Advil DUAL ACTION WITH Acetaminophen

HALEON

Clinical Study Summary

In the treatment of postsurgical dental pain, FDC IBU/APAP 250/500 mg provided significantly better analgesia over 0-8 hours than placebo or either drug alone

Results from two phase 3, randomized, parallel-group, double-blind, placebo-controlled studies

Searle, S., et al., 2020.

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Background

93% of individuals across the globe grapple with pain, underscoring the importance of healthcare providers' role in pain management. Oral NSAIDs are widely recommended as front-line treatment for acute pain management.

The American Dental Association recommends the combination of acetaminophen and ibuprofen to effectively manage mild to moderate dental pain[1]

- A previous pilot study demonstrated that various fixed-dose combinations of ibuprofen (IBU) and acetaminophen (APAP) provided analgesic efficacy comparable to a higher dose of IBU, with the same safety profile[2]
- This results in a total daily IBU dose of 750 mg and a total daily APAP dose of 1500 mg, considerably lower than the currently approved OTC maximum daily doses for the agents (1200 and 4000 mg, respectively)

Study Objective

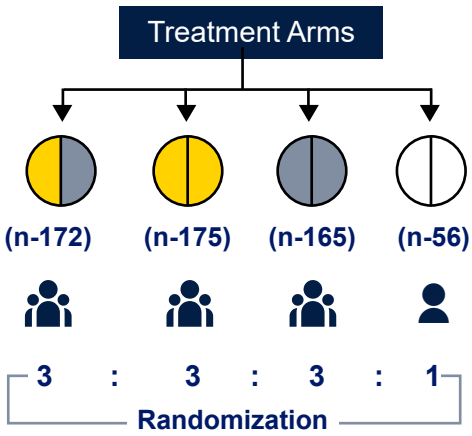
To determine if FDC IBU/APAP 250/500 mg:

1. Provided superior analgesia to its individual components, sustained with multiple doses (study 1 & 2)
2. Had a rapid onset of analgesia (starts within 30 minutes) (studies 1 and 2)
3. 8-hour dosing interval was appropriate (studies 1 & 2)

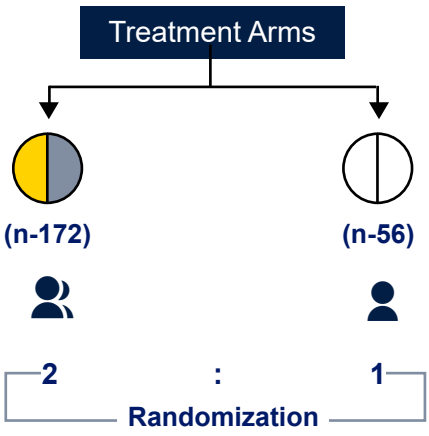
Study Design and Methodology

Study 1 (Single dose) and Study 2 (Multiple dose) were single-center, phase 3, randomized, double-blind, placebo-controlled, conducted in healthy population aged 18 - 40 years who experienced **moderate to severe postsurgical oral dental pain** following extraction of ≥3 third molars

Study 1 (Single dose)



Study 2 (Multiple dose)



FDC (IBU/APAP 250/500 mg) | IBU 250 mg | APAP 650 mg | Placebo

Study 1 (Single dose) and Study 2 (Multiple dose):

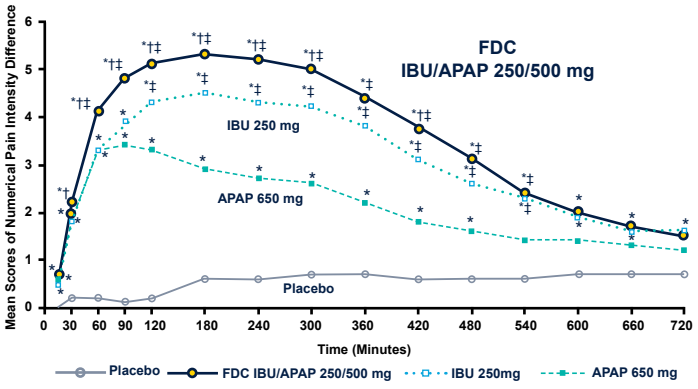
Primary endpoint: Sum of pain intensity difference scores based on the 11-point numerical pain severity rating (SPID[11]) during the interval from baseline to 8 hours and during 0-24 hours for study 1 and study 2 respectively

Key Secondary endpoints: $SPID[11]_{0\text{-}8,\ 6\text{-}8}$, Time to first perceptible pain relief (TFPR), Time to meaningful pain relief (TMPR), duration of pain relief, the cumulative proportion of treatment failures at 6 and 8 hours

Results

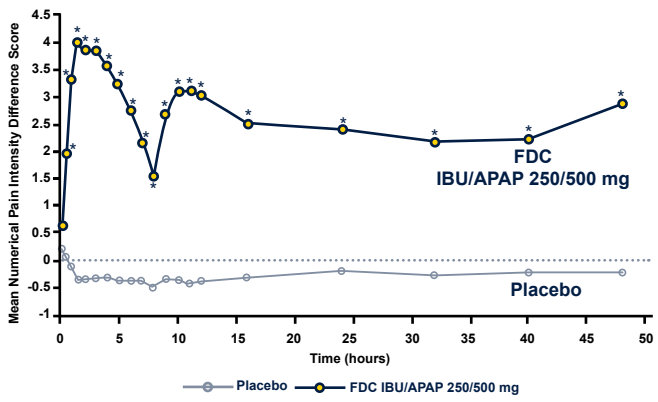
FDC IBU/APAP 250/500 mg provided significantly better analgesia over 0-8 hours than placebo, IBU 250 mg alone, and APAP 650 mg alone with efficacy sustained over a period of 2 days

Study 1 (Single dose)



*Significantly better than placebo at the 0.05 level. †Significantly better than IBU 250 mg at the 0.05 level. ‡ Significantly better than APAP 650 mg at the 0.05 level.

Study 2 (Multiple dose)



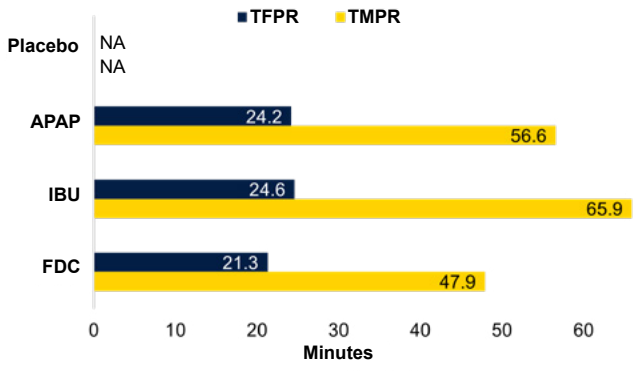
*P< 0.05 versus placebo. APAP indicates acetaminophen; FDC, fixed-dose combination; IBU, ibuprofen

- In the single dose study, FDC IBU/APAP 250/500 mg was significantly better for SPID[11]$_{0-8}$ than placebo, IBU alone, and APAP alone (P<0.001, P=0.008, and P<0.001), respectively and for SPID[11]$_{0-24}$ compared to placebo (P<0.001) in the multiple dose study

					
Study 1 (Single dose)	SPID[11] $_{0-8}$	**34.3**	**28.9**	**19.4**	**4.1**
Study 2 (Multiple dose)	SPID[11] $_{0-24}$	**64.6**			**-7.1**

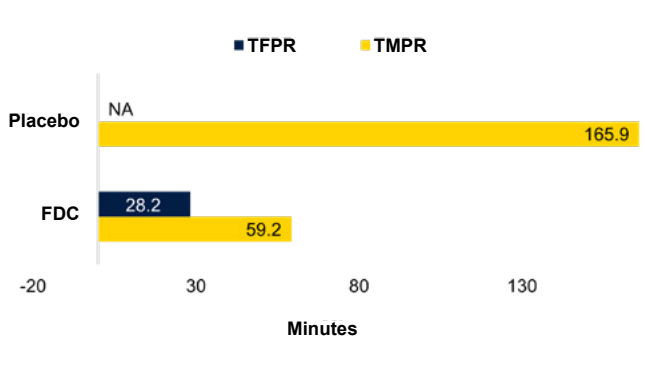
FDC IBU/APAP 250/500 mg provides a rapid onset of pain relief that starts within 30 minutes, a crucial attribute for any analgesic used for acute pain

Study 1 (Single dose)



Lower the value of TFPR and TMPR, the more rapid the onset of pain relief

Study 2 (Multiple dose)

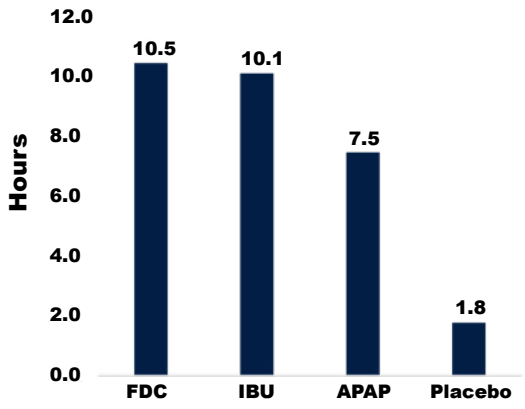


- TFPR was 21.3 and 28.2 minutes for the FDC in studies 1 and 2, respectively, and numerically better than either IBU (24.6 minutes) or APAP alone (24.2 minutes) in study 1
- For both studies, TMPR with FDC IBU/APAP 250/500 mg (47.9, 59.2 mins) was significantly faster than IBU (65.9 mins, P=0.003), APAP (56.6 mins; P=0.031) and placebo (NA; 165.9, P<0.001)

Abbreviations: SPID[11]: Sum of pain intensity difference scores based on the 11-point numerical pain severity rating during the different interval; **TFPR:** Time to first perceptible pain relief; TMPR: Time to meaningful pain relief

The FDC IBU/APAP 250/500 mg provided longer-lasting pain relief and significantly superior analgesia compared to placebo and APAP 650 mg in the single dosage study, both of which persisted in the multiple dose research, support the 8-hour dosing interval

Study 1 (Single dose)



	Median duration of pain relief #	Cumulative proportion of treatment failures after 8 hours
	10.5 hrs	24.4%
	10.1 hrs (P=0.069*)	33.1% (P=0.064*)
	7.5 hrs (P<0.001*)	51.5% (P<0.001*)
	1.8 hrs (P<0.001*)	69.6% (P<0.001*)

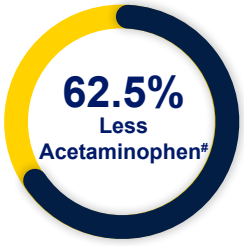
#assessed using median time to treatment failure; *Depicted P values are comparison of FDC with respect to other treatment groups

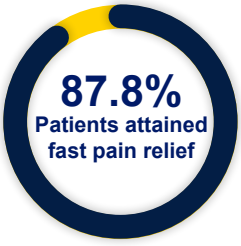
Conclusion

FDC IBU/APAP 250/500 mg, is well-tolerated, and more effective analgesic for pain management compared with standard OTC dosing of either agent alone

- FDC IBU/APAP 250/500 mg provided significantly greater analgesic efficacy across primary endpoints than either ibuprofen 250 mg or acetaminophen 650 mg alone
- Offers a rapid onset of analgesia that starts within 30 minutes, sustained over an 8-hour dosing interval
- The adverse events profile of the FDC IBU/APAP 250/500 mg was comparable to or better than those of the two components alone

Greater relief with a lower maximum daily dose of each medication





*the maximum daily allowance of ibuprofen alone is 1200 mg

#the maximum daily allowance of acetaminophen alone is 4000 mg

**8 hours of effective pain relief with a fast onset of action

FDC IBU/APAP 250/500 mg offers effective pain relief, targeting multiple pain pathways. It offers an effective alternative to opioid-based medications, that does not have the risk of opioid-related complications.

References

1. Kraglund, F. (2014). The Journal of the American Dental Association, 145(9), 966-968
2. Mehlisch DR, Aspley S, Daniels SE, Bandy DP. Clin Ther. 2010 May;32(5):882-95.