CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 211-733
Drug Name:	Ibuprofen/acetaminophen
Indication(s):	Pain reliever (b) (4)
Applicant:	Pfizer, Inc.
Date(s):	Received: January 31, 2019 PDUFA: November 30, 2019
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Feng Li, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
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Project Manager:	Kristen Hardin
Keywords:	NDA review, Clinical Studies

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1. EXECUTIVE SUMMARY

Pfizer, Inc. submitted a New Drug Application (NDA) for a fixed-dose combination (FDC) product consisting of ibuprofen 125 mg and acetaminophen 250 mg intended for over-the-counter (OTC) use. The proposed indications are 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). The proposed dosing regimen is two FDC tablets every 8 hours. The application relies on three confirmatory efficacy studies, study (b) (4) B5061003, and B5061004, to demonstrate the efficacy of the FDC.

Study B5061003 was a single-dose dental pain study to support the pain relief indication. This was a single-center, 12-hour, factorial, randomized, double-blind, efficacy and safety study of the FDC compared to IBU 250 mg, APAP 650 mg, and placebo in healthy male and female subjects aged 18 to 40 years who experienced post-operative pain following surgical extraction of 3 or more third molar teeth. The primary efficacy endpoint was the time-weighted sum of pain intensity difference from baseline during 0 to 8 hours (SPID8), which was analyzed using an ANCOVA model, with treatment group, sex, baseline categorical pain as factors, and baseline numerical pain as a continuous covariate. The study demonstrated the analgesic efficacy of the FDC as well as the contribution of each component with statistical significance. Secondary endpoints were also consistently in favor of the FDC.

Study B5061004 was conducted to demonstrate the multiple-dose analgesic efficacy of the FDC. It was a single-center, multiple dose, randomized, placebo-controlled, double-blind study in subjects 18 to 40 years of age who experienced post-operative pain following surgical extraction of 3 or more third molar teeth. The primary efficacy endpoint was the time-weighted sum of pain intensity difference from baseline to 24 hours (SPID24). The primary analysis model was the same ANCOVA model as in study B5061003. The study demonstrated the multiple-dose

efficacy in terms of SPID24 with statistical significance in comparison to placebo. Findings in secondary endpoints were supportive consistently.

The primary efficacy results from the three studies are summarized in the table below.

Study	Endpoint	Statistics	Placebo	IBU/APAP	IBU	APAP*
[redacted] (b) (4)						
B5061003	SPID8	N	56	172	175	165
		LSM (SE)	4.3(2.6)	34.4 (1.5)	28.7(1.5)	19.6 (1.6)
		Compared to placebo		30.1	24.4	15.3
		95% CI		(24.1, 36.0)	(18.5, 30.4)	(9.4, 21.3)
		p-value		<0.001	<0.001	<0.001
		Compared to FDC			5.7	14.8
		95% CI			(1.5, 9.8)	(10.6, 19.0)
		p-value			0.008	<0.001
B5061004	SPID24	N	41	82	NA	NA
		LSM (SE)	-8.1 (9.4)	64.8 (6.7)		
		Compared to placebo		72.9		
		95% CI		(50.1, 95.7)		
		p-value		<0.001		

* [redacted] (b) (4) APAP 650 mg for study B5061003; LSM: least square mean
SE: standard error; CI: confidence interval; NA: not applicable

Based on my review, there was evidence from the two dental pain studies to support the analgesic efficacy of the FDC. [redacted] (b) (4)

If this product is approved for the pain relief indication only [redacted] (b) (4)

The review team needs to consider the overall benefit-risk profiles and potential safety concerns of its OTC use while making decision.

2. INTRODUCTION

2.1 Overview

Pfizer has developed this fixed-dose combination (FDC) consisting of ibuprofen 125 mg and 250 mg of acetaminophen intended for over-the-counter (OTC) use. The proposed product indications are 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) The proposed dosing regimen is 2 FDC tablets every 8 hours (for a total daily dose of 750 mg of ibuprofen and 1500 mg of acetaminophen).

The division and the applicant discussed the clinical development program for the FDC under IND 112,538 on several occasions.

- At the pre-IND meeting occurred on September 20, 2011, the division informed the applicant (b) (4) would be acceptable (b) (4)
- At the End-of-Phase 2 meeting occurred on May 15, 2014, the division stated that the proposed clinical development program of two dental pain studies including one full factorial single-dose study, and one one-factorial multiple dose study appeared acceptable. The division further advised the applicant to evaluate the efficacy of the FDC over the last 2 hours of the dosing interval and time to rescue would be an important endpoint to support the proposed dosing interval.
- At the meeting occurred on April 3, 2017, the division agreed (b) (4)
- At the pre-NDA meeting occurred on March 19, 2018, the division informed the applicant the Integrated Summary of Efficacy (ISE) is required for the NDA submission. The division further advised the applicant to include analyses that evaluate summed pain intensity differences over the last two to four hours of the dosing interval and provide pain intensity over time curve for each of the treatments. The applicant asked if the agency would consider labelling the product for the pain indication only (b) (4) The division responded that this would be a review issue.

This statistical review focuses on efficacy results of (b) (4) the single-dose dental pain study B5061003, and the multiple-dose dental pain study B5061004.

2.2 Data Sources

All data were supplied electronically by the applicant as SAS transport files and can be found at the following location in the CDER electronic document room (EDR): \\Cdsesub1\evsprod\NDA211733\0001\m5\datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The datasets and associated define files were of acceptable quality and were sufficient for validating study results.

3.2 Evaluation of Efficacy

(b) (4)

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3.2.2 Study B5061003

3.2.2.1 Study Design and Endpoints

This was a single-center, 12-hour, full factorial, randomized, double-blind, parallel group, efficacy and safety study of a single-dose of the FDC compared to IBU 250 mg, APAP 650 mg, and placebo in healthy male and female subjects aged 18 to 40 years who were experiencing post-operative pain following surgical extraction of 3 or more third molar teeth.

All eligible subjects must have had a baseline pain score of at least moderate on the 4-point categorical scale, confirmed by a Visual Analog Pain Severity Rating Scale (VAS PSR) of at least 50 mm on a 100 mm VAS scale, to be eligible for entry. Baseline pain severity was rated using an 11-point numerical scale. Upon completion of the baseline scales, eligible subjects were randomly assigned in a ratio of 1:3:3:3 to a single dose of placebo, FDC (IBU 250 mg/APAP 500 mg), IBU 250 mg, or APAP 650 mg. The randomization was stratified by sex and baseline pain severity (moderate versus severe).

At 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours post-dose, subjects provided self-ratings of pain severity using an 11-point numerical PSR (same as a 11-point NRS) and a 4-point categorical PSR. At 12 hours, subjects also completed a Global Evaluation of the study medication. Additionally, subjects evaluated the time to first perceptible relief and time to meaningful relief using a double stopwatch method for up to 12 hours post-dose or until the time of first rescue medication use, whichever was sooner.

Subjects not experiencing adequate pain 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 or codeine sulfate orally. Subjects who took rescue medication remained at the study site for the full 12-hour duration and continued to perform their efficacy assessments.

The primary efficacy endpoint was the time-weighted sum of pain intensity difference (PID) based on 11-point numerical PSR from 0 to 8 hours (SPID8). Secondary endpoints included time-weighted sum of PID during 6 to 8 hours (SPID6_8), duration of relief, as measured by the time to treatment failure (time to first dose of rescue or drop out due to lack of efficacy), and time to onset of meaningful relief.

3.2.2.2 Statistical Methodology

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. The primary analysis population included all randomized subjects who were dosed and had a baseline temperature assessment (mITT).

Intermittent missing pain scores were imputed using linear interpolation by calculating the weighted average of the values immediately preceding and subsequent to the time point window, with weights inversely proportional to the duration between the analyzed time point and the actual time.

All assessments completed after a subject took the first dose of rescue medication were ignored. The pain scores after the time of rescue medication were replaced with the score recorded at the time of rescue medication or the baseline value, whichever was worse (WOCF). If a subject discontinued due to lack of efficacy or an adverse event, the missing values were imputed with the baseline value (BOCF). If a subject discontinued due to other reasons, the last observation was carried forward for the missing values (LOCF). Since this a single-dose study, subjects remained in the clinic, the amount of missing values were minimal (<1%).

Duration of relief was estimated by the time to treatment failure. Treatment failure was defined as taking rescue medication or discontinuing the study due to lack of efficacy.

Time to meaningful relief was defined as the elapsed time from dosing until the subject pressed the second stopwatch labeled meaningful relief; otherwise, the subject was considered censored. The censoring was at 12 hours if the subject did not depress the stopwatch by the end of the scheduled evaluation or became treatment failure prior to depressing the second stopwatch. The censoring was at the time of the dropout if the subject withdrew for non-efficacy related reasons.

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 568 subjects were randomized, 56 to placebo, 172 to the FDC, 175 to IBU 250 mg, and 165 to APAP 650 mg. Most subjects (99%) completed the study. A total of 8 subjects (1%) discontinued early, 1 due to AE and 7 subjects no longer willing to participate in the study (Table 3).

The treatment groups were comparable in the demographics (Table 4). Most subjects were White females. The mean age was 19.5 years and the mean baseline pain about 7.7.

Table 3: Patient Disposition – Study B5061003

	Total	**Placebo**	**IBU/APAP**	**IBU 250**	**APAP 650**
Randomized (full analysis set)	**568**	**56**	**172**	**175**	**165**
Completed, n (%)	560 (99%)	55 (98%)	172 (100%)	173 (99%)	160 (97%)
Discontinued, n(%)	8 (1%))	1 (2%)	0	2 (1%)	5 (3%)
Reason for discontinuation					
Adverse event	1	0	0	1 (0.6%)	0
Withdrawal by subject	7 (1%)	1 (2%)	0	1 (0.6%)	5 (3%)

Source: Reviewer

Table 4: Summary of Demographics and Baseline Characteristics -Study B5061003

Characteristics	Placebo N=56	IBU/APAP N=172	IBU 250 N=175	APAP 650 N=165
Sex				
Female	34 (61%)	102 (59%)	102 (58%)	97 (59%)
Male	22 (39%)	70 (41%)	73 (42%)	68 (41%)
Age (years)				
Mean (SD)	19.6 (3.0)	19.3 (1.8)	19.7 (2.7)	19.4 (2.1)
Median	18.0	18.0	19.0	18.0
Min, Max	18.0, 30.0	18.0, 27.0	18.0, 33.0	18.0, 28.0
Race, n (%)				
White	53 (95%)	161 (94%)	164 (94%)	159 (96%)
Other	2 (4%)	8 (5%)	7 (4%)	2 (1%)
Asian	1 (2%)	2 (1%)	3 (2%)	2 (1%)
Black or African American	0	1 (1%)	1 (1%)	2 (1%)
Baseline Pain (11 point scale)				
Mean (SD)	7.7 (1.1)	7.7 (1.1)	7.8 (1.2)	7.7 (1.1)
Median	8.0	8.0	8.0	8.0
Min, Max	5.0, 10.0	6.0, 10.0	5.0, 10.0	6.0, 10.0

Source: Reviewer; SD: standard deviation

3.2.2.4 Results and Conclusions

I was able to reproduce the applicant's primary efficacy analysis results (Figure 4). The FDC was superior to placebo, IBU 250 mg, and APAP 650 mg in terms of SPID8 with statistical significance. Both IBU 250 mg and APAP 650 mg were also better than placebo with statistical significance. It seems that IBU 250 mg contributed more in pain reduction than APAP 650 mg. The difference between IBU 250 mg and APAP 650 mg in SPID8 achieved nominal statistical significance.

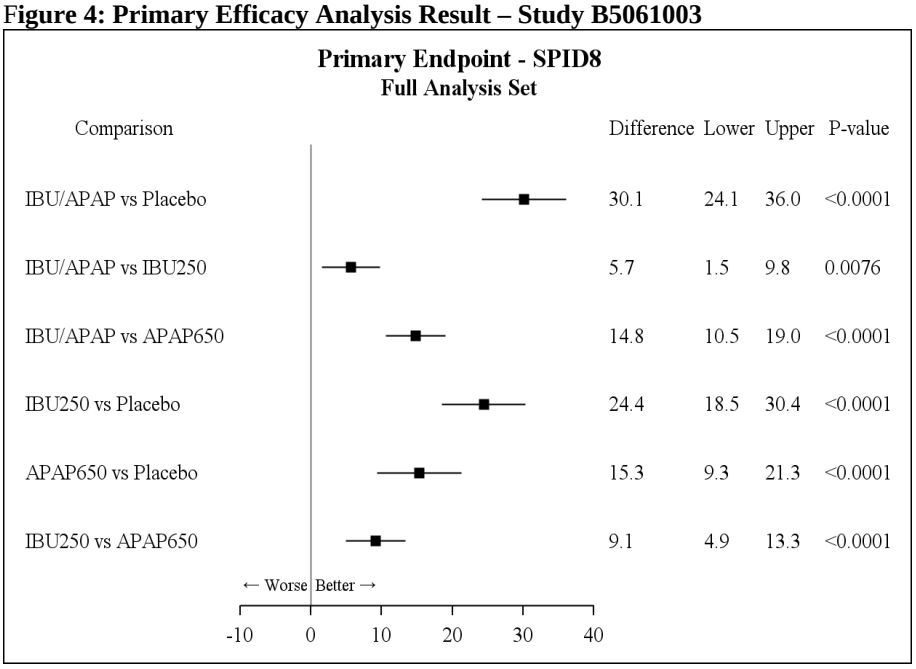
Duration of relief measured by time to treatment failure (taking rescue medication or dropout due to lack of efficacy) is presented in Figure 5. The median time to treatment failure was less than 2 hours for the placebo group, around 9 hours for the APAP 650 mg group, more than 10 hours for both the FDC and IBU 250 mg group. Treatment failure was mainly due to taking rescue medication as no subjects discontinued due to lack of efficacy.

For the primary efficacy analysis, all the pain scores after taking the first rescue medication were considered as missing and imputed with a WOCF approach, which is not appropriate as the dental pain could resolve gradually overtime even without any treatment.

To investigate the robustness of the study conclusion to the method for handling pain scores after taking rescue medication, I conducted analyses base on different methods to handling pain scores measured after taking rescue medication. One analysis utilized all observed pain scores regardless of rescue use. The other two analyses replaced pain scores within a therapeutic window of the rescue medication with the last assessment prior to taking the rescue. The two

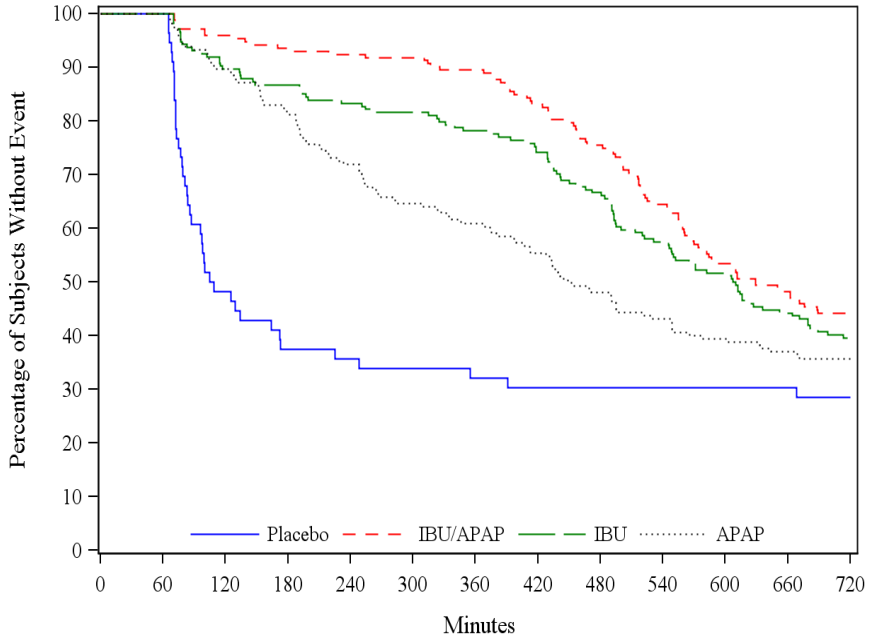
analyses differed in the assumed lengths of the therapeutic window of the rescue medication. The study conclusion remained the same using the aforementioned methods for handling pain assessments after taking rescue medication, despite that the estimated treatment effects differed.

Figure 4: Primary Efficacy Analysis Result – Study B5061003



Source: reviewer

Figure 5: Duration of Relief Measured by Time to Treatment Failure -Study B5061003



Source: reviewer

The FDC was superior to placebo, IBU 250 mg, and APAP 650 mg with nominal statistical significance in time to onset of meaningful pain relief. The median time to onset of meaningful relief was about 50 minutes. The FDC was also better than placebo and APAP 650 mg with nominal statistical significance, and numerically better than IBU 250 mg in SPID6_8, which supported the dosing regimen of every 8 hours for acute pain management.

3.2.3 Study B5061004

3.2.3.1 Study Design and Endpoints

The design and analysis of this study was like Study B5061003 except that this was a two-arm, placebo-controlled, multiple dose study of 48 hours. It was a single-center, in-patient, multiple dose, randomized, double-blind, parallel group trial in subjects (18 to 40 years of age, inclusive) who experienced post-operative pain following surgical extraction of 3 or more third molar teeth. Following surgery, subjects rested at the study center until they experienced post-surgical pain of at least moderate severity.

Eligible subjects with a qualifying baseline pain were randomized in a ratio of 2:1 to either the FDC or placebo. Pain intensity assessments were scheduled to be completed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 32, 40, and 48 hours post-first dose.

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 or codeine sulfate. Subjects who took rescue medication during the evaluation period remained at the study site and continued to perform their efficacy assessments.

The primary efficacy endpoint was the time-weighted sum of pain intensity difference from baseline to 24 hours (SPID24) based on the 11-point numerical pain scale. Secondary endpoints included SPID6_8, duration of relief, as measured by the time to treatment failure (time to first dose of rescue, the second dose of study drug, or drop out due to lack of efficacy), and time to onset of meaningful relief.

3.2.3.2 Statistical Methodology

The primary analysis population (ITT) included all randomized subjects who were dosed with study medication and provided a baseline assessment. Same as in Study B5061003, 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. Secondary efficacy endpoints were defined and analyzed similarly as in Study B5061003.

All assessments completed more than a minute after a subject took rescue medication were ignored and set to missing. Missing efficacy scores after taking rescue medication, dropout due to AE, or dropout due to lack of efficacy were imputed using a WOCF. For other missing efficacy scores, a LOCF approach was applied.

3.2.3.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 123 subjects were randomized, 41 to placebo and 82 to the FDC. Overall, about 9% of the subjects discontinued the study early, primarily due to withdraw by subject (Table 5).

The demographic and baseline characteristics were comparable between the two randomized treatment groups (Table 6). About 55% of subjects were female and more than 80% were white, with a mean age of 22 years.

Table 5: Patient Disposition – Study B5061004

	Total	**Placebo**	**IBU/APAP**
Randomized (full analysis set)	**123**	**41**	**82**
Completed, n (%)	112 (91%)	36 (88%)	76 (93%)
Discontinued, n(%)	11 (9%))	5 (12%)	6 (7%)
Reason for discontinuation			
Adverse event	1 (1%)	0	1 (1%)
Non-compliance with study drug	1 (1%)	1 (2%)	0
Withdrawal by subject	9 (7%)	4 (10%)	5 (6%)

Source: Reviewer

Table 6: Summary of Demographics and Baseline Characteristics – Study B5061004

Characteristics	**Placebo N=41**	**IBU/APAP N=82**
Sex		
Female	22 (54%)	45 (55%)
Male	19 (46%)	37 (45%)
Age (years)		
Mean (SD)	21.8 (4.1)	21.8 (3.7)
Median	21.0	21.0
Min, Max	18.0, 38.0	18.0, 34.0
Race, n (%)		
White	35 (85%)	77 (94%)
Other	5 (12%)	2 (2%)
Black or African American	1 (2%)	2 (2%)
Asian	0	1 (1%)
Baseline Pain (11 point scale)		
Mean (SD)	7.7 (1.2)	7.6 (1.3)
Median	8.0	7.0
Min, Max	4.0, 10.0	5.0, 10.0

Source: reviewer

3.2.3.4 Results and Conclusions

The FDC was statistically significantly better than placebo in SPID24 based on the primary analysis. In addition, the difference between the FDC and placebo in SPID6_8 was also nominally significant (Table 7) indicating there was still an effect up to 8 hours. Analyses using different methods for handling pain scores after taking rescue medications or dropout yielded same conclusion for the primary endpoint SPID24. Missing values due to dropout was about 5%.

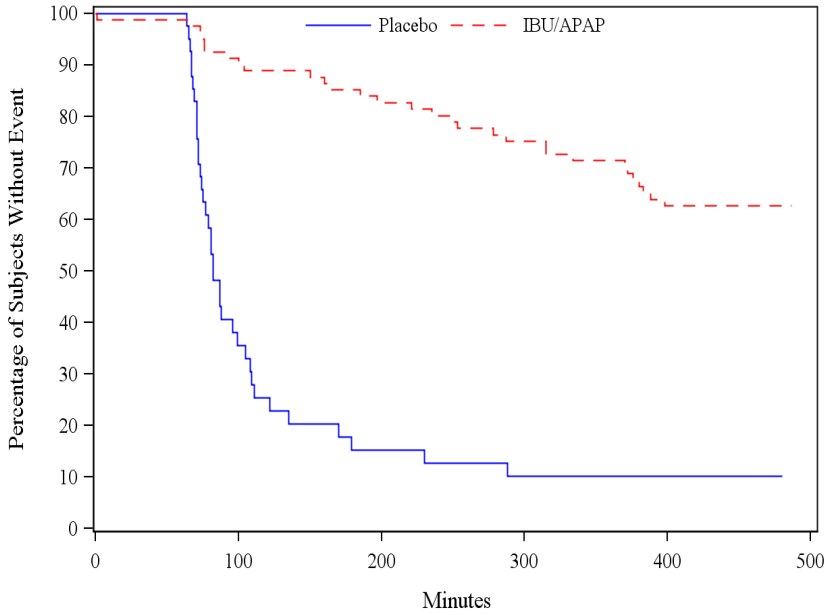
Table 7: Efficacy Results for SPID24 and SPID6_8 – Study B5061004

Endpoint	Statistics	**Placebo N=41**	**IBU/APAP N=82**
SPID24	Mean (SD)	-7.1 (54.5)	64.6 (64.6)
	LS mean (SE)	-8.1 (9.4)	64.8 (6.7)
	Difference from placebo		72.9
	95% CI		(50.1, 95.7)
	P-value		<0.001
SPID6_8	Mean (SD)	-1.3 (6.4)	6.5 (7.9)
	LS mean (SE)	-1.5 (1.1)	6.5 (0.8)
	Difference from placebo		7.9
	95% CI		(5.2, 10.6)
	P-value		<0.001

SD: standard deviation; SE: standard error; LS mean: least square mean from ANCOVA; CI: confidence interval
Source: reviewer

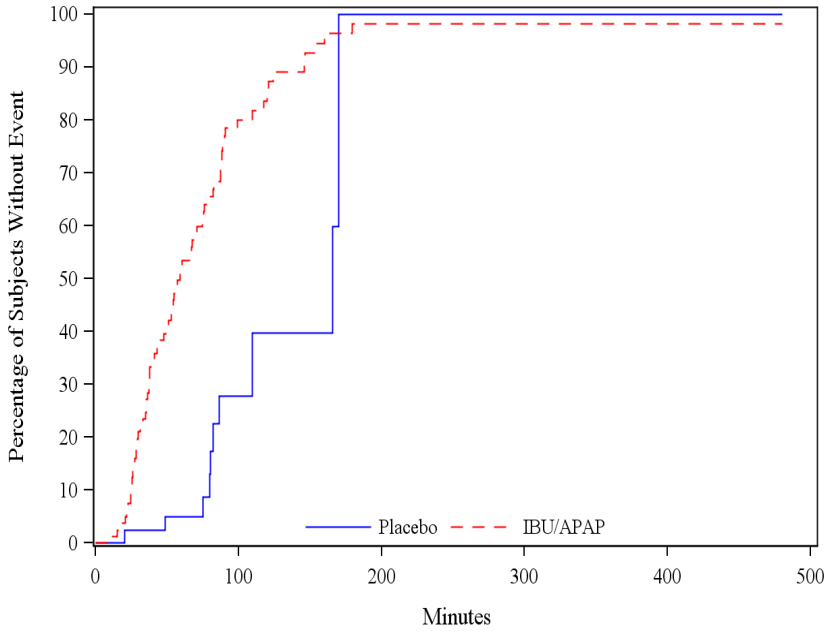
The Kaplan-Meier plot of time to treatment failure is presented in Figure 6. A lower percentage of subjects experienced treatment failure in the FDC treatment group (37%) when compared to placebo (88%). The duration of relief was significantly longer for the FDC treatment group. Subjects in the FDC group experienced faster onset of pain relief (Figure 7). The median time to onset of meaningful pain relief was within one hour for the FDC group and more than 2 hours for placebo group.

Figure 6: Duration of Relief Measured by Time to Treatment Failure – Study B5061004



Source: Reviewer

Figure 7: Time to Onset of Meaningful Pain Relief – Study B5061004



Source: Reviewer

3.3 Evaluation of Safety

The evaluation of the safety data was conducted by the clinical reviewer, Dr. Timothy Jiang. The safety profile appears consistent with findings for each component. One safety concern for this combination product is the potential of exceeding the safety limit of each component especially acetaminophen (b) (4) products. Please refer to Dr. Jiang's review for more detailed information.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Sex, Age and Race

(b) (4)

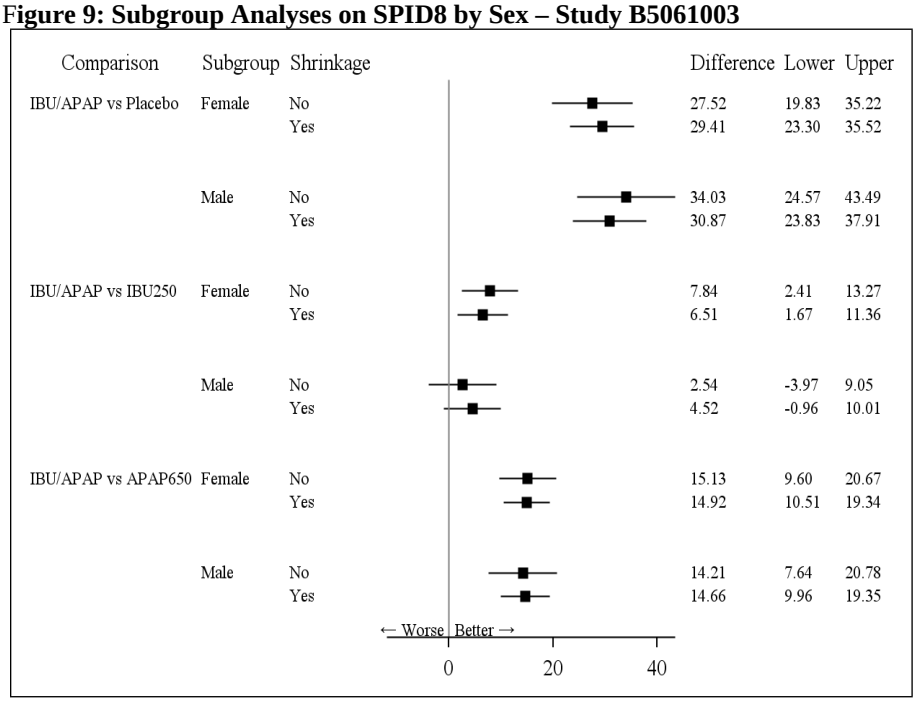
oth study B5061003 and B5061004 enrolled subjects ages from 18 to 40 years old and more than 90% of the subjects were White. Subgroup analyses were only performed by sex for both studies (Figures 9 and 10). No issues were identified from the subgroup analyses.

There was some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same prior within study to derive shrinkage estimates for all subgroups (see Appendix for details).

The results of the sample estimates and the shrinkage estimates of treatment effects in the same subgroups, are presented in the same figures. There were no apparent treatment by subgroup interaction effects.

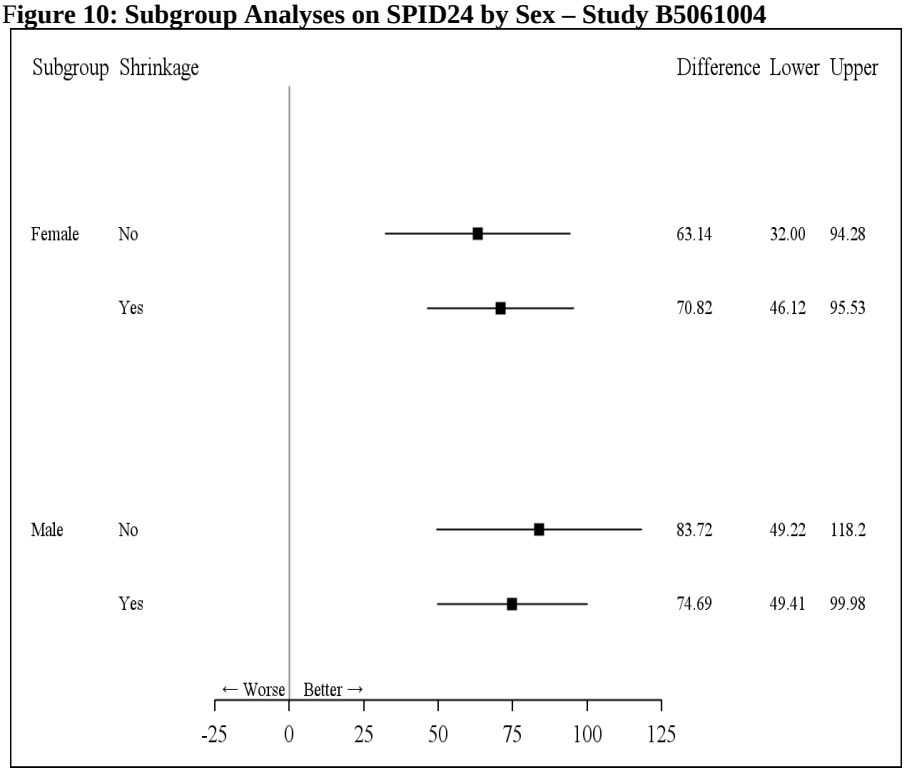
(b) (4)

Figure 9: Subgroup Analyses on SPID8 by Sex – Study B5061003



Source: reviewer

Figure 10: Subgroup Analyses on SPID24 by Sex – Study B5061004



Source: reviewer

4.2 Other Special/Subgroup Populations

No other special subgroup analyses were conducted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

(b) (4)

Another statistical issue common to all three studies (pain (b) (4)) was that inappropriate imputation methods were employed to handle intercurrent events during the study. Specifically, for subjects who took rescue medication, a WOCF approach was implemented to replace all observed efficacy assessments after taking the first rescue medication. For subjects who discontinued treatments early, a single imputation (WOCF, BOCF or LOCF) was applied depending on the dropout reasons. No estimand or adequate justification to the methods was provided. However, since subjects remained in clinic for the duration of the study and efficacy assessments were collected regardless of rescue or early discontinuation, there was very little missing efficacy assessments. Analyses utilizing all observed primary efficacy measures were performed and the results supported the study conclusions from the primary analyses. Further analyses replacing efficacy assessments within the therapeutic window of the rescue medication with the pre-rescue measure also did not change the study conclusion. Therefore, my concerns were alleviated.

5.2 Collective Evidence

The submission relied on three studies to support the proposed (b) (4) pain reduction indication. (b) (4)

(b) (4)

However, the two dental pain studies did provide consistent findings to support the analgesic efficacy. The single-dose dental pain study utilized a factorial design comparing the FDC with placebo, IBU 250 mg and APAP 650 mg. The study demonstrated that the FDC was better than placebo, IBU 250 mg and APAP 650 mg with statistical significance in SPID8. The secondary endpoints including duration of relief, time to onset of meaningful pain relief, SPID6_8 were consistently in favor of the FDC in comparison to either placebo or each component. The multiple-dose dental pain study was a placebo-controlled study designed to demonstrate the multiple-dose analgesic efficacy. The study showed that the FDC was better than placebo in analgesic efficacy during the 24-hour period based on the primary endpoint, SPID24. As noted in the single dose dental pain study, this effect was supported by the secondary endpoints.

5.3 Conclusions and Recommendations

Overall, the two dental pain studies have demonstrated that the FDC was better than placebo and each component in terms of the analgesic efficacy. (b) (4)

Based on these results, there is only substantial evidence to support the pain indication. However, if this product is approved only for the pain indication, there will be a safety concern if a consumer takes another product containing acetaminophen (b) (4). The review team will need to decide based on overall benefit-risk profile and potential post-marketing safety concern.

5.4 Labeling Recommendations

Not applicable as this is a non-prescription product.

Appendix

Bayesian hierarchical modeling produces shrinkage estimates of the individual study treatment effects by removing the within study variability. Further, treatment effects are regarded as exchangeable, which allows them to be different but related. Therefore, shrinkage estimates tend to be more precise and provide narrower confidence/credible intervals. Below is the model used in the analysis for sex and race groups:

$$Y_i \sim N(\mu_i, \sigma_i^2), i = 1, 2$$

$$\mu_i \sim N(\mu, \tau^2), i = 1, 2$$

$$\mu \sim N(0, D^2),\ 1/\tau^2 \sim \text{Gamma}(0.01, 0.01)$$

The magnitude of D^2 depends on the residual variance within study. For example, in Study B5061003, D = 39 and in Study B5061004, D=121.

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/s/

FENG LI
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DAVID M PETULLO
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I concur.