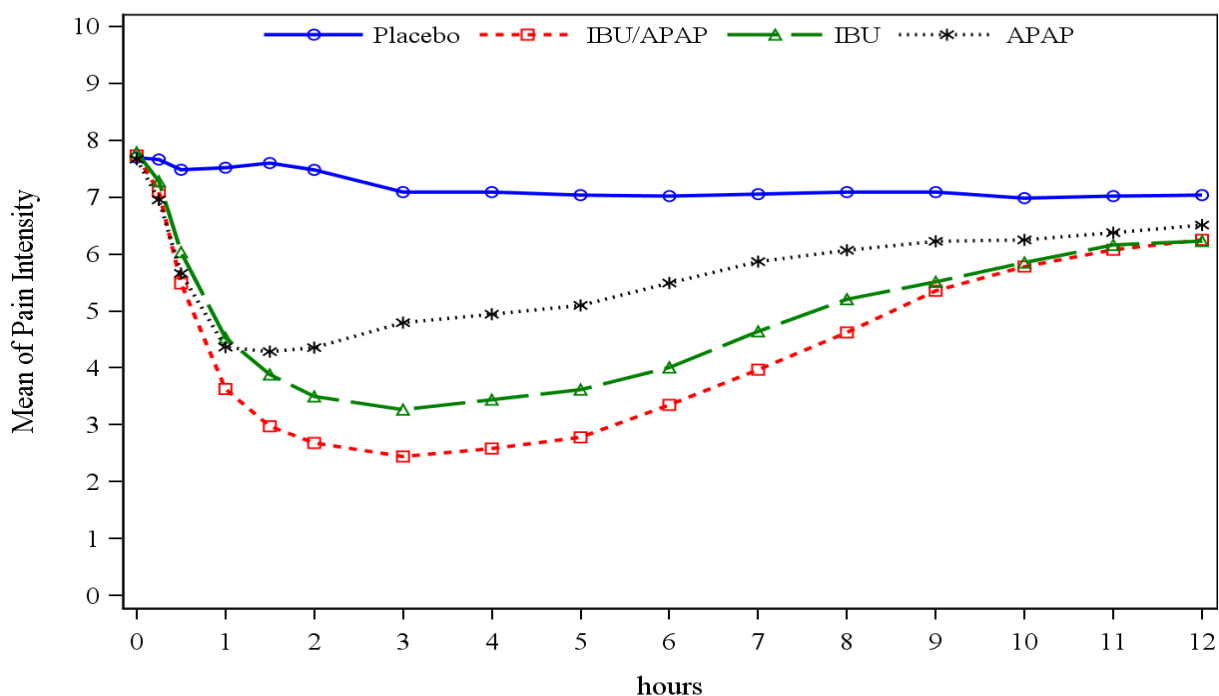
| Planned Treatment | Medication Name | N   | N (%) of Subjects Rescued |
|-------------------|-----------------|-----|---------------------------|
| Placebo           | CODEINE         | 56  | 2 (3.6%)                  |
|                   | TRAMADOL        | 56  | 39 (70%)                  |
| IBU 250/APAP500   | CODEINE         | 172 | 10 (5.8%)                 |
|                   | TRAMADOL        | 172 | 95 (55%)                  |
| IBU 250           | CODEINE         | 175 | 8 (4.6%)                  |
|                   | TRAMADOL        | 175 | 101 (58%)                 |
| APAP 650          | CODEINE         | 165 | 10 (6%)                   |
|                   | TRAMADOL        | 165 | 103 (62%)                 |

Source: Dr. Li (modified)

Pain Intensity over Time:

At the request of the clinical team, Dr. Li, the statistical reviewer, conducted pain intensity over time using different way of imputations as the figures below:

Figure 7 Pain Intensity over Time (Pre-specified, WOCF; Study B5061003)



Source: Dr. Feng Li

In terms of assessing pain intensity during hour 6-8 using pre-specified WOCF approach, i.e. replacing all pain scores after the first rescue, the separation between the FDC and IBU is apparent. See comments regarding different methods of amputation for details from Dr. Li's review.

Time to Meaningful Relief

The results for time to onset of meaningful relief are summarized in the table and figure below. Compared to placebo, the time to meaningful relief was significantly faster for all treatment groups ( $p < 0.001$  for all comparisons; only 28.6% of the placebo subjects reported meaningful relief). Furthermore, subjects in the FDC IBU 250 mg/APAP 500 mg treatment group reported meaningful relief significantly sooner (median: 47.9 minutes) than both IBU 250 mg (median: 65.9 minutes;  $p = 0.003$ ) and APAP 650 mg (median: 56.6 minutes;  $p < 0.001$ ) alone. By the end

Clinical Review  
 NDA 211733  
 Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

of the study, a higher percentage of subjects had achieved meaningful relief in the FDC treatment group (85.5%) when compared to both IBU 250 mg (79.4%) and APAP 650 mg (71.5%).

Table 13 Time to Meaningful Relief (Study B5061003)

|                                   | <b>Placebo</b>                            | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>IBU<br/>250 mg</b>                     | <b>APAP<br/>650 mg</b> | <b>P-value<sup>a</sup></b> |                        |
|-----------------------------------|---|---|---|------------------------|----------------------------|------------------------|
|                                   | <b>N = 56</b>                             | <b>N = 172</b>                            | <b>N = 175</b>                            | <b>N = 165</b>         |                            |                        |
| Median (minutes) <sup>b</sup>     | N/A                                       | 47.9                                      | 65.9                                      | 56.6                   | <0.001*                    |                        |
| 95% CI (median) <sup>b</sup>      | N/A                                       | (41.6, 57.4)                              | (57.2, 81.6)                              | (50.5, 84.6)           |                            |                        |
| Number(%) with event <sup>c</sup> | 16 (28.6%)                                | 147 (85.5%)                               | 139 (79.4%)                               | 118<br>(71.5%)         |                            |                        |
| <b>Pairwise Comparisons</b>       |   |   |   |                        |                            |                        |
|                                   | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>IBU<br/>250 mg</b>  | <b>APAP<br/>650 mg</b>     | <b>IBU<br/>250 mg</b>  |
|                                   | <b>vs</b>                                 | <b>vs</b>                                 | <b>vs</b>                                 | <b>vs</b>              | <b>vs</b>                  | <b>vs</b>              |
|                                   | <b>Placebo</b>                            | <b>IBU<br/>250 mg</b>                     | <b>APAP<br/>650 mg</b>                    | <b>Placebo</b>         | <b>Placebo</b>             | <b>APAP<br/>650 mg</b> |
| P-value <sup>a</sup>              | <0.001 F                                  | 0.003 F                                   | 0.031 F                                   | <0.001 F               | <0.001 F                   | 0.631                  |

Source: Table 14.2.2.5.1.

\* p ≤ 0.05 for treatment effect.

Abbreviations: APAP = acetaminophen; CI = confidence interval; FDC = fixed-dose combination;

IBU = ibuprofen; mg = milligram; N = number of subjects; N/A = not applicable; PSR = pain severity rating.

<sup>a</sup> P-values using the Gehan-Wilcoxon test, stratified by sex and baseline categorical PSR terms.

<sup>b</sup> Using the method of Simon and Lee, Cancer Treatment Report 66:37-42, 1982.

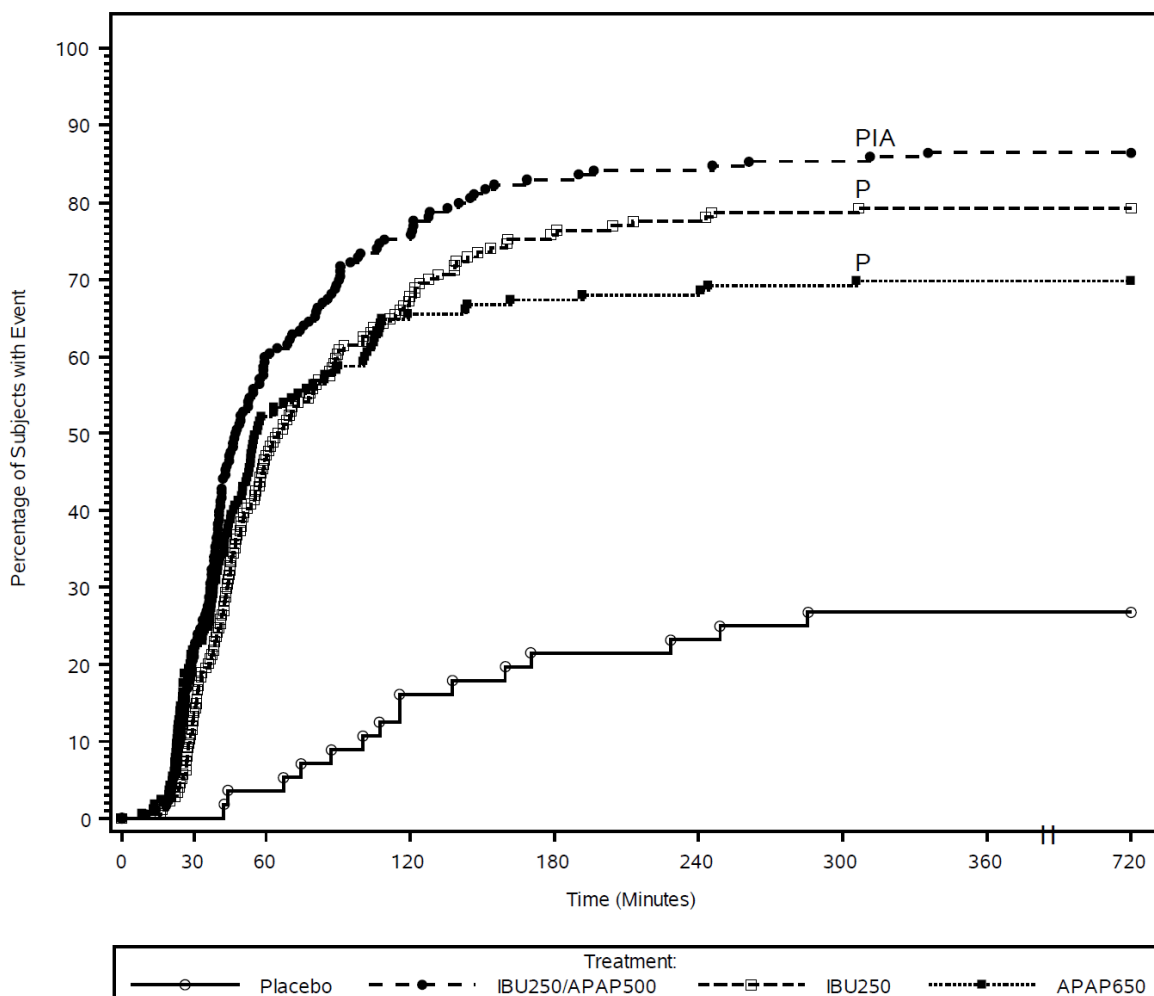
<sup>c</sup> Number(%) of subjects with Meaningful Relief.

F: First treatment significantly better than second at 0.05 level. f: First treatment significantly better than second but technically ineligible.

S: Second treatment significantly better than first at 0.05 level. s: Second treatment significantly better than first but technically ineligible.

Applicant's Study Report (Page 61)

Figure 8 Time to Meaningful Relief (Study B5061003)



P: Significantly better than Placebo at the 0.05 level.  
 I: Significantly better than IBU 250 mg at the 0.05 level.  
 A: Significantly better than APAP 650 mg at the 0.05 level.  
 Abbreviations: APAP = acetaminophen; IBU = ibuprofen; mg = milligram.

Applicant's Study Report (Page 62)

Reviewer's comments.

The onset is within 60 min (48 minutes, median time, by meaningful pain relieve) which is satisfactory, which is especially for important for an OTC product given there is no professional label instruction. It seems that APAP contributed the onset more than IBU.

Time to Perceptible Relief

The results for time to perceptible relief confirmed are summarized in the table and figure below. Compared to placebo, the results for the time to perceptible relief were similar to those of meaningful relief in that all treatment groups were significantly faster ( $p < 0.001$  for all comparisons; only 28.6% subjects reported first perceptible relief for placebo). Median times to perceptible relief were similar across all treatment groups.

Table 14 Time to Perceptible Relief (Study B5061003)

|                                    | <b>Placebo</b>                            | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>IBU<br/>250 mg</b>                     | <b>APAP<br/>650 mg</b> | <b>P-value<sup>a</sup></b> |                        |
|------------------------------------|---|---|---|------------------------|----------------------------|------------------------|
|                                    | <b>N = 56</b>                             | <b>N = 172</b>                            | <b>N = 175</b>                            | <b>N = 165</b>         |                            |                        |
| Median (minutes) <sup>b</sup>      | N/A                                       | 21.3                                      | 24.6                                      | 24.2                   | <0.001*                    |                        |
| 95% CI (median) <sup>b</sup>       | N/A                                       | (18.7, 24.2)                              | (22.3, 27.8)                              | (20.7, 29.9)           |                            |                        |
| Number (%) with event <sup>c</sup> | 16 (28.6)                                 | 149 (86.6)                                | 139 (79.4)                                | 118 (71.5)             |                            |                        |
| <b>Pairwise Comparisons</b>        |   |   |   |                        |                            |                        |
|                                    | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>FDC IBU<br/>250 mg/APAP<br/>500 mg</b> | <b>IBU<br/>250 mg</b>  | <b>APAP<br/>650 mg</b>     | <b>IBU<br/>250 mg</b>  |
|                                    | <b>vs</b>                                 | <b>vs</b>                                 | <b>vs</b>                                 | <b>vs</b>              | <b>vs</b>                  | <b>vs</b>              |
|                                    | <b>Placebo</b>                            | <b>IBU<br/>250 mg</b>                     | <b>APAP<br/>650 mg</b>                    | <b>Placebo</b>         | <b>Placebo</b>             | <b>APAP<br/>650 mg</b> |
| P-value <sup>a</sup>               | <0.001 F                                  | 0.088                                     | 0.133                                     | <0.001 F               | <0.001 F                   | 0.887                  |

Source: Table 14.2.3.1.1.

\*  $p \leq 0.05$  for treatment effect.

Abbreviations: APAP = acetaminophen; CI = confidence interval; FDC = fixed-dose combination; IBU = ibuprofen; mg = milligram; N = number of subjects; PSR = pain severity rating; N/A = not applicable.

<sup>a</sup> P-values using the Gehan-Wilcoxon test, stratified by sex and baseline categorical PSR terms.

<sup>b</sup> Using the method of Simon and Lee, Cancer Treatment Report 66:37-42, 1982.

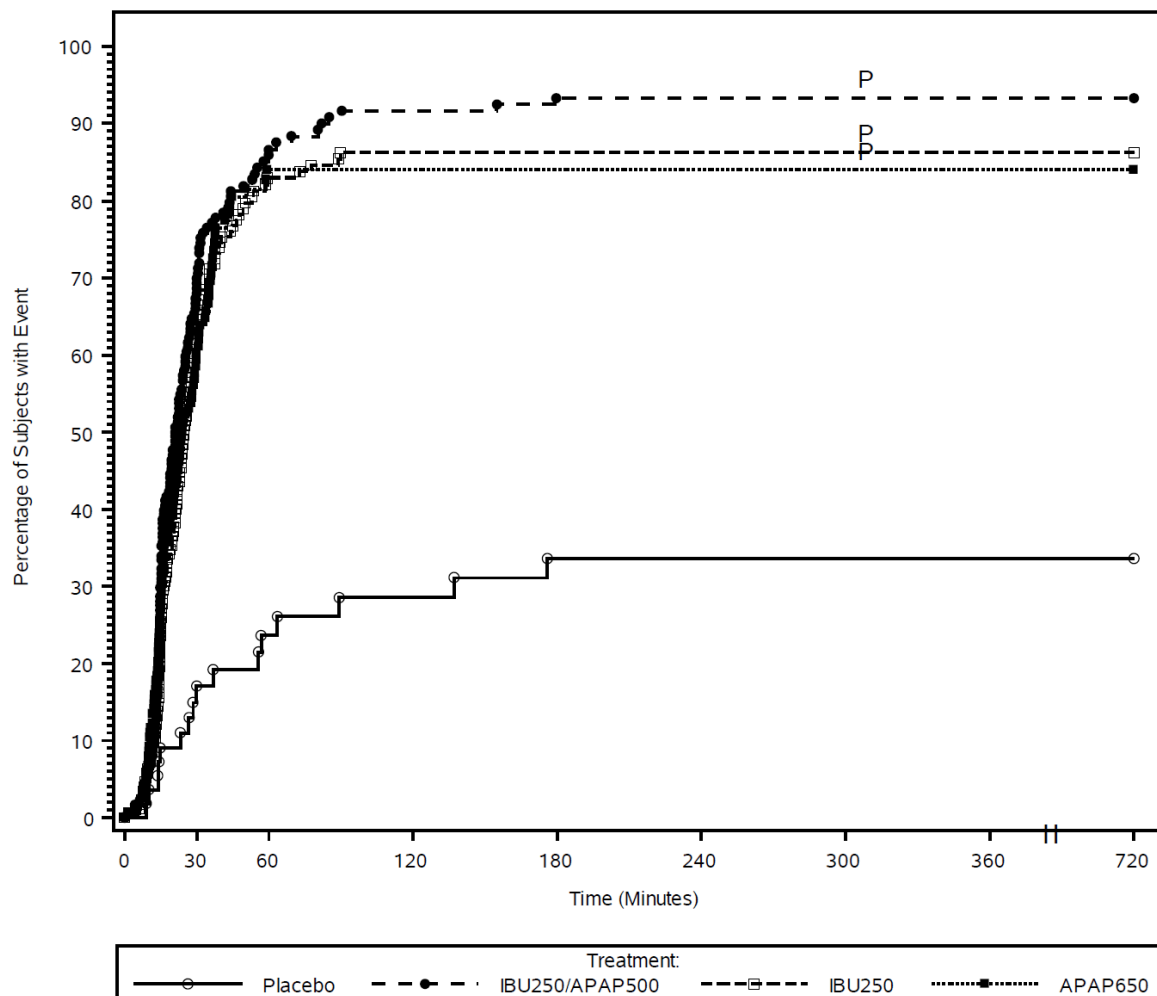
<sup>c</sup> Number (%) of subjects with first perceptible relief confirmed by meaningful relief.

F: First treatment significantly better than second at 0.05 level. f: First treatment significantly better than second but technically ineligible.

S: Second treatment significantly better than first at 0.05 level. s: Second treatment significantly better than first but technically ineligible.

Applicant's Study Report (Page 64)

Figure 9 Time to First Perceptible Relief (Study B5061003)



P: Significantly better than Placebo at the 0.05 level.

I: Significantly better than IBU 250 mg at the 0.05 level.

A: Significantly better than APAP 650 mg at the 0.05 level.

Abbreviations: APAP = acetaminophen; IBU = ibuprofen; mg = milligram.

Applicant's Study Report (Page 65)

PRR Scored on the 5-Point Categorical PRR Scale

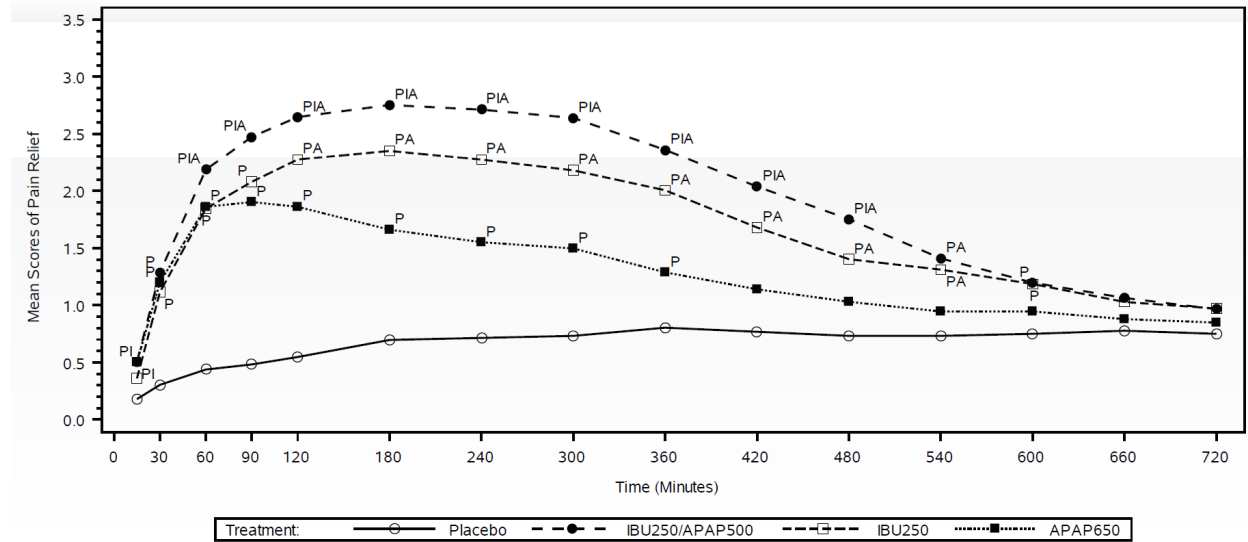
Pain relief rating scores over time are presented in the figure below. Compared to placebo, significantly better PRR scores were observed for the FDC IBU 250 mg/APAP 500 mg and IBU 250 mg treatment groups from 15 minutes (FDC IBU/APAP) and 30 minutes (IBU 250 mg) to

Clinical Review  
NDA 211733  
Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

540 minutes post-dose. Similarly, significantly better PRR scores were observed for the APAP 650 mg treatment group from 15 to 360 minutes post-dose when compared to placebo. The FDC treatment group had significantly better PRR scores from 60 to 480 minutes post-dose when compared to both IBU 250 mg and APAP 650 mg alone.

Clinical Review  
NDA 211733  
Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

Figure 10 Pain Relief Rating Score over Time (Study B5061003)

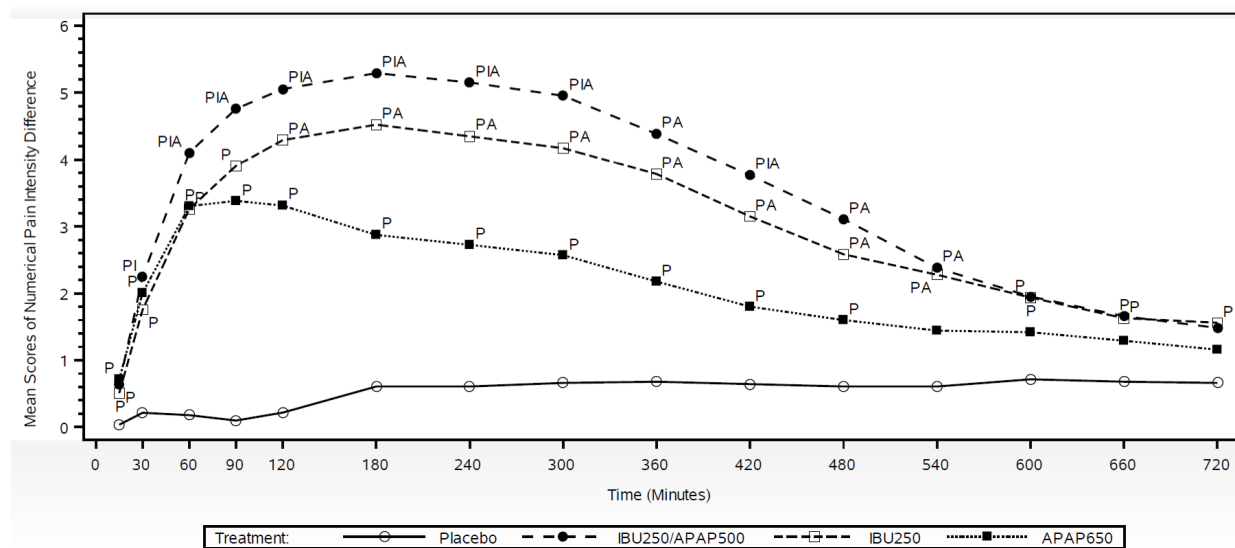


Source: Applicant's Study Report (page 67)

PID Scored on the 11-Point Numerical PSR

PID numerical data over time follows the similar pattern as PRR Scored on the 5-Point Categorical PRR Scale as below. Compared to placebo, significantly better numerical PID scores were observed for the FDC IBU 250 mg/APAP 500 mg and IBU 250 mg treatment groups from 15 to 600 minutes post-dose. Significantly better numerical PID scores were observed for the APAP 650 mg treatment group from 15 to 480 minutes post-dose when compared to placebo. In addition, the FDC IBU 250 mg/APAP 500 mg treatment group had significantly better numerical PID scores from 60 to 420 minutes post-dose when compared to both IBU 250 mg and APAP 650 mg alone.

Figure 11 Numerical Pain Intensity Difference Scores over Time

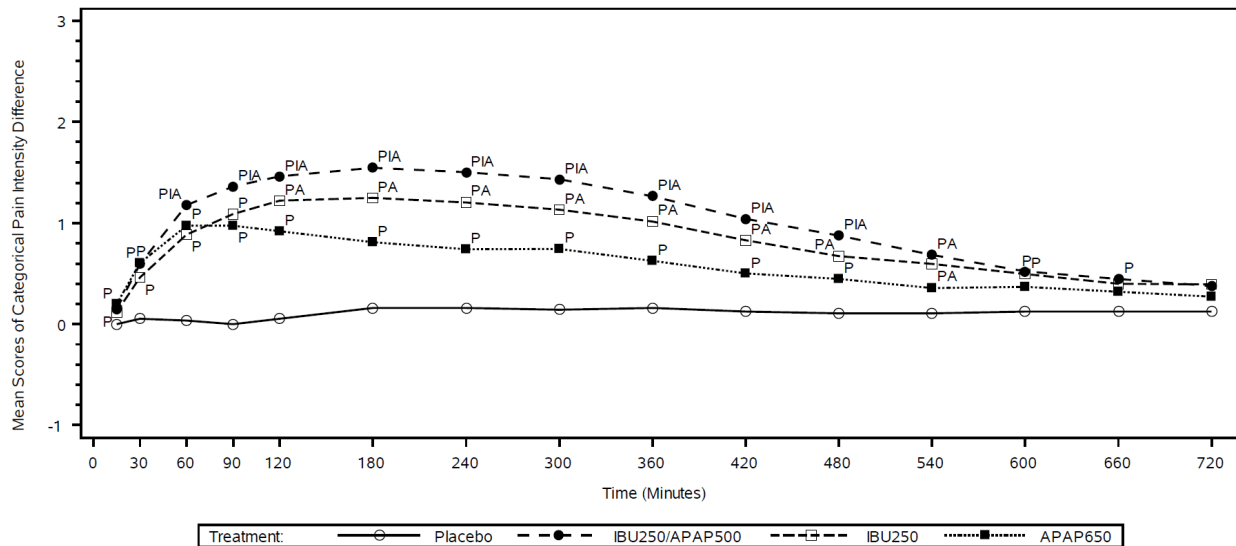


Source: Applicant’s Study Report (page 69)

PID Scored on the 4-Point Categorical PSR

PID categorical data over time are presented also follows the similar pattern as PRR Score on the 5-Point Categorical PRR Scale as below. Like the numerical PID results, significantly better categorical PID scores were observed for the FDC IBU 250mg/APAP 500 mg and IBU 250 mg treatment groups from 15 minutes (FDC IBU/APAP) and 30 minutes (IBU 250 mg) to 600 minutes post-dose when compared to placebo. Likewise, significantly better categorical PID scores were observed for the APAP 650 mg treatment group from 15 to 480 minutes post-dose when compared to placebo. Also consistent with the numerical PID results, the FDC IBU 250 mg/APAP 500 mg treatment group had significantly better categorical PID scores (from 60 to 480 minutes post-dose) than IBU 250 mg and APAP 650 mg alone.

Figure 12 Categorical Pain Intensity Difference Scores over Time



Source: Applicant's Study Report (page 71)

Dose/Dose Response

N/A

Durability of Response

N/A

Persistence of Effect

N/A

Additional Analyses Conducted on the Individual Trial

Additional analysis on pain intensity over time and use of rescue by the Agency has been incorporated into the secondary efficacies as above.

Reviewer's Efficacy Conclusions:

- The Combination Rule of the FDC is fulfilled in terms of analgesic efficacy by the single-dose dental study using SPID 8.
- The FDC has adequate onset of action with meaningful pain relief of 48 minutes (median time), which is essential for an acute analgesic.
- The FDC appears to persist over the proposed dosing interval of 8 hours (although each individual component is generally dosed at shorter interval).

## 6.2. B5061004

### 6.2.1. Study Design

#### Study title:

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

#### Overview and Objective

This study compared the efficacy and safety of FDC of IBU 250 mg/APAP 500 mg (administered as 2 tablets of IBU 125 mg/APAP 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 or more third molar teeth. It should be noted that based on once per day dosing, the proposed maximum daily doses of IBU and APAP in the current FDC are 250 mg IBU/500 mg APAP, both of which are meaningfully less than the currently approved OTC total daily doses of both IBU (1200 mg) and APAP (4000 mg).

The objective of the study was to compare the analgesic efficacy and safety of FDC IBU 250 mg/APAP 500 mg (administered as 2 tablets of IBU 125 mg/APAP 250 mg) every 8 hours compared to placebo in a 48-hour period following extraction of 3 or more third molar teeth.

#### Trial Design

Overall Study Design and Plan: Description and Flow Chart This was 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 250 mg/APAP 500 mg group and 34 subjects for placebo group [a ratio of 2:1]). Subjects were adult males and females (18 to 40 years of age, inclusive) who experienced post-operative pain following surgical extraction of 3 or more third molar teeth. Following extraction of 3 or more third molar teeth, subjects rested quietly at the study center until they experienced post-surgical pain of at least moderate severity. At that time, subjects assessed their pain intensity and severity using categorical, numerical, and/or visual scales. Subjects with a qualifying baseline pain threshold within approximately five hours of completion of surgery were entered into the study.

Upon completion of the baseline scales, eligible subjects received an oral dose of study medication 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,

Clinical Review  
NDA 211733  
Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

32, 40, and 48 hours post-baseline, subjects provided self-ratings of pain severity using categorical and numerical pain severity ratings (PSRs). Subjects also provided a self-rating of pain relief at each time point (except at baseline) using a categorical pain relief rating (PRR) scale. At 24 and 48 hours, or at the time of first rescue medication on each respective day, subjects also completed a Global Evaluation of the study medication. Additionally, subjects also evaluated the time to first perceptible relief and time to meaningful relief using a double stopwatch method up to eight hours post-baseline (i.e., up to the second dose administration) or until the time of first rescue medication use, whichever was sooner. A review of any reported AEs was also completed. The schedule of activities as below provides an overview of the protocol visits and procedures.

Reviewer's Comments:

While not described in the study procedure, it is disclosed in Applicant's Summary of Clinical Efficacy that this study is conducted without allowing food from one hour before and two hours after the scheduled dosing.

Table 15 Schedule of Study (Study B5061004)

| Visit Identifier   | Time (hours)           |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   | 28 Calendar Days After Last Dose |
|--|------------------------|---------|---|------|-----|-----|-------------------|------------------------------|-----|-----------------------|------|------|------|------|------|---|----------------------------------|
|  | Screening <sup>a</sup> | 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 |   |                                  |
| Informed consent   | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Inclusion and exclusion criteria   | x                      | x       |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Demographic information  | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Medical history  | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Physical examination   | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Screening laboratory tests <sup>b</sup>                                  | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Hematology   | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Blood chemistry  | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Urinalysis   | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Coagulation  | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Serum pregnancy test   | x                      |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Urine pregnancy test <sup>c</sup>  |                        | x       |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Surgical procedure   |                        | x       |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Surgical trauma scale  |                        | x       |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Vital signs (HR, BP, T, RR) <sup>d</sup>                                 | x                      |         | x   |      |     |     |                   |                              | x   |                       |      |      |      |      |      | x |                                  |
| Randomization <sup>e</sup>   |                        |         | x   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Dosing   |                        |         | x   |      |     |     |                   |                              | x   |                       | x    | x    | x    | x    |      |   |                                  |
| Pain evaluations   |                        |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| VAS pain severity rating <sup>f</sup>                                    |                        |         | x   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Categorical pain severity rating <sup>g</sup>                            |                        |         | x   | x    | x   | x   | x                 | x                            | x   | x                     | x    | x    | x    | x    | x    |   |                                  |
| Numerical pain severity rating <sup>h</sup>                              |                        |         | x   | x    | x   | x   | x                 | x                            | x   | x                     | x    | x    | x    | x    | x    |   |                                  |
| Categorical pain relief rating <sup>i</sup>                              |                        |         |   | x    | x   | x   | x                 | x                            | x   | x                     | x    | x    | x    | x    | x    |   |                                  |
| Time to 'first perceptible' relief <sup>j</sup>                          |                        |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Time to 'meaningful' relief <sup>k</sup>                                 |                        |         |   |      |     |     |                   |                              |     |                       |      |      |      |      |      |   |                                  |
| Patient global evaluation <sup>l</sup>                                   |                        |         |   |      |     |     |                   |                              |     |                       |      | 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 <sup>m</sup>                   |

Clinical Review  
NDA 211733  
Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

|                             |  |   |
|-----------------------------|--|---|
| Follow-up call <sup>m</sup> |  | x |
|-----------------------------|--|---|

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Subjects had to meet all inclusion criteria and not meet any exclusion criteria to participate in this study.

Inclusion Criteria:

- Males and females 18 to 40 years of age (inclusive)
- Outpatients who had undergone surgical extraction of three or more third molars, of which at least two must have been a partial or complete bony mandibular impaction.
- Subject must have had 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 five hours after surgery is completed.
- 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.
- Examined by the attending dentist or physician and medically cleared to participate in the study
- In good health and had no contraindications to the study or rescue medication.
- Female subjects were not pregnant, as verified by a urine-based pregnancy test, or breast-feeding female subjects.
- Male subjects able to father children and female subjects of childbearing potential who were, in the opinion of the investigator, sexually active at risk for pregnancy with their partner(s) must have agreed 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.
- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative/parent(s)/legal guardian) had been informed of all pertinent aspects of the study.
- Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria:

- Presence or history of any significant hepatic, renal, endocrine, cardiovascular, neurological, psychiatric, gastrointestinal, pulmonary, hematologic, or metabolic disorder determined by the investigator to have placed the subject at increased risk, including the presence or history within two years of screening of the following medical conditions/disorders:
  - Gastrointestinal ulcer or gastrointestinal bleeding;
  - Paralytic ileus or other gastrointestinal obstructive disorders;
  - Bleeding disorder.
- Clinically significant abnormalities on the screening laboratory tests determined by the

investigator or designee that would have placed the subject at increased risk.

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or study medication administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the subject inappropriate for entry into this study.
- Subjects at risk for excessive bleeding, i.e., those on anticoagulant therapy, etc.
- Acute localized dental alveolar infection at the time of surgery that could have confounded the post-surgical evaluation.
- Hypersensitivity to IBU, naproxen, aspirin, or any other NSAID; or to APAP, tramadol, other opioids, or to their combinations.
- Use of a prescription or OTC drug with which administration of IBU or any other NSAID; APAP; codeine, tramadol, or any other opioid is contraindicated (including: opioids, antipsychotics, antianxiety agents, or other CNS depressants [including alcohol]).
- Use of prescription or OTC antihistamines within 24 hours prior to taking study medication. (Note exceptions: loratadine, desloratadine, cetirizine, levocetirizine, fexofendadine, and azelastine).
- Use of a bisphosphonate (i.e., pamidronate, risedronate, alendronate, or ibandronate) within the past five years.
- Prior use of any type of analgesic or NSAID within five half-lives of that drug or less before taking the first dose of study medication, except for pre-anesthetic medication and anesthesia for the procedure.
- Were currently taking a monoamine oxidase inhibitor (MAOI), antipsychotic, or any other neuroleptic or had taken:
  - A MAOI within two months of screening (Note: subjects were not to discontinue taking an MAOI solely for qualifying for the study);
  - An antipsychotic or other neuroleptic within 14 days of surgery (Note: subjects were not to discontinue taking these medications solely for qualifying for the study);
  - Subjects who were currently taking any selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor or selective norepinephrine reuptake inhibitor (SNRI), or tricyclic antidepressant (TCA), and were not on a stable dose of this medication for at least 30 days prior to screening or did not maintain this dose throughout the study and their condition was judged by the investigator to not be well-controlled (Note: subjects were not to discontinue taking these medications solely for the purpose of qualifying for the study).

Treatments Administered Study medication was administered to the subject within seven minutes of the completion of the baseline pain assessments and, thereafter, every eight hours by the third-party dispenser. No other study personnel were present at the time of dosing. After the subject was blindfolded, while the subject was sitting up, the dispenser gave the two tablets to the blindfolded subject with 6 to 8 ounces of room temperature water (time = 0).

Subjects swallowed the study medication whole.

## Study Endpoints

### Primary Efficacy Evaluation:

SPID0-24 (time-weighted sum of Pain Intensity Difference [PID] scores PID based on the 11-point Numerical PSR scale) from 0 to 24 hours.

### Key Secondary Efficacy Evaluations:

- SPID (time-weighted sum of PID 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, or discontinuation due to AE or lack of efficacy;
- Time to onset of "meaningful" relief for the first dose

## Statistical Analysis Plan

Primary efficacy endpoint SPID 0-24 hours was analyzed by an analysis of covariance (ANCOVA) model.

### Analysis Methods for Secondary Endpoints:

- SPID based on the 11-point Numerical PSR scale from 0-8, 6-8, 0-16, 8-16, and 0-48 hours were analyzed using the main effects ANCOVA model like the primary endpoint.
- Time to first onset of "meaningful" relief for the first dose and duration of relief after first dose (as measured by the time from first dose to first use of rescue medication or second dose, or discontinuation due to AE or lack of efficacy) were analyzed using the Gehan-Wilcoxon test for testing difference between the 2 treatment groups.

## Protocol Amendments

No protocol amendments were issued during the study, and no change to the conduct of the study was implemented.

### 6.2.2. Study Results

#### Compliance with Good Clinical Practices

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory

requirements were followed, in particular, those affording greater protection to the safety of trial participants.

#### Financial Disclosure

The Applicant's submission included the completed "Certification: Financial Interests and Arrangements of Clinical Investigators" form (Form FDA 3455). The Applicant indicated that the investigators at each site are certified as having no Financial Arrangement as defined in 21 CFR 54.2.

#### Patient Disposition

Disposition of Subjects Subject disposition is summarized in the table below. Subjects were assigned to placebo and FDC IBU 250 mg/APAP 500 mg in a ratio of 1:2 and stratified by sex and baseline pain (moderate vs severe). A total of 203 subjects were screened, out of which 123 subjects were randomized and included in the full analysis and safety sets. Forty-one (41) and 82 subjects were randomized to placebo and FDC IBU 250 mg/APAP 500 mg treatment groups, respectively. In total, 11 subjects discontinued from the study: one subject discontinued from the FDC IBU 250 mg/APAP 500 mg group due to an AE of emesis, one subject discontinued from the placebo group due to medication error without an associated AE, and nine subjects were no longer willing to participate in the study.

Table 16 Disposition (Study B5061004)

|   | <b>Total</b><br><b>N = 123</b> | <b>Placebo</b><br><b>N = 41</b> | <b>FDC IBU 250 mg/<br/>APAP 500 mg</b><br><b>N = 82</b> |
|---|--------------------------------|---------------------------------|---|
| Screened: 203                                     |                                |                                 |   |
| Randomized  | 123 (100.00%)                  | 41 (100.00%)                    | 82 (100.00%)  |
| Completed   | 112 (91.06%)                   | 36 (87.80%)                     | 76 (92.68%)   |
| Discontinued                                      | 11 (8.94%)                     | 5 (12.20%)                      | 6 (7.32%)   |
| Adverse event                                     | 1 (0.81%)                      | 0                               | 1 (1.22%)   |
| Medication error without associated adverse event | 1 (0.81%)                      | 1 (2.44%)                       | 0 (0.00%)   |
| Death   | 0                              | 0                               | 0   |
| Protocol violation                                | 0                              | 0                               | 0   |
| Lost to follow-up                                 | 0                              | 0                               | 0   |
| Does not meet entrance criteria                   | 0                              | 0                               | 0   |
| No longer willing to participate in Study         | 9 (7.32%)                      | 4 (9.76%)                       | 5 (6.10%)   |
| Withdrawn due to pregnancy                        | 0                              | 0                               | 0   |
| No longer meets eligibility criteria              | 0                              | 0                               | 0   |
| Other   | 0                              | 0                               | 0   |
| Full Analysis Set                                 | 123 (100.00%)                  | 41 (100.00%)                    | 82 (100.00%)  |
| Per Protocol Set                                  | 110 (89.43%)                   | 36 (87.80%)                     | 74 (90.24%)   |
| Safety Set  | 123 (100.00%)                  | 41 (100.00%)                    | 82 (100.00%)  |

## Applicant's Study Report (Page 47)

### Protocol Violations/Deviations

A total of 103 protocol deviations were recorded for a total of 54 subjects. Most protocol deviations were related to procedures/tests (101), most of which included test results not performed per protocol or followed up appropriately, tests performed outside of the allowed protocol window, assessments not completed during the study period, ice pack removal less than 30 minutes prior to post-dose assessments, and subjects eating or drinking at times outside of the allowed protocol window. One (1) randomization deviation and 1 study medication deviation were also recorded.

There were significant protocol violations identified in two randomized subjects who took at least one dose of the study medication. Subject (b) (6) consumed food prior to the scheduled pain assessment at two hours post the first dose, and Subject (b) (6) used ice pack prior to the scheduled pain assessment at two hours post the first dose.

### Reviewer's comments:

There is significant amount of protocol deviations (a total of 103) in a total of 54 subjects. Most protocol deviations (101) were related to protocol/tests, which are not expected to affect the overall efficacy results.

### Demographic Characteristics

Treatment groups were comparable with respect to the demographic characteristics as the table below. A total of 67 subjects (54.47%) were female and 56 subjects (45.53%) were male. Most of the study population was White (112 subjects, 91.06%), followed by Other (mixed racial origins; 7 subjects, 5.69%), Black (3 subjects, 2.44%), and Asian (1 subject, 0.81%). Most subjects were of non-Hispanic/Latino ethnicity (95 subjects, 77.24%). The mean age was 21.8 years (SD: 3.84; range: 18-38 years).

Clinical Review  
 NDA 211733  
 Ibuprofen/Acetaminophen Fixed Dose Combination Tablets

Table 17 Demographics (Study B5061004)

|                        | <b>Total</b>   | <b>Placebo</b> | <b>FDC IBU 250 mg/<br/>APAP 500 mg</b> |
|------------------------|----------------|----------------|--|
|                        | <b>N = 123</b> | <b>N = 41</b>  | <b>N = 82</b>                          |
| <b>Sex</b>             |                |                |  |
| Male                   | 56 (45.53%)    | 19 (46.34%)    | 37 (45.12%)                            |
| Female                 | 67 (54.47%)    | 22 (53.66%)    | 45 (54.88%)                            |
| <b>Age (year)</b>      |                |                |  |
| Mean                   | 21.8           | 21.8           | 21.8                                   |
| SD                     | 3.84           | 4.09           | 3.73                                   |
| Median                 | 21.0           | 21.0           | 21.0                                   |
| Min                    | 18             | 18             | 18                                     |
| Max                    | 38             | 38             | 34                                     |
| <b>Race</b>            |                |                |  |
| White                  | 112 (91.06%)   | 35 (85.37%)    | 77 (93.90%)                            |
| Black                  | 3 (2.44%)      | 1 (2.44%)      | 2 (2.44%)                              |
| Asian                  | 1 (0.81%)      | 0              | 1 (1.22%)                              |
| Other                  | 7 (5.69%)      | 5 (12.20%)     | 2 (2.44%)                              |
| <b>Ethnicity</b>       |                |                |  |
| Hispanic or Latino     | 28 (22.76%)    | 12 (29.27%)    | 16 (19.51%)                            |
| Not Hispanic or Latino | 95 (77.24%)    | 29 (70.73%)    | 66 (80.49%)                            |

Source: [Table 14.1.2](#).

Abbreviations: APAP = acetaminophen; FDC = fixed-dose combination; IBU = ibuprofen;  
 max = maximum; mg = milligram; min = minimum; N = number of subjects; SD = standard deviation.

Source: Applicant's Study Report (Page 49)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Treatment groups were comparable with respect to all baseline pain assessments (Table 5). The baseline mean pain intensity (VAS) was 73.6 mm. Respectively, 53.66% and 46.34% of subjects rated their pain at baseline as moderate or severe. The baseline mean pain severity on the numerical scale was 7.6 (median: 8.0; range: 4-10).

Table 18 Baseline Characteristics (Study B5061004)

|                                    | <b>Total</b>   | <b>Placebo</b> | <b>FDC IBU 250 mg/<br/>APAP 500 mg</b> |
|------------------------------------|----------------|----------------|--|
|                                    | <b>N = 123</b> | <b>N = 41</b>  | <b>N = 82</b>                          |
| <b>Pain intensity (VAS) (mm)</b>   |                |                |  |
| Mean                               | 73.6           | 74.0           | 73.4                                   |
| SD                                 | 13.11          | 11.54          | 13.89                                  |
| Median                             | 73.0           | 74.0           | 71.5                                   |
| Min                                | 50             | 50             | 50                                     |
| Max                                | 100            | 98             | 100                                    |
| <b>Pain severity (categorical)</b> |                |                |  |
| Moderate                           | 66 (53.66%)    | 22 (53.66%)    | 44 (53.66%)                            |
| Severe                             | 57 (46.34%)    | 19 (46.34%)    | 38 (46.34%)                            |
| <b>Pain severity (numerical)</b>   |                |                |  |
| Mean                               | 7.6            | 7.7            | 7.6                                    |
| SD                                 | 1.25           | 1.17           | 1.29                                   |
| Median                             | 8.0            | 8.0            | 7.0                                    |
| Min                                | 4              | 4              | 5                                      |
| Max                                | 10             | 10             | 10                                     |

Source: [Table 14.1.5](#).

Abbreviations: APAP: acetaminophen; FDC = fixed-dose combination; IBU = ibuprofen; max = maximum; mg = milligram; min = minimum; mm = millimeter; N = number of subjects; SD = standard deviation; VAS = visual analog scale.

Applicant's Study Report (Page 51)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study treatment was administered under the supervision of qualified investigative site personnel who ensured that each subject ingested the study medication as instructed.

All concomitant medications used during the study were recorded in the eCRF. Antibiotics were permitted at the discretion of the investigator. Restrictions on prior and concomitant medications are described in exclusion criteria.

Subjects not experiencing adequate relief after the 1-hour time point evaluation were permitted to take rescue medication at the discretion of the investigator. Rescue medication included either tramadol hydrochloride (immediate release tablets) 50 to 100 mg orally or codeine sulfate (immediate release tablets) 15 to 60 mg orally. If needed, subjects received

additional doses of rescue medication (i.e., tramadol every four to six hours as needed [prn] within 48 hours after first dose of study medication or codeine sulfate every four hours prn within 8 hours after dosing with study medication) at the study center based on the discretion of the investigator. The total maximum daily dose of tramadol hydrochloride that may have been taken at the study center was 400 mg. The total maximum daily dose of codeine sulfate that may have been taken at the study center was 360 mg. Subjects did not take any rescue medication home with them. Subjects who took rescue medication during the evaluation period remained at the study site and continued to perform their efficacy assessments. Rescue medication was administered within five minutes of rescue assessments being performed. Subjects who took rescue medication within one hour after dosing were considered discontinued and were replaced. The use of rescue medication was recorded in the appropriate section of the CRF. The date, time, name of rescue medication taken, and reasons for use were recorded.

#### Efficacy Results – Primary Endpoint

The treatment difference in SPID 24 between FDC IBU 250 mg/APAP 500 mg and placebo based on the ANCOVA model was significant; the FDC IBU 250 mg/APAP 500 mg was superior to placebo in terms of SPID 24 ( $p < 0.001$ ).

Table 19 Primary Efficacy: SPID 24 (Study B5061004)

|                                       | Placebo             |                      | FDC IBU 250 mg/<br>APAP 500 mg |                       |        |
|---------------------------------------|---------------------|----------------------|--------------------------------|-----------------------|--------|
|                                       | N = 41              |                      | N = 82                         |                       |        |
| Mean (SD)                             | -7.05 (54.525)      |                      | 64.58 (64.554)                 |                       |        |
| Median                                | -16.00              |                      | 67.25                          |                       |        |
| Range                                 | (-71.0, 161.8)      |                      | (-44.8, 206.0)                 |                       |        |
| LSM (SE) <sup>a</sup>                 | -8.13 (9.426)       |                      | 64.76 (6.676)                  |                       |        |
| FDC IBU 250 mg/APAP 500 mg vs Placebo |                     | P-value              |                                | RMSE <sup>b</sup>     |        |
| Diff <sup>c</sup>                     | 95% CI <sup>c</sup> | P-value <sup>a</sup> | Trt*Sex <sup>d</sup>           | Trt*Base <sup>e</sup> |        |
| 72.89                                 | (50.075, 95.707)    | <0.001*              | 0.380                          | 0.444                 | 60.188 |

Source: Applicant’s Study Report (Page 53)

Reviewer’s comment: The Applicant’s analysis of the primary efficacy endpoint has been confirmed by the Agency’s statistical reviewer, Dr. Li. The primary efficacy confirmed the multiple dose efficacy of the FDC compared to placebo with statistical significance in SPID 24, the agency preferred endpoint for acute indication.

#### Efficacy Results – Secondary and other relevant endpoints

The Sponsor conducted several secondary efficacy analyses. It must be noted that the Applicant

















































