

EXCEDRIN[®] EXTRA STRENGTH

Clinical Trial Proposal (Tension Headache Model)

I. Title

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose study comparing the efficacy of two different formulations of Excedrin[®] Extra Strength with Extra Strength Tylenol[®] and placebo in the acute treatment of episodic tension-type headache.

II. Rationale

This study is designed to determine whether two different formulations of Excedrin[®] ES are superior to ES Tylenol[®] (APAP 1000) and to placebo in the acute treatment of episodic tension-type headache. One formulation of Excedrin[®] ES contains ASA 500 mg, APAP 500 mg, and caffeine 130 mg per two-tablet dose (EES 130), and the second formulation contains ASA 500 mg, APAP 500 mg, and caffeine 65 mg per two-tablet dose (EES 65).

In six well-controlled clinical trials—four in episodic tension-type headache and two in postoperative dental pain—EES 130 was significantly superior to APAP 1000 as measured by the standard efficacy measures of total pain relief (TOTPAR) and sum of pain intensity differences from baseline (SPID) (Docket submission #77N-0094; 12/21/88). However, the efficacy of EES 65 relative to both EES 130 and APAP 1000 has never been studied in a comparative clinical trial.

This study is designed to test the superiority of EES 65 over APAP 1000 by detecting a clinically and statistically significant difference in the 4-hour weighted sum of pain-relief scores (TOTPAR4). It is anticipated that the mean TOTPAR4 for EES 130 will be significantly greater than that for placebo and for APAP 1000, and numerically greater than that for EES 65.

This study will also provide information on the dose-response relationship between APAP 1000, EES 65, and EES 130. A positive dose response in this trial would provide evidence for increased analgesic adjuvancy with increased caffeine dose and provide information on the dose-response relationship between EES 130, EES 65, and APAP 1000.

III. Study Objectives

- A. Compare a single dose of Excedrin[®] ES containing 65 mg caffeine (EES 65) with 1000 mg of APAP and placebo.
- B. Compare a single dose of Excedrin[®] ES containing 130 mg caffeine (EES 130) with 1000 mg of acetaminophen (APAP) and placebo.
- C. Evaluate dose-response relationship between EES 130 and EES 65.

The primary comparison in this study is that between EES 65 and APAP 1000. As the superiority of EES 130 vs. APAP 1000 has been previously established, the purpose of EES 130 in this study is as the "gold standard" positive control. The test of EES 130 vs. APAP 1000 is only being conducted to confirm the sensitivity of the study and is secondary to that of EES 65 vs. APAP 1000.

IV. Study Design

- A. Multicenter, randomized, double-blind, placebo-controlled, parallel-group, single-dose study.
- B. Treatment Arms
 1. EES 130 (ASA 250 mg/APAP 250 mg/Caffeine 65 mg per tablet x 2)
 2. EES 65 (ASA 250 mg/APAP 250 mg/Caffeine 32.5 mg per tablet x 2)
 3. APAP 1000 (APAP 500 mg per tablet x 2)
 4. Placebo tablets
- C. Number of Sites: 12 to 20
- D. Subjects: 400 subjects per treatment arm (1600 total)
- E. Visits
 1. Screening & Enrollment
 2. Follow-Up

V. Inclusion Criteria

- A. Must be 18 years of age or older.
- B. Women of child-bearing potential must be sterilized or using an acceptable birth-control method. (Urine pregnancy test on day of screening must be negative.)
- C. Must suffer an average of at least four—but not more than ten—episodic tension-type headache (IHS 2.1) per month.
- D. Tension headaches must, on average, last at least four hours without treatment.
- E. Must have no more than one migraine headache per month.
- F. Must be able to distinguish one headache type from another.
- G. Tension headaches must be at least moderate in intensity.
- H. Must be in good general health based upon medical history.
- I. Must give written informed consent prior to enrollment.
- J. Must be able to communicate meaningfully with study personnel.

VI. Exclusion Criteria

- A. Emotional disorder of such severity as to preclude participation.
- B. Unwilling or unable to ingest tablets.
- C. Unwilling or unable to fully participate in study.
- D. Tension headaches caused or exacerbated by recent head or neck trauma.
- E. Sensitivity or idiosyncratic response to APAP, any NSAID, or any xanthine.
- F. Taking any concomitant medications (e.g., psychotropics, antidepressants, sedative-hypnotics, steroidal or nonsteroidal anti-inflammatory drugs, analgesics) which could confound quantification of analgesia.
- G. Recent history of alcohol or drug abuse.
- H. Significant history of malignancy, gastrointestinal ulcers and/or bleeding, inflammatory bowel disease, metabolic disease, hematologic disease, or disease of the pancreas, heart, kidney, lungs, liver, nervous system.
- I. Medical condition requiring chronic administration of analgesics, steroids, or NSAIDs. (ASA \leq 325 mg qD for MI prophylaxis permitted.)
- J. Used investigational drug or device during 30 days preceding enrollment.
- K. Enrolled in another study or previous enrollment in same study.

VII. Efficacy Evaluations

- A. Recorded Variables
 1. Pain Intensity
 - a. Scale: None, Mild, Moderate, Severe.
 - b. Assessments: 15, 30, 45, 60, 90, 120, 180, and 240 minutes.
 2. Pain Relief
 - a. Scale: None, A Little, Some, A Lot, Complete.
 - b. Assessments: 15, 30, 45, 60, 90, 120, 180, and 240 minutes.
 3. Time to Meaningful Relief
 4. Other measures, including muscle stiffness, psychic tension, degree of relaxation, and interference with daily activities.
- B. Calculated Variables
 1. PID, peak PID, SPID.
 2. Pain relief scores, peak PAR, TOTPAR.
 3. Time to onset of meaningful pain relief.
 4. Time to taking backup medication.

VIII. Safety Evaluation

- A. Analysis of adverse events (AEs).
- B. AEs may be either spontaneously reported or elicited during questioning and examination of subjects.
- C. All identified AEs must be recorded and described on the appropriate page of the case report form.

IX. Study Procedures

- A. Informed Consent
- B. Review of Inclusion and Exclusion Criteria to Determine Eligibility.
- C. Stop Watch, Diary, and Study Medication
 - 1. Dispensing
 - 2. Training
- D. Baseline Diary Assessment
 - 1. Pain intensity (must be at least moderate)
 - 2. Date and time of assessment
 - 3. Dosing with study medication
- E. Subsequent Diary Assessments
 - 1. 15, 30, 45, 60, 90, 120, 180, and 240 minutes after dosing
 - 2. Pain intensity level
 - 3. Degree of pain relief
 - 4. Onset of meaningful pain relief (stop watch)
- F. Rescue
 - Preferred after two hours, but permitted anytime.
- G. Follow-Up Visit
 - 1. Document AEs.
 - 2. Return materials.

X. Statistical Methods

- A. Primary Efficacy Variable: TOTPAR4
- B. Primary Data Set: Intent-to-Treat
- C. Sample Size Calculation:

400 subjects per treatment group will provide $\geq 90\%$ power with a Type I error rate of 5% (two-tailed) to detect a 1.2-unit difference in TOTPAR4 between any two treatments.
- D. Analysis Methods
 - 1. Analyses of PIDs, PARs, SPIDs, and TOTPARs will be done via ANCOVA model with factors for treatment, center, and baseline pain intensity as covariate.
 - 2. Time to meaningful pain relief will be analyzed using Wilcoxon Rank sums and nonparametric survival techniques for comparing waiting-time distributions.
 - 3. Linear contrast to estimate slope of the dose response regression line will be calculated using the three active treatment groups.

Study Procedure Flow Chart

STUDY EVENTS & PROCEDURES	Screening & Enrollment (V1)	Treatment Phase	Follow-Up (V2)
Informed Consent	X		
Diagnostic Interview	X		
Medical History	X		
Medication History	X		
Physical Exam (incl. neuro)	X		
Urine Pregnancy Test (WOCBP)	X	X	
Inclusion/Exclusion Criteria	X		
Enroll Subject/Assign Subject Number	X		
Issue Stopwatch & Diary	X		
Subject Training	X		
Dispense Study Medication	X		
Subject Self-Rates & Self-Treats Headache Episode		X	
Investigator Reviews Subject Diary			X
Document Adverse Experiences			X
Collect/Inventory Study Materials			X
Patient Status			X

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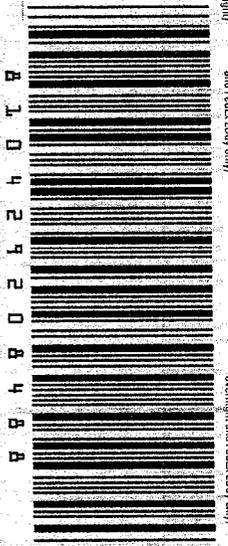
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