

**Analgesic Adjuvancy  
of Caffeine**

# **The Analgesic Adjuvancy Of Caffeine in Combination with Acetaminophen**

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### Abbreviations

AE	Adverse Event
AF EXCEDRIN	Acetaminophen 1000mg plus caffeine 130mg
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
APAP	Acetaminophen
ASA	Acetylsalicylic acid (Aspirin)
BMS	Bristol-Myers Squibb
CAF	Caffeine
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
IHS	International Headache Society
IRB	Institutional Review Board
ITT	Intent-to-Treat
MAXPAR	Maximum Pain Relief
MAXPID	Maximum Pain Intensity Difference
OTC	Over-the-Counter
PAR	Pain Relief
%SPID	Percent Sum of Pain Intensity Difference
PI	Pain Intensity
PID	Pain Intensity Difference
SPID	Sum of Pain Intensity Differences
TOTPAR	Total Pain Relief
TYLENOL	Acetaminophen 1000mg

## EXECUTIVE SUMMARY

### 1.0 SCOPE OF THIS SUMMARY

This document provides data from three new, parallel, double-blind, randomized, placebo-controlled trials that demonstrate caffeine adjuvancy with acetaminophen (APAP). One trial was conducted in the tension headache model (HPD-H203) and two trials were conducted in the dental pain model (HPD-D104 and HPD-D105). The new tension headache trial (HPD-H203), was conducted to confirm results of the earlier crossover design headache trials.

Data from these three new trials confirm the positive caffeine adjuvancy findings of previously submitted studies in headache, dental, and postpartum bioassay pain models.

Overall, BMS has completed a total of 17 clinical studies that specifically examined the analgesic adjuvancy of caffeine in combination with APAP. Fourteen (14) of these studies have previously been submitted to FDA. The 17 studies are summarized in Table 1.0, where they are classified in two ways. First they are classified as either head-to-head direct comparison studies, or as bioassay relative potency comparison studies, based on the analytical methodology employed to evaluate response differences between treatments. The studies are further classified according to the pain model investigated: tension-type headache pain, postoperative dental pain, and postpartum pain.

Table 1.0 BMS Clinical Study Program Caffeine's Analgesic Adjuvancy With Acetaminophen							
Pain Model Study No.	Study Design Features <sup>A</sup>	Subjects N	Treatment Groups			Study Dates	Submission Dates To FDA Initial (Follow-Up)
			No. <sup>B</sup>	APAP mg	APAP mg +CAF mg		
<b>Head-to-Head Direct Comparison Studies</b>							
<b>Tension-Type Headache Pain</b>							
HPD-H203	DB, PG, R, PC	1104	3	1000	1000 +130	10/97-5/98	NEW
170-01-88	DB, CO, R, PC	441	3	1000	1000 +130	2/88-1/89	11/16/89 (5/93, 5/95)
170-02-88	DB, CO, R, PC	442	3	1000	1000 +130	2/88-10/88	11/16/89 (5/93, 5/95)
<b>Postoperative Dental Pain</b>							
HPD-D104	DB, PG, R, PC	1009	3	1000	1000 +130	3/97-12/97	NEW
HPD-D105	DB, PG, R, PC	1015	3	1000	1000 +65	4/97-12/97	NEW
171-01-88	DB, PG, R, PC	534	3	1000	1000 +130	1/88-9/88	11/16/89 (5/93)

Table 1.0 (cont.) BMS Clinical Study Program Caffeine's Analgesic Adjuvancy With Acetaminophen									
Pain Model Study No	Study Design Features <sup>A</sup>	Subjects N	Treatment Groups			Study Dates	Submission Dates To FDA Initial (Follow-Up)		
			No. <sup>B</sup>	APAP mg	APAP mg +CAF mg				
<b>Bioassay Relative Potency Comparison Studies</b>									
<b>Postpartum Pain</b>									
2255	DB, PG, R, PC	739	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	77-79	9/27/82 (11/83, 2/85, 11/89, 5/93, 5/95)		
2576	DB, PG, R, PC	699	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	7/79-6/81	9/27/82 (11/83, 2/85, 11/89, 5/93)		
2577	DB, PG, R, PC	227	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	9/79-9/81	9/27/82 (11/83, 2/85, 11/89, 5/93)		
2578	DB, PG, R, PC	373	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	11/79-2/82	9/27/82 (11/83, 2/85, 11/89, 5/93)		
2579	DB, PG, R, PC	434	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	1/80-3/81	9/27/82 (11/83, 2/85, 11/89, 5/93)		
2580	DB, PG, R, PC	538	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	4/80-4/81	9/27/82 (11/83, 2/85, 11/89, 5/93)		
2581	DB, PG, R, PC	414	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	1985	10/30/1986		
<b>Postoperative Dental Pain</b>									
2569	DB, PG, R	173	4		1000, 1500 +130, +195	10/80-10/81	9/27/82 (11/89, 5/93)		
2711	DB, CO, R, PC	48	5	500	0, 500 +65, +65		9/27/82 (11/83, 2/85)		
2570	DB, PG, R, PC	196	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	2/80-9/81	10/30/86 (11/89, 5/93)		
2571	DB, PG, R, PC	386	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	3/80-1/83	10/30/86 (11/89, 5/93)		

<sup>A</sup> DB = Double-Blind; PG = Parallel-Groups; CO = Crossover; R = Randomized; PC = Placebo-Controlled

<sup>B</sup> Number of treatment groups includes Placebo treatment group for each study, except Postoperative Dental Pain Study No. 2569, which was not placebo-controlled

## 2.0 FOCUS OF THIS SUMMARY

This document provides two levels of evidence supporting the adjuvancy of caffeine when combined with APAP. Primary support consists of six head-to-head trials. Three of these trials are the new trials HPD-H203, HPD-D104, and HPD-D105. The other three trials (170-01-88, 170-02-88, and 171-01-88) were submitted to the FDA in 1989.

Secondary support includes data from 11 bioassay studies that were submitted to the agency in 1982 and 1986.

### Primary Support – Head-to-Head Trials

HPD-H203 (tension-type headache) HPD-D104 (dental pain) and HPD-D105 (dental pain) are new head-to-head studies, as mentioned above, while Studies 170-01-88, 170-02-88 (tension-type headache) and 171-01-88 (dental pain) are previously submitted APAP/CAF vs. APAP head-to-head studies. These six

studies, considered individually, provide substantial evidence of the analgesic adjuvant effect of caffeine given in combination with APAP, and when pooled, allow an accurate estimate of the magnitude of caffeine's adjuvant effect. This estimate is consistent with the prior published estimate.

These six head-to-head comparisons of APAP/CAF with APAP alone were adequately designed and powered to show both the analgesic adjuvant effect of caffeine and superiority of the active treatments over placebo in the different pain models. Considered together, they constitute substantial evidence of the analgesic adjuvancy of caffeine in combination with APAP and support Category I status in the Internal Analgesic Monograph.

### **Secondary Support - Bioassay Trials**

In addition to the six head-to-head studies mentioned above, BMS has completed a total of 11 double-blind, randomized, placebo-controlled, parallel groups, relative potency single-dose bioassays comparing multiples of APAP/CAF in a fixed 500 mg/65 mg ratio with corresponding multiples of APAP alone. Four of these studies were conducted in a dental pain model (Studies 2711 and 2569-2571), while the other seven were conducted in a postpartum pain model (Studies 2255 and 2576-2581).

FDA concluded that, in the aggregate, these bioassay trials do not constitute substantial evidence that caffeine potentiates the analgesic effect of APAP. The Agency's criticism was that intra-study APAP/CAF vs. APAP pairwise comparisons by APAP dose did not show consistent superiority for the combination. However, it should be noted that the studies were neither designed nor powered to sustain such analyses.

The BMS dental pain relative potency studies showed weak and inconsistent evidence of an analgesic adjuvant effect of caffeine combined with APAP, probably as a result of lesser sensitivity of the dental pain model. To the extent that these studies are supportive of the analgesic adjuvancy of caffeine combined with APAP, they will be discussed briefly, but are not the primary focus of this summary.

The postpartum studies, on the other hand, provide strong evidence of caffeine's analgesic adjuvancy effect for APAP, and these studies will be considered in greater detail below in Section 4.3.

### 3.0 DISCUSSION/SUMMARY AND CONCLUSIONS

#### 3.1 Discussion/Summary

During the past three decades, BMS has submitted considerable evidence in support of caffeine adjuvancy. In 1995, the FDA issued a Feedback Letter to Industry, which concluded that while caffeine was an adjuvant when combined with ASA alone or with the combination of ASA/APAP, there was insufficient evidence to demonstrate that caffeine was an adjuvant when combined with APAP alone. FDA based this decision on concern about potential differential carryover effects in the crossover tension headache trials. In August 1995, BMS responded to the April 1995 FDA Feedback Letter, affirming the position that previously submitted clinical information provided substantial evidence of caffeine adjuvancy with APAP.

Since that time BMS has conducted three new, randomized, double-blind, placebo-controlled, head-to-head clinical trials assessing the analgesic adjuvant effect of caffeine when combined with APAP. One study was conducted in a tension headache model (HPD-H203), while the other two were conducted in a dental model (HPD-D104 and HPD-D105). The new, parallel design, tension headache trial (HPD-H203) was conducted to confirm the results of the earlier crossover design headache trials. Results of these 3 new trials considered in conjunction with results of earlier trials in tension-type headache, dental pain and postpartum pain models constitute strong evidence for caffeine adjuvancy with APAP, and provide a firm basis for the conclusion that caffeine potentiates the analgesic effectiveness of APAP, to a clinically relevant degree.

#### Efficacy Summary

##### Headache Model

Caffeine adjuvancy with APAP was demonstrated in the new, parallel design, headache trial (HPD-H203) which confirmed the results of the earlier crossover headache trials (170-01-88, 170-02-88). Similarly, the pooled analysis of headache studies, HPD-H203 and the first treated headache of the crossover trials, 170-01-88 and 170-02-88, also demonstrated caffeine adjuvancy with APAP (Figure A and Figure B).

- Study HPD-H203, the new, parallel, double-blind, randomized, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID from 75 minutes through 4 hours, and to placebo from 30 minutes through 4 hours (Figure A). APAP/CAF was superior to APAP alone and to placebo for SPID4 and MAXPID.
  - APAP/CAF was statistically superior to APAP alone for PAR from 75 minutes through 4 hours, and to placebo from 45 minutes

through 4 hours (Figure B). APAP/CAF was statistically superior to APAP alone and placebo for TOTPAR4 and MAXPAR.

- Studies 170-01-88 and 170-02-88, two earlier crossover, double-blind, randomized, placebo-controlled trials each demonstrated caffeine adjuvancy with APAP as evidenced by:
  - 170-01-88
    - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
    - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
  - 170-02-88
    - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
    - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
- Pooled analysis of headache studies (HPD-H203; and first treated headache of the cross-over trials, 170-01-88 and 170-02-88) demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF statistically superior to APAP alone for PID from 60 minutes through 4 hours (Figure A) and to placebo from 30 minutes through 4 hours. APAP/CAF was statistically superior to APAP alone and to placebo for MAXPID, SPID1 and SPID4.
  - APAP/CAF statistically superior to APAP alone and to placebo for PAR at 30 minutes and from 60 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1, and TOTPAR4.

#### Dental Pain Model

Caffeine adjuvancy with APAP was demonstrated in two new dental studies (HPD-D105, HPD-D104).

In Study HPD-D104, statistical significance in favor of APAP/CAF over APAP alone was achieved at fewer timepoints than in Study D105. In an earlier dental study (171-01-88), while both APAP/CAF and APAP alone were significantly superior to placebo, the combination APAP/CAF was not significantly better than APAP alone due, in part, to the small sample size. However, the treatment effect observed in Study 171-01-88 was in favor of APAP/CAF over APAP and was similar in magnitude to that seen in HPD-D104 and HPD-D105.

Similarly, the pooled analysis of dental trials, HPD-D104, HPD-D105, 171-01-88, demonstrated caffeine adjuvancy with APAP (Figure C and Figure D).

- Study HPD-D105 (APAP 1000mg/CAF 65mg) a new, parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and placebo for MAXPID, SPID1, AND SPID4.
  - APAP/CAF was statistically superior to APAP alone for PAR from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- Study HPD-D104 (APAP 1000mg/CAF 130mg) a new, parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID at 30 minutes, and to placebo from 15 minutes through 4 hours (Figure C).
  - APAP/CAF was statistically superior to APAP alone for PAR at 15, 30, 60 and 75 minutes, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP for TOTPAR1, and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- In Study 171-01-88 (APAP 1000mg/CAF 130mg), an earlier parallel, randomized, double-blind, placebo-controlled trial, although statistically significant differences from APAP alone were not demonstrated due to the small sample size; treatment effects, however, were in the range of those seen in HPD-D104 and HPD-D105, and favored APAP/CAF over APAP alone (Figure C and Figure D).
- Pooled analysis of all dental studies, HPD-D104, HPD-D105, and 171-01-88, demonstrated caffeine adjuvancy as evidenced by:
  - APAP/CAF statistically superior to APAP alone for PID from 30 minutes through 3 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPID, SPID1, and SPID4.
  - APAP/CAF was statistically superior to APAP alone for PAR from 15 min through 3 hours (Figure D), and to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.

### Postpartum Pain Model

Caffeine adjuvancy was demonstrated in the pooled postpartum/bioassay trials.

- Studies 2255, 2576, 2577, 2578, 2579, 2580 demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF statistically superior to APAP with relative potency estimates of 1.28 for SPID4 and 1.31 for TOTPAR4, indicating approximately 1300mg APAP would be required to provide comparable relief to APAP 1000mg/CAF 130mg.

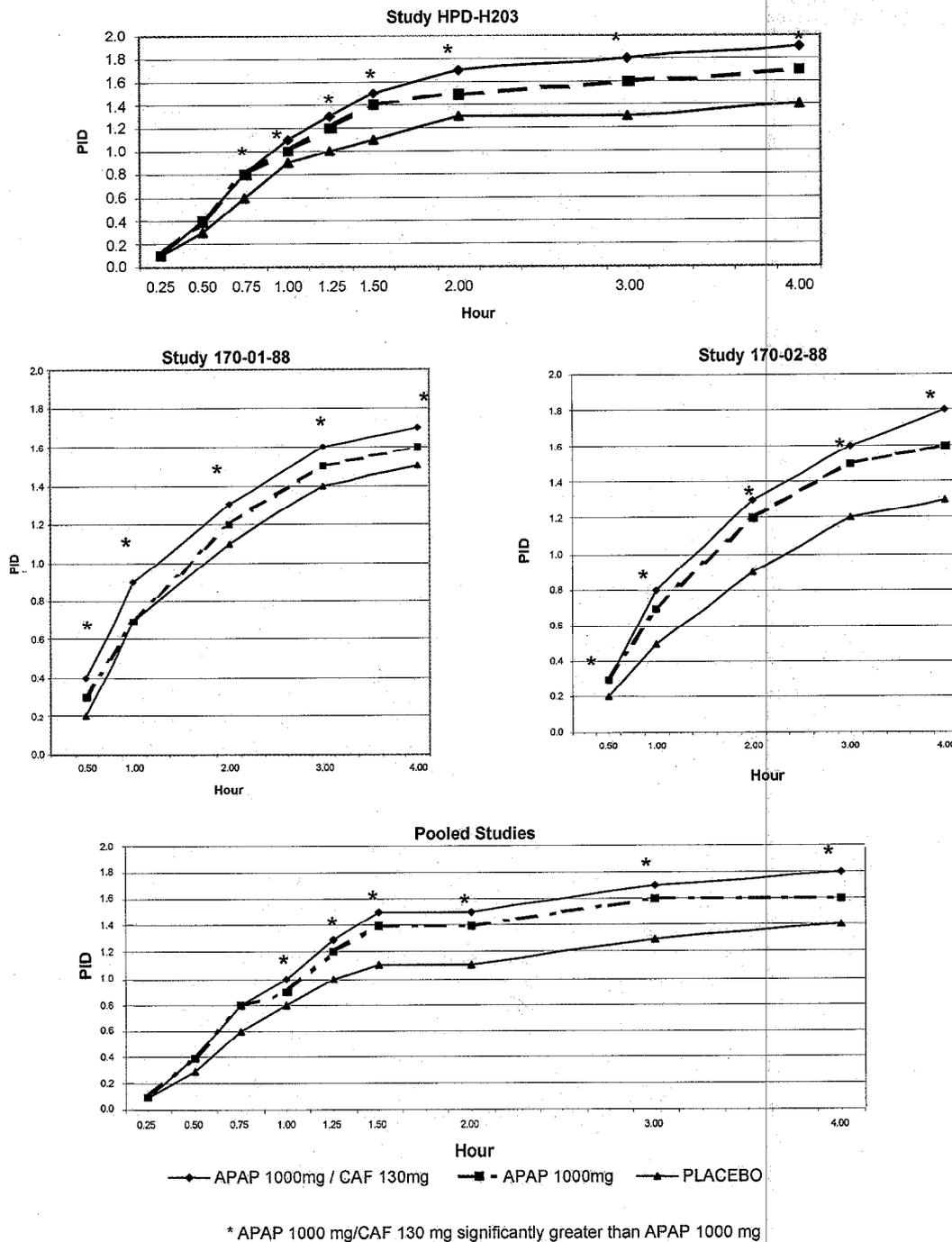
### Safety Summary

Although incidence rates for both gastrointestinal and nervous system were slightly higher for APAP/CAF than for APAP alone in the head-to-head studies, none of the adverse events in either of the categories was of a serious nature. Overall, the APAP/CAF combination was well tolerated by the subjects in these trials. Adverse events were consistent with the safety profile of the individual components. Since 1990, the APAP 1000 mg/CAF 130 mg combination has been marketed in the U.S. by BMS as Aspirin Free Excedrin<sup>®</sup>. Since that time, more than 2.5 billion tablets have been sold. The safety event profile is well characterized.

### **3.2 Conclusions**

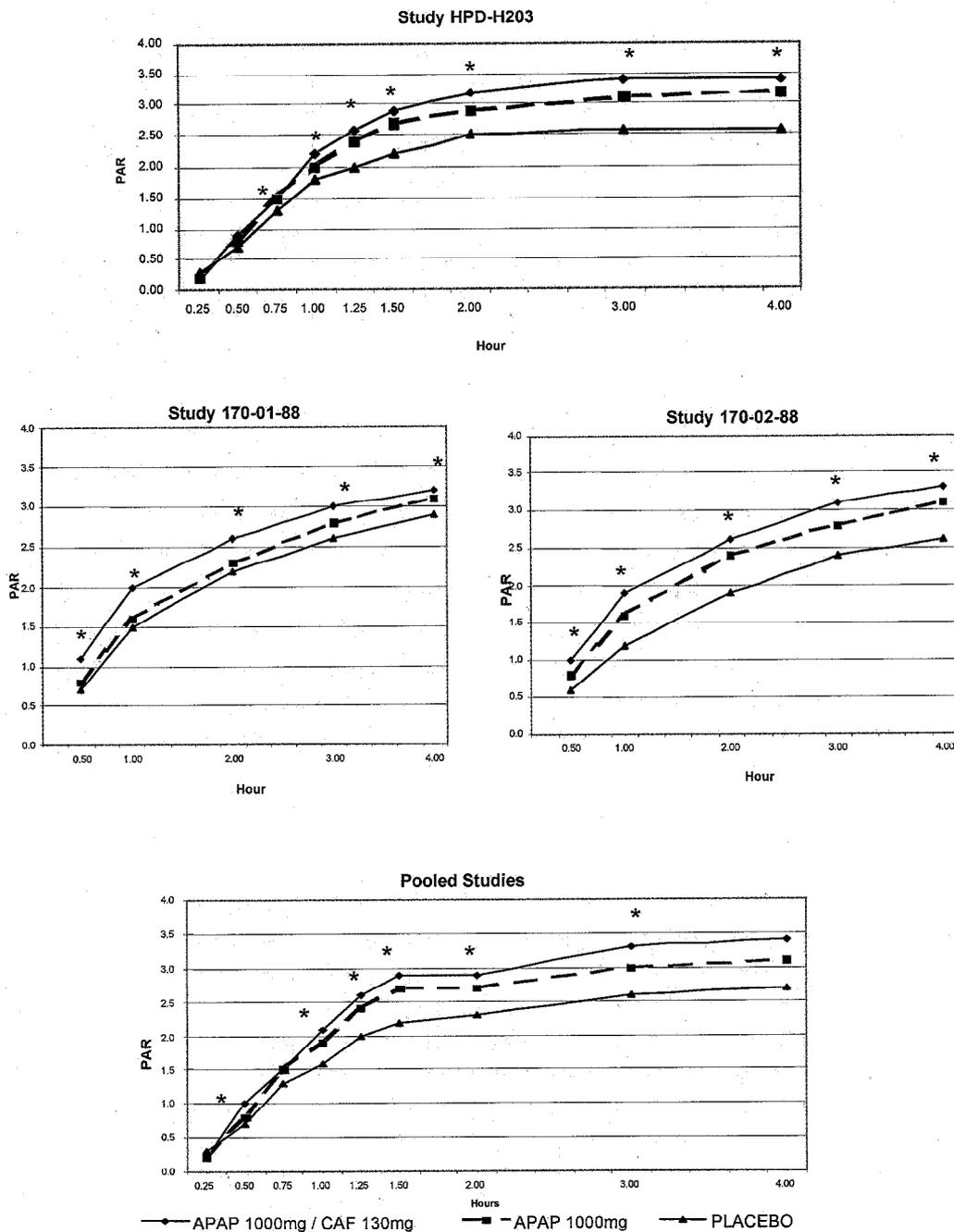
- Caffeine adjuvancy with APAP has been demonstrated in a variety of pain models (headache, dental, postpartum) and study designs (parallel, cross-over, bioassay) as evidenced by statistically significant increases in pain relief and decreases in pain intensity compared to APAP alone.
- Caffeine adjuvancy with APAP allows consumers to obtain better pain relief than could be expected with the analgesic base alone.
- Caffeine adjuvancy with APAP, currently the most commonly used analgesic in the U.S., provides a meaningful benefit to consumers.
- The combination of APAP with caffeine is safe and well tolerated with demonstrated caffeine adjuvancy.

Figure A  
Pain Intensity Difference  
Tension Headache (ITT)



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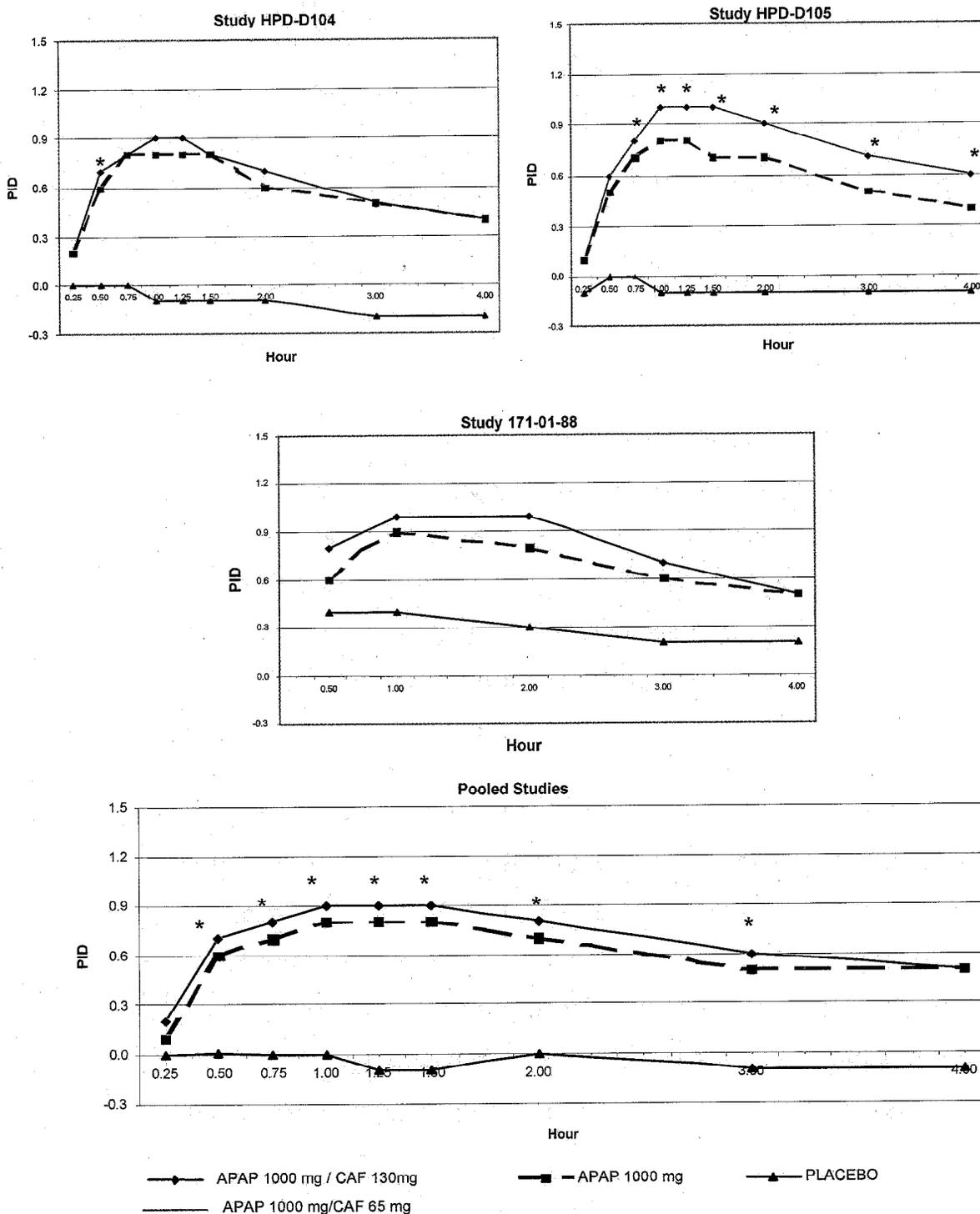
### Figure B Pain Relief Tension Headache (ITT)



\* APAP 1000 mg/CAF 130 mg significantly greater than APAP 1000 mg

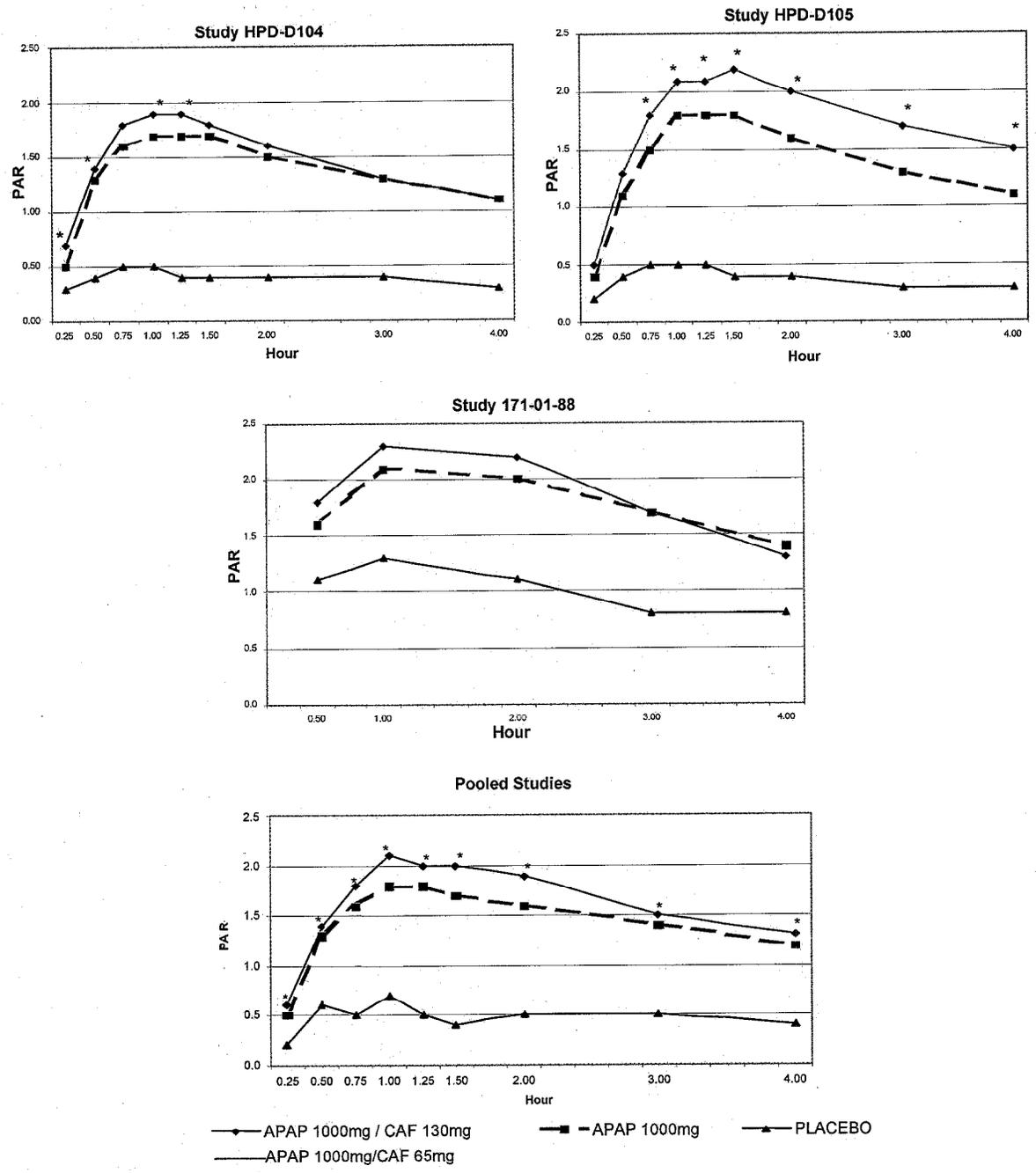
**BRISTOL-MYERS SQUIBB**  
Hillside, New Jersey 07205

Figure C  
Pain Intensity Difference  
Dental Pain (ITT)



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Figure D  
Pain Relief  
Dental Pain (ITT)



\* APAP 1000 mg/CAF significantly greater than APAP 1000 mg

# The Analgesic Adjuvancy of Caffeine in Combination with Acetaminophen

## 1.0 INTRODUCTION

This document is an integrated summary of evidence from three new clinical trials supporting caffeine adjuvancy with acetaminophen (APAP) and previously submitted trials.

### 1.1 Scientific Rationale

Caffeine has been a constituent of OTC and prescription analgesic drug products since the early 1900s. The medical literature provides strong evidence that caffeine enhances the analgesic effects of ASA, APAP, and ASA/APAP combinations in a variety of pain models<sup>1-5</sup>. The effect of caffeine as an analgesic adjuvant has been studied in numerous trials. In 1984, Laska et al published a meta-analysis of the results of 30 clinical bioassay studies in more than 10,000 subjects which demonstrated that caffeine enhances the pain relieving potency of caffeinated analgesic formulations (Laska 1984) containing APAP and ASA. The authors analyzed the relative potency of caffeinated and non-caffeinated analgesics in studies conducted from 1975-1981 utilizing various pain models. They concluded that the addition of caffeine to APAP, ASA, and the combination of APAP and ASA resulted in a 41% increase in analgesic activity [Relative potency 1.41 (95% confidence interval 1.23-1.63)]. The significance of these findings is that it would require approximately 40% more analgesic base (e.g., 1400 mg APAP alone) to provide pain relief equivalent to that provided by the caffeinated analgesic (e.g., APAP 1000mg/CAF 130mg; ASA 500mg/APAP 500mg/CAF 130mg). APAP/ASA/CAF 130mg has also been shown to be more efficacious than ibuprofen. In a multi-center, double-blind study by Goldstein et al, the combination of APAP 500mg/ASA 500mg/ CAF 130mg demonstrated superior overall analgesic efficacy and faster onset of meaningful pain relief than ibuprofen 400mg in the treatment of acute migraine attacks (Goldstein 2001).

The addition of caffeine to analgesics allows consumers to receive greater pain relief than could be expected with the analgesic base alone. In addition, given the known safety concerns associated with excessive analgesic use, such as hepatotoxicity with APAP and gastrointestinal (GI) bleeding with ASA, the "analgesic sparing" effect of caffeine may actually offer a significant therapeutic benefit. Clearly, caffeine adjuvancy provides a desirable benefit to consumers.

### 1.2 Background

The safety and efficacy of caffeine as an analgesic adjuvant was initially reviewed by FDA's Advisory Review Panel for OTC Internal Analgesic,

Antipyretic and Antirheumatic Drug Products (Panel) during the period 1972 through 1977. Although the Panel stated that the inclusion of caffeine theoretically "could be a factor in analgesic abuse," it concluded that (a) there was "insufficient evidence" to justify a warning regarding caffeine, and (b) the "potential benefits outweigh this risk" (42 FR 35484-85). The Panel thus placed caffeine in Category I for safety. With respect to effectiveness, the Panel found there was some evidence to suggest that caffeine-containing analgesics were more effective than non-caffeinated analgesics alone (42 FR 35483). Because the data available at that time were considered limited, however, the Panel concluded that additional clinical studies were required to conclusively determine that caffeine was an effective analgesic adjuvant when used in combination with aspirin (ASA), acetaminophen (APAP), or ASA/APAP combinations (42 FR 35482). Accordingly, the Panel placed caffeine in Category III for effectiveness with the expectation that it could attain Category I status when one or more adequate and well-controlled studies demonstrated caffeine adjuvancy [*i.e.*, that caffeine, when added to an analgesic base, provides a statistically significant contribution to the overall effectiveness of the analgesic product (42 FR 35483, 35489)].

Subsequently, Bristol-Myers Squibb (BMS) engaged in a continuing dialogue with the Agency to address the Panel's and FDA's concerns regarding the efficacy of caffeine as an analgesic adjuvant. As part of that dialogue, BMS conducted new trials and submitted significant new data and information in filings dating from 1973 through 1988. The submissions included adequate and well-controlled studies involving different designs (bioassay, parallel head-to-head, crossover head-to-head), different pain models (tension headache, dental, postpartum), and different analgesic bases (APAP, ASA/APAP combinations). The adequacy of the new data and information, individually and collectively, was attested to by leading experts from various scientific disciplines, including analgesiologists, headache specialists, statisticians, and pharmacologists.

These filings included a 1982 Citizen Petition to reopen the administrative record to include new clinical studies designed to address the Agency's concerns. While the Petition was denied in 1983, the Agency requested and received further detail on several of the studies submitted in the Citizen Petition. The following year, Laska et al. provided a meta-analysis of the results of studies conducted by BMS in over 10,000 subjects, comparing the potency of various analgesic bases combined with caffeine, relative to an analgesic alone. A series of meetings, discussions and submissions followed over the next few years.

In 1988, FDA published the Proposed Rule for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for OTC Human Use (53 FR 46204, Nov. 16, 1988). Based upon comments on the caffeine dose, FDA agreed to change "the Panel's recommended single dose of 65mg caffeine to 75mg caffeine as an analgesic adjuvant, not to exceed a single adult dose of 150mg or a maximum daily dose of 600mg" (53 FR 46251). In making this change, the Agency noted

that a 150mg single adult dose was well within the 100-200mg dose range for caffeine recommended by the Sleep-Aid Panel for stimulant drug products (53 FR 46244).

In response to the 1988 Proposed Rule, BMS submitted additional data supporting the efficacy of caffeine as an analgesic adjuvant. In 1988, BMS submitted data from six adequate and well-controlled clinical trials which showed that the combination of ASA (500mg), APAP (500mg), and caffeine (130mg) provided superior analgesic efficacy to APAP (1000mg) alone, and that this difference was statistically and clinically significant. The following year, BMS submitted the results from three adequate and well-controlled clinical trials (two headache studies and one dental pain study) comparing the efficacy of a combination containing APAP (1000mg) and caffeine (130mg) with APAP (1000mg) alone. The two crossover headache studies yielded statistically significant results demonstrating that caffeine provides a positive contribution to the effectiveness of APAP. Although the results of the parallel design dental study did not achieve statistical significance, the differences between the caffeinated and non-caffeinated products were supportive of caffeine's adjuvancy.

In an April 18, 1995 Feedback Letter to Industry, the Office of OTC Drug Evaluation (Office) concluded that caffeine was an effective analgesic adjuvant when combined with ASA or ASA/APAP combinations. The Office concluded that caffeine had not been shown to be an effective analgesic adjuvant when combined with APAP alone. This decision was based on the Office's conclusion that the statistically significant differences between the caffeinated and non-caffeinated analgesics observed in the crossover headache studies could be due to a biasing carryover effect. The Office also rejected previously submitted relative potency bioassay studies on the basis that most did not demonstrate statistically significant differences between APAP/caffeine combinations versus APAP alone. Moreover, the Office, in its April 1995 Feedback Letter, advised BMS that it would recommend to the Commissioner that the single dose of caffeine considered Generally Recognized As Safe (GRAS) for use as an analgesic adjuvant be established at 64 or 65mg, rather than the 150mg proposed in the Agency's Proposed Rule. This recommendation was based upon the Office's conclusion that it would be "prudent" to limit the caffeine dose on the theoretical basis that analgesics containing more than 65mg of caffeine per analgesic dose might foster analgesic misuse. In order to reduce this potential risk, the Office concluded that "the final monograph will include the minimum effective dose of caffeine, as established by the data, as the maximum allowed safe dose until such time as more definitive studies of caffeine's ability to foster analgesic misuse are conducted."

On August 21, 1995, BMS submitted a comprehensive response to the Office's 1995 feedback letter setting forth the scientific basis supporting the Category I status of caffeine 130mg as an analgesic adjuvant in combination with APAP

alone. In addition, BMS concluded that there was no evidence that analgesics containing 130mg of caffeine would promote analgesic misuse any more than those containing 64 or 65mg per dose or those containing no caffeine at all. Thus, there was no adequate scientific or legal basis to limit the acceptable caffeine dose for analgesics to 65mg, particularly when a large body of the data supporting the efficacy of caffeine was derived using a 130mg dose of caffeine.

In 1997, FDA again reviewed caffeine 130mg safety as part of its review of NDA 20-802 for Excedrin<sup>®</sup> Migraine. Three adequate and well-controlled clinical studies examined the safety and efficacy of single dose Excedrin<sup>®</sup> Migraine (ASA 500mg, APAP 500mg, caffeine 130mg) versus placebo for the pain associated with migraine headache. In July 1997, the NDA was the subject of a joint meeting of the Advisory Committees on Nonprescription Drugs and Arthritis Drugs, with representation from the Peripheral and Central Nervous System Drugs Advisory Committee. The Committees voted to approve the application, which was approved in January 1998 with a dosing regimen of 2 tablets (ASA 500mg, APAP 500mg, caffeine 130mg) every 6 hours, not to exceed 8 tablets in 24 hours. On October 7, 1999, Supplement No. 002 to NDA 20-802 was approved to expand the indication to treat the entire migraine complex, with a dosing regimen in line with prescription migraine treatments, *i.e.*, 2 tablets in a 24-hour period.

Additionally, BMS conducted three new clinical trials, one in a tension headache model and two in a dental model. These three studies were designed to conclusively establish caffeine adjuvancy with APAP. As such, the new tension headache study was conducted as a parallel group study designed to confirm the earlier crossover studies, thereby addressing the Agency's concern about potential carryover effect. The two new parallel group dental studies were conducted to supplement the earlier dental study.

The individual study reports for these trials are included in Appendices A, B and C of this Citizen Petition. The efficacy data from these three trials, as well as data from previously submitted trials, are presented in this integrated summary.

### **1.3 Scope Of This Summary**

This document includes data from three new, parallel, double-blind, randomized, placebo-controlled trials that demonstrate caffeine adjuvancy with APAP. One trial was conducted in the tension headache model (HPD-H203) and two trials were conducted in the dental pain model (HPD-D104 and HPD-D105). The new tension headache trial (HPD-H203), was conducted to confirm results of the earlier crossover design headache trials.

Data from these three new trials confirm the positive caffeine adjuvancy findings of previously submitted studies in headache, dental, and postpartum/bioassay pain models.

Overall, BMS has completed a total of 17 clinical studies that specifically examined the analgesic adjuvancy of caffeine in combination with APAP. Fourteen (14) of these studies have previously been submitted to FDA. The 17 studies are summarized in Table 1.0, where they are classified in two ways. First they are classified as either head-to-head direct comparison studies, or as bioassay relative potency comparison studies, based on the analytical methodology employed to evaluate response differences between treatments. The studies are further classified according to the pain model investigated: tension-type headache pain, postoperative dental pain, and postpartum pain.

Table 1.0 BMS Clinical Study Program Caffeine's Analgesic Adjuvancy With Acetaminophen								
Pain Model Study No.	Study Design Features <sup>A</sup>	Subjects N	Treatment Groups			Study Dates	Submission Dates To FDA Initial (Follow-Up)	
			No. <sup>B</sup>	APAP mg	APAP mg +CAF mg			
<b>Head-to-Head Direct Comparison Studies</b>								
<b>Tension-Type Headache Pain</b>								
HPD-H203	DB, PG, R, PC	1104	3	1000	1000 +130	10/97-5/98	NEW	
170-01-88	DB, CO, R, PC	441	3	1000	1000 +130	2/88-1/89	11/16/89 (5/93, 5/95)	
170-02-88	DB, CO, R, PC	442	3	1000	1000 +130	2/88-10/88	11/16/89 (5/93, 5/95)	
<b>Postoperative Dental Pain</b>								
HPD-D104	DB, PG, R, PC	1009	3	1000	1000 +130	3/97-12/97	NEW	
HPD-D105	DB, PG, R, PC	1015	3	1000	1000 +65	4/97-12/97	NEW	
171-01-88	DB, PG, R, PC	534	3	1000	1000 +130	1/88-9/88	11/16/89 (5/93)	
<b>Bioassay Relative Potency Comparison Studies</b>								
<b>Postpartum Pain</b>								
2255	DB, PG, R, PC	739	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	77-79	9/27/82 (11/83, 2/85, 11/89, 5/93, 5/95)	
2576	DB, PG, R, PC	699	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	7/79-6/81	9/27/82 (11/83, 2/85, 11/89, 5/93)	
2577	DB, PG, R, PC	227	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	9/79-9/81	9/27/82 (11/83, 2/85, 11/89, 5/93)	
2578	DB, PG, R, PC	373	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	11/79-2/82	9/27/82 (11/83, 2/85, 11/89, 5/93)	
2579	DB, PG, R, PC	434	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	1/80-3/81	9/27/82 (11/83, 2/85, 11/89, 5/93)	
2580	DB, PG, R, PC	538	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	4/80-4/81	9/27/82 (11/83, 2/85, 11/89, 5/93)	
2581	DB, PG, R, PC	414	7	500, 1000, 1500	500, 1000, 1500 +65, +130, +195	1985	10/30/1986	

Table 1.0 (cont.) BMS Clinical Study Program Caffeine's Analgesic Adjuvancy With Acetaminophen							
Pain Model Study No.	Study Design Features <sup>A</sup>	Subjects N	Treatment Groups			Study Dates	Submission Dates To FDA Initial (Follow-Up)
<b>Postoperative Dental Pain</b>							
2569	DB, PG, R	173	4		1000, 1500 +130, +195	10/80-10/81	9/27/82 (11/89, 5/93)
2711	DB, CO, R, PC	48	5	500	0, 500 +65, +65		9/27/82 (11/83, 2/85)
2570	DB, PG, R, PC	196	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	2/80-9/81	10/30/86 (11/89, 5/93)
2571	DB, PG, R, PC	386	7	500, 1000, 2000	500, 1000, 2000 +65, +130, +260	3/80-1/83	10/30/86 (11/89, 5/93)

<sup>A</sup> DB = Double-Blind; PG = Parallel-Groups; CO = Crossover; R = Randomized; PC = Placebo-Controlled

<sup>B</sup> Number of treatment groups includes Placebo treatment group for each study, except Postoperative Dental Pain Study No. 2569, which was not placebo-controlled

#### 1.4 Focus Of This Summary

This document provides two levels of evidence supporting the adjuvancy of caffeine when combined with APAP. Primary support consists of six head-to-head trials. Three of these trials are the new trials HPD-H203, HPD-D104, and HPD-D105. The other three trials (170-01-88, 170-02-88, and 171-01-88) were submitted to the FDA in 1989.

Secondary support includes data from 11 bioassay studies that were submitted to the agency in 1982 and 1986.

#### Primary Support – Head-to-Head Trials

HPD-H203 (tension-type headache) HPD-D104 (dental pain) and HPD-D105 (dental pain) are new head-to-head studies, as mentioned above, while Studies 170-01-88, 170-02-88 (tension-type headache) and 171-01-88 (dental pain) are previously submitted APAP/CAF v. APAP head-to-head studies. These six studies, considered individually, provide substantial evidence of the analgesic adjuvant effect of caffeine given in combination with APAP, and when pooled allow an accurate estimate of the magnitude of caffeine's adjuvant effect. This estimate is consistent with the prior published estimate described above.

These six head-to-head comparisons of APAP/CAF with APAP alone were adequately designed and powered to show both the analgesic adjuvant effect of caffeine and superiority of the active treatments over placebo in the different pain models. Considered together, they constitute substantial evidence of the analgesic adjuvancy of caffeine in combination with APAP and support Category I status in the Internal Analgesic Monograph.

## **Secondary Support - Bioassay Trials**

In addition to the six head-to-head studies mentioned above, BMS has completed a total of 11 double-blind, randomized, placebo-controlled, parallel groups, relative potency single-dose bioassays comparing multiples of APAP/CAF in a fixed 500 mg/65 mg ratio with corresponding multiples of APAP alone. Four of these studies were conducted in a dental pain model (Studies 2711 and 2569-2571), while the other seven were conducted in a postpartum pain model (Studies 2255 and 2576-2581).

FDA concluded that in the aggregate, these bioassay trials do not constitute substantial evidence that caffeine potentiates the analgesic effect of APAP. The Agency's criticism was that intra-study APAP/CAF v. APAP pairwise comparisons by APAP dose did not show consistent superiority for the combination. However, it should be noted that the studies were neither designed nor powered to sustain such analyses.

The BMS dental pain relative potency studies showed weak and inconsistent evidence of an analgesic adjuvant effect of caffeine combined with APAP, probably as a result of lesser sensitivity of the dental pain model. To the extent that these studies are supportive of the analgesic adjuvancy of caffeine combined with APAP, they will be discussed briefly, but are not the primary focus of this summary.

The postpartum studies, on the other hand, when considered together, provide strong evidence of caffeine's analgesic adjuvancy effect for APAP, and these studies will be considered in greater detail below in Section 4.3.

## **2.0 METHODS**

### **2.1 Pain Models**

Headache and dental models were used to compare the analgesic effectiveness of APAP/CAF with that of APAP in the three new studies as they are representative of painful conditions common in the general population which are usually treated with OTC analgesics (single ingredient or combination formulations).

The headache model utilized the muscle-contraction (tension-type) headache indication. In the new 1997 parallel-groups study, subjects with headache pain were selected using diagnostic criteria for tension-type headache developed by the International Headache Society (IHS)<sup>7</sup>. In the 1988 crossover studies, subjects with headache pain were selected according to diagnostic criteria for tension-type headache developed by the Ad Hoc Committee on the Classification of Headache, the precursor to the IHS criteria<sup>8</sup>.

Studies using the dental pain model enrolled subjects experiencing postoperative pain secondary to one or more of a group of specific dental surgical procedures (e.g., third molar extraction), performed under general or local anesthesia.

The six studies in the two pain models that constitute primary support for caffeine's ability to potentiate the analgesic effectiveness of APAP were single-dose, randomized, double-blind, and placebo-controlled. Active treatments were always APAP/CAF and APAP. Inclusion criteria included: moderate or severe pain, no complicating illness(es), and the ability to tolerate study medications. In general, other analgesics were prohibited from four to eight hours before and during study participation.

## **2.2 Analgesic Response Measures**

All of the six primary studies followed standard general methodological guidelines and outcome measures for evaluation of analgesic drugs. After giving informed consent, subjects were instructed to evaluate baseline pain intensity on a 4-point ordinal scale with 0 representing no pain (none) and 3, (severe pain), at baseline and to evaluate pain again, using the same scale, after ingesting a single dose of study drug. Measurements were collected hourly for four hours. Studies HPD-H203, -D104 and -D105 also included pain evaluations every 15 minutes for the first 90 minutes post-dosing. At post-medication times, subjects were also asked to evaluate the amount of relief afforded by the study medication (with respect to baseline pain) using a five-point pain relief scale calibrated from 0 (none) to 4 (complete). Subjects were permitted to take rescue medication (any OTC or prescription medication prescribed by their physicians) if study medication did not provide sufficient relief from pain.

Several widely-used and generally accepted summary measures of analgesic effect were derived from the primary outcome measures (pain intensity and pain relief). Pain intensity indices included: difference from baseline for pain intensity score at each post-medication observation point (pain intensity difference, or PID); maximum PID for the observation period (MAXPID); and the weighted sum (weighting for each evaluation was proportional to the time elapsed from the prior evaluation point) of PID scores during the four-hour study period (SPID). Pain relief indices included: magnitude of pain relief at each post-medication observation point (PAR); maximum PAR for the observation period (MAXPAR); and the weighted sum (weighted as for SPID) of PAR scores during the four-hour study period (total pain relief or TOTPAR).

### **2.3 Effectiveness Analysis Methods for Individual Studies and for Pooled Study Results**

In this report, individual study results from both the parallel and crossover studies are presented as protocol specified analyses.

For the parallel tension headache and dental studies, pain relief scores and all scores calculated as differences from baseline (including pain intensity difference from baseline), were analyzed for each time point using two-way analysis of covariance with treatment group and investigator as the two main factors and baseline pain intensity as the covariate.

For the crossover tension headache studies, pain relief scores and all scores calculated as differences from baseline (including pain intensity difference from baseline) were analyzed at each time point using two-way analysis of variance with factors for subject within sequence, period, and treatment. Expanded models were used to assess the influence of other factors, including investigative site, and the possibility of carryover effect from the first period to the second period. Additional terms considered in the expanded models included, investigator-by-period; investigator-by-treatment; and period-by-sequence interactions.

In addition to the protocol specified analyses for the crossover tension headache studies, analyses using data from the first treated headache only and from the first period treated headaches only were carried out. These analyses were conducted to: a) address FDA criticism that carryover effects may have biased the primary analyses, and b) facilitate pooling of the results with those from the parallel design tension headache study. Individual study results for the first treated headache are presented in Appendix 1. Individual study results using both first period treated headaches were similar to those using only the first treated headache and are not presented.

To integrate results of the individual tension headache studies, data from the first headache only for the crossover studies were pooled with those of the parallel-groups design study. The major efficacy variables, pain relief and pain intensity difference from baseline were analyzed using an analysis of covariance model with factors for protocol, investigator, treatment group, and baseline pain intensity as the covariate.

To integrate results of the parallel-groups design dental pain studies, an analysis of covariance model was used with factors for protocol, investigator, treatment group, and baseline pain intensity as the covariates. Caffeine adjuvancy in the pooled database was analyzed using three levels for the treatment group: APAP/CAF, APAP alone, and placebo. This analysis concentrates on the effect of adding caffeine (65mg or 130mg) to APAP, regardless of caffeine dose.

### 3.0 DEMOGRAPHIC AND BASELINE PAIN CHARACTERISTICS OF STUDY POPULATIONS

#### 3.1 Tension Headache

Table 3.1 summarizes demographic attributes and baseline pain intensity for the parallel-groups study, HPD-H203, together with corresponding information obtained from the pooled crossover studies, 170-01-88 and 170-02-88 (first headache only). There were no significant intra-study, inter-treatment group or inter-study differences ( $p > 0.12$ ) for these variables, nor did the pooled treatment groups differ significantly with respect to any of these variables. Subjects in the three studies ranged in age from 18 to 77 years of age, with a mean of 34.3 years. Most of the subjects were female (74%), white (84%), and experienced moderate headache pain intensity (79%) at baseline.

<b>Characteristic</b>	<b>APAP1000/ CAF130 (N=788)</b>	<b>APAP1000 (N=796)</b>	<b>Placebo (N=401)</b>	<b>Total (N=1985)</b>	<b>p-value<sup>B</sup></b>
<b>Gender</b>					0.298
Male	209 (26.5%)	196 (24.6%)	115 (28.7%)	520 (26.2%)	
Female	579 (73.5%)	600 (75.4%)	286 (71.3%)	1465 (73.8%)	
<b>Race</b>					0.322
Caucasian	671 (85.2%)	674 (84.7%)	329 (82.0%)	1674 (84.3%)	
Black	71 (9.0%)	65 (8.2%)	43 (10.7%)	179 (9.0%)	
Hispanic	40 (5.1%)	51 (6.4%)	25 (6.2%)	116 (5.8%)	
Other	6 (0.8%)	6 (0.8%)	4 (1.0%)	16 (0.8%)	
<b>Age</b>					0.947
Mean	34.3	34.3	34.2	34.3	
SD	10.01	9.92	10.01	9.97	
Range	18-77	18-67	18-65	18-77	
<b>Baseline Pain Intensity</b>					0.470
None	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.1%)	
Mild	1 (0.1%)	2 (0.3%)	0 (0.0%)	3 (0.2%)	
Moderate	632 (80.2%)	629 (79.0%)	316 (78.8%)	1577 (79.4%)	
Severe	155 (19.7%)	165 (20.7%)	84 (20.9%)	404 (20.4%)	

<sup>A</sup>First headache only for studies 170-01-88 and 170-02-88

<sup>B</sup>P-value for age from analysis of variance model with factors of protocol, site and treatment group. P-values for gender, race, baseline pain intensity from Cochran-Mantel-Haenszel test for general association, adjusted for protocol and site. For the variable race, the p-value was calculated after combining the Black, Hispanic, and Other categories.

### 3.2 Dental Pain

Demographic attributes and baseline pain intensity for the pooled dental pain studies (HPD-D104, HPD-D105, and 171-01-88) are summarized in Table 3.2.

The treatment groups in the individual studies did not differ significantly with respect to the various demographic attributes or baseline pain intensity, nor did the pooled treatment groups differ significantly for any of these variables. Subjects in the three studies ranged in age from 15 to 64 years, with a mean of 23.7 years. Most of the subjects were female (58%), white (73%), and experienced moderate pain intensity at baseline (73%).

<b>Characteristic</b>	<b>APAP1000/ CAF65/130<sup>B</sup> (N=1020)</b>	<b>APAP1000 (N=1021)</b>	<b>Placebo (N=514)</b>	<b>Total (N=2555)</b>	<b>p-value<sup>A</sup></b>
Gender					0.577
Male	428 (42.0%)	430 (42.1%)	203 (39.5%)	1061 (41.5%)	
Female	592 (58.0%)	591 (57.9%)	311 (60.5%)	1494 (58.5%)	
Race					0.571
Caucasian	758 (74.3%)	750 (73.5%)	369 (71.8%)	1877 (73.5%)	
Black	98 (9.6%)	90 (8.8%)	52 (10.1%)	240 (9.4%)	
Hispanic	128 (12.5%)	136 (13.3%)	68 (13.2%)	332 (13.0%)	
Other	36 (3.5%)	45 (4.4%)	25 (4.9%)	106 (4.1%)	
Age					0.157
Mean	23.5	24.0	23.5	23.7	
SD	6.68	7.07	5.99	6.71	
Range	15-60	15-64	15-55	15-64	
Baseline Pain Intensity					0.962
Moderate	742 (72.7%)	748 (73.3%)	375 (73.0%)	1865 (73.0%)	
Severe	278 (27.3%)	273 (26.7%)	139 (27.0%)	690 (27.0%)	

<sup>A</sup> P-value for age from analysis of variance model with factors of protocol, site and treatment group. P-value for gender, race, baseline pain intensity from Cochran-Mantel-Haenszel test for general association, adjusted for protocol and site. For the variable race, the p-value was calculated after combining the following categories: Black, Hispanic, and Other.

<sup>B</sup> APAP1000/CAF65/130 is the pool of treatment groups APAP1000/CAF130 (HPD-D104 and 171-01-88) and APAP1000/CAF65 (HPD-D105).

## 4.0 EFFICACY RESULTS

### 4.1 Efficacy Results for the Tension Headache Studies

Table 4.1 summarizes design attributes, treatment-assignment, study drug doses and outcome measures for the three head-to-head tension-type headache studies.

<b>Table 4.1</b>				
<b>Tension-Type Headache Studies HPD-H203, 170-01-88, and 170-02-88</b>				
<b>Description Year Conducted</b>	<b>Subjects Total N Treatment Sequence N*</b>	<b>APAP/CAF Dose mg</b>	<b>APAP Dose mg</b>	<b>Outcome Measures</b>
HPD-H203 - Multi-Center Randomized (2:2:1) Placebo-Controlled Parallel Groups 1997	1104 438 APAP/CAF 441 APAP 225 PLACEBO	1000/130	1000	PID PAR SPID TOTPAR
170-01-88 - Multi-center Randomized (2:2:1) Placebo-Controlled 2-Period Incomplete Crossover 1988	441 129 APAP/CAF--APAP 136 APAP--APAP/CAF 44 APAP/CAF--PLACEBO 45 PLACEBO--APAP/CAF 43 APAP--PLACEBO 44 PLACEBO--APAP	1000/130	1000	PID PAR SPID TOTPAR
170-02-88 - Multi-center Randomized (2:2:1) Placebo-Controlled 2-Period Incomplete Crossover 1988	442 130 APAP/CAF--APAP 133 APAP--APAP/CAF 48 APAP/CAF--PLACEBO 44 PLACEBO--APAP/CAF 44 APAP--PLACEBO 43 PLACEBO--APAP	1000/130	1000	PID PAR SPID TOTPAR

\*For crossover studies, 1<sup>st</sup> period treatment – 2<sup>nd</sup> period treatment.

Efficacy results for the new parallel-groups design tension headache study, HPD-H203 demonstrated caffeine adjuvancy with APAP and corroborate findings in the two earlier crossover design tension headache studies, 170-01-88 and 170-02-88. All analyses for the individual studies and for the pooled studies were performed for the set of all randomized subjects who had data (intent-to-treat-population). Complete individual study results for 170-01-88 and 170-02-88 were previously submitted to the FDA in 1989. Complete individual study results for HPD-H203 are provided in further detail in Appendix A of this submission.

#### 4.1.1 Pain Intensity Difference (PID)

In study HPD-H203, APAP/CAF was statistically superior to APAP alone from 75 minutes through 4 hours, and superior to placebo from 30 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPID and SPID4 (Table 4.1.1.1 and Figure 4.1.1). Similarly, in studies 170-01-88 and 170-02-88, APAP/CAF was statistically superior to APAP alone and to placebo for PID from 30 minutes through 4 hours, MAXPID, SPID1, and SPID4 (Tables 4.1.1.2-4.1.1.3 and Figure 4.1.1). Mean PID, MAXPID, and SPID estimates from analyses of the first-treated-headache only and for the two headaches treated during the first treatment period for the crossover studies 170-

01-88 and 170-02-88 (Appendix 1) are similar to those obtained when all treated headaches are analyzed under the crossover design.

The pooled efficacy results for HPD-H203, 107-01-88, and 170-02-88 show clear, consistent evidence of significantly superior effectiveness of APAP/CAF over both APAP alone and placebo for reducing tension-type headache pain intensity. The APAP/CAF combination was significantly superior to APAP alone from 60 minutes through 4 hours and placebo from 30 minutes through 4 hours. APAP/CAF was also statistically superior to APAP and placebo for MAXPID, SPID1, and SPID4 (Table 4.1.1.4 and Figure 4.1.1).

The data show clinically significant treatment effects favoring APAP/CAF over APAP alone. The incremental mean SPID4 treatment effect for APAP/CAF over that of APAP alone, calculated as  $100 \times [(\text{mean SPID4 APAP/CAF} - \text{mean SPID4 placebo}) / (\text{mean SPID4 APAP} - \text{mean SPID4 placebo})]$  is about 62% for the pooled results; thus indicating a 62% decrease in pain intensity versus APAP alone in the tension headache model.

Table 4.1.1.1  
 TENSION HEADACHE -- PROTOCOL HPD-H203  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	P-VALUES @			OVERALL TREATMENT EFFECT	P-VALUES @		
	APAP1000/CAF130 MEAN (STD) N=438	APAP1000 MEAN (STD) N=440	PLACEBO MEAN (STD) N=225		APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY DIFFERENCE (PID) *							
15 MIN	0.1 ( 0.27)	0.1 ( 0.30)	0.1 ( 0.36)	0.843	0.565	0.881	0.746
30 MIN	0.4 ( 0.61)	0.4 ( 0.62)	0.3 ( 0.57)	0.097	0.831	0.041	0.061
45 MIN	0.8 ( 0.76)	0.8 ( 0.75)	0.6 ( 0.73)	0.034	0.599	0.011	0.035
60 MIN	1.1 ( 0.84)	1.0 ( 0.80)	0.9 ( 0.81)	0.002	0.073	<0.001	0.048
75 MIN	1.3 ( 0.84)	1.2 ( 0.83)	1.0 ( 0.86)	<0.001	0.027	<0.001	0.008
90 MIN	1.5 ( 0.84)	1.4 ( 0.83)	1.1 ( 0.92)	<0.001	0.007	<0.001	0.002
2 HRS	1.7 ( 0.84)	1.5 ( 0.86)	1.3 ( 0.93)	<0.001	0.008	<0.001	<0.001
3 HRS	1.8 ( 0.79)	1.6 ( 0.87)	1.3 ( 1.02)	<0.001	0.004	<0.001	<0.001
4 HRS	1.9 ( 0.80)	1.7 ( 0.87)	1.4 ( 1.04)	<0.001	0.010	<0.001	<0.001
MAX PID	1.9 ( 0.71)	1.8 ( 0.75)	1.5 ( 0.88)	<0.001	0.009	<0.001	<0.001
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #							
1-HOUR	0.6 ( 0.53)	0.6 ( 0.52)	0.5 ( 0.52)	0.017	0.387	0.005	0.034
4-HOUR	5.8 ( 2.58)	5.3 ( 2.75)	4.4 ( 3.17)	<0.001	0.007	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR,  
 AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 4.1.1.2  
 TENSION HEADACHE -- PROTOCOL 170-01-88  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=344	APAP1000 MEAN (STD) N=345	PLACEBO MEAN (STD) N=168	OVERALL TREATMENT EFFECT	P-VALUES *		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
BASELINE PAIN @ INTENSITY	2.3 (0.36)	2.3 (0.34)	2.3 (0.38)	0.651	0.517	0.399	0.697
PAIN INTENSITY @ DIFFERENCE (PID)							
30 MIN	0.4 (0.50)	0.3 (0.46)	0.2 (0.38)	<0.001	0.014	<0.001	0.061
1 HR	0.9 (0.69)	0.7 (0.64)	0.7 (0.60)	<0.001	<0.001	<0.001	0.838
2 HRS	1.3 (0.72)	1.2 (0.69)	1.1 (0.73)	0.002	0.005	0.002	0.291
3 HRS	1.6 (0.69)	1.5 (0.72)	1.4 (0.76)	0.004	0.013	0.003	0.210
4 HRS	1.7 (0.70)	1.6 (0.74)	1.5 (0.80)	0.001	0.030	<0.001	0.041
MAXPID	1.8 (0.65)	1.7 (0.67)	1.6 (0.72)	<0.001	0.011	<0.001	0.060
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #							
1-HOUR	0.6 (0.56)	0.5 (0.51)	0.4 (0.45)	<0.001	<0.001	<0.001	0.311
4-HOUR	5.3 (2.39)	4.8 (2.38)	4.4 (2.49)	<0.001	0.001	<0.001	0.144

\* P-VALUES ARE BASED ON THE FOLLOWING CROSSOVER MODEL:  
 RESPONSE = OVERALL MEAN + SUBJECT WITHIN SEQUENCE EFFECT + PERIOD EFFECT + TRT EFFECT +  
 ERROR

@ ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 4.1.1.3  
TENSION HEADACHE -- PROTOCOL 170-02-88  
PAIN INTENSITY DIFFERENCE FROM BASELINE  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=348	APAP1000 MEAN (STD) N=346	PLACEBO MEAN (STD) N=173	OVERALL TREATMENT EFFECT	P-VALUES*		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
BASELINE PAIN @							
INTENSITY	2.3 (0.33)	2.3 (0.35)	2.3 (0.32)	0.756	0.780	0.581	0.455
PAIN INTENSITY @							
DIFFERENCE (PID)							
30 MIN	0.3 (0.45)	0.3 (0.44)	0.2 (0.38)	<0.001	0.005	<0.001	0.019
1 HR	0.8 (0.63)	0.7 (0.62)	0.5 (0.57)	<0.001	<0.001	<0.001	<0.001
2 HRS	1.3 (0.65)	1.2 (0.68)	0.9 (0.71)	<0.001	<0.001	<0.001	<0.001
3 HRS	1.6 (0.65)	1.5 (0.69)	1.2 (0.79)	<0.001	<0.001	<0.001	<0.001
4 HRS	1.8 (0.67)	1.6 (0.73)	1.3 (0.83)	<0.001	<0.001	<0.001	<0.001
MAXPID	1.8 (0.60)	1.7 (0.67)	1.4 (0.77)	<0.001	<0.001	<0.001	<0.001
SUM OF PAIN							
INTENSITY							
DIFFERENCE							
(SPID) #							
1-HOUR	0.6 (0.50)	0.5 (0.49)	0.3 (0.44)	<0.001	<0.001	<0.001	<0.001
4-HOUR	5.3 (2.15)	4.7 (2.29)	3.8 (2.51)	<0.001	<0.001	<0.001	<0.001

\* P-VALUES ARE BASED ON THE FOLLOWING CROSSOVER MODEL:

RESPONSE = OVERALL MEAN + SUBJECT WITHIN SEQUENCE EFFECT + PERIOD EFFECT + TRT EFFECT + ERROR

@ ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 4.1.1.4  
 TENSION HEADACHE -- POOLED DATA  
 STUDIES HPD-H203, 170-01-88, 170-02-88<sup>a</sup>  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130		APAP1000		PLACEBO		OVERALL TREATMENT EFFECT	P-VALUES @		
	N	MEAN (STD)	N	MEAN (STD)	N	MEAN (STD)		APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY DIFFERENCE (PID) *										
15 MIN	438	0.1 ( 0.27)	440	0.1 ( 0.30)	225	0.1 ( 0.36)	0.843	0.565	0.881	0.746
30 MIN	787	0.4 ( 0.59)	796	0.4 ( 0.60)	401	0.3 ( 0.55)	<0.001	0.235	<0.001	0.003
45 MIN	438	0.8 ( 0.76)	440	0.8 ( 0.75)	225	0.6 ( 0.73)	0.034	0.599	0.011	0.035
60 MIN	787	1.0 ( 0.82)	795	0.9 ( 0.79)	401	0.8 ( 0.81)	<0.001	0.002	<0.001	0.001
75 MIN	438	1.3 ( 0.84)	440	1.2 ( 0.83)	225	1.0 ( 0.86)	<0.001	0.027	<0.001	0.008
90 MIN	438	1.5 ( 0.84)	440	1.4 ( 0.83)	225	1.1 ( 0.92)	<0.001	0.007	<0.001	0.002
2 HRS	787	1.5 ( 0.84)	796	1.4 ( 0.86)	401	1.1 ( 0.93)	<0.001	0.001	<0.001	<0.001
3 HRS	783	1.7 ( 0.80)	790	1.6 ( 0.86)	401	1.3 ( 0.97)	<0.001	0.002	<0.001	<0.001
4 HRS	782	1.8 ( 0.77)	789	1.6 ( 0.89)	400	1.4 ( 1.00)	<0.001	<0.001	<0.001	<0.001
MAX PID	787	1.9 ( 0.71)	796	1.7 ( 0.78)	401	1.5 ( 0.87)	<0.001	<0.001	<0.001	<0.001
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #										
1-HOUR	787	0.6 ( 0.56)	795	0.5 ( 0.56)	401	0.4 ( 0.54)	<0.001	0.021	<0.001	<0.001
4-HOUR	787	5.5 ( 2.58)	796	5.0 ( 2.78)	401	4.2 ( 3.06)	<0.001	<0.001	<0.001	<0.001

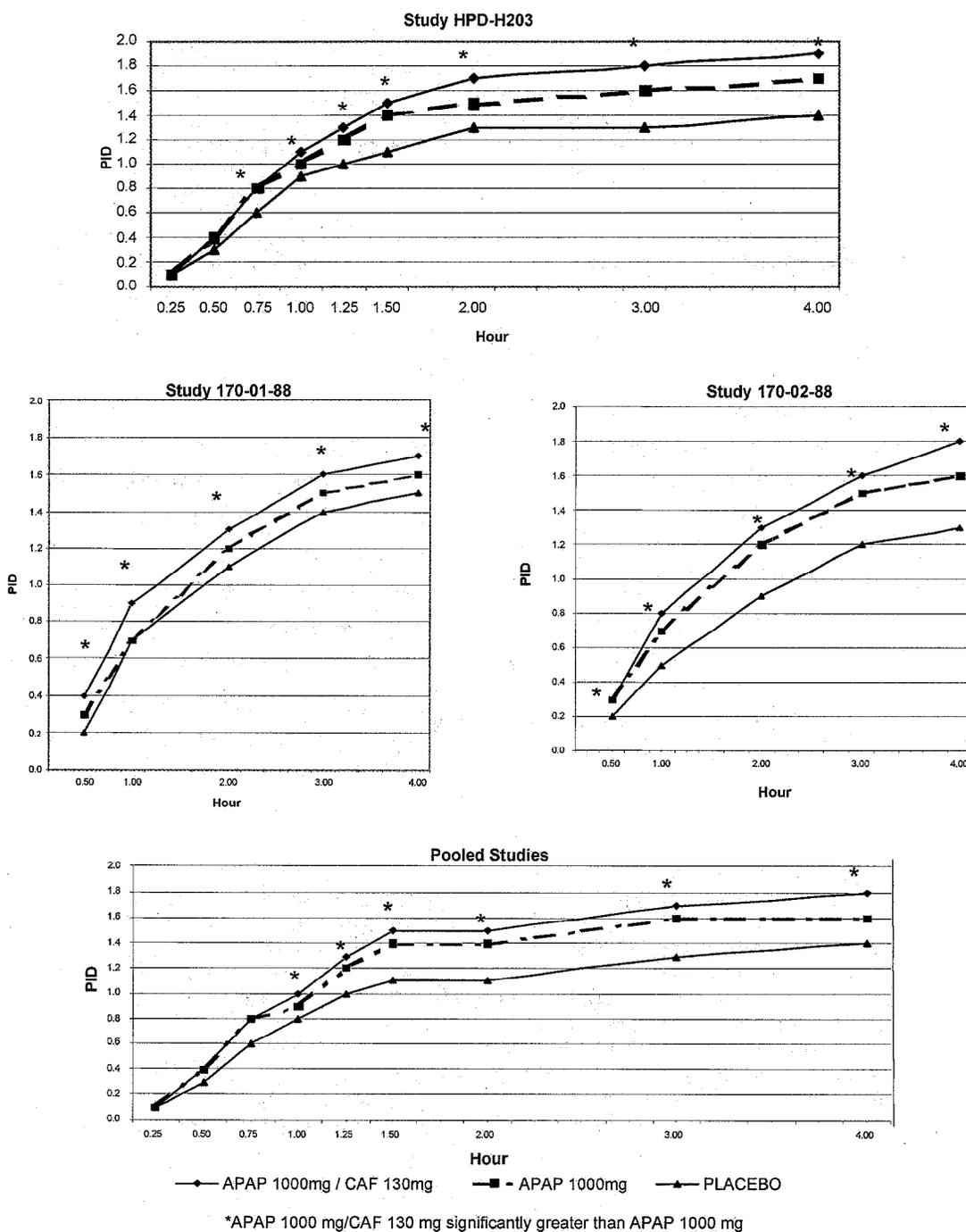
@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR PROTOCOL, TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

<sup>a</sup> FIRST HEADACHE ONLY FOR STUDIES 170-01-88 AND 170-02-88

# SPID=WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Figure 4.1.1  
Pain Intensity Difference  
Tension Headache (ITT)



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#### 4.1.2 Pain Relief (PAR)

In study HPD-H203, there was significantly greater pain relief for APAP/CAF versus APAP alone for PAR from 75 minutes through 4 hours, and versus placebo from 45 minutes through 4 hours. APAP/CAF was statistically superior to APAP alone and to placebo for MAXPAR and TOTPAR4 (Table 4.1.2.1 and Figure 4.1.2). In studies 170-01-88 and 170-02-88, APAP/CAF was significantly superior to APAP and placebo for PAR from 30 minutes through 4 hours, and for MAXPAR, TOTPAR1, and TOTPAR4 (Tables 4.1.2.2-4.1.2.3 and Figure 4.1.2). Mean PAR, MAXPAR, and TOTPAR estimates from analyses of the first-treated-headache only or for the two headaches treated during the first treatment period for the crossover studies 170-01-88 and 170-02-88 (Appendix 1) are similar to those obtained when all treated headaches are analyzed under the crossover design.

In the pooled analyses of the headache studies, APAP/CAF was statistically superior to APAP alone and to placebo for PAR at 30 minutes and from 60 minutes through 4 hours, as well as for MAXPAR, TOTPAR1 and TOTPAR4 (Table 4.1.2.4 and Figure 4.1.2).

These results also showed clinically significant treatment effects favoring APAP/CAF over APAP alone. The incremental mean TOTPAR4 treatment effect for APAP/CAF over that of APAP alone, calculated as  $100 \times [(\text{mean TOTPAR4 APAP/CAF} - \text{mean TOTPAR4 placebo}) / (\text{mean TOTPAR4 APAP} - \text{mean TOTPAR4 placebo})]$  is about 64% for the pooled results; thus indicating a 64% increase in pain relief versus APAP alone in the tension headache model.

Table 4.1.2.1  
TENSION HEADACHE -- PROTOCOL HPD-H203  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=438	APAP1000 MEAN (STD) N=440	PLACEBO MEAN (STD) N=225	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
15 MIN	0.2 ( 0.54)	0.2 ( 0.58)	0.3 ( 0.66)	0.338	0.759	0.151	0.235
30 MIN	0.9 ( 1.08)	0.8 ( 1.08)	0.7 ( 1.01)	0.155	0.318	0.055	0.272
45 MIN	1.5 ( 1.36)	1.5 ( 1.32)	1.3 ( 1.32)	0.063	0.602	0.021	0.06
60 MIN	2.2 ( 1.44)	2.0 ( 1.39)	1.8 ( 1.47)	0.003	0.148	<0.001	0.023
75 MIN	2.6 ( 1.41)	2.4 ( 1.42)	2.0 ( 1.55)	<0.001	0.036	<0.001	0.002
90 MIN	2.9 ( 1.35)	2.7 ( 1.41)	2.2 ( 1.60)	<0.001	0.014	<0.001	<0.001
2 HRS	3.2 ( 1.28)	2.9 ( 1.41)	2.5 ( 1.64)	<0.001	0.005	<0.001	<0.001
3 HRS	3.4 ( 1.18)	3.1 ( 1.42)	2.6 ( 1.69)	<0.001	<0.001	<0.001	<0.001
4 HRS	3.4 ( 1.20)	3.2 ( 1.43)	2.6 ( 1.75)	<0.001	0.004	<0.001	<0.001
MAXPAR	3.5 ( 1.07)	3.3 ( 1.22)	2.9 ( 1.52)	<0.001	0.01	<0.001	<0.001
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.2 ( 0.97)	1.1 ( 0.95)	1.0 ( 0.98)	0.056	0.342	0.016	0.104
4-HOUR	11.0 ( 3.99)	10.2 ( 4.56)	8.6 ( 5.45)	<0.001	0.004	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Table 4.1.2.2  
 TENSION HEADACHE -- PROTOCOL 170-01-88  
 PAIN RELIEF  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130			APAP1000			PLACEBO			P-VALUES *		
	MEAN (STD) N=344	MEAN (STD) N=345	MEAN (STD) N=168	OVERALL TREATMENT EFFECT	APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO					
PAIN RELIEF @												
30 MIN	1.1 (0.94)	0.8 (0.93)	0.7 (0.79)	<0.001	<0.001	<0.001	0.299					
1 HR	2.0 (1.14)	1.6 (1.11)	1.5 (1.05)	<0.001	<0.001	<0.001	0.607					
2 HRS	2.6 (1.13)	2.3 (1.13)	2.2 (1.11)	<0.001	<0.001	<0.001	0.360					
3 HRS	3.0 (1.03)	2.8 (1.11)	2.6 (1.13)	<0.001	<0.001	<0.001	0.054					
4 HRS	3.2 (1.00)	3.1 (1.09)	2.9 (1.13)	<0.001	0.006	<0.001	0.019					
MAXPAR	3.3 (0.96)	3.1 (1.01)	3.0 (1.06)	<0.001	0.004	<0.001	0.027					
TOTAL PAIN RELIEF (TOTPAR) #												
1-HOUR	1.5 (0.99)	1.2 (0.96)	1.1 (0.86)	<0.001	<0.001	<0.001	0.415					
4-HOUR	10.4 (3.76)	9.4 (3.83)	8.8 (3.83)	<0.001	<0.001	<0.001	0.104					

\* P-VALUES ARE BASED ON THE FOLLOWING CROSSOVER MODEL:

RESPONSE = OVERALL MEAN + SUBJECT WITHIN SEQUENCE EFFECT + PERIOD EFFECT + TRT EFFECT + ERROR

@ ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORES

Table 4.1.2.3  
TENSION HEADACHE -- PROTOCOL 170-02-88  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=348	APAP1000 MEAN (STD) N=346	PLACEBO MEAN (STD) N=173	OVERALL TREATMENT EFFECT	P-VALUES *		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF @							
30 MIN	1.0 (0.92)	0.8 (0.88)	0.6 (0.78)	<0.001	0.002	<0.001	<0.001
1 HR	1.9 (1.10)	1.6 (1.05)	1.2 (0.99)	<0.001	<0.001	<0.001	<0.001
2 HRS	2.6 (1.05)	2.4 (1.09)	1.9 (1.16)	<0.001	<0.001	<0.001	<0.001
3 HRS	3.1 (0.97)	2.8 (1.08)	2.4 (1.26)	<0.001	<0.001	<0.001	<0.001
4 HRS	3.3 (0.96)	3.1 (1.08)	2.6 (1.30)	<0.001	<0.001	<0.001	<0.001
MAXPAR	3.4 (0.86)	3.2 (0.97)	2.7 (1.23)	<0.001	<0.001	<0.001	<0.001
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.4 (0.96)	1.2 (0.92)	0.9 (0.83)	<0.001	<0.001	<0.001	<0.001
4-HOUR	10.5 (3.45)	9.5 (3.68)	7.8 (4.12)	<0.001	<0.001	<0.001	<0.001

\* P-VALUES ARE BASED ON THE FOLLOWING CROSSOVER MODEL:

RESPONSE = OVERALL MEAN + SUBJECT WITHIN SEQUENCE EFFECT + PERIOD EFFECT + TRT EFFECT + ERROR

@ ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORES

TABLE 4.1.2.4  
 TENSION HEADACHE -- POOLED DATA  
 STUDIES HPD-H203, 170-01-88, 170-02-88<sup>a</sup>  
 PAIN RELIEF  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130		APAP1000		PLACEBO		OVERALL TREATMENT EFFECT	P-VALUES @		
	N	MEAN (STD)	N	MEAN (STD)	N	MEAN (STD)		APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN										
RELIEF *										
15 MIN	438	0.2 ( 0.54)	440	0.2 ( 0.58)	225	0.3 ( 0.66)	0.338	0.759	0.151	0.235
30 MIN	786	1.0 ( 1.12)	796	0.8 ( 1.07)	401	0.7 ( 1.01)	<0.001	0.016	<0.001	0.024
45 MIN	438	1.5 ( 1.36)	440	1.5 ( 1.32)	225	1.3 ( 1.32)	0.063	0.602	0.021	0.060
60 MIN	787	2.1 ( 1.41)	795	1.9 ( 1.37)	401	1.6 ( 1.42)	<0.001	0.003	<0.001	<0.001
75 MIN	438	2.6 ( 1.41)	440	2.4 ( 1.42)	225	2.0 ( 1.55)	<0.001	0.036	<0.001	0.002
90 MIN	438	2.9 ( 1.35)	440	2.7 ( 1.41)	225	2.2 ( 1.60)	<0.001	0.014	<0.001	<0.001
2 HRS	787	2.9 ( 1.33)	796	2.7 ( 1.41)	401	2.3 ( 1.57)	<0.001	<0.001	<0.001	<0.001
3 HRS	783	3.3 ( 1.20)	790	3.0 ( 1.38)	401	2.6 ( 1.60)	<0.001	<0.001	<0.001	<0.001
4 HRS	782	3.4 ( 1.18)	789	3.1 ( 1.40)	400	2.7 ( 1.65)	<0.001	<0.001	<0.001	<0.001
MAXPAR	787	3.5 ( 1.08)	796	3.3 ( 1.25)	401	2.9 ( 1.48)	<0.001	<0.001	<0.001	<0.001
TOTAL PAIN										
RELIEF										
(TOTPAR) #										
1-HOUR	786	1.3 ( 1.07)	795	1.2 ( 1.03)	401	1.0 ( 1.02)	<0.001	0.005	<0.001	0.002
4-HOUR	786	10.8 ( 4.11)	796	9.9 ( 4.58)	401	8.5 ( 5.22)	<0.001	<0.001	<0.001	<0.001

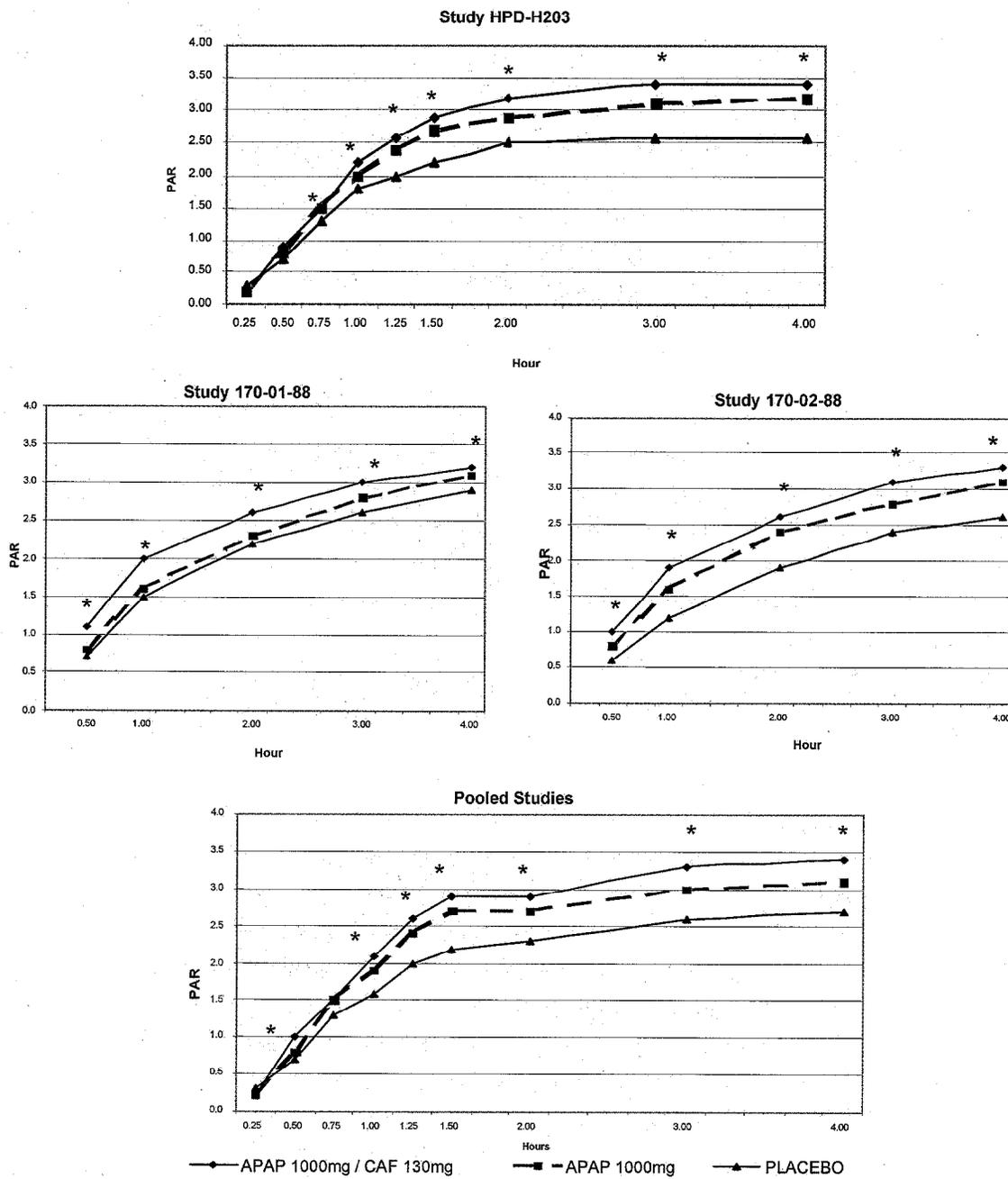
@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR PROTOCOL, TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

<sup>a</sup> FIRST HEADACHE ONLY FOR STUDIES 170-01-88 AND 170-02-88

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Figure 4.1.2  
Pain Relief  
Tension Headache (ITT)



\*APAP 1000 mg/CAF 130 mg significantly greater than APAP 1000 mg

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## 4.2 Efficacy Results for the Postoperative Dental Pain Studies

Table 4.2.1 summarizes design attributes, treatment assignment, study drug doses and outcome measures for the three head-to-head dental pain studies.

Table 4.2.1 Dental Pain Studies HPD-D104 and -D105 and 171-01-88				
Description Year Conducted	Subjects Total N Per Group N	APAP/CAF Dose mg	APAP Dose mg	Outcome Measures
HPD-D104 - Multi-Center Randomized (2:2:1) Placebo-Controlled Parallel-Groups 1997	1009 403 APAP/CAF 403 APAP 203 PLACEBO	1000/130	1000	PID PAR SPID TOTPAR
HPD-D105 - Multi-Center Randomized (2:2:1) Placebo-Controlled Parallel-Groups 1997	1015 407 APAP/CAF 404 APAP 204 PLACEBO	1000/65	1000	PID PAR SPID TOTPAR
171-01-88 - Multi-Center Randomized (2:2:1) Placebo-Controlled Parallel-Groups 1988	534 212 APAP/CAF 214 APAP 108 PLACEBO	1000/130	1000	PID PAR SPID TOTPAR

Efficacy results for the new parallel-groups postoperative dental pain studies, HPD-D104 and HPD-D105, demonstrate caffeine adjuvancy with APAP and corroborate findings of the earlier dental pain study, 171-01-88. As with the tension type headache pain studies, pooling of results for the three studies was carried out in order to obtain a more accurate estimate of the incremental analgesic effect of caffeine in APAP/CAF combinations.

Study HPD-D105 employed a caffeine dose of 65 mg, while the two other parallel-group dental pain studies, HPD-D104 and 171-01-88, used a caffeine dose of 130 mg. Inclusion of HPD-D105 results in a pooled analysis is supported by the fact that the study design and target condition were similar to those in Studies HPD-D104 and 171-01-88. In addition, the demographic attributes of the treated populations were similar in all three studies.

While the 65 mg dose of CAF used in combination with 1000 mg APAP in Study HPD-D105 showed a more prominent and consistent adjuvant effect than the 130 mg caffeine dose in Study HPD-D104, it is important to note that these caffeine doses were assessed in independent studies with different investigators.

Therefore, since the caffeine doses were not included in a single head-to-head trial, the results of the studies should not be directly compared. Despite this variability between studies, these studies support the analgesic effect of caffeine when combined with APAP, at either dose, 65mg or 130mg.

All analyses for the individual studies and for the pooled studies were performed for the set of all randomized subjects who had data (intent-to-treat population). Complete individual study results for 171-01-88 were previously submitted to the FDA in 1989. Complete individual study results for HPD-D104 and HPD-D105 are presented in Appendix B and C, respectively, in this submission.

#### **4.2.1 Pain Intensity Difference from Baseline (PID)**

In Study HPD-D104, APAP/CAF was statistically superior to APAP alone for PID at 30 minutes, and to placebo from 15 minutes through 4 hours (Table 4.2.1.1 and Figure 4.2.1). In study HPD-D105, APAP/CAF was statistically superior to APAP alone for PID from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and placebo for MAXPID, SPID1, and SPID4 (Table 4.2.1.2 and Figure 4.2.1). In Study 171-01-88, statistically significant differences versus APAP alone were not demonstrated at any time point, however, this may be due to the small sample size of the study (Table 4.2.1.3 and Figure 4.2.1). However, treatment effects favoring APAP/CAF over APAP alone were in the range of those seen in HPD-D104 and HPD-D105.

Caffeine adjuvancy was demonstrated in the pooled analysis of all three dental studies: HPD-D104, HPD-D105 and 171-02-88. APAP/CAF was statistically superior to APAP alone for PID from 30 minutes through 3 hours, and superior to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPID, SPID1 and SPID4 (Table 4.2.1.4 and Figure 4.2.1).

Clinically significant treatment effects favoring APAP/CAF over APAP alone are demonstrated by these studies. The incremental mean SPID4 treatment effect for APAP/CAF over that of APAP alone, calculated as  $100 \times [(mean\ SPID4\ APAP/CAF - mean\ SPID4\ placebo) / (mean\ SPID4\ APAP - mean\ SPID4\ placebo)]$  is about 7% for the pooled results; thus indicating a 7% decrease in pain intensity versus APAP alone in the dental model.

TABLE 4.2.1.1  
 DENTAL PAIN -- PROTOCOL HPD-D104  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=401	APAP1000 MEAN (STD) N=403	PLACEBO MEAN (STD) N=202	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY DIFFERENCE (PID) *							
15 MIN	0.2 ( 0.63)	0.2 ( 0.51)	0.0 ( 0.44)	<0.001	0.491	<0.001	<0.001
30 MIN	0.7 ( 0.75)	0.6 ( 0.74)	0.0 ( 0.59)	<0.001	0.025	<0.001	<0.001
45 MIN	0.9 ( 0.85)	0.8 ( 0.81)	-0.0 ( 0.69)	<0.001	0.318	<0.001	<0.001
60 MIN	0.9 ( 0.90)	0.8 ( 0.86)	-0.1 ( 0.75)	<0.001	0.062	<0.001	<0.001
75 MIN	0.9 ( 0.94)	0.8 ( 0.93)	-0.1 ( 0.73)	<0.001	0.087	<0.001	<0.001
90 MIN	0.8 ( 0.98)	0.8 ( 0.93)	-0.1 ( 0.72)	<0.001	0.120	<0.001	<0.001
2 HRS	0.7 ( 0.98)	0.6 ( 0.95)	-0.2 ( 0.70)	<0.001	0.267	<0.001	<0.001
3 HRS	0.5 ( 0.94)	0.5 ( 0.94)	-0.2 ( 0.73)	<0.001	0.815	<0.001	<0.001
4 HRS	0.4 ( 0.92)	0.4 ( 0.93)	-0.2 ( 0.72)	<0.001	0.642	<0.001	<0.001
MAX PID	1.2 ( 0.86)	1.2 ( 0.83)	0.3 ( 0.70)	<0.001	0.419	<0.001	<0.001
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #							
1-HOUR	0.7 ( 0.68)	0.6 ( 0.63)	-0.0 ( 0.54)	<0.001	0.076	<0.001	<0.001
4-HOUR	2.3 ( 3.08)	2.2 ( 2.99)	-0.5 ( 2.49)	<0.001	0.563	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

TABLE 4.2.1.2  
 DENTAL PAIN -- PROTOCOL HPD-D105  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF65 MEAN (STD) N=407	APAP1000 EAN (STD) N=404	PLACEBO MEAN (STD) N=204	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY DIFFERENCE (PID) *							
15 MIN	0.1 ( 0.57)	0.1 ( 0.53)	-0.1 ( 0.50)	<0.001	0.169	<0.001	<0.001
30 MIN	0.6 ( 0.76)	0.5 ( 0.71)	-0.0 ( 0.57)	<0.001	0.309	<0.001	<0.001
45 MIN	0.8 ( 0.79)	0.7 ( 0.78)	-0.0 ( 0.67)	<0.001	0.016	<0.001	<0.001
60 MIN	1.0 ( 0.84)	0.8 ( 0.84)	-0.1 ( 0.73)	<0.001	0.003	<0.001	<0.001
75 MIN	1.0 ( 0.88)	0.8 ( 0.89)	-0.1 ( 0.74)	<0.001	<0.001	<0.001	<0.001
90 MIN	1.0 ( 0.92)	0.8 ( 0.93)	-0.1 ( 0.77)	<0.001	<0.001	<0.001	<0.001
2 HRS	0.9 ( 0.92)	0.7 ( 0.94)	-0.1 ( 0.74)	<0.001	<0.001	<0.001	<0.001
3 HRS	0.7 ( 0.93)	0.5 ( 0.94)	-0.1 ( 0.74)	<0.001	<0.001	<0.001	<0.001
4 HRS	0.6 ( 0.92)	0.4 ( 0.93)	-0.1 ( 0.74)	<0.001	0.006	<0.001	<0.001
MAX PID	1.3 ( 0.86)	1.1 ( 0.85)	0.3 ( 0.77)	<0.001	0.014	<0.001	<0.001
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #							
1-HOUR	0.6 ( 0.64)	0.5 ( 0.62)	-0.0 ( 0.54)	<0.001	0.017	<0.001	<0.001
4-HOUR	2.9 ( 2.97)	2.2 ( 3.03)	-0.4 ( 2.55)	<0.001	<0.001	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 4.2.1.3  
 DENTAL PAIN -- PROTOCOL 171-01-88  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) 212	APAP1000 MEAN (STD) 214	PLACEBO MEAN (STD) 108	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY DIFFERENCE (PID) *							
30 MIN	0.8 (0.81)	0.6 (0.73)	0.4 (0.77)	<0.001	0.124	<0.001	0.004
1 HR	1.0 (0.86)	0.9 (0.83)	0.4 (1.00)	<0.001	0.208	<0.001	<0.001
2 HRS	1.0 (0.98)	0.8 (0.95)	0.3 (0.99)	<0.001	0.152	<0.001	<0.001
3 HRS	0.7 (1.01)	0.6 (0.97)	0.2 (0.96)	<0.001	0.637	<0.001	<0.001
4 HRS	0.5 (1.04)	0.5 (1.00)	0.2 (1.02)	0.001	0.620	0.002	<0.001
MAX PID	1.3 (0.85)	1.2 (0.83)	0.8 (0.96)	<0.001	0.297	<0.001	<0.001
SUM OF PAIN # INTENSITY DIFFERENCE (SPID)							
1-HOUR	0.9 (0.77)	0.8 (0.71)	0.4 (0.81)	<0.001	0.125	<0.001	<0.001
4-HOUR	3.0 (3.36)	2.8 (3.24)	1.1 (3.49)	<0.001	0.431	<0.001	<0.001

@ P-VALUES FROM ANALYSIS OF COVARIANCE MODEL WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 4.2.1.4

Aspirin Free Excedrin -- Dental Pain  
Pain Intensity Difference  
Intent-To-Treat Population  
(Studies HPD-D104 & HPD-D105 & 171-01-88 Pooled)

VARIABLE	APAP1000/CAF <sup>A</sup>		APAP1000		PLACEBO		OVERALL TREATMENT EFFECT	P-VALUES @		
	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)		APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
Pain Intensity Difference (PID) *										
15 Min	808	0.2 (0.60)	807	0.1 (0.52)	406	-0.0 (0.47)	<0.001	0.134	<0.001	<0.001
30 Min	1020	0.7 (0.77)	1021	0.6 (0.73)	514	0.1 (0.65)	<0.001	0.005	<0.001	<0.001
45 Min	808	0.8 (0.82)	807	0.7 (0.80)	406	-0.0 (0.68)	<0.001	0.016	<0.001	<0.001
60 Min	1020	0.9 (0.87)	1021	0.8 (0.84)	514	0.0 (0.82)	<0.001	<0.001	<0.001	<0.001
75 Min	808	0.9 (0.91)	807	0.8 (0.90)	406	-0.1 (0.73)	<0.001	<0.001	<0.001	<0.001
90 Min	808	0.9 (0.95)	807	0.8 (0.92)	406	-0.1 (0.74)	<0.001	<0.001	<0.001	<0.001
2 Hrs	1020	0.8 (0.96)	1020	0.7 (0.94)	514	-0.0 (0.80)	<0.001	<0.001	<0.001	<0.001
3 Hrs	1020	0.6 (0.94)	1020	0.5 (0.93)	514	-0.1 (0.80)	<0.001	0.019	<0.001	<0.001
4 Hrs	1020	0.5 (0.93)	1020	0.5 (0.93)	514	-0.1 (0.81)	<0.001	0.242	<0.001	<0.001
Max PID	1020	1.2 (0.86)	1021	1.1 (0.84)	514	0.4 (0.81)	<0.001	0.010	<0.001	<0.001
Sum of Pain Intensity Differences (SPID) #										
1-Hour	1020	0.7 (0.69)	1021	0.6 (0.65)	514	0.1 (0.63)	<0.001	<0.001	<0.001	<0.001
4-Hour	1020	2.7 (3.09)	1020	2.3 (3.03)	514	-0.1 (2.81)	<0.001	0.003	<0.001	<0.001

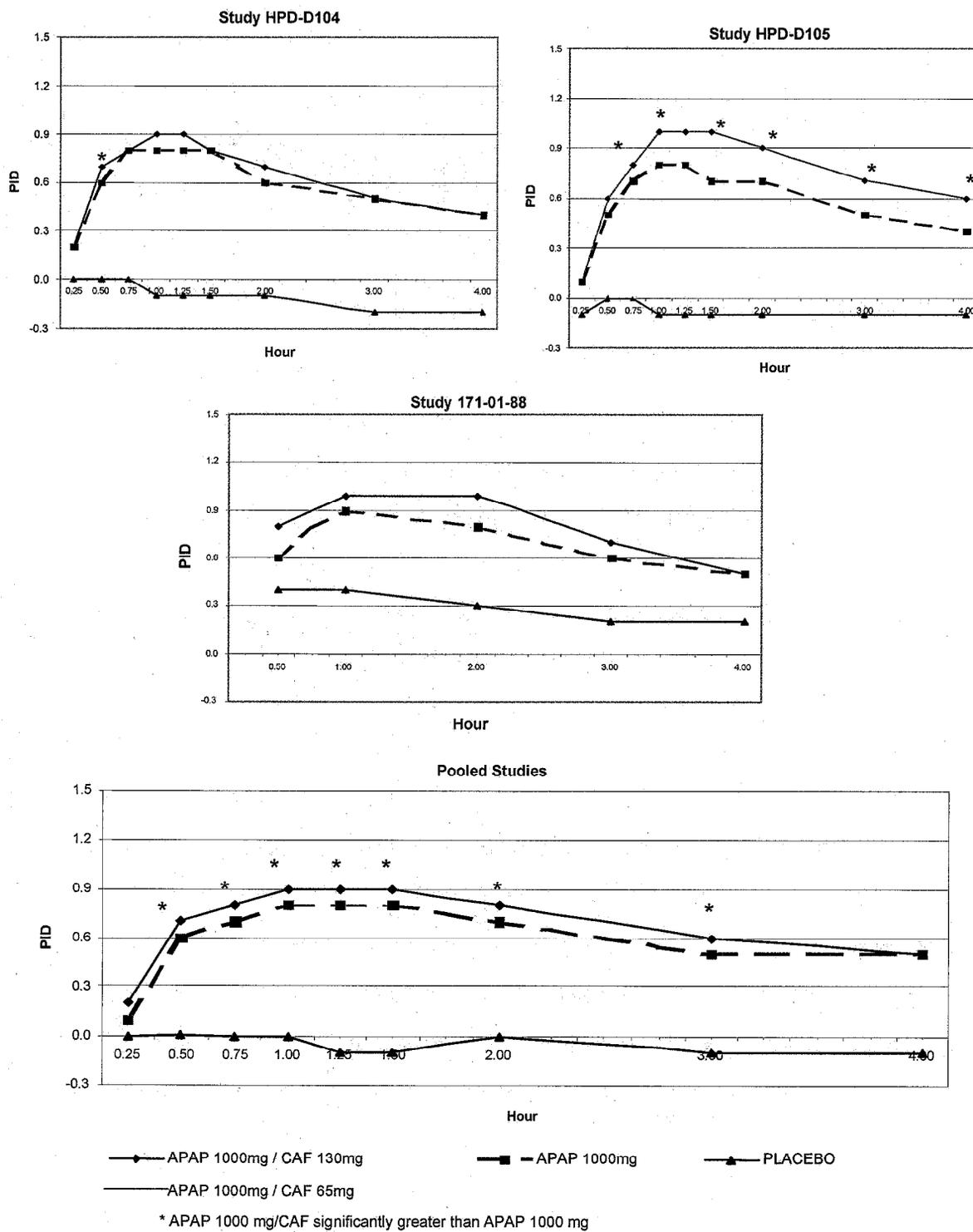
@ P-value from analysis of covariance with factors of treatment, protocol, investigator, and baseline pain intensity as the covariate.

<sup>A</sup> APAP1000/CAF is the pool of treatment groups APAP1000/CAF130 (HPD-D104 and 171-01-88) and APAP1000/CAF65 (HPD-D105).

\* Arithmetic mean and standard deviation (Std) are based on raw data.

# SPID = Weighted sum of PIDs. The weight used at each time point is equal to the time elapsed from the previous time point.

Figure 4.2.1  
Pain Intensity Difference  
Dental Pain (ITT)



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#### 4.2.2 Pain Relief (PAR)

In Study HPD-D104, the PAR scores were significantly greater for APAP/CAF than for APAP alone at 15, 30, 60, and 75 minutes post dose, and superior to placebo from 15 minutes through 4 hours (Table 4.2.2.1 and Figure 4.2.2). In addition, APAP/CAF was statistically superior to APAP for TOTPAR1, and to placebo for MAXPAR, TOTPAR1, and TOTPAR4. Similarly, in Study HPD-D105, APAP/CAF was significantly superior to APAP alone for PAR from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours. In addition, APAP/CAF was significantly superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4 (Table 4.2.2.2 and Figure 4.2.2). While there were no statistically significant differences between the APAP/CAF combination and APAP alone for any endpoint in Study 171-01-88 (Table 4.2.2.3 and Figure 4.2.2), the magnitude of the treatment effect for caffeine (APAP/CAF vs. APAP alone difference) was in the range of that seen in the other two studies.

When results for all three studies are pooled, statistically significant differences are seen in favor of APAP/CAF vs. APAP alone for PAR scores from 15 minutes through 3 hours, and to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1 and TOTPAR4 (Table 4.2.2.4 and Figure 4.2.2).

Clinically significant treatment effects favoring APAP/CAF over APAP alone were demonstrated by these studies. The incremental mean TOTPAR4 treatment effect for APAP/CAF over that of APAP alone, calculated as  $100 \times \frac{(\text{mean TOTPAR4 APAP/CAF} - \text{mean TOTPAR4 placebo})}{(\text{mean TOTPAR4 APAP} - \text{mean TOTPAR4 placebo})}$  is about 16% for the pooled results; thus indicating a 16% increase in pain relief versus APAP alone in the dental model.

TABLE 4.2.2.1  
DENTAL PAIN -- PROTOCOL HPD-D104  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130			OVERALL TREATMENT EFFECT	P-VALUES @		
	MEAN (STD) N=401	APAP1000 MEAN (STD) N=403	PLACEBO MEAN (STD) N=202		APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
15 MIN	0.7 ( 0.89)	0.5 ( 0.72)	0.3 ( 0.54)	<0.001	0.006	<0.001	<0.001
30 MIN	1.4 ( 1.12)	1.3 ( 1.08)	0.4 ( 0.68)	<0.001	0.028	<0.001	<0.001
45 MIN	1.8 ( 1.24)	1.6 ( 1.18)	0.5 ( 0.78)	<0.001	0.081	<0.001	<0.001
60 MIN	2.0 ( 1.29)	1.8 ( 1.27)	0.6 ( 0.85)	<0.001	0.016	<0.001	<0.001
75 MIN	1.9 ( 1.42)	1.8 ( 1.40)	0.5 ( 0.88)	<0.001	0.049	<0.001	<0.001
90 MIN	1.8 ( 1.49)	1.7 ( 1.45)	0.4 ( 0.87)	<0.001	0.155	<0.001	<0.001
2 HRS	1.6 ( 1.52)	1.5 ( 1.49)	0.4 ( 0.90)	<0.001	0.253	<0.001	<0.001
3 HRS	1.3 ( 1.49)	1.3 ( 1.50)	0.4 ( 0.95)	<0.001	0.840	<0.001	<0.001
4 HRS	1.1 ( 1.48)	1.1 ( 1.49)	0.3 ( 0.92)	<0.001	0.954	<0.001	<0.001
MAXPAR	2.4 ( 1.34)	2.3 ( 1.31)	0.9 ( 1.12)	<0.001	0.239	<0.001	<0.001
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.5 ( 0.99)	1.3 ( 0.92)	0.4 ( 0.63)	<0.001	0.01	<0.001	<0.001
4-HOUR	5.6 ( 4.74)	5.3 ( 4.66)	1.6 ( 2.95)	<0.001	0.371	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

TABLE 4.2.2.2  
 DENTAL PAIN -- PROTOCOL HPD-D105  
 PAIN RELIEF  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF65 MEAN (STD) N=407	APAP1000 MEAN (STD) N=404	PLACEBO MEAN (STD) N=204	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN							
RELIEF *							
15 MIN	0.5 ( 0.76)	0.4 ( 0.69)	0.2 ( 0.56)	<0.001	0.357	<0.001	0.002
30 MIN	1.3 ( 1.09)	1.1 ( 1.01)	0.4 ( 0.65)	<0.001	0.054	<0.001	<0.001
45 MIN	1.8 ( 1.19)	1.5 ( 1.15)	0.5 ( 0.72)	<0.001	0.003	<0.001	<0.001
60 MIN	2.1 ( 1.25)	1.8 ( 1.22)	0.5 ( 0.83)	<0.001	<0.001	<0.001	<0.001
75 MIN	2.2 ( 1.33)	1.8 ( 1.32)	0.5 ( 0.89)	<0.001	<0.001	<0.001	<0.001
90 MIN	2.2 ( 1.39)	1.8 ( 1.43)	0.4 ( 0.94)	<0.001	<0.001	<0.001	<0.001
2 HRS	2.0 ( 1.46)	1.6 ( 1.49)	0.4 ( 0.93)	<0.001	<0.001	<0.001	<0.001
3 HRS	1.7 ( 1.52)	1.3 ( 1.51)	0.3 ( 0.97)	<0.001	<0.001	<0.001	<0.001
4 HRS	1.5 ( 1.56)	1.1 ( 1.50)	0.3 ( 0.98)	<0.001	<0.001	<0.001	<0.001
MAXPAR	2.6 ( 1.30)	2.3 ( 1.32)	0.8 ( 1.18)	<0.001	0.002	<0.001	<0.001
TOTAL PAIN							
RELIEF							
(TOTPAR) #							
1-HOUR	1.4 ( 0.94)	1.2 ( 0.89)	0.4 ( 0.61)	<0.001	0.003	<0.001	<0.001
4-HOUR	6.6 ( 4.74)	5.3 ( 4.70)	1.5 ( 3.06)	<0.001	<0.001	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS FOR TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Table 4.2.2.3

Aspirin Free Excedrin -- Dental Pain  
Pain Relief  
Intent-To-Treat Population  
(Study: 171-01-88)

VARIABLE	APAP1000/CAF130 Mean (Std) N = 212	APAP1000 Mean (Std) N = 214	PLACEBO Mean (Std) N = 108	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
Relief *							
30 Min	1.8 (1.25)	1.6 (1.23)	1.1 (1.18)	<0.001	0.337	<0.001	<0.001
60 Min	2.3 (1.25)	2.1 (1.34)	1.3 (1.38)	<0.001	0.168	<0.001	<0.001
2 Hrs	2.2 (1.48)	2.0 (1.51)	1.1 (1.43)	<0.001	0.249	<0.001	<0.001
3 Hrs	1.7 (1.60)	1.7 (1.59)	0.8 (1.36)	<0.001	0.951	<0.001	<0.001
4 Hrs	1.3 (1.65)	1.4 (1.64)	0.8 (1.39)	0.001	0.380	0.004	<0.001
MAXPAR	2.7 (1.24)	2.6 (1.31)	1.7 (1.49)	<0.001	0.290	<0.001	<0.001
Total Pain Relief (TOTPAR) #							
1-Hour	2.0 (1.14)	1.9 (1.20)	1.2 (1.20)	<0.001	0.201	<0.001	<0.001
4-Hour	7.2 (5.09)	7.0 (5.22)	4.0 (4.81)	<0.001	0.729	<0.001	<0.001

@ P-value from analysis of covariance with factors of treatment, investigator site, and baseline pain intensity as the covariate.

\* Arithmetic mean and standard deviation (Std) are based on raw data.

# TOTPAR = Weighted sum of pain relief. The weight used at each time point is equal to the time elapsed from the previous time point.

Table 4.2.2.4

Aspirin Free Excedrin -- Dental Pain  
Pain Relief  
Intent-To-Treat Population  
(Studies HPD-D104 & HPD-D105 & 171-01-88 Pooled)

VARIABLE	APAP1000/CAF <sup>A</sup>		APAP1000		PLACEBO		-----P-VALUES @-----			
	N	Mean (Std)	N	Mean (Std)	N	Mean (Std)	OVERALL TREATMENT EFFECT	APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
Relief *										
15 Min	808	0.6 (0.83)	807	0.5 (0.71)	406	0.2 (0.55)	<0.001	0.008	<0.001	<0.001
30 Min	1020	1.4 (1.15)	1021	1.3 (1.10)	514	0.6 (0.85)	<0.001	0.003	<0.001	<0.001
45 Min	808	1.8 (1.21)	807	1.6 (1.17)	406	0.5 (0.75)	<0.001	<0.001	<0.001	<0.001
60 Min	1020	2.1 (1.27)	1021	1.8 (1.27)	514	0.7 (1.02)	<0.001	<0.001	<0.001	<0.001
75 Min	808	2.0 (1.38)	807	1.8 (1.36)	406	0.5 (0.88)	<0.001	<0.001	<0.001	<0.001
90 Min	808	2.0 (1.45)	807	1.7 (1.44)	406	0.4 (0.90)	<0.001	<0.001	<0.001	<0.001
2 Hrs	1020	1.9 (1.50)	1020	1.6 (1.51)	514	0.5 (1.08)	<0.001	<0.001	<0.001	<0.001
3 Hrs	1020	1.5 (1.53)	1020	1.4 (1.53)	514	0.5 (1.07)	<0.001	0.010	<0.001	<0.001
4 Hrs	1020	1.3 (1.55)	1020	1.2 (1.53)	514	0.4 (1.07)	<0.001	0.053	<0.001	<0.001
MAXPAR	1020	2.5 (1.31)	1021	2.4 (1.32)	514	1.0 (1.28)	<0.001	0.001	<0.001	<0.001
Total Pain Relief (TOTPAR) #										
1-Hour	1020	1.5 (1.03)	1021	1.4 (1.01)	514	0.6 (0.84)	<0.001	<0.001	<0.001	<0.001
4-Hour	1020	6.3 (4.85)	1020	5.7 (4.84)	514	2.0 (3.59)	<0.001	<0.001	<0.001	<0.001

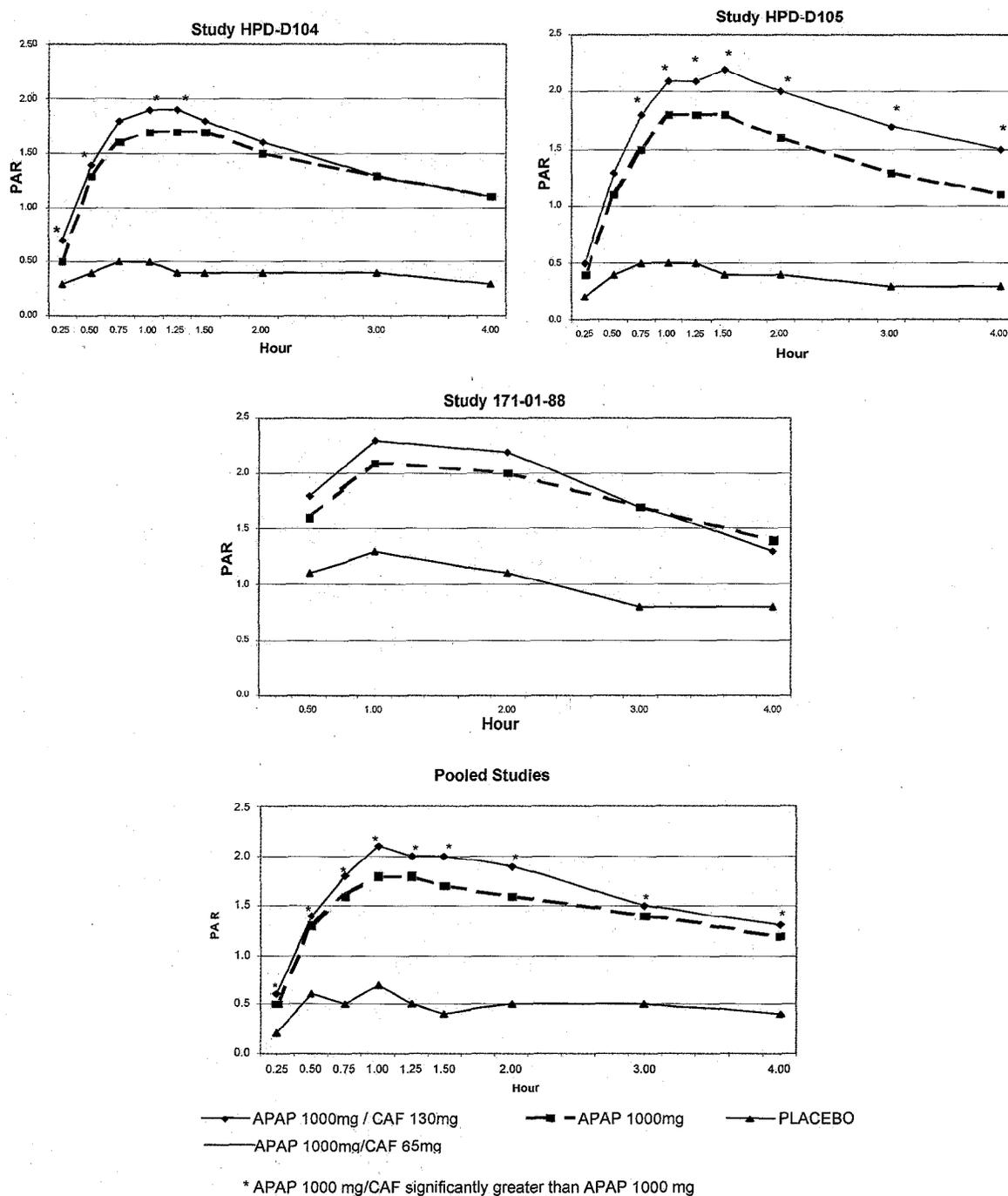
@ P-value from analysis of covariance with factors of treatment, protocol, investigator, and baseline pain intensity as the covariate.

<sup>A</sup> APAP1000/CAF is the pool of treatment groups APAP1000/CAF130 (HPD-D104 and 171-01-88) and APAP1000/CAF65 (HPD-D105).

\* Arithmetic mean and standard deviation (Std) are based on raw data.

# TOTPAR = Weighted sum of pain relief. The weight used at each time point is equal to the time elapsed from the previous time point.

Figure 4.2.2  
Pain Relief  
Dental Pain (ITT)



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### 4.3 Efficacy Results in Bioassay Trials – Secondary Support

#### 4.3.1 Background

In addition to the six head-to-head studies described above, BMS completed a total of 11 other assessments of the magnitude of the analgesic adjuvant effect of caffeine combined with APAP in the early to mid 1980s. These studies employed single-dose, double-blind, randomized, placebo-controlled, parallel-groups bioassay relative potency comparisons of multiples of APAP/CAF in a fixed 500 mg/65mg ratio to corresponding multiples of the APAP doses alone. Four (2711 and 2569-2571) of the studies were carried out in a postoperative (third molar extraction) dental-pain model and seven (2255 and 2576-2581) were carried out in a postpartum pain model. This section will focus on postpartum pain although a brief discussion of dental studies is included for completeness.

#### Dental

The four dental pain model studies were all either flawed in design or found only weak evidence of the analgesic potentiating activity of caffeine. Study 2569 did not include a placebo group; Study 2570 showed a non-significantly greater potency for the APAP/CAF combinations in SPID analyses (potency ratio 1:49;95% CI 0.40-3.41). Study 2571 found no significant APAP/CAF v. APAP difference with respect to TOTPAR (relative potency 0.89; 95% CI 0.55-2.29). Study 2711, a two-phase relative potency study was conducted in an unvalidated, periodontal scaling-induced pain model, and although it showed all actives superior to placebo, but indistinguishable from one another in the second phase, it failed to show any of the active treatments superior to placebo in the first phase. Thus, these studies add little of substance to support the analgesic adjuvancy of caffeine in APAP/CAF combination and are not discussed further.

#### Postpartum

Salient details of the postpartum pain studies, including key results, are summarized in Table 4.3.1. The six studies summarized in this table entered a total of 3010 subjects. Study 2581 is not included in this table or further discussed in this document, because although all active treatments were significantly superior to placebo, the study also found "negative" dose-response relationships for both the APAP/CAF combinations and APAP alone. Therefore, a combination/monotherapy potency ratio could not be calculated from the study results.

### 4.3.2 Methods

The relative potency assessments in the studies in Table 4.3.1 were made by comparing the analgesic potencies of the fixed ratio APAP/CAF combinations to those for the corresponding APAP monotherapies. Pain intensity was measured at baseline and hourly postdose for four hours on a four-point scale. For each post-baseline time point, the difference from baseline (PID) was calculated. PAR was measured hourly postdose for four hours using a five-point scale.

Potency estimates were derived from fitted dose-response regression lines, constructed using summary measures for SPID4 and TOTPAR4. These summary variables are estimates of the areas under the mean time-effect curves for each test dose constructed using the weighted sums of the SPIDs or PARs, respectively (weighting was by length of time in hours between successive evaluations). Calculation of a potency ratio required a pair of linear, dose response curves with significant and parallel slopes. As an approach to accounting for different initial pain intensities, in addition to standard analyses of SPID results, individual patient SPIDs were "normalized" by reference to the maximum achievable SPID (MSPID) as  $\%SPID = 100 \times (SPID/MSPID)$ .

These studies were designed to allow calculation of potency ratios and associated 95% confidence intervals (CIs) for the active treatment pairs (APAP/CAF v. APAP) and were not intended to assess APAP/CAF v. APAP differences in pairwise comparisons for the dose pairs.

### 4.3.3 Results

For the %SPID4 pairwise comparisons in Table 4.3.1, the combination was arithmetically superior to monotherapy in 15 of 18 instances, tied with monotherapy in one, and arithmetically inferior in two. Corresponding results for the 18 SPID4 pair comparisons are 11, four and three; and for the 15 TOTPAR comparisons, 12, one and two.

Table 4.3.2 summarizes the potency ratio results for SPID4 and TOTPAR4, standard summary measures of analgesic efficacy, and also includes results of pooled analyses of the SPID4 and TOTPAR4 potency ratios. The pooled APAP/CAF to APAP potency ratio for SPID4 is 1.28 and for TOTPAR4 is 1.31: both potency estimates are statistically significant. Thus, approximately 1300mg APAP would be required to provide comparable relief to APAP 1000mg/CAF 130mg. These potency ratios are very similar to APAP/CAF vs. APAP effectiveness ratios found in the BMS studies described above in Sections 4.1 and 4.2.

#### 4.3.4 Discussion/Conclusions

FDA's primary critique of BMS' postpartum pain relative potency bioassay studies was that the studies were not consistent in showing significant superiority of the combinations to their respective APAP monotherapy comparators. However, as pointed out above, these studies were neither designed nor powered to sustain pairwise comparisons for the individual dose pairs. In fact, in aggregate, the postpartum studies provide strong evidence of caffeine's analgesic adjuvancy when combined with APAP.

**Table 4.3.1**  
**BMS Single-Dose, Double-Blind, Randomized, Placebo-Controlled, Parallel-Groups APAP/CAF v. APAP Postpartum Relative Potency Bioassay Studies Completed in 1981<sup>1</sup>**

Protocol #	Study Treatments <sup>2</sup> (APAP/CAF) (APAP)	Subjects (n)	Results
			Pain Parameters <sup>4</sup>
2255	1, 2, 4 tabs (500/65) 1, 2, 4 tabs Placebo	739	%SPID4: 14, 30*, 54*#; 13*, 27*, 38*; 9 SPID4: 1.2, 2.5, 4.7, 1.1, 2.3, 3.3, 0.7 TOTPAR4: 3.6, 5.3*, 7.8*#; 3.3, 5.5, 6.5*; 2.1
2576	1, 2, 3 tabs (500/65) 1, 2, 3 tabs Placebo	699	%SPID4: 40*, 43*, 41*; 40*, 41*, 46*; 32 SPID4: 4.1, 4.3, 4.1, 4.1, 4.2, 4.8, 3.2 TOTPAR4: 7.4*, 8.1*, 7.7*; 7.5*; 7.6*, 8.6*; 5.6
2577	1, 2, 3 tabs 1, 2, 3 tabs Placebo	227	%SPID4: 44*, 52*, 62*; 43*, 58*, 48*; 30 SPID4: 4.2, 4.5, 5.5, 3.9, 5.5, 4.7, 2.7
2578	1, 2, 3 tabs (500/65) 1, 2, 3 tabs Placebo	373	%SPID4: 43, 54*, 57*; 36, 45*, 49*; 33 SPID4: 4.6*, 4.9*, 6.2*; 4.0, 5.1*, 5.5*; 3.4 TOTPAR4: 8.2*, 10.3*#, 10.4*; 7.1, 8.2*, 9.1*; 6.*
2579	1, 2, 3 tabs (500/65) 1, 2, 3 tabs Placebo	404	%SPID4: 47, 48, 53*, 44, 47, 49*; 41 SPID4: 5.6, 5.7, 6.5*; 5.4, 5.7*, 5.9*; 4.9 TOTPAR4: 8.8*, 9.0*, 9.9*; 8.4, 8.8, 9.3*; 7.6
2580	1, 2, 3 tabs (500/65) 1, 2, 3 tabs Placebo	538	%SPID4: 46*, 47*, 51*; 43*, 46*, 50*; 30 SPID4: 5.2*, 5.3*, 5.7*; 4.9*, 5.3*, 5.7*; 3.3 TOTPAR4: 9.1*, 9.1*, 9.9*; 8.4, 9.1*, 9.7*; 6.0

<sup>1</sup>In all studies, subjects assessed pain intensity (when measured), and, pain relief (when measured) at baseline, and 1, 2, 3 and 4 hours after dosing.

<sup>2</sup>APAP/CAF tabs contained 500mg APAP and 65 mg CAF and identical APAP tabs contained only 500 mg APAP.

<sup>3</sup>PR = significant potency ratio. \*./# = Dose Response significant, p $\leq$  0.05 ("+"), or nonsignificant ("-")/Dose Response Curves parallel ("+"), or nonparallel ("-").

<sup>4</sup>Under Pain Parameters, the order of observations is APAP/CAF 1, 2, 3 (or 4) tabs; APAP 1, 2, 3 (or 4) tabs; placebo.

\*Significantly better than placebo.

\*\*95% CI excludes 1.0.

;/#Significantly (p $\leq$  0.05) different from corresponding APAP multiple.

**Table 4.3.2**  
**Acetaminophen Plus Caffeine vs. Acetaminophen Alone**  
**Relative Potency (95% Confidence Intervals)**  
**Derived From:**

<b>Study</b>	<b>SPID4</b>	<b>TOTPAR4</b>
2255	1.31*(1.12-1.54)	1.20*(1.01-1.44)
2576	0.51 (Indeterminate)	0.76 (Indeterminate)
2577	1.05 (0.36-4.68)	Not collected
2578	1.73*(1.12-3.57)	2.13*(1.36-5.17)
2579	1.54 (0.60-355)	1.61 (0.60->500)
2580	1.16 (0.19-154)	1.34 (0.53-13.7)
Pool	1.28*(1.09-1.54)	1.31*(1.10-1.59)

\*Significant at 0.05 level

Pool = Entire pool including all caffeine levels

## 5.0 SAFETY OF APAP/CAF IN THE HEAD-TO-HEAD STUDIES

Safety results for the relative potency studies have been submitted to FDA previously, and showed no serious or unexpected adverse events. In the summaries below, safety results for the six head-to-head studies are grouped by pain model (i.e., tension-type headache and dental pain). All adverse events in these summaries were "treatment emergent" (defined as any new or worsening illness, sign or symptom complained of by the subject or noted by the investigator during the course of treatment, regardless of the investigator's assessment of the relationship between the event and study drug), and a serious adverse event (SAE) is defined as an AE that meets at least one of the following criteria: fatal, life threatening, permanently disabling, resulting in hospitalization, leading to prolonged hospitalization, congenital anomaly, cancer, or overdose.

For the tension headache studies, safety results from the parallel-groups study, HPD-H203, are summarized separately from those obtained in the crossover studies (Table 5.0). For both the parallel-groups and pooled crossover studies, the proportion of subjects reporting any adverse event was significantly ( $p < 0.05$ ) greater for APAP 1000mg/CAF 130mg than for either APAP 1000mg or placebo. The proportion of subjects reporting gastrointestinal events and nervous system adverse events was also significantly ( $p < 0.05$ ) greater for the combination than for APAP 1000mg alone.

No SAEs were reported in these studies.

<b>Table 5.0</b>			
<b>Incidence of AEs in Tension Headache Studies</b>			
<b>N (%)</b>			
<b>Parallel-Groups Study HPD-H203</b>			
<b>Event</b>	<b>Aspirin-Free Excedrin® APAP 1000mg/ CAF 130mg (N = 438)</b>	<b>Extra-Strength Tylenol® APAP 1000mg (N = 441)</b>	<b>Placebo (N = 225)</b>
Adverse Events	52 (12%)	27 (6%)	12 (5%)
Gastrointestinal	22 (5%)	6 (1%)	5 (2%)
Nervous	28 (6%)	15 (3%)	6 (3%)
<b>CrossOver Studies 170-01-88, 170-02-88</b>			
<b>Event</b>	<b>Aspirin-Free Excedrin® APAP 1000mg/ CAF 130mg (N = 692)</b>	<b>Extra-Strength Tylenol® APAP 1000mg (N = 691)</b>	<b>Placebo (N = 341)</b>
Adverse Events	144 (21%)	90 (13%)	41 (12%)
Gastrointestinal <sup>A</sup>	59 (9%)	45 (7%)	19 (6%)
Nervous	50 (7%)	10 (1%)	2 (1%)

<sup>A</sup> In this table, adverse events from studies 170-01-88 and 170-02-88 categorized here as gastrointestinal events were categorized as stomach discomfort in the original study reports.

For the dental studies, no statistically significant differences in incidence of adverse events were detected between any of the treatment groups (Table 5.1). The incidences and patterns for AEs in the APAP1000/CAF130 APAP1000/CAF65 groups were similar.

No SAEs were reported in these studies and no discontinuations were prompted by AEs.

<b>Table 5.1</b>				
<b>Incidence of AEs in Dental Pain</b>				
<b>Studies HPD-D104, HPD-D105, 171-01-88</b>				
<b>N (%)</b>				
<b>Event</b>	<b>Aspirin-Free Excedrin® APAP 1000mg/ CAF 130mg (N = 615)</b>	<b>Aspirin-Free Excedrin® APAP 1000mg/ CAF 65mg (N = 407)</b>	<b>Extra-Strength Tylenol® APAP 1000mg (N = 1021)</b>	<b>Placebo (N = 515)</b>
Adverse Events	160 (26%)	101 (25%)	262 (26%)	137 (27%)
Gastrointestinal <sup>A</sup>	108 (18%)	67 (16%)	178 (17%)	101 (20%)
Nervous	22 (4%)	20 (5%)	32 (3%)	12 (2%)

<sup>A</sup> In this table, adverse events from study 171-01-88 categorized here as gastrointestinal events were categorized as stomach discomfort in the original study report.

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The APAP/CAF combination was well tolerated by the subjects in these trials. Adverse events were consistent with the safety profile of the individual components.

## **6.0 DISCUSSION/SUMMARY AND CONCLUSIONS**

### **6.1 Discussion/Summary**

During the past three decades, BMS has submitted considerable evidence in support of caffeine adjuvancy. In 1995, the FDA issued a Feedback Letter to Industry, which concluded that while caffeine was an adjuvant when combined with ASA alone or with the combination of ASA/APAP, there was insufficient evidence to demonstrate that caffeine was an adjuvant when combined with APAP alone. FDA based this decision on concern about potential differential carryover effects in the crossover tension headache trials. In August 1995, BMS responded to the April 1995 FDA Feedback Letter, affirming the position that previously submitted clinical information provided substantial evidence of caffeine adjuvancy with APAP.

Since that time BMS has conducted three new, randomized, double-blind, placebo-controlled, head-to-head clinical trials assessing the analgesic adjuvant effect of caffeine when combined with APAP. One study was conducted in a tension headache model (HPD-H203), while the other two were conducted in a dental model (HPD-D104 and HPD-D105). The new, parallel design, tension headache trial (HPD-H203) was conducted to confirm the results of the earlier crossover design headache trials. Results of these 3 new trials considered in conjunction with results of earlier trials in tension-type headache, dental pain and postpartum pain models constitute strong evidence for caffeine adjuvancy with APAP, and provide a firm basis for the conclusion that caffeine potentiates the analgesic effectiveness of APAP, to a clinically relevant degree.

#### **6.1.1 Efficacy Summary**

##### Headache Model

Caffeine adjuvancy with APAP was demonstrated in the new, parallel design, headache trial (HPD-H203) which confirmed the results of the earlier crossover headache trials (170-01-88, 170-02-88). Similarly, the pooled analysis of headache studies HPD-H203, and the first treated headache of the crossover trials, 170-01-88, and 170-02-88 also demonstrated caffeine adjuvancy with APAP (Figure A and Figure B).

- Study HPD-H203, the new, parallel, double-blind, randomized, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID from 75 minutes through 4 hours, and to placebo from 30 minutes through 4

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- hours (Figure A). APAP/CAF was superior to APAP alone and to placebo for SPID4 and MAXPID.
- APAP/CAF was statistically superior to APAP alone for PAR from 75 minutes through 4 hours, and to placebo from 45 minutes through 4 hours (Figure B). APAP/CAF was statistically superior to APAP alone and placebo for TOTPAR4 and MAXPAR.
- Studies 170-01-88 and 170-02-88, two earlier crossover, double-blind, randomized, placebo-controlled trials each demonstrated caffeine adjuvancy with APAP as evidenced by:
    - 170-01-88
      - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
      - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
    - 170-02-88
      - APAP/CAF was statistically superior to APAP alone and placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1, and SPID4.
      - APAP/CAF was statistically superior to APAP alone and to placebo for PAR from 30 minutes through 4 hours (Figure B), MAXPAR, TOTPAR1 and TOTPAR4.
  - Pooled analysis of headache studies (HPD-H203; and first treated headache of the cross-over trials, 170-01-88 and 170-02-88) demonstrated caffeine adjuvancy with APAP as evidenced by:
    - APAP/CAF statistically superior to APAP from 60 minutes through 4 hours and to placebo for PID from 30 minutes through 4 hours (Figure A), MAXPID, SPID1 and SPID4.
    - APAP/CAF statistically superior to APAP alone and to placebo for PAR at 30 minutes and from 60 minutes through through 4 hours (Figure B), MAXPAR, TOTPAR1, and TOTPAR4.

### Dental Pain Model

Caffeine adjuvancy with APAP was demonstrated in two new dental studies (HPD-D105, HPD-D104).

In Study HPD-D104, statistical significance in favor of APAP/CAF over APAP alone was achieved at fewer timepoints than in Study D105. In an earlier dental study (171-01-88), while both APAP/CAF and APAP alone were significantly superior to placebo, the combination APAP/CAF was not significantly better than APAP alone due, in part, to the small sample size. However, the treatment effect observed in Study 171-01-88 was in favor of APAP/CAF over APAP and was similar in magnitude to that seen in HPD-D104 and HPD-D105. Similarly, the pooled analysis of dental trials, HPD-D104, HPD-D105, 171-01-88, demonstrated caffeine adjuvancy with APAP (Figure C and Figure D).

- Study HPD-D105 (APAP 1000mg/CAF 65mg) a new, parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and placebo for MAXPID, SPID1, AND SPID4.
  - APAP/CAF was statistically superior to APAP alone for PAR from 45 minutes through 4 hours, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- Study HPD-D104 (APAP 1000mg/CAF 130mg) a new, parallel, randomized, double-blind, placebo-controlled trial demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF was statistically superior to APAP alone for PID at 30 minutes, and to placebo from 15 minutes through 4 hours (Figure C).
  - APAP/CAF was statistically superior to APAP alone for PAR at 15, 30, 60 and 75 minutes, and to placebo from 15 minutes through 4 hours (Figure D). APAP/CAF was statistically superior to APAP for TOTPAR1, and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.
- In Study 171-01-88 (APAP 1000mg/CAF 130mg), an earlier parallel, randomized, double-blind, placebo-controlled trial, although statistically significant differences from APAP alone were not demonstrated due to the

small sample size; treatment effects, however, were in the range of those seen in HPD-D104 and HPD-D105, and favored APAP/CAF over APAP alone (Figure C and Figure D).

- Pooled analysis of all dental studies, HPD-D104, HPD-D105, and 171-01-88, demonstrated caffeine adjuvancy as evidenced by:
  - APAP/CAF statistically superior to APAP alone for PID from 30 minutes through 3 hours, and to placebo from 15 minutes through 4 hours (Figure C). APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPID, SPID1, and SPID4.
  - APAP/CAF was statistically superior to APAP alone for PAR from 15 min through 3 hours (Figure D), and to placebo from 15 minutes through 4 hours. APAP/CAF was also statistically superior to APAP alone and to placebo for MAXPAR, TOTPAR1, and TOTPAR4.

### Postpartum Pain Model

Caffeine adjuvancy was demonstrated in the pooled postpartum/bioassay trials.

- Studies 2255, 2576, 2577, 2578, 2579, 2580 demonstrated caffeine adjuvancy with APAP as evidenced by:
  - APAP/CAF statistically superior to APAP with relative potency estimates of 1.28 for SPID4 and 1.31 for TOTPAR4; indicating approximately 1300mg APAP would be required to provide comparable relief to APAP 1000mg/CAF 130mg.

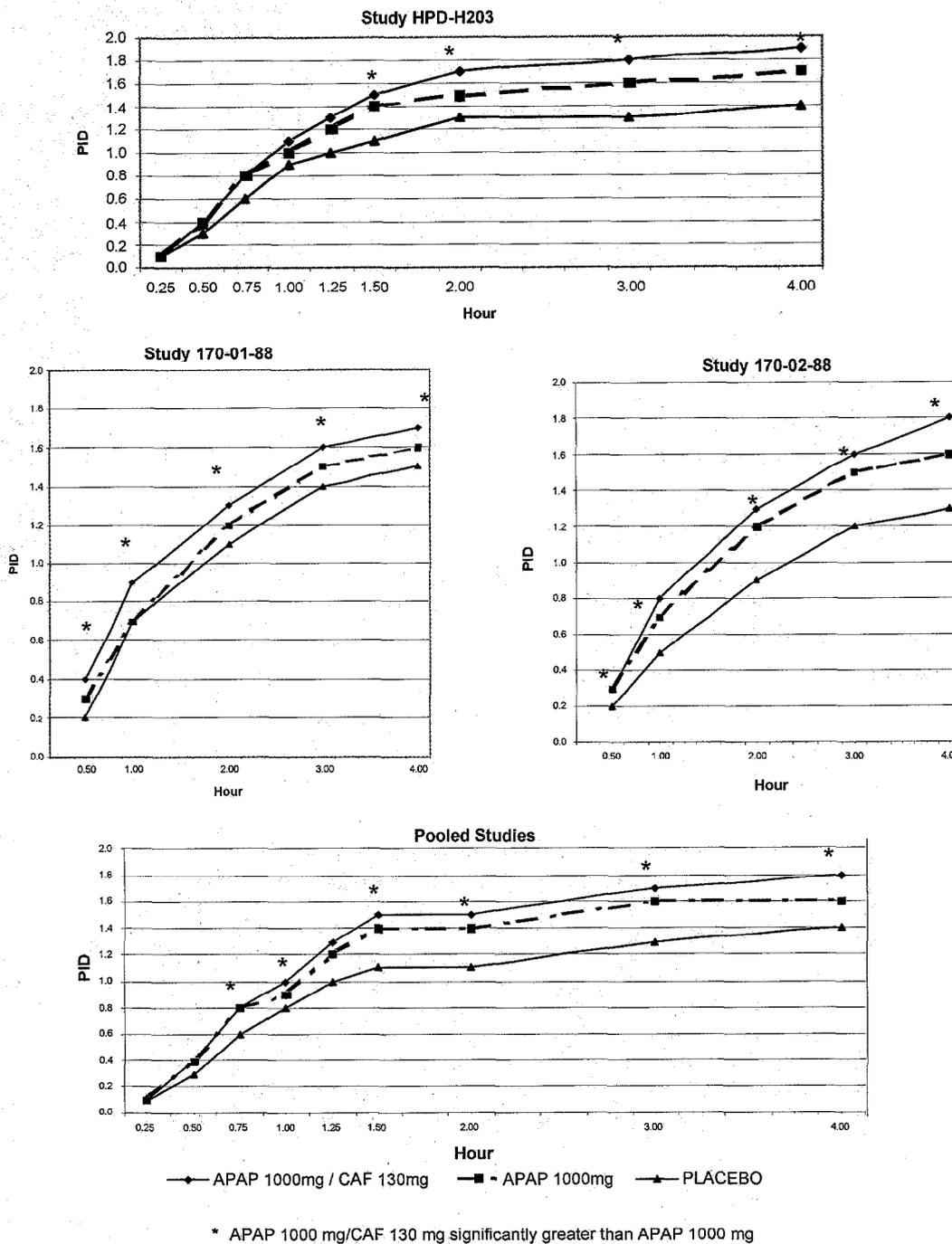
### **6.1.2 Safety Summary**

Although incidence rates for both gastrointestinal and nervous system were slightly higher for APAP/CAF than for APAP alone in the head-to-head studies, none of the adverse events in either of the categories was of a serious nature. Overall, the APAP/CAF combination was well tolerated by the subjects in these trials. Adverse events were consistent with the safety profile of the individual components. Since 1990, the APAP 1000mg/CAF 130mg combination has been marketed in the U.S. by BMS as Aspirin Free Excedrin®. Since that time, more than 2.5 billion tablets have been sold. The safety event profile is well characterized.

## 6.2 Conclusions

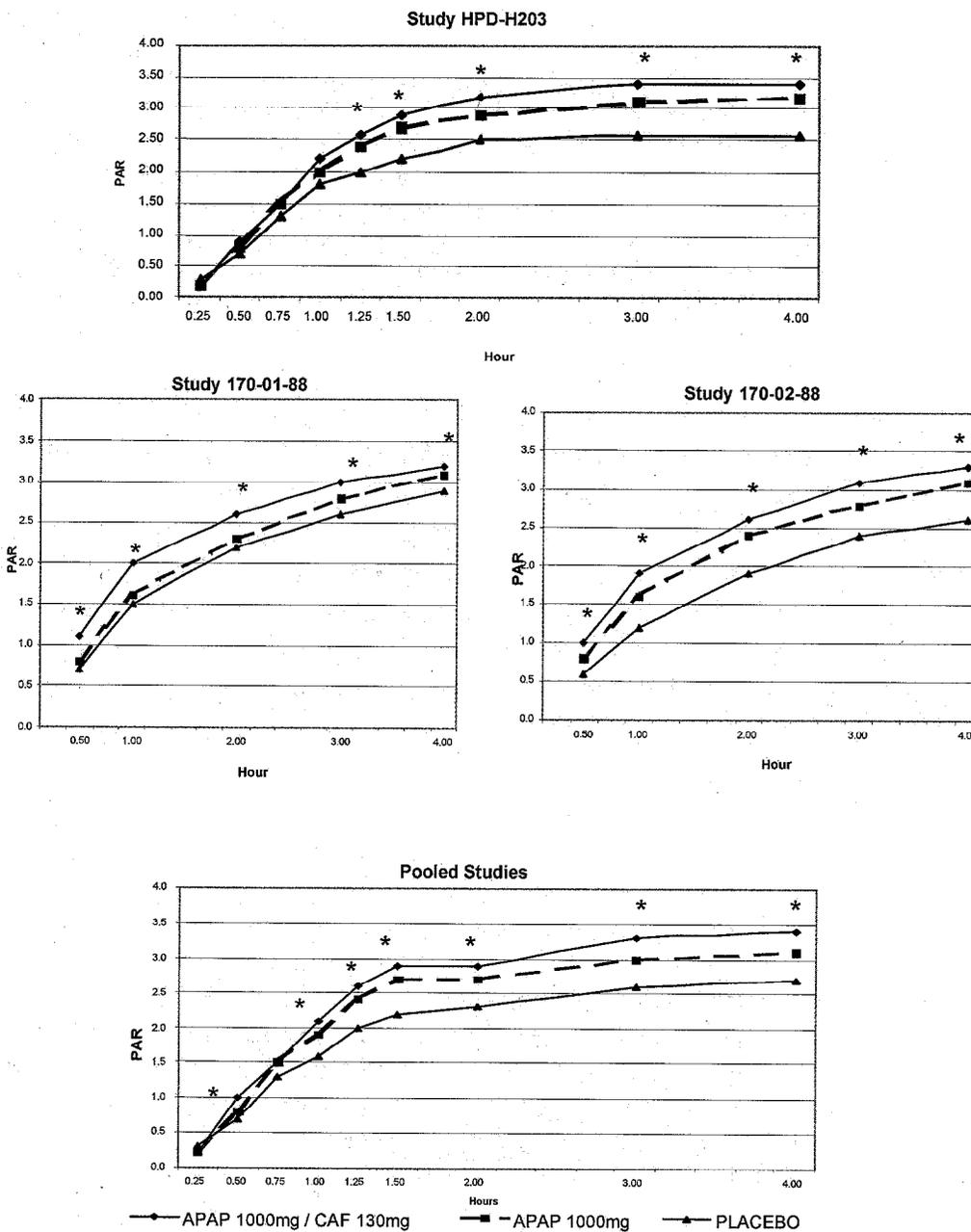
- Caffeine adjuvancy with APAP has been demonstrated in a variety of pain models (headache, dental, postpartum) and study designs (parallel, cross-over, bioassay) as evidenced by statistically significant increases in pain relief and decreases in pain intensity compared to APAP alone.
- Caffeine adjuvancy with APAP allows consumers to obtain better pain relief than could be expected with the analgesic base alone.
- Caffeine adjuvancy with APAP, currently the most commonly used analgesic in the U.S., provides a meaningful benefit to consumers.
- The combination of APAP with caffeine is safe and well tolerated with demonstrated caffeine adjuvancy.

**Figure A**  
**Pain Intensity Difference**  
**Tension Headache (ITT)**



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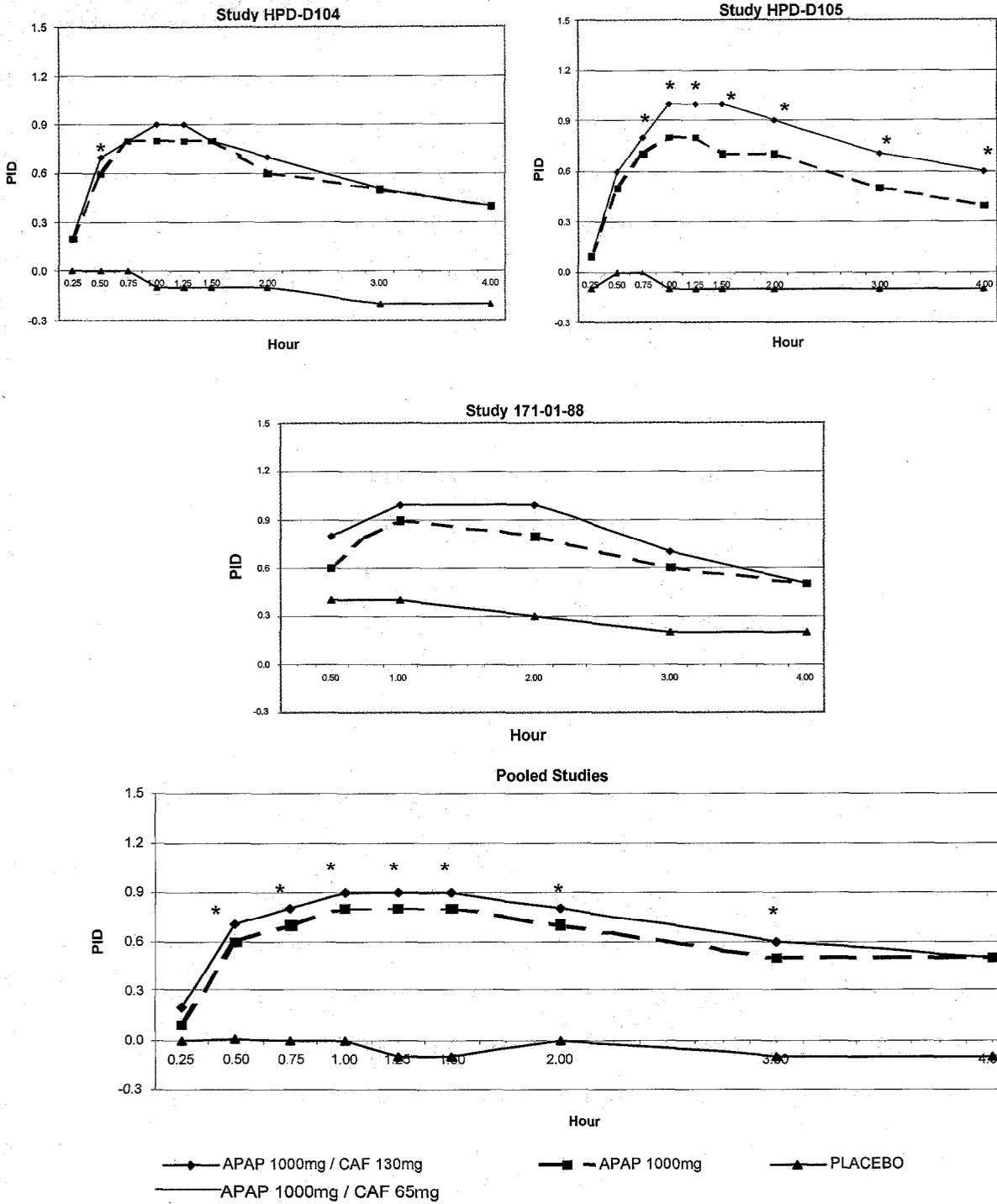
Figure B  
Pain Relief  
Tension Headache (ITT)



APAP 1000 mg/CAF 130 mg significantly greater than APAP 1000 mg  
\*

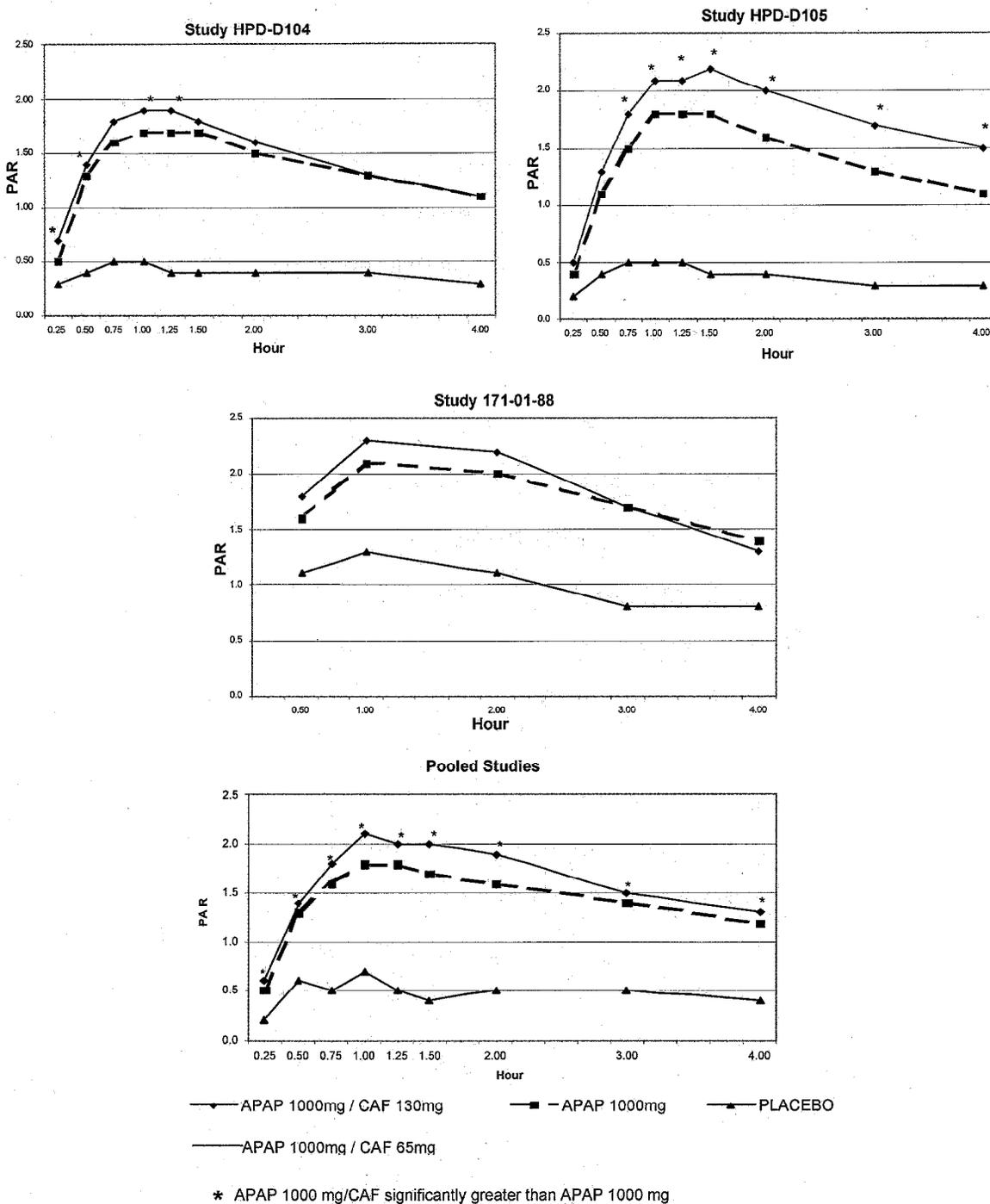
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Figure C  
Pain Intensity Difference  
Dental Pain (ITT)



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Figure D  
Pain Relief  
Dental Pain (ITT)



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## 7.0 REFERENCES

1. Beaver WT. Mild analgesics: A review of their clinical pharmacology, II. *Am J Med Sci* 1966;251:576-599.
2. Beaver WT. Aspirin and acetaminophen as constituents of analgesic combinations. *Arch Intern Med* 1981;141:293-300.
3. AMA Drug Evaluations, Fifth Edition, American Medical Association, Chicago. 1983;67-167.
4. Aaron H, Gardener LI, Hirsch J. Non-narcotic analgesics. *Med Lett Drugs Ther* 1966;8:7-8.
5. When are drug combinations justified? *Drug Ther Bull* 1981;18:37-40.
6. Laska EM, Sunshine A, Zigelboim I, Roure C, Marrero I, Wanderling J, Olson N. Effect of caffeine on acetaminophen analgesia. *Clin Pharmacol Ther* 1983;33:498-508.
7. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;8(Suppl 7):1-96.
8. Ad Hoc Committee on Classification of Headache. Classification of headache. *J Am Med Assoc*, 1962;179:717-718.

**APPENDIX 1**

Table 1	Tension Headache – Protocol 170-01-88 <sup>a</sup> Pain Intensity Difference from Baseline Intent-to-Treat Population
Table 1.1	Tension Headache – Protocol 170-01-88 <sup>a</sup> Pain Intensity Difference from Baseline Intent to-To-Treat Population
Table 2	Tension Headache – Protocol 170-02-88 <sup>a</sup> Pain Intensity Difference from Baseline Intent-to-Treat Population
Table 2.1	Tension Headache – Protocol 170-02-88 <sup>a</sup> Pain Intensity Difference from Baseline Intent-To-Treat Population
Table 5	Tension Headache – Protocol 170-01-88 <sup>a</sup> Pain Relief Intent-To-Treat Population
Table 6	Tension Headache – Protocol 170-02-88 <sup>a</sup> Pain Relief Intent-To-Treat Population
Table 8.1	Tension Headache – Protocol 170-01-88 <sup>a</sup> Pain Relief Intent-To-Treat Population
Table 8.2	Tension Headache – Protocol 170-02-88 <sup>a</sup> Pain Relief Intent-To-Treat Population

Table 1  
TENSION HEADACHE -- PROTOCOL 170-01-88\*  
PAIN INTENSITY DIFFERENCE FROM BASELINE  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=172	APAP1000 MEAN (STD) N=179	PLACEBO MEAN (STD) N= 89	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY							
DIFFERENCE (PID) *							
30 MIN	0.4 ( 0.61)	0.3 ( 0.61)	0.2 ( 0.52)	0.014	0.128	0.004	0.095
60 MIN	0.9 ( 0.76)	0.8 ( 0.78)	0.7 ( 0.79)	0.013	0.025	0.007	0.383
2 HRS	1.3 ( 0.80)	1.2 ( 0.81)	1.1 ( 0.88)	0.082	0.051	0.069	0.821
3 HRS	1.5 ( 0.79)	1.4 ( 0.85)	1.4 ( 0.92)	0.162	0.132	0.089	0.646
4 HRS	1.7 ( 0.76)	1.5 ( 0.93)	1.5 ( 0.99)	0.088	0.046	0.091	0.963
MAX PID	1.7 ( 0.73)	1.6 ( 0.82)	1.6 ( 0.83)	0.116	0.044	0.195	0.720
SUM OF PAIN INTENSITY							
DIFFERENCE (SPID) #							
1-HOUR	0.7 ( 0.62)	0.5 ( 0.64)	0.4 ( 0.58)	0.006	0.032	0.002	0.176
4-HOUR	5.2 ( 2.61)	4.6 ( 2.89)	4.5 ( 2.93)	0.032	0.032	0.023	0.594

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a FIRST HEADACHE ONLY

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 1.1  
 TENSION HEADACHE -- PROTOCOL 170-01-88<sup>a</sup>  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=172	APAP1000 MEAN (STD) N=179	PLACEBO MEAN (STD) N= 89	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY							
DIFFERENCE (PID) *							
30 MIN	0.4 ( 0.50)	0.3 ( 0.50)	0.2 ( 0.41)	0.009	0.079	0.002	0.107
60 MIN	0.9 ( 0.68)	0.7 ( 0.69)	0.7 ( 0.61)	0.005	0.013	0.003	0.337
2 HRS	1.3 ( 0.70)	1.2 ( 0.74)	1.2 ( 0.72)	0.136	0.069	0.131	0.982
3 HRS	1.6 ( 0.66)	1.5 ( 0.76)	1.5 ( 0.71)	0.096	0.037	0.162	0.750
4 HRS	1.7 ( 0.68)	1.6 ( 0.80)	1.6 ( 0.72)	0.245	0.100	0.328	0.707
MAX PID	1.8 ( 0.65)	1.7 ( 0.71)	1.7 ( 0.66)	0.158	0.059	0.268	0.661
SUM OF PAIN INTENSITY							
DIFFERENCE (SPID) #							
1-HOUR	0.6 ( 0.55)	0.5 ( 0.55)	0.5 ( 0.47)	0.002	0.017	0.001	0.174
4-HOUR	5.1 ( 2.34)	4.8 ( 2.59)	4.7 ( 2.32)	0.046	0.026	0.054	0.919

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

<sup>a</sup> AVERAGE OF THE TWO FIRST PERIOD HEADACHES ONLY

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 2  
TENSION HEADACHE -- PROTOCOL 170-02-88<sup>a</sup>  
PAIN INTENSITY DIFFERENCE FROM BASELINE  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=177	APAP1000 MEAN (STD) N=177	PLACEBO MEAN (STD) N= 87	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS LACEBO
PAIN INTENSITY DIFFERENCE (PID) *							
30 MIN	0.3 ( 0.51)	0.3 ( 0.56)	0.2 ( 0.51)	0.046	0.402	0.014	0.072
60 MIN	0.8 ( 0.75)	0.7 ( 0.72)	0.4 ( 0.71)	<0.001	0.171	<0.001	0.003
2 HRS	1.2 ( 0.76)	1.2 ( 0.82)	0.8 ( 0.88)	<0.001	0.521	<0.001	<0.001
3 HRS	1.5 ( 0.78)	1.5 ( 0.83)	1.1 ( 0.88)	<0.001	0.608	<0.001	<0.001
4 HRS	1.8 ( 0.71)	1.6 ( 0.88)	1.2 ( 0.91)	<0.001	0.023	<0.001	<0.001
MAX PID	1.8 ( 0.65)	1.7 ( 0.77)	1.3 ( 0.88)	<0.001	0.084	<0.001	<0.001
SUM OF PAIN INTENSITY DIFFERENCE (SPID) #							
1-HOUR	0.6 ( 0.57)	0.5 ( 0.58)	0.3 ( 0.52)	<0.001	0.202	<0.001	0.006
4-HOUR	5.1 ( 2.44)	4.8 ( 2.70)	3.5 ( 2.83)	<0.001	0.174	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a FIRST HEADACHE ONLY

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 2.1  
 TENSION HEADACHE -- PROTOCOL 170-02-88 a  
 PAIN INTENSITY DIFFERENCE FROM BASELINE  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=178	APAP1000 MEAN (STD) N=177	PLACEBO MEAN (STD) N= 87	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN INTENSITY							
DIFFERENCE (PID) *							
30 MIN	0.3 ( 0.43)	0.3 ( 0.48)	0.1 ( 0.33)	<0.001	0.584	<0.001	0.001
60 MIN	0.8 ( 0.60)	0.7 ( 0.60)	0.5 ( 0.52)	<0.001	0.165	<0.001	<0.001
2 HRS	1.2 ( 0.63)	1.2 ( 0.66)	0.9 ( 0.72)	<0.001	0.626	<0.001	<0.001
3 HRS	1.5 ( 0.67)	1.5 ( 0.65)	1.2 ( 0.81)	<0.001	0.661	<0.001	<0.001
4 HRS	1.7 ( 0.68)	1.6 ( 0.71)	1.3 ( 0.83)	<0.001	0.064	<0.001	<0.001
MAX PID	1.8 ( 0.62)	1.7 ( 0.62)	1.4 ( 0.78)	<0.001	0.180	<0.001	<0.001
SUM OF PAIN INTENSITY							
DIFFERENCE (SPID) #							
1-HOUR	0.6 ( 0.48)	0.5 ( 0.50)	0.3 ( 0.38)	<0.001	0.258	<0.001	<0.001
4-HOUR	5.1 ( 2.16)	4.8 ( 2.21)	3.8 ( 2.52)	<0.001	0.260	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a AVERAGE OF THE TWO FIRST PERIOD HEADACHES ONLY

# SPID = WEIGHTED SUM OF PAIN INTENSITY DIFFERENCE FROM BASELINE

Table 5  
TENSION HEADACHE -- PROTOCOL 170-01-88<sup>a</sup>  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=172	APAP1000 MEAN (STD) N=179	PLACEBO MEAN (STD) N= 89	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
30 MIN	1.2 ( 1.19)	0.9 ( 1.10)	0.7 ( 1.01)	0.006	0.026	0.002	0.212
60 MIN	2.1 ( 1.34)	1.7 ( 1.35)	1.5 ( 1.38)	0.002	0.006	0.002	0.363
2 HRS	2.6 ( 1.35)	2.4 ( 1.36)	2.3 ( 1.45)	0.101	0.133	0.044	0.426
3 HRS	3.0 ( 1.27)	2.8 ( 1.29)	2.7 ( 1.36)	0.126	0.217	0.047	0.329
4 HRS	3.2 ( 1.27)	3.0 ( 1.32)	3.0 ( 1.39)	0.357	0.303	0.180	0.621
PEAK RELIEF	3.3 ( 1.19)	3.1 ( 1.25)	3.1 ( 1.27)	0.284	0.153	0.222	0.958
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.6 ( 1.18)	1.3 ( 1.15)	1.1 ( 1.10)	0.001	0.007	<0.001	0.253
4-HOUR	10.5 ( 4.53)	9.6 ( 4.61)	9.0 ( 4.66)	0.042	0.073	0.018	0.364

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a FIRST HEADACHE ONLY

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Table 6  
TENSION HEADACHE -- PROTOCOL 170-02-88<sup>a</sup>  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=177	APAP1000 MEAN (STD) N=177	PLACEBO MEAN (STD) N= 87	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
30 MIN	1.0 ( 1.10)	0.8 ( 1.00)	0.6 ( 1.00)	0.015	0.183	0.004	0.067
60 MIN	1.9 ( 1.37)	1.7 ( 1.32)	1.1 ( 1.24)	<0.001	0.209	<0.001	0.003
2 HRS	2.6 ( 1.29)	2.5 ( 1.39)	1.9 ( 1.46)	<0.001	0.321	<0.001	0.002
3 HRS	3.2 ( 1.15)	2.9 ( 1.37)	2.4 ( 1.56)	<0.001	0.091	<0.001	<0.001
4 HRS	3.5 ( 1.01)	3.1 ( 1.38)	2.5 ( 1.59)	<0.001	0.015	<0.001	<0.001
PEAK RELIEF	3.5 ( 1.00)	3.2 ( 1.30)	2.6 ( 1.55)	<0.001	0.040	<0.001	<0.001
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.4 ( 1.13)	1.2 ( 1.09)	0.9 ( 1.01)	<0.001	0.160	<0.001	0.007
4-HOUR	10.7 ( 3.97)	9.8 ( 4.61)	7.6 ( 5.08)	<0.001	0.062	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a FIRST HEADACHE ONLY

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Table 8.1  
 TENSION HEADACHE -- PROTOCOL 170-01-88<sup>a</sup>  
 PAIN RELIEF  
 INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=172	APAP1000 MEAN (STD) N=179	PLACEBO MEAN (STD) N= 89	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
30 MIN	1.2 ( 0.99)	0.9 ( 0.94)	0.7 ( 0.78)	<0.001	0.002	<0.001	0.146
60 MIN	2.0 ( 1.13)	1.6 ( 1.11)	1.6 ( 1.08)	<0.001	<0.001	<0.001	0.689
2 HRS	2.5 ( 1.14)	2.4 ( 1.10)	2.3 ( 1.13)	0.086	0.066	0.059	0.697
3 HRS	3.0 ( 1.06)	2.8 ( 1.07)	2.7 ( 1.11)	0.078	0.058	0.056	0.724
4 HRS	3.2 ( 1.02)	3.0 ( 1.10)	3.0 ( 1.08)	0.294	0.152	0.242	0.995
PEAK RELIEF	3.3 ( 0.98)	3.1 ( 1.01)	3.1 ( 1.03)	0.164	0.086	0.146	0.961
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.6 ( 1.00)	1.3 ( 0.96)	1.1 ( 0.86)	<0.001	<0.001	<0.001	0.342
4-HOUR	10.3 ( 3.85)	9.4 ( 3.80)	9.2 ( 3.78)	0.013	0.012	0.014	0.671

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a AVERAGE OF THE TWO FIRST PERIOD HEADACHES ONLY

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE

Table 8.2  
TENSION HEADACHE -- PROTOCOL 170-02-88<sup>a</sup>  
PAIN RELIEF  
INTENT-TO-TREAT POPULATION

VARIABLE	APAP1000/CAF130 MEAN (STD) N=178	APAP1000 MEAN (STD) N=177	PLACEBO MEAN (STD) N= 87	OVERALL TREATMENT EFFECT	P-VALUES @		
					APAP/CAF VS APAP	APAP/CAF VS PLACEBO	APAP VS PLACEBO
PAIN RELIEF *							
30 MIN	1.0 ( 0.88)	0.9 ( 0.88)	0.5 ( 0.69)	<0.001	0.170	<0.001	0.001
60 MIN	1.8 ( 1.04)	1.6 ( 1.07)	1.2 ( 0.94)	<0.001	0.118	<0.001	<0.001
2 HRS	2.6 ( 1.03)	2.4 ( 1.10)	1.9 ( 1.17)	<0.001	0.210	<0.001	<0.001
3 HRS	3.1 ( 0.99)	2.9 ( 1.10)	2.4 ( 1.27)	<0.001	0.098	<0.001	<0.001
4 HRS	3.3 ( 0.98)	3.1 ( 1.13)	2.6 ( 1.25)	<0.001	0.046	<0.001	<0.001
PEAK RELIEF	3.4 ( 0.92)	3.2 ( 0.98)	2.7 ( 1.23)	<0.001	0.114	<0.001	<0.001
TOTAL PAIN RELIEF (TOTPAR) #							
1-HOUR	1.4 ( 0.91)	1.3 ( 0.92)	0.9 ( 0.75)	<0.001	0.114	<0.001	<0.001
4-HOUR	10.3 ( 3.44)	9.7 ( 3.72)	7.8 ( 4.08)	<0.001	0.065	<0.001	<0.001

@ P-VALUE FROM ANALYSIS OF COVARIANCE WITH FACTORS OF TREATMENT, INVESTIGATOR, AND BASELINE PAIN INTENSITY AS THE COVARIATE

\* ARITHMETIC MEAN AND STANDARD DEVIATION (STD) BASED ON RAW DATA

a AVERAGE OF THE TWO FIRST PERIOD HEADACHES ONLY

# TOTPAR = WEIGHTED SUM OF PAIN RELIEF SCORE