

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: 20802**

**STATISTICAL REVIEW(S)**



responder at a predetermined evaluation time (1/2, 1, 2, 3, 4, 6 hours post baseline) if that patient's pain was reduced to mild or none at that evaluation time. Thus, PRS is not a direct patient judgment, but is an inferred judgment based the pain intensity scale.

The sponsor summarized efficacy results at 2 and 6 hours (Vol. 1.1, Section 2.H.3, pages 110, 117, 125). For all three studies, the sponsor concluded that for PID and PRS, Excedrin was statistically more effective in the relief of migraine pain than placebo. Statistical results computed by this reviewer confirm those of the sponsor.

#### IV. Reviewer's Statistical Analyses and Results

Beside a routine check of the sponsor's statistical findings, this reviewer looked into the sponsor's selection of evaluable migraine patients. The purpose of my patient re-selection is not intended to improve that of the sponsor; my purpose is to examine statistical robustness by an alternative patient selection. My patient selection, unlike the sponsor's (see Vol. 1.1, Section 2.H.2, pages 98, 100), is not based on migraine expertise, but rather on a computer reading of patient data which sought to fit the IHS migraine criteria. For reference, the IHS (International Headache Society) criteria for migraine with and without aura and a by-study listing of mismatched patients is given in the appendix of this review (pages 11, 12).

Included in my own analyses are all and only those patients whose interview response data strictly satisfied my implementation of the IHS criteria and who, in addition, had the minimal amount of data necessary for a statistical analysis. While this brought about a modest difference in patients the sponsor and I selected for analysis, the sponsor's statistical findings were confirmed by my own. First, I will briefly characterize the differences between my patient selection and the sponsor's followed by patient demographics. Reviewer's analytical results for the primary efficacy variables are found on pages 5-10.

#### A. FDA/Bristol-Myers Patient Inclusion Comparison

	Patient Inclusion Counts for Statistical Analyses		
	Study 840	Study 841	Study 842
Bristol-Meyers	378	427	415
FDA Reviewer	365	418	397
Total No. Patients involved	387	435	420
No. Mismatched Pts.	31	25	28
Mismatch Percentage *	8.0%	5.7%	6.7%

\* Computed as  $100 \times [\text{No. Mismatched Pts.} / \text{Total No. Patients}]$ . Mismatched patients are listed by study on appendix page 12.

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**B. Patient Counts - Strict Migraine Patient Demographics**

Demographic	Drug Taken	Study 840	Study 841	Study 842
Female/Male:	Excedrin	136/47	154/52	166/34
	placebo	141/41	172/40	164/33
White/Other:	Excedrin	142/41	175/31	180/20
	placebo	152/30	188/24	174/23
Age<60/Age≥60:	Excedrin	181/2	199/7	193/7
	placebo	179/3	200/12	191/6
No Aura/Aura:	Excedrin	157/26	163/43	169/31
	placebo	154/28	166/46	168/29

While these counts do not give a complete view of the balance of patient allocation demographics to Excedrin and to placebo, these counts do not indicate cause for concern.

Reviewer's statistical methods were as follows. As was done by the sponsor, PID and PRS were analyzed at each time-point. Note in (A), (B), and (C) below that when there is but one investigator, the model term for investigator is automatically redundant.

- (A) The primary analysis of PID used an ANCOVA model of the form:  

$$PID(\text{time}) = \mu + \text{Drug}(i) + \text{Investigator}(j) + \beta \cdot \text{BaselinePI} + \text{Error}.$$
 Interactions were checked by a model that further included terms for drug by investigator and drug by baseline Pain Intensity. Excedrin was found in all three studies to provide statistically superior pain reductions (PID) to placebo from 1 to 6 hours inclusive.
- (B) The primary analysis of Patient Response Status made use of an ANCOVA model as well as a logistic model of the form:  $PRS(\text{time}) = \mu + \text{Drug}(i) + \text{Investigator}(j) + \text{Error}.$  Interaction of drug with investigator was checked by including a drug by investigator model term. Excedrin was found to provide statistically superior pain relief (PRS) to placebo from 1 to 6 hours inclusive.
- (C) Analyses were performed to explore the effects of Age, Race, Sex, and the existence of Aura accompanying migraine on relief from pain. The effects of Age, Race, and Sex were done as a group by including, in the corresponding models identified in (A) and (B) above, terms for these 3 main effects along with their individual interactions with drug effect. Third and higher order interactions were ignored. The effect of Aura was isolated from the effect of Age, Race, and Sex by including in the models identified in (A) and (B), an indicator variable for the existence of aura along with its interaction with drug effect. Age, Race, Sex, and Aura appear to have no substantive effect on the action of Excedrin in migraine. The results of these analyses for Age, Race, Sex, and Aura should not be considered to have confirmatory value because these studies were neither designed nor powered to detect these effects.

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**V. Reviewer's Comments**

The three studies and the resulting data examined by this reviewer provide adequate statistical evidence that Excedrin is effective in relieving the pain of migraine. This inferential conclusion is based on both the sponsor's and my own statistical analyses of the two agreed upon primary efficacy variables (pain intensity, patient response status) and that FDA combination drug policy is not to be applied to this case.

*Richard A. Stein*

Richard A. Stein, Ph.D.  
Mathematical Statistician

This review contains 4 pages of text, and 8 pages of appended tables, and figures.

Concur:

*Hoi M. Leung*

Hoi M. Leung, PhD  
Team Leader

*Ralph Harkins*

Ralph Harkins, PhD  
Director, Div. of Biometrics IV

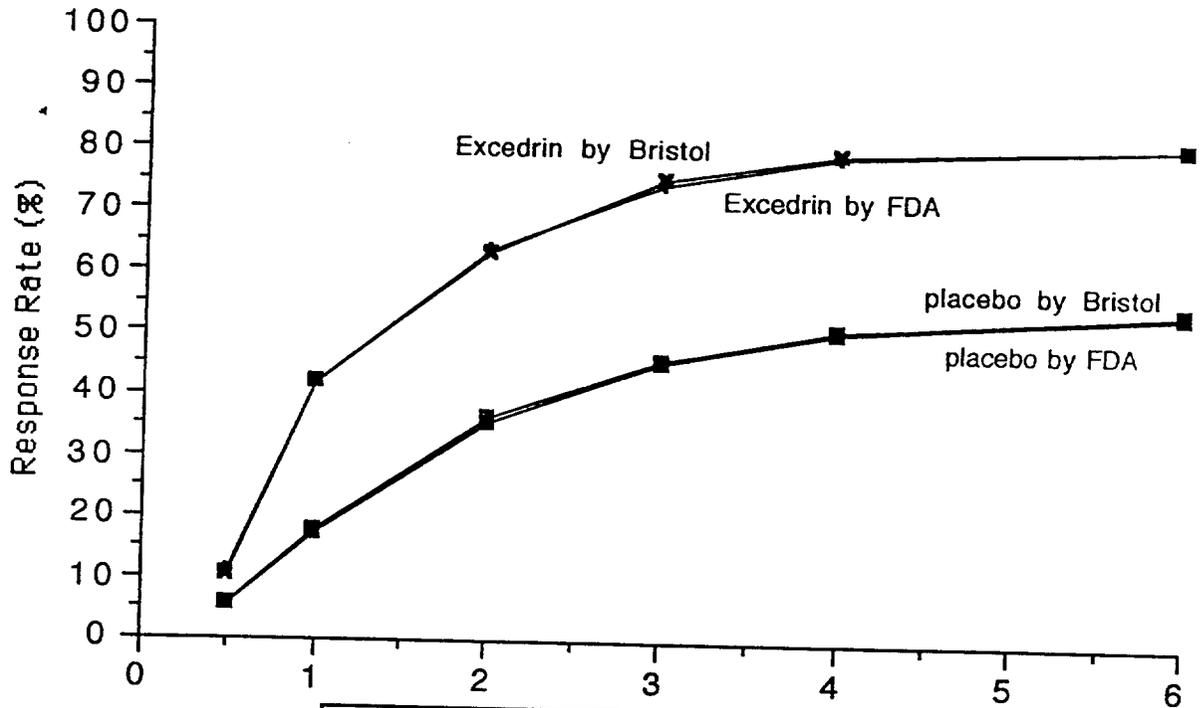
Archival: NDA 20-802  
cc: HFD-550/Rudolph Widmark, MD, PhD  
HFD-550/Chin Koerner, CSO  
HFD-550/Div. File  
HFD-340/Div. Sci. Inv.  
HFD-725/Richard Stein, PhD  
HFD-725/Div. File

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# Appendix

## Study 840 - Summary of Results

### Proportion of Patients Responding to Excedrin and to placebo

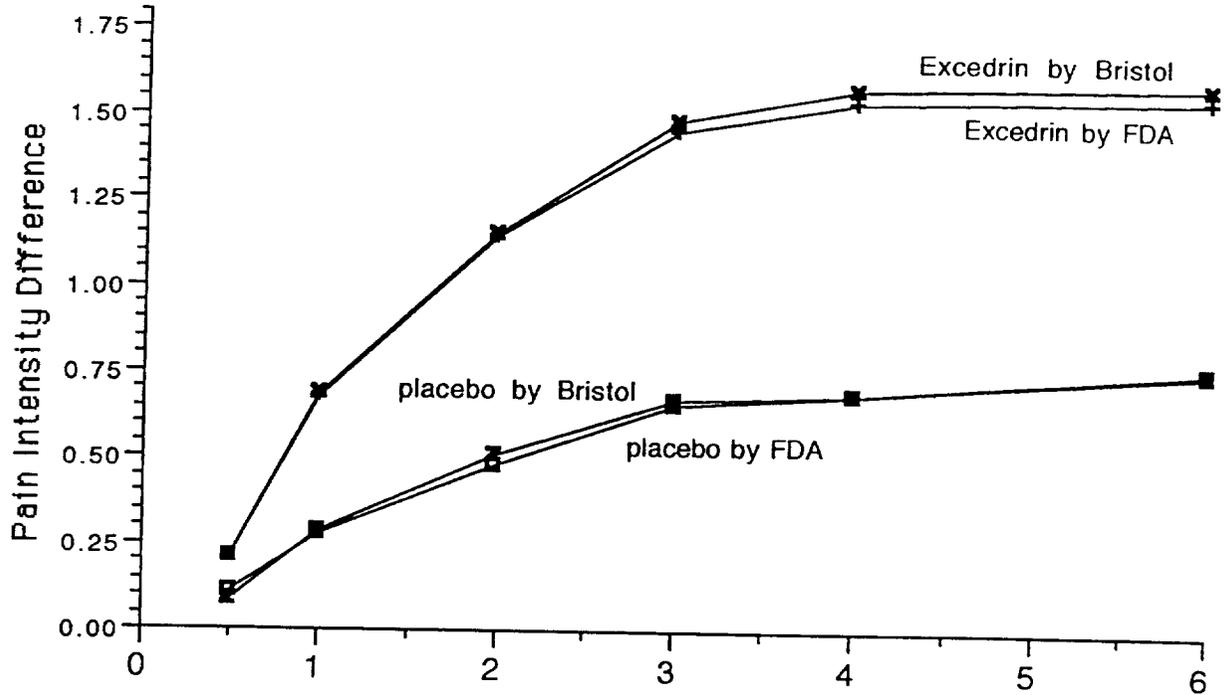


Drug	No. Pts.	Time after taking Drug [Hours]					
		0.5	1	2	3	4	6
Excedrin *	187	10.7%	42.2%	63.6%	75.4%	79.7%	81.8%
placebo	191	5.8%	17.8%	36.6%	46.1%	51.3%	55.0%
Excedrin **	183	10.9%	42.1%	63.9%	74.9%	79.2%	81.4%
placebo	182	6.0%	17.6%	35.9%	45.9%	50.8%	54.4%
P-Value **		0.08	<.0001	<.0001	<.0001	<.0001	<.0001

\* Using Sponsor's Evaluability Criteria

\*\* Using FDA reviewer's "strict migraine" Approach

## Study 840 Pain Intensity Difference

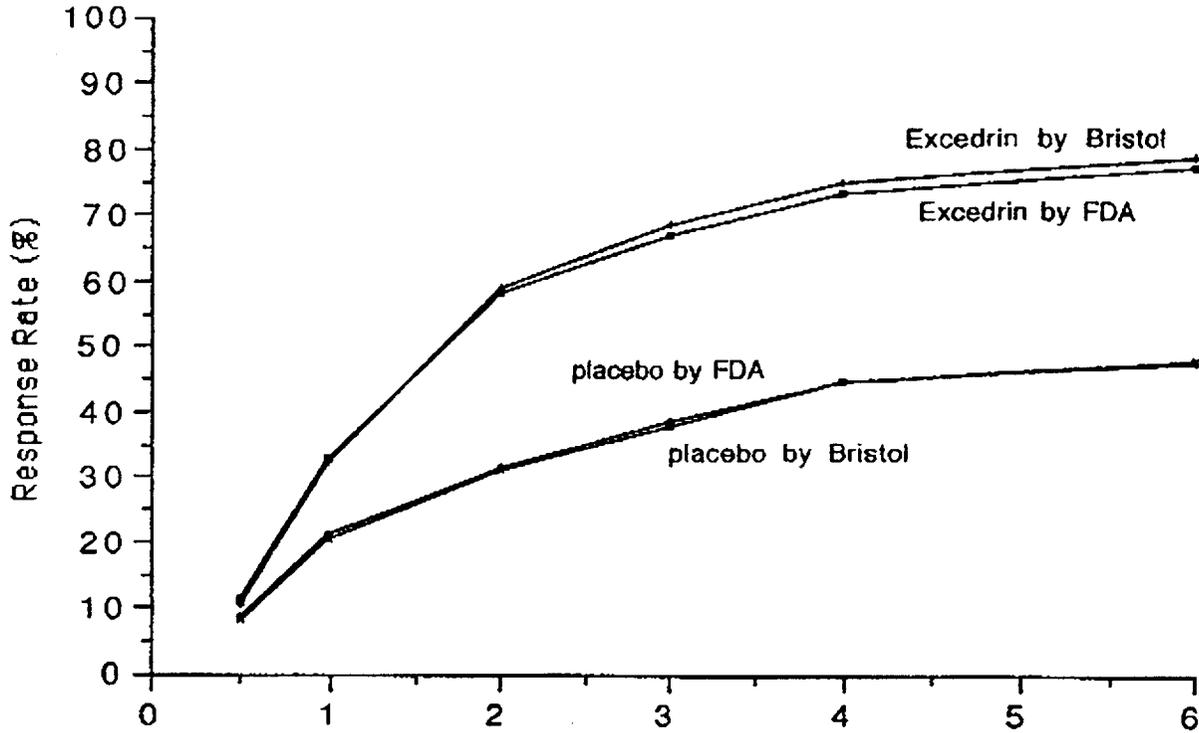


Drug	N Pts	Time after taking Drug [Hours]						
		0.00 †	0.50	1	2	3	4	6
Excedrin *	187	2.37	0.21	0.70	1.16	1.49	1.58	1.60
placebo	191	2.41	0.09	0.29	0.51	0.67	0.69	0.76
Excedrin **	183	2.36	0.21	0.68	1.15	1.45	1.54	1.56
placebo	182	2.42	0.11	0.28	0.48	0.66	0.69	0.77
P-Value **		0.27	0.02	<.0001	<.0001	<.0001	<.0001	<.0001

- † Pain Intensity at Baseline
- \* Using Sponsor's Evaluability Criteria
- \*\* Using FDA reviewer's "strict migraine" Approach

### Study 841 - Summary of Results

#### Proportion of Patients Responding to Excedrin and to placebo

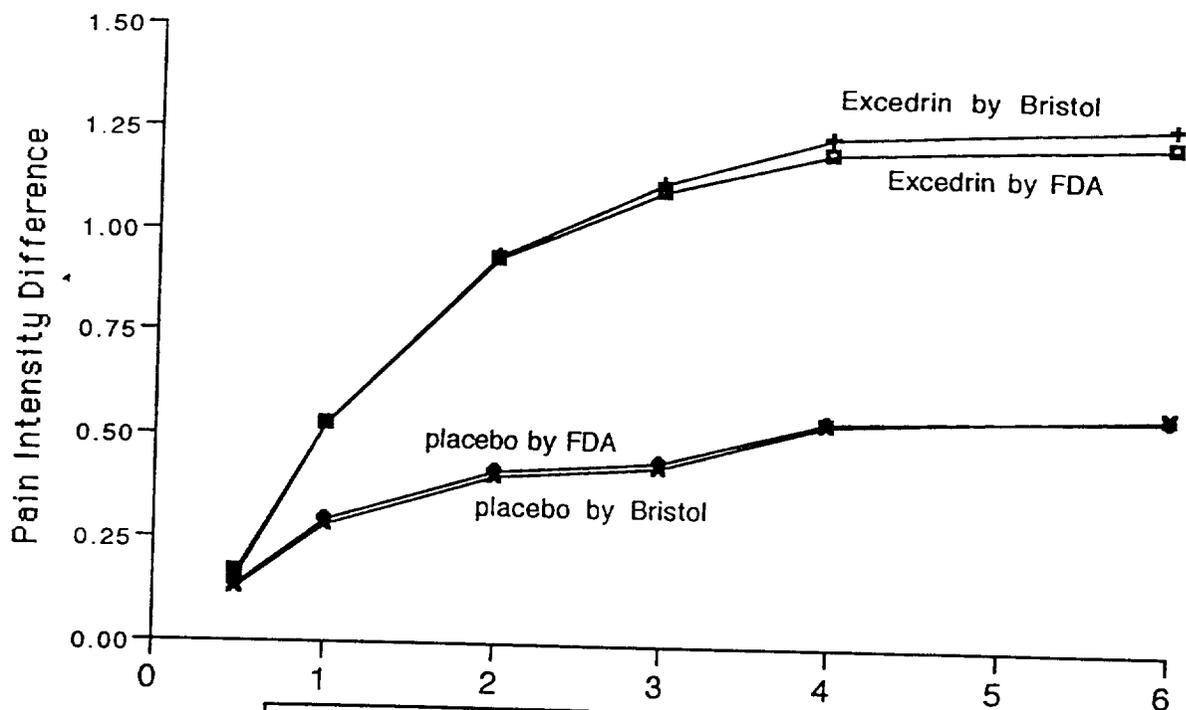


		Time after taking Drug [Hours]					
Drug	No. Pts.	0.5	1	2	3	4	6
Excedrin *	206	10.7%	32.5%	59.2%	68.4%	74.8%	78.2%
placebo	212	8.6%	20.5%	31.2%	38.0%	44.3%	47.5%
Excedrin **	206	11.7%	33.0%	58.3%	67.0%	73.3%	76.7%
placebo	212	9.0%	21.2%	31.6%	38.7%	44.3%	47.2%
P-Value **		0.43	<.01	<.0001	<.0001	<.0001	<.0001

\* Using Sponsor's Evaluability Criteria

\*\* Using FDA reviewer's "strict migraine" Approach

## Study 841 Pain Intensity Difference

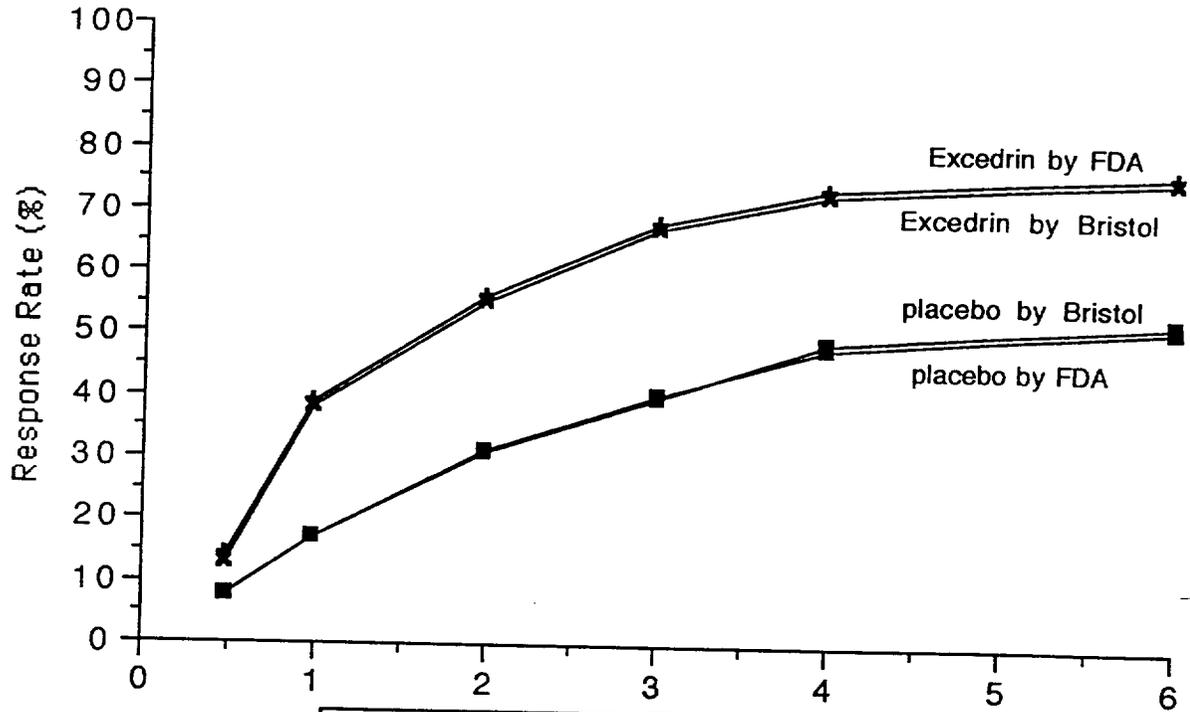


Drug	N Pts	Time after taking Drug [Hours]						
		0.00 †	0.50	1	2	3	4	6
Excedrin *	206	2.33	0.16	0.53	0.94	1.13	1.24	1.28
placebo	212	2.29	0.14	0.29	0.41	0.43	0.54	0.57
Excedrin **	206	2.33	0.17	0.53	0.93	1.10	1.20	1.23
placebo	212	2.31	0.14	0.30	0.42	0.45	0.55	0.57
P-Value **			0.69	<.001	<.0001	<.0001	<.0001	<.0001

- † Pain Intensity at Baseline
- \* Using Sponsor's Evaluability Criteria
- \*\* Using FDA reviewer's "strict migraine" Approach

## Study 842 - Summary of Results

### Proportion of Patients Responding to Excedrin and to placebo

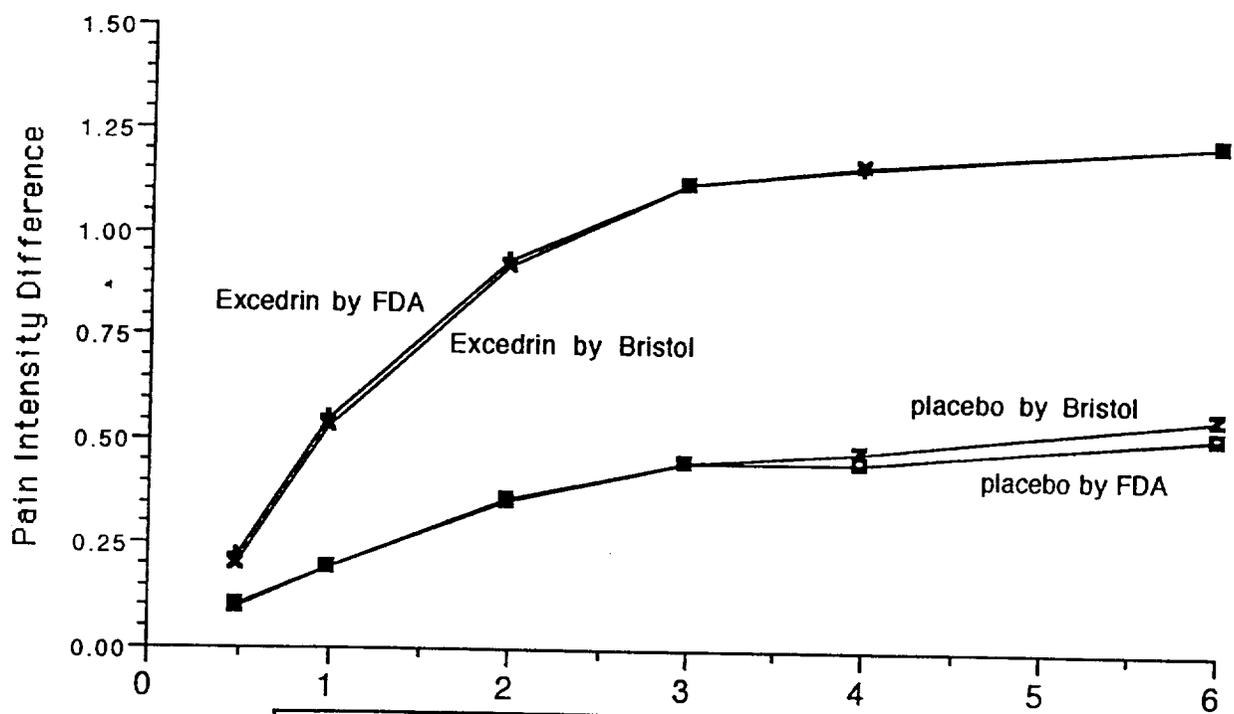


Drug	No. Pts.	Time after taking Drug [Hours]					
		0.5	1	2	3	4	6
Excedrin *	209	12.9%	38.3%	55.5%	67.5%	73.2%	76.1%
placebo	206	7.8%	17.5%	31.1%	40.3%	49.0%	52.9%
Excedrin **	200	14.5%	39.5%	56.5%	68.5%	74.0%	77.0%
placebo	197	8.1%	17.3%	31.5%	40.6%	48.2%	52.3%
P-Value **		0.04	<.0001	<.0001	<.0001	<.0001	<.0001

\* Using Sponsor's Evaluability Criteria

\*\* Using FDA reviewer's "strict migraine" Approach

## Study 842 Pain Intensity Difference



Drug	N. Pts	Time after taking Drug [Hours]						
		0.00 †	0.50	1	2	3	4	6
Excedrin *	209	2.31	0.21	0.54	0.92	1.12	1.17	1.22
placebo	206	2.30	0.10	0.19	0.36	0.46	0.48	0.57
Excedrin **	200	2.30	0.22	0.56	0.94	1.13	1.16	1.23
placebo	197	2.30	0.11	0.20	0.36	0.45	0.46	0.53
P-Value **		0.98	0.01	<.0001	<.0001	<.0001	<.0001	<.0001

† Pain Intensity at Baseline  
 \* Using Sponsor's Evaluability Criteria  
 \*\* Using FDA reviewer's "strict migraine" Approach

**MIGRAINE CRITERIA  
INTERNATIONAL HEADACHE SOCIETY (IHS)**

**1.1 Migraine Without Aura (Common Migraine)**

- A. At least 5 attacks fulfilling criteria B-D:
- B. Headache attacks, lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following 4 characteristics:
  - 1. Unilateral location
  - 2. Pulsating quality
  - 3. Moderate or severe intensity (inhibits or prohibits daily activities)
  - 4. Aggravation by walking stairs or similar routine physical activities
- D. During headache at least one of the following:
  - 1. Nausea and/or vomiting,
  - 2. Photophobia and phonophobia.
- E. At least one of the following:
  - 1. History, physical and neurological examinations do not suggest organic disorder,
  - 2. History, physical and neurological examinations do suggest organic disorder, but such disorder is ruled out by appropriate investigations,
  - 3. Organic disorder is present, but migraine attacks do not occur de novo in close temporal relation to the disorder.

**1.2 Migraine With Aura (Classical Migraine)**

- A. At least 2 attacks fulfilling criteria B.
- B. At least three of the following four characteristics:
  - 1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction,
  - 2. At least one aura symptom develops gradually over more than 4 minutes or, two or more symptoms occur in succession,
  - 3. No aura symptom lasts more than 60 minutes. If more than one symptom is present, accepted duration is proportionally eased,
  - 4. Headache follows aura with a free interval of less than 60 minutes, but may begin before the aura.
- C. At least one from 1.1.E. (above).

## Patients Not Analyzed in Common: Bristol/Reviewer

The following is a by-study list of patient ID numbers that are not common to the statistical efficacy analyses of Bristol and of this reviewer.

### Study -840

#### 22 Patients Included by Bristol but Excluded by FDA

1019\*, 1021, 1024, 1050, 1065, 1126, 1138, 1154, 1171, 1177, 1192, 1223, 1235, 1269, 1294, 1312, 1313, 1321, 1335, 1343, 1427, 1434

#### 9 Patients Excluded by Bristol but Included by FDA

1043, 1053, 1181, 1187, 1262, 1318, 1330, 1347, 1430

### Study -841

#### 17 Patients Included by Bristol but Excluded by FDA

2020, 2027, 2042, 2044, 2109, 2117, 2160, 2209, 2318, 2464, 2473, 2486, 2494, 2540, 2561, 2595, 2612

#### 8 Patients Excluded by Bristol but Included by FDA

2124, 2211, 2265, 2279, 2321, 2533, 2591, 2600

### Study 842

#### 23 Patients Included by Bristol but Excluded by FDA

3014, 3015, 3041, 3143, 3151, 3176, 3189, 3190, 3217, 3221, 3224, 3232, 3235, 3286, 3306, 3313, 3366, 3434, 3515, 3517, 3518, 3537, 3538

#### 5 Patients Excluded by Bristol but Included by FDA

3177, 3287, 3291, 3450, 3567

- \* As an example, patient 1019 was included in the sponsor's efficacy evaluation of Response Status and Pain Intensity. This patient was excluded by this reviewer because this patient, who did not have aura, responded YES only to question C-1 of the 4 criteria under point C of IHS criteria given on the previous page.

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# Statistical Review and Evaluation

NDA: 20-802

Drug Name: Excedrin Extra Strength

Applicant: Bristol-Myers Products

Statistical Reviewer: Richard A. Stein

Review #2, Date: 6/3/97

Correspondence Date: 1/14/97

FDA Stamp Date: 1/15/97

Reviewing Medical Officer: Rudolph Widmark, MD

Volumes Reviewed: 1.1, 1.33, 1.34, 1.37, 1.40, 1.50

Indication: For temporary relief of pain associated with: headache, including migraine headache, toothache, muscular aches, backache, colds, minor arthritis, and menstrual discomfort.

This report is an analytical extension of my first review of Excedrin dated 5/23/97.

**Patient Response Status** is analyzed here using a modified definition of "responder". In my first review, a patient was judged to respond when that patient's pain intensity was reduced to a rating of mild or none. In this review, a patient is a responder at a predetermined evaluation time (1/2, 1, 2, 3, 4, 6 hours post baseline) only if that patient's pain is reduced to "none".

## Reviewer's Statistical Analyses and Results

The statistical model and methods used here are the same as in my original memo of 5/23/97. The table below puts together my former results adjoined with my latest results.

It can be seen on the last 3 lines of each table below that modifying the definition of a responder leads to different estimates of the proportion responding, but does not effectively modify the original overall statistical conclusions.

Study 840		Time after taking Drug [Hours]					
Drug	No. Pts.	0.5	1	2	3	4	6
Excedrin ☞	187	10.7%	42.2%	63.6%	75.4%	79.7%	81.8%
placebo	191	5.8%	17.8%	36.6%	46.1%	51.3%	55.0%
Excedrin *	183	10.9%	42.1%	63.9%	74.9%	79.2%	81.4%
placebo	182	6.0%	17.6%	35.9%	45.9%	50.8%	54.4%
P-Value *		0.08	<.0001	<.0001	<.0001	<.0001	<.0001
Excedrin ***	183	0.5%	5.5%	25.7%	41.0%	50.8%	56.8%
placebo	182	0.5%	2.2%	5.5%	13.3%	20.4%	25.8%
P-Value ***		0.99	0.10	<.0001	<.0001	<.0001	<.0001

☞ Using Sponsor's Evaluability Criteria

\* Using FDA "strict migraine" Approach with Responders as Pain = "None" or "Mild".

\*\*\* Using FDA "strict migraine" Approach with Responders as Pain = "None".

Study 841		Time after taking Drug [Hours]					
Drug	No. Pts.	0.5	1	2	3	4	6
Excedrin $\oplus$	206	10.7%	32.5%	59.2%	68.4%	74.8%	78.2%
placebo	212	8.6%	20.5%	31.2%	38.0%	44.3%	47.5%
Excedrin $*$	206	11.7%	33.0%	58.3%	67.0%	73.3%	76.7%
placebo	212	9.0%	21.2%	31.6%	38.7%	44.3%	47.2%
P-Value $*$		0.43	<.01	<.0001	<.0001	<.0001	<.0001
Excedrin $**$	206	0.0%	5.8%	16.5%	28.2%	35.9%	41.7%
placebo	212	1.9%	3.8%	8.5%	10.8%	15.6%	20.3%
P-Value $**$		0.05	0.38	0.01	<.0001	<.0001	<.0001

Study 842		Time after taking Drug [Hours]					
Drug	No. Pts.	0.5	1	2	3	4	6
Excedrin $\oplus$	209	12.9%	38.3%	55.5%	67.5%	73.2%	76.1%
placebo	206	7.8%	17.5%	31.1%	40.3%	49.0%	52.9%
Excedrin $*$	200	14.5%	39.5%	56.5%	68.5%	74.0%	77.0%
placebo	197	8.1%	17.3%	31.5%	40.6%	48.2%	52.3%
P-Value $*$		0.04	<.0001	<.0001	<.0001	<.0001	<.0001
Excedrin $**$	200	0.0%	5.5%	21.0%	33.0%	36.5%	42.5%
placebo	197	0.0%	1.0%	5.1%	8.1%	13.2%	17.8%
P-Value $**$		0.99	0.01	<.0001	<.0001	<.0001	<.0001

- $\oplus$  Using Sponsor's Evaluability Criteria
- $*$  Using FDA "strict migraine" Approach with Responders as Pain = "None" or "Mild".
- $**$  Using FDA "strict migraine" Approach with Responders as Pain = "None".

*Richard A. Stein*

Richard A. Stein, Ph.D.  
Mathematical Statistician

This review contains 3 pages of text mixed with tables.

Concur:

*Hoi M. Leung*  
Hoi M. Leung, PhD  
Team Leader

*for Hoi M. Leung*  
Ralph Harkins, PhD  
Director, Div. of Biometrics IV

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HFD-550/Chin Koerner, CSO S. Cook  
HFD-550/Div. File  
HFD-340/Div. Sci. Inv.  
HFD-725/Richard Stein, PhD  
HFD-725/Div. File

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