A Study of the Fixed Dose Combination of Ibuprofen and Acetaminophen for the Treatment of Moderate and Severe Dental Pain

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Background

- Ibuprofen (IBU) and acetaminophen (APAP) are oral analgesics with distinct mechanisms of action (MoA).
- **Ibuprofen** is a nonsteroidal anti-inflammatory drug (NSAID), which targets the cyclooxygenase (COX)-1 and COX-2 enzymes peripherally to prevent prostaglandin formation needed to send pain signals to the brain.
- **Acetaminophen** is a centrally acting analgesic that is thought to block prostaglandin and other brain signal factors to raise the pain threshold.
- Ibuprofen (125 mg) and APAP (250 mg), as two distinct active ingredients, when combined in a fixed dose combination (FDC) offer efficacy advantages and potential tolerability differentiation versus either active ingredient alone (based on lower maximum daily exposure to the active ingredients when used in combination versus when given alone).

Methodology

- The FDC (dosed as two tablets every 8 hours – 250/500 mg per dose) was studied in a pivotal, single-dose Dental Pain Clinical Study (third molar extraction) to evaluate its effectiveness treating acute pain, and its tolerability. The single dose dental pain study included four arms:
  - IBU/APAP 250/500 mg [n=172]
  - IBU 250 mg [n=175]
  - APAP 650 mg [n=165]
  - Placebo (PBO) [n=56]
- The study subjects had moderate (n=255, 44.9%) or severe (n=313, 55.1%) pain at baseline.
- The '**Third Molar Extraction Dental Pain Study Model**' is a well-defined study model for the evaluation of treatment of dental pain, which is also recognized more broadly as a study model to evaluate acute pain, which can be extrapolated to other pain types. Third molar extraction causes a level of pain that is well characterized in severity, duration, and consistency between patients. These properties make the dental pain study model predicable in its ability to evaluate and differentiate the effectiveness of treatment options for pain.

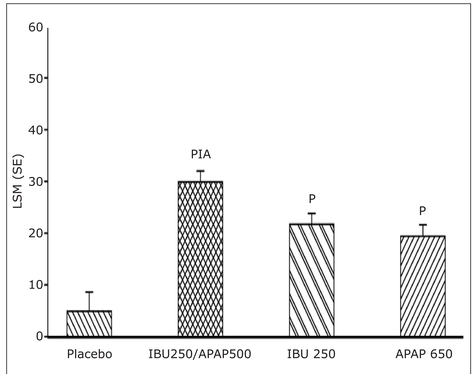
Objective

- The objective of this analysis was to compare subjects with moderate pain versus severe pain with a focus on three key endpoints from the pivotal study that are clinically meaningful to pain sufferers:

1. Summary of pain intensity difference' (SPID 0-8 hours)
2. Time to 'meaningful pain relief' (MPR)
3. Treatment failure at 8 hours (TF8)

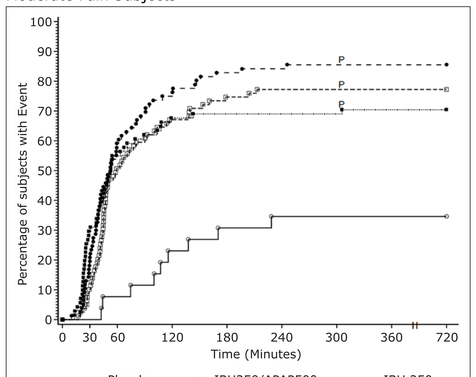
Results

Figure 1. Mean SPID 0-8 Hours – Moderate Pain Subjects



P: Significantly better than Placebo at the 0.05 level.
I: Significantly better IBU 250 mg at the 0.05 level.
A: Significantly better than APAP 650 mg at the 0.05 level.

Figure 2. Median Time (Minutes) to Meaningful Pain Relief – Moderate Pain Subjects



P: Significantly better than Placebo at the 0.05 level.

Table 1. Percent with Treatment Failure at 8 Hours – Moderate Pain Subjects

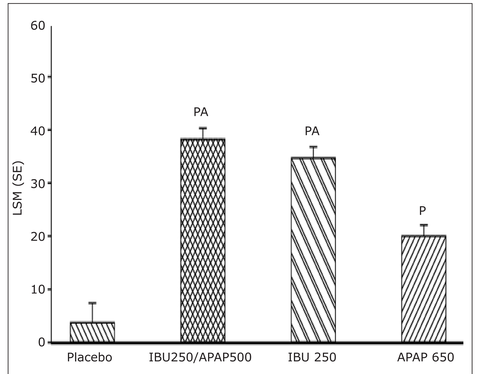
Placebo N=26	IBU250/ APAP500 N=78	IBU250 N=80	APAP650 N=71	p-value
15 (57.7%)	18 (23.1%)	26 (32.5%)	32 (45.1%)	0.003*

Pairwise comparisons

	IBU250/ APAP500 vs. Placebo	IBU250/ APAP500 vs. IBU250	IBU250/ APAP500 vs. APAP650	IBU250 vs. Placebo	APAP650 vs. Placebo	IBU250 vs. APAP650
TrT diff+	-34.61	-9.70	-22.08	-24.78	-12.76	-12.58
95% CI+	(-56.05, -13.16)	(-23.34, 3.95)	(-36.94. -7.23)	(-47.20, -2.35)	(-35.06, 9.53)	(-27.99, 2.83)
p-value	0.002	0.164	0.004	0.030	0.262	0.110

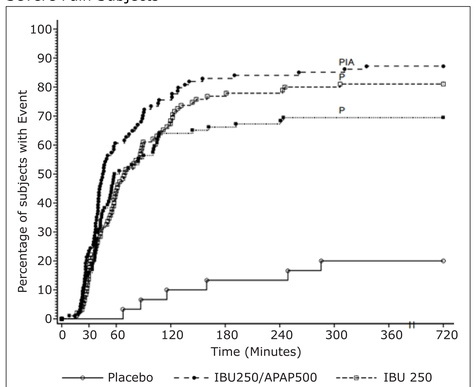
*p ≤ 0.05 for treatment effect.

Figure 3. Mean SPID 0-8 Hours – Severe Pain Subjects



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

Figure 4. Median Time (Minutes) to Meaningful Pain Relief – Severe Pain Subjects



P: Significantly better than Placebo at the 0.05 level.
I: Significantly better BU 250 mg at the 0.05 level.
A: Significantly better than APAP 650 mg at the 0.05 level.

Table 2. Percent with Treatment Failure at 8 Hours – Severe Pain Subjects

Placebo N=30	IBU250/ APAP500 N=94	IBU250 N=95	APAP650 N=94	p-value
24 (80.0%)	24 (25.5%)	32 (33.7%)	53 (56.4%)	< 0.001*

Pairwise comparisons

	IBU250/ APAP500 vs. Placebo	IBU250/ APAP500 vs. IBU250	IBU250/ APAP500 vs. APAP650	IBU250 vs. Placebo	APAP650 vs. Placebo	IBU250 vs. APAP650
TrT diff+	-54.41	-8.21	-30.85	-46.14	-23.44	-22.62
95% CI+	(-71.25, -37.58)	(-21.12, 4.71)	(-44.14. -17.56)	(-63.37, -28.91)	(-40.97, -5.92)	(-36.32, -8.91)
p-value	< 0.001	0.213	< 0.001	< 0.001	0.009	0.001

*p ≤ 0.05 for treatment effect.

Results

Moderate Pain Subjects

The results for the key three endpoints were:

1. Mean SPID 0-8 hours was significantly better with IBU/APAP (29.8) than APAP (19.1 [p<0.001]), IBU (21.7 [p=0.006]), and PBO (4.9 [p<0.001]); **Figure 1**
2. Median time (minutes) to MPR was faster with IBU/APAP (52.7) than APAP (53.0 [p=0.741]), IBU (59.0 [p=0.084]), and PBO (>720 [p<0.001]); **Figure 2**
3. Percent with TF8 was less with IBU/APAP (23.1%) than APAP (45.1% [p=0.004]), IBU (32.5% [p=0.164]), and PBO (57.7% [p=002]); **Table 1**

Severe Pain Subjects

The results for the key three endpoints were:

1. Mean SPID 0-8 hours was better with IBU/APAP (38.1) than APAP (19.7 [p<0.001]), IBU (34.8 [p=0.233]), and PBO (3.4 [p<0.001]); **Figure 3**
2. Median time (minutes) to MPR was faster with IBU/APAP (45.5) than APAP (60.8 [p=0.018]), IBU (69.7 [p=0.018]), and PBO (>720 [p<0.001]); **Figure 4**
3. Percent with TF8 was less with IBU/APAP (25.5%) than APAP (56.4% [p<0.001]), IBU (33.7% [p=0.213]), and PBO (80.0% [p<001]); **Table 2**

Safety

- The safety profile of IBU/APAP was comparable to that observed with PBO, and sometimes better than the individual components, in the pivotal studies.
- Among the most commonly observed adverse events (AEs) in the single dose study, the rates (n/%) with IBU/APAP versus PBO were nausea (17/9.9% versus 17/30.4%), vomiting (7/4.1% versus 11/19.6%), dizziness (5/2.9% versus 4/7.1%), and flushing (0/0% versus 2/3.6%).
- IBU/APAP had lower rates for all these AEs compared to IBU alone and APAP alone.

Conclusion

- The combination of IBU/APAP offers two active ingredients, with different MoA, to deliver more robust pain relief than the individual components when used at OTC dosing.
- FDC IBU/APAP 250/500 mg demonstrated in this analysis that it was effective in moderate and severe pain.
- Importantly, effectiveness of the IBU/APAP was maintained in the subset with severe pain at baseline.
- Dental pain is a recognized model for evaluating treatments for acute pain, and this study confirmed the effectiveness of the FDC IBU/APAP 250/500 mg.
- Equally important was the good tolerability of the product demonstrated in the study.
- The benefit/risk profile of IBU/APAP supports its consideration as a first line pain relief option.

Abbreviations:

AEs: Adverse events; **APAP**: Acetaminophen; **COX:** Cyclooxygenase; **FDC:** Fixed dose combination; **IBU:** Ibuprofen; **MoA:** Mechanisms of action; **MPR:** Meaningful pain relief; **NSAID:** Nonsteroidal anti-inflammatory drug; **PBO:** Placebo; **SPID:** Summary of pain intensity difference; **TF8:** Treatment failure at 8 hours