CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-317

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 12/15/00

NDA:	21-317
Name of Drug:	Extra Strength Bayer Migraine (500 mg Buffered Aspirin Caplets)
Indication of Drug:	Migraine
Sponsor:	Bayer, Morristown, NJ
Type of Document:	New NDA
Reviewer:	Hong Zhao, Ph.D

Filing of NDA

Introduction

This product is intended for OTC use as a treatment for migraine. It is a bilayer caplet which combines aspirin and calcium carbonate in an immediate release formulation. According to the sponsor, this product has been marketed, in accordance with the Internal Analgesic Monograph, for nearly ten years.

The sponsor has conducted clinical trials in patients suffering from migraine to establish the safety and efficacy of plain aspirin tablets. A bioequivalence study between the clinical plain aspirin and the proposed buffered aspirin has been conducted to support the approval of the buffered aspirin as Extra Strength Bayer Migraine (500 mg Buffered Aspirin Caplets).

Bioequivalence Study

Protocol S99-102: *Comparative, Randomized, 2-Way Crossover Bioavailability Study of Commercial Extra Strength Bayer Plus Buffered Aspirin and Commercial Extra Strength Bayer Aspirin Caplets in Healthy Adults Under Fasting Conditions Following Administration of A Single Oral Dose.*

Dissolution Test

Dissolution test for both products was performed using the methods from the respective USP monographs for Coated and Uncoated Aspirin tablets. The method for 500 mg buffered Aspirin caplet dissolution testing is the method described in the compendial monograph for buffered Aspirin Tablets.

Only one time point (at 30 minutes, 6 units tested) dissolution data on [redacted] for unbuffered caplet has been provided in the submission. The volume of dissolution medium used for reference product dissolution testing is not provided.

Comment 1

In the NDA submission, individual concentration-time data were provided on only 6 subjects and PK results for each individual subject were not found; both assay validation report and representative [redacted] chromatograms were not found; dissolution data were

provided only means on 6 units of each biobatch tested. Therefore, the sponsor is requested to provide the following information:

- Individual concentration-time data and individual pharmacokinetic results for all subjects in the study,
- Assay validation report and representative [redacted] chromatograms,
- Detail description of dissolution methods used, dissolution profiles and individual dissolution data for 12 units of each of the batches used in the BE study.

On its face, this NDA is fileable.

Filing Meeting was held on February 6, 2001 at Corporate S400. OTC Project Manager for this NDA agreed to convey the above Comment to the sponsor.

Hong Zhao, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

cc: NDA21-317 (Aspirin Tablets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

/s/

Hong Zhao
2/13/01 10:36:37 AM
BIOPHARMACEUTICS

Raman Baweja
2/13/01 11:10:39 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Date of Document: 12/15/00, 4/9/01

NDA:	21-317
Name of Drug:	Extra Strength Bayer Migraine (500 mg Buffered Aspirin Caplets)
Indication of Drug:	Migraine
Sponsor:	Bayer, Morristown, NJ
Type of Document:	New NDA
Reviewer:	Hong Zhao, Ph.D.

Introduction

Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory properties. Aspirin is approved for the temporary relief of headache, pain and fever of colds, muscle aches and pains, menstrual pain, toothache pain, and minor aches and pains of arthritis. The recommended dose regimen for aspirin is one 500 mg caplet taken every 4 to 6 hours, as needed, up to a maximum of 8 caplets per 24 hours.

Extra Strength Bayer Migraine (Extra Strength Bayer Plus Buffered Aspirin Caplets, 500 mg) is intended for OTC use for the treatment of migraine pain and associated symptoms (nausea, light and sound sensitivity), and improving ability to resume normal activities. The recommended dose regimen for migraine indication is: "Adults 18 years and over: Take 2 caplets with a full glass of water. Do not exceed 8 caplets in 24 hours unless directed by a doctor. Under 18 year of age: Consult a doctor". Currently available OTC migraine treatments contain either ibuprofen or a combination of aspirin, acetaminophen and caffeine. This will be the first product available in the U.S. formulated with 500 mg of aspirin alone and clinical proven for migraine treatment.

This product is a bilayer caplet that combines aspirin and calcium carbonate in an immediate release formulation. According to the sponsor, this product has been marketed in the US for several years under the OTC analgesic/antipyretic monograph under the name "Extra Strength Bayer Plus (ESBP)". The sponsor has conducted clinical trials in patients suffering from migraine to establish the safety and efficacy of plain aspirin caplets (Extra Strength Bayer Aspirin, ESBA). A bioequivalence study between the proposed buffered aspirin (ESBP) and the clinical plain aspirin (ESBA) was conducted.

Clinical Trials

Three clinical safety and efficacy trials were conducted (S98-072, S98-073, S-98-074). The study design for these studies is prospective, randomized, double-blind, parallel group, single dose, placebo controlled clinical trial. A total of 707 patients received Extra Strength Bayer Aspirin, 2x500 mg caplets and 706 patients received placebo. The duration of treatment was one migraine attack of moderate to severe intensity and subsequent evaluation of pain and symptoms for 6 hours post-dosing. Headache recurrence up to 24 hours post-dosing was also evaluated.

The primary efficacy variable was the percent of subjects who experienced a change in pain intensity from a baseline evaluation of moderate (2) or severe (3), to mild (1) or none (0), at 2 hours post-dosing. The secondary efficacy variables were the reduction of the symptoms of nausea, photophobia, and phonophobia throughout the 6-hour study period for the subset of subjects whose migraine attack included the symptom prior to dosing.

Bioequivalence Study Review

***Protocol S99-102**: Comparative, Randomized, 2-Way Crossover Bioavailability Study of Commercial Extra Strength Bayer Plus Buffered Aspirin and Commercial Extra Strength Bayer Aspirin Caplets in Healthy Adults Under Fasting Conditions Following Administration of A Single Oral Dose.*

Study Design

Twenty-five healthy volunteers (of 25 subjects, 11 males and 14 females with age range from 19 to 45 years, 84% were Caucasians and the rests are Hispanics) completed the study. A single oral dose of study medication (test product: Commercial Extra Strength Bayer Plus Buffered Aspirin Caplet, 500 mg, Lot 201299N; reference product: Commercial Extra Strength Bayer Aspirin Caplet, 500 mg, Lot 201589N) was administered in a fasting state. There was a 7-day washout period between treatments. Blood samples were collected up to 12 hours at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 90 minutes and 2, 3, 4, 6, 8, 10, and 12 hours post each dosing for plasma salicylic acid concentration determination.

Selection of Analyte in the Study

The analyte selected as the indicating variable of bioequivalence was salicylic acid. The scientific justification provided by the sponsor are as follows: Since acetylsalicylic acid is rapidly converted to salicylic acid by hydrolysis and first-pass metabolism, peak plasma concentrations of acetylsalicylic acid are extremely sensitive to minor variations in solid dosage form dissolution and disintegration. In contrast, peak plasma concentrations of salicylic acid are relatively stable compared to acetylsalicylic acid and are considered to be a superior indicating variable for comparative bioequivalence. Hence, the current bioequivalence study is based on plasma salicylic acid concentration only.

Analytical Method

An [redacted] method with UV detection was utilized for the analysis of salicylic acid in human [redacted] plasma. The assay was conducted over the concentration range of [redacted] system. The validation work included three separate days of analysis, each containing two sets of eight standards and three sets of 6 quality control (QC) samples. Precision and accuracy of the method was evaluated as well as specificity, stability, linearity, carryover, and sensitivity. In addition, the potential conversion of acetylsalicylic acid (ASA) to salicylic acid (SA) was evaluated by analysis of duplicate 10 µg/ml ASA stability samples during each validation run and there was less that 10% breakdown of any of the ASA controls analyzed during the stability study. The lower limit of

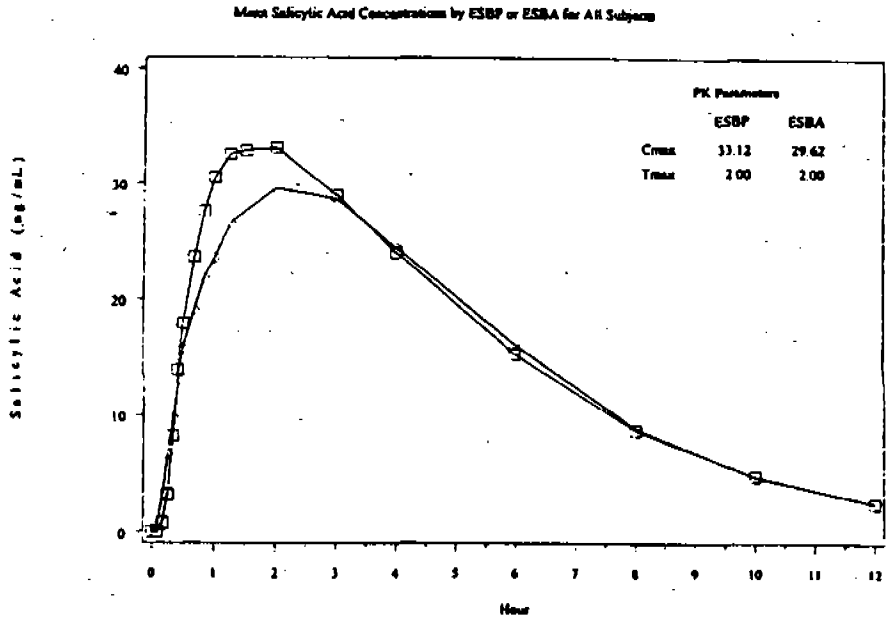
quantitation (LLOQ) was [redacted] for salicylic acid. The assay for salicylic acid in human plasma met all requirements for use for bioavailability (BA)/bioequivalence (BE) and pharmacokinetic (PK) studies.

Results

The study results shown in the following table and PK profiles demonstrate bioequivalence between Extra Strength Bayer Plus Aspirin Caplet (buffered) and Extra Strength Bayer Aspirin Caplet (unbuffered):

N=25 Parameter	T (Buffered) Mean±SD	R (Unbuffered) Mean±SD	Geometric Mean Ratio (T/R)	90% CI
C_{max} (µg/ml)	34.8±8.6	33.2±7.8	1.045	99.8-109.4
AUC_t (µg.h/ml)	190±64	183±64	1.038	100.5-107.3
AUC_{inf} (µg.h/ml)	199±73	191±72	1.038	100.3-107.4
T_{max} (h)	1.7±0.5	1.9±0.9		
$T_{1/2}$ (h)	2.1±0.5	2.1±0.4		

Means were derived from least squares means.



Mean Salicylic Acid Concentrations after administration of 500 mg Extra Strength Bayer Plus (ESBP, buffered Aspirin) or 500 mg Extra Strength Bayer Aspirin (ESBA) (N=25).

Extra Strength Bayer Plus (buffered Aspirin) reached maximum concentration sooner than Extra Strength Bayer Aspirin (1.65 hours vs. 1.91 hours). According to the sponsor, both formulations at 500 mg single doses were well tolerated. There were no clinical significant changes in laboratory tests.

Pharmacokinetic data analysis by gender has been conducted by this reviewer. The results are shown in the following table:

Gender	C_{max} (μg/ml)	AUC_t (μg.hr/ml)	AUC_{inf} (μg.hr/ml)	T_{max} (h)	$t_{1/2}$ (h)
ESBP					
Male (N=11)	29.3±4.8	148±24	152±25	1.7±0.6	1.9±0.2
Female (N=14)	39.1±8.6	221±66	232±78	1.6±0.4	2.3±0.6
(F-M/M)x100%	33%	49%	53%		
ESBA					
Male (N=11)	29.5±5.2	148±24	152±26	1.7±0.6	2.0±0.2
Female (N=14)	36.1±8.3	212±71	225±80	2.1±1.1	2.2±0.5
(F-M/M)x100%	22%	43%	48%		

The data analysis reveals that systemic exposure after 500 mg Aspirin was higher in female subjects than male subjects (20-30% higher in C_{max} and approximately 50% higher in AUC). Body weight difference between male and female subjects may contribute partly to this exposure difference since female subjects usually have less body weight, therefore higher dose per kilogram body weight in this case. Calculation of dose normalized exposure is not possible due to only mean body weight for all subjects was provided in the submission.

Subgroup pharmacokinetic data analysis by race was not conducted due to limited sample size (4 Hispanics vs. 21 Caucasians), however, plasma concentration profiles obtained from these 4 Hispanic subjects appear not different from these obtained from other subjects (Caucasians).

Dissolution Test Review

Dissolution Methods

Dissolution tests for both products were performed using the methods from the respective USP monographs for buffered and unbuffered Aspirin caplets:

Dosage form: 500 mg Aspirin USP, buffered with Calcium Carbonate USP, Caplet
Apparatus: [redacted]
Medium: [redacted]
Specification: Q= [redacted] in 30 minutes

Dosage form: 500 mg Aspirin USP unbuffered Caplet
Apparatus: [redacted]
Medium: [redacted]
Specification: Q= [redacted] in 30 minutes

[redacted]

Dissolution Results

Dissolution data for twelve individual caplets from both biobatches shown below met the specification of [redacted] of the drug released in 30 minutes.

	% of the drug Dissolved				
Time (min)	5	10	15	20	30
Lot 201589N	[redacted]				
Lot 201299N	[redacted]				

Lot 201589N-Bayer Aspirin Caplet, 500 mg (R); Lot 201299N-Bayer Plus Caplet (buffered), 500 mg (T).

Comment 1

Bioequivalence has been demonstrated between the proposed Extra Strength Bayer Plus 500 mg (buffered aspirin) and the clinical Extra Strength Bayer Aspirin, 500 mg (plain unbuffered aspirin).

Comment 2

Systemic exposure after 500 mg Aspirin was higher in female healthy subjects than male healthy subjects (20-30% higher in C_{max} and approximately 50% higher in AUC).

Recommendation

From an OCPB perspective, the application is acceptable.

Hong Zhao, Ph.D. _____

RD/FT Initialed by Raman Baweja, Ph.D. _____

cc: NDA21-317 (Aspirin Caplets), HFD-120, HFD-860 (Zhao, Baweja, Mehta), Central Documents Room (CDR-Biopharm)

Appendix

Human Pharmacokinetics

Orally administered aspirin is absorbed rapidly, partly from the stomach, but mostly from the upper intestine. The rate of absorption is determined by many factors: the disintegration and dissolution rate of the dosage form, the pH at the mucosal surfaces, and gastric emptying time. Salicylates are absorbed by passive diffusion, primarily of nondissociated salicylic acid, across gastrointestinal membranes, and the rate of absorption is influenced by gastric pH. Increasing gastric pH increases salicylate dissociation; however, increased gastric pH increases the solubility of salicylates, thus enhancing dissolution of the dosage form. The overall effect is to enhance absorption. As a result, there is little meaningful difference between the rates of absorption of aspirin, sodium salicylate, and buffered preparations of salicylates. The presence of food delays absorption of salicylates.

Ingested aspirin is mainly absorbed as acetylsalicylic acid, but some enters the systemic circulation as salicylic acid because of hydrolysis by esterases in the gastrointestinal mucosa and the liver. Hydrolysis in the plasma, liver and erythrocytes results in rapid disappearance of detectable acetylsalicylic acid. For example, 30 minutes after an aspirin dose of 650 mg, only 27% of the total plasma salicylate are in the acetylated form. As a result, plasma concentrations of acetylsalicylic acid are always low and rarely exceed 20 μg/ml at ordinary therapeutic doses. Both aspirin and salicylate have pharmacological activity; only aspirin has an anti-platelet effect.

After absorption, salicylate is distributed throughout most body tissues and most transcellular fluids, primarily by pH-dependent passive processes. The volume of distribution of usual doses of aspirin in normal subjects is about 170 ml/kg, increasing to about 500 ml/kg at high therapeutic doses because of saturation of binding sites on plasma protein. At normal clinical doses, 80% to 90% of the salicylate is bound to plasma proteins, especially albumin; this fraction declines as plasma concentrations are increased.

Salicylate is mainly eliminated by hepatic metabolism; the metabolites include salicyluric acid, salicyl phenolic glucuronide, salicylic acyl glucuronide, gentisic acid and gentisuric acid. Salicylate is also excreted unchanged in the urine; the amount excreted by this route increases with increasing dose and also depends on urinary pH, about 30% of a dose being excreted in alkaline urine compared with 2% of a dose in acidic urine. Renal excretion involves glomerular filtration, active renal tubular secretion, and passive tubular reabsorption. The plasma half-life of aspirin is approximately 30 minutes, and the plasma half-life of salicylate is 2 to 3 hours in low doses and about 12 hours at usual anti-inflammatory doses.

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/s/

Hong Zhao
6/5/01 01:21:28 PM
BIOPHARMACEUTICS

Raman Baweja
6/5/01 02:34:36 PM
BIOPHARMACEUTICS

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW OF NDA

Brand Name:	**Bayer® Migraine**
Generic Name:	**Acetylsalicylic Acid**
Sponsor:	**Bayer Corporation**
Indication:	**Acute Migraine**
NDA Number:	**21-317**
Original Receipt Date:	**12/19/2000**
Clinical Reviewers:	**Kevin A. Prohaska, D.O.**
Review Author:	**Kevin A. Prohaska, D.O.**
Review Completed:	**06/12/01**

Table of Contents

1. Review Sources

The following sources were used for my review:

Volume 1:	NDA Index, Draft Labeling, and Study Synopses
Volume 5-8:	Study report S98-072
Volume 9-12:	Study report S98-073
Volume 12-16:	Study report S98-074
Volume 16:	Integrated Summaries for Efficacy and Safety
IND 57459	Serial 000 through 012 and Division File
Supplement BZ	Containing the datasets in electronic format.

Subject data listings and case report forms for each study can be found at the end of each individual study report in Module 3 and Annex II respectively. Additionally, the sponsor provided the Integrated Summary of Efficacy (ISE), Integrated Summary of Safety (ISS), and each study report as PDF files with the original NDA submission.

2. Background

The sponsor of this NDA requests approval of over-the-counter Extra Strength Bayer® Aspirin 500 mg (ESBA), to be marketed under the name "Bayer® Migraine [redacted] associated symptoms (nausea, phonophobia, photophobia) in adults 18 years and older. The submission includes additional labeling intended for the migraine headache population.

Currently, Extra Strength Bayer® Aspirin 500 mg is indicated for "relief of headache, painful discomfort and fever of colds, muscular aches and pains, temporary relief of minor pains of arthritis, toothache and pain following dental procedures, and menstrual pain" in children and adults 12 years of age and older. Professional labeling includes indications for a wide variety of vascular conditions (TIA, Acute Ischemic Stroke, Unstable Angina Pectoris, Chronic Stable Angina Pectoris, Acute Myocardial Infarction, and prevention of recurrent Myocardial Infarction), several post-revascularization procedures (Coronary Artery Bypass Graft, Percutaneous Transluminal Coronary Angioplasty, and Corotid Endarterectomy), and multiple rheumatological disorders (Rheumatoid Arthritis, Juvenile Rheumatoid Arthritis, Spondyloarthropathies, Osteoarthritis, and the Arthritis and Pleurisy of Systemic Lupus Erythematosus).

The sponsor states that an "*FDA Advisory Panel for Internal Analgesics acknowledged a reasonable risk benefit ratio for up to four grams of aspirin per day for the temporary relief of pain not to exceed ten days unless directed by your doctor, longer term use has been approved by the FDA under the direction of a doctor for cardiovascular and rheumatologic uses.*"

Approved dosing of Extra Strength Bayer® Aspirin in adults and children 12 years of age and older, is 1 to 2 tablets/caplets/gelcaps with water every 4 to 6 hours as needed. Maximum

dose is not to exceed eight tablets/caplets/gelcaps (4 grams) per 24 hours. Aspirin 500 mg is available worldwide.

This application contains the results of three randomized, placebo-controlled, double blind clinical studies of ESBA 1000 mg in the treatment of migraine pain and its associated symptoms. All three studies were of similar design except study S98-072 and S98-074 were multicenter, and S98-073 was a single center study. Also included in the safety evaluation is the bioavailability study, S99-102. See Table 1: Study Overview, for details. The sponsor also supplies a Global Safety Review of published articles on the use and safety of aspirin in the prophylaxis and treatment of migraine going back approximately 40 years.

Table 1: Study Overview

Study Number	Dates	# of subjects enrolled	Age of subjects
S98-072	3/31/1999 to 1/11/2000	485	19 to 64
S98-073	4/08/1999 to 4/11/2000	446	18 to 60
S98-074	3/29/1999 to 2/18/2000	482	18 to 72
S99-102	1/14/2000 to 1/22/2000	26	18 to 45

2.1 Indication

Acute migraine with and without aura in adults 18 years of age or older.

2.2 Administrative History

The following sequence of events occurred:

1. December 15, 1998, IND [redacted]'s submitted for the evaluation of [redacted] in migraine.
2. February 4, 1999, a meeting occurred between the sponsor, the Division of Neuropharmacological Drug Products, and the Division of OTC Drug Products.
3. July 1, 1999, a teleconference occurred with the sponsor.
4. September 21, 2000, a pre-NDA meeting occurred with the sponsor.
5. December 19, 2000, the sponsor submits the NDA.
6. February 6, 2001, a 45-day filing meeting occurred between the Division of Neuropharmacological Drug Products, and the Division of OTC Drug Products.
7. April 9, 2001, the sponsor submits the electronic datasets.
8. June 12, 2001, a meeting occured between the Division of Neuropharmacological Drug Products, and the Division of OTC Drug Products.

Specific details regarding each meeting can be found in the Division Files for IND [redacted] and NDA 21317.

The Division of Over the Counter Drug Products is responsible for the primary review of this New Drug Application. The Division of Neuropharmacological Drug Products (HFD-120)

has been consulted to review the safety and efficacy data. By agreement the Division of Over the Counter Drug Products is responsible to review the Global Safety Review submitted by the sponsor. A brief review of the original protocol and important amendments can be found in Appendix B -.

2.3 Proposed Labeling

The sponsor plans to market a single formulation under two trade names, Extra Strength Bayer® Migraine Plus Buffered Caplets (500 mg), [redacted]
Bayer® Migraine will be packaged in 24, 50 and 100 counts [redacted]

Table 2 is a copy of the proposed draft labeling and referenced support for each claim. The draft labeling for the carton and bottle are analogous.

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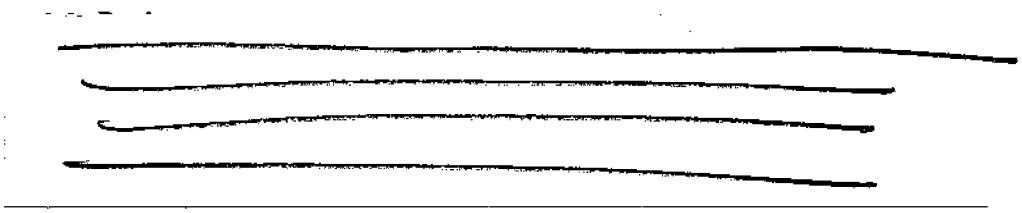
1 page(s) of revised draft labeling has been redacted from this portion of the review.



3. Review of Efficacy

3.1 Background and Methodology

The NDA application contains the results of three clinical safety and efficacy trials, S98-072, S98-073, and S98-074. All three studies were adequate and well controlled trials that by design were capable of demonstrating efficacy. Each trial was of similar design and treated a single migraine with study medication. Subjects with a migraine history, meeting the International Headaches Society diagnostic criteria for migraine headache with and without aura, were randomized to either placebo or Extra Strength Bayer® Aspirin 1000 mg. All studies were double blinded. Study S98-072 and S98-074 were multicenter studies and study S98-073 was a single center study.

To be eligible for entry into the study subjects were required to be at least 18 years of age, diagnosed with migraine before the age of 50, have a migraine history of at least one year, and have at least one but not more than six migraines per month. Additionally, subjects were expected to be able to differentiate their usual migraine headache from other forms of headache and have no more than 15 headache days per month.

Subjects were excluded from participating in the studies if their migraine pattern was such that they did not respond to over-the-counter medication and/or prescription medication. Additionally, subjects were excluded if they experienced vomiting >20% of the time during migraines, experienced migraines variants (basilar artery migraine, ophthalmoplegic migraine, or cluster migraine), or had a recent change (3 months) in their migraine prophylaxis therapy.

These inclusion and exclusion criterion resulted in the most severe or unstable migraineurs from participating in these studies. These criterion resulted in the three studies being populated by subjects likely to take over-the-counter therapies for their migraine headaches.

For study S98-072, potential candidates were identified via a random telephone screening procedure, followed by a screening history and physical (population based recruiting). For study S98-073 and S98-074, potential subjects were identified through private practice records, research databases, referrals, and local advertising (conventional recruiting).

Eligible subjects were given a single dose of blinded medication at randomization. Patients were asked to treat a single headache of moderate to severe intensity within eight weeks of randomization. Efficacy variables were assessed at 30 minutes, one, two, three, four, five, and six hours post-dosing with study medication. Headache recurrence was followed out to 24 hours. Safety was assessed by the recording of adverse events in a patient diary through

hour 24. Additionally, any adverse event occurring after 24 hours and reported by the subject at Visit 2 was recorded on the Adverse Event Case Report Form. Follow up (Visit 2) was to occur within seven days of the treatment day but preferably the next day following the treated migraine.

Subjects were encouraged to not use rescue medication for at least two hours after dosing with study medication, however they were permitted to use rescue medication at any time. Immediately prior to taking any rescue medication subjects were instructed to complete the migraine assessment form. All subjects taking rescue medication before two hours post-dosing were considered treatment failures. Extra Strength Bayer®Aspirin 500 mg, two caplets, was chosen for the study since it is the maximum dose approved in the United States for other chronic pain conditions. Additional information regarding the original protocols and important amendments can be found in Appendix B -.

Table 3 below summarizes the subjects enrolled and their disposition in the three clinical trials. Those who did not take study medication and failed to return, or took study medication greater than 8 weeks after randomization were excluded from analysis and labeled nonevaluable. All patients that took study medication were included in the safety analysis and are labeled ITT_{ALL} (the sponsor uses All ITT). ITT_{ALL} includes 1191 subjects; 595 placebo treated subjects and 596 Extra Strength Bayer® Aspirin treated subjects. This population also includes 11 subjects that took study medication but did not follow-up or return the migraine diary, hence there are no post-treatment assessments available. Such individuals traditionally would not be included in an ITT analysis recommended by the Division of Neuropharmacological Drug Productsfor migraine studies since there is no valid post-treatment observations. Efficacy analyses using ITT_{ALL} can be found at the end of each study report with minimal commentary by the sponsor. The sponsor uses ITT_{ALL} as their primary population for safety analysis.

The primary efficacy analysis population is labeled by the sponsor as Confirmed Migraine ITT (I use ITT_{CM} in this review). All patients that took study medication but incorrectly treated a non-migraine headache (10 subjects), or took study medication and failed to follow up (11 subjects), were excluded from the sponsor's primary efficacy analysis population. ITT_{CM} included 586 Extra Strength Bayer® Aspirin treated subjects and 584 placebo treated subjects. The sponsor does not provide a safety analysis using ITT_{CM}.

Table 3: Summary of Subject Enrollment and Evaluability

	S98-072		S98-073		S98-074	
	ESBA	**Placebo**	**ESBA**	**Placebo**	**ESBA**	**Placebo**
Enrolled/Randomized	243	242	224	222	240	242
Nonevaluable	38	38	25	39	48	34
Took study medication (ITT_{ALL})	205	204	199	183	192	208
Excluded from confirmed migraine ITT (ITT_{CM})	4	4	2	3	4	4
Confirmed Migraine (ITT_{CM})	201	200	197	180	188	204

Source: Sponsor Table 1.1 studies S98-072, S98-073, S98-074.

3.2 Demographics and Baseline Characteristics

Across all studies and treatments, 79% of the population are female and 21% are male. This is consistent with other migraine studies and reflects the 3:1 preponderance of migraine diagnosis in women compared to men in the general population. The vast majority of subjects was Caucasain (79%). The mean age of the subjects was 36.60 years and >99% were in the 18 to <65 year age group. There were no subjects less than 18 years of age in any of the three clinical trials and only 9 subjects 65 years of age or older in the three clinical trials combined. The distributions of the demographic parameters of the subject's are similar between all three clinical trials (Sponsor Table ISE I-8, page 139).

The demographic profile of each clinical trial by treatment can be found in Table 4 for the ITT_{ALL} population. Within each study, treatment groups had comparable demographic characteristics, with one exception. In Study S98-073 there was a significant difference ($p=0.034$) among treatment groups in the distribution of subjects by age with placebo treated subjects having a lower mean age (29.61 years) compared to the ESBA treated group (31.78 years). Otherwise there were no other statistically significant differences among treatment groups in demographics characteristics at baseline. Similar results were seen with the ITT_{CM} population.

Table 4: Demographic profile of each trial by treatment group (ITT_{ALL}).

	S98-072			S98-073			S98-074		
	ESBA (n=205)	**Placebo (n=204)**	**p**	**ESBA (n=199)**	**Placebo (n=183)**	**p**	**ESBA (n=192)**	**Placebo (n=208)**	**p**
Age									
Mean	37.42	37.78	0.706	31.78	29.61	0.034	41.66	40.74	0.380
Range	20-58	19-64		18-60	18-58		18-66	18-72	
Age Group									
18-64	205	204		199	183		191	200	
≥65	0	0		0	0		1	8	
Gender									
Male	44(21%)	42(21%)	0.815	40(20%)	45(25%)	0.293	42(22%)	38(18%)	0.335
Female	161(79%)	162(79%)		159(80%)	138(75%)		150(78%)	170(82%)	
Race									
White	158(77%)	156(76%)	0.774	152(76%)	127(69%)	0.125	167(87%)	178(86%)	0.756
Black	44(21%)	46(23%)		24(12%)	12(7%)		11(6%)	18(9%)	
Hispanic	1(0%)	0(0%)		21(11%)	39(21%)		3(2%)	7(3%)	
Asian	2(1%)	1(0%)		2(1%)	2(1%)		7(4%)	3(1%)	
Other	0(0%)	1(0%)		0(0%)	3(2%)		4(2%)	2(1%)	

Source, Sponsor Table 2.1.1, Study reports S98-072, S98-073, S98-074.

Table 5 outlines the distribution of subjects for each baseline migraine characteristic by treatment arm and study. The baseline characteristics of nausea, photophobia, and phonophobia are evenly distributed between both treatment groups within each study. Across all treatments and studies, 68% of the subjects reported a migraine headache of moderate intensity at baseline. There are no statistical difference between placebo and ESBA treated groups with respect to the distribution of subjects reporting moderate headache at baseline in the pooled analysis ($p=0.440$)[1] or within each individual study ($p\geq 0.603$). Between studies, study S98-074 has relatively more subjects (78%) in the combined treatment groups reporting a migraine of moderate intensity at baseline than either study S98-072 (62%) or study S98-073 (64%).

[1] Source: Sponsor's Table ISE C-8, page 70.

Table 5: Baseline Migraine Characteristics by treatment group and study.[1] (ITT_{ALL})

Symptom	S98-072			S98-073			S98-074		
	ESBA N=205	Placebo N=204	p	ESBA N=199	Placebo N=183	p	ESBA N=192	Placebo N=208	p
Pain Intensity, n(%)									
Moderate	123(60)	127(63)	0.603	125(63)	116(64)	0.898	146(76)	161(79)	0.676
Severe	81(40)	75(37)		72(37)	65(36)		45(24)	44(21)	
Nausea, n(%)									
None	88(43)	92(46)	0.769	73(37)	73(40)	0.624	68(36)	68(33)	0.880
Mild	69(34)	65(32)		77(39)	66(36)		80(42)	93(45)	
Moderate	44(22)	41(20)		41(21)	37(20)		35(18)	37(18)	
Severe	3(1)	4(2)		6(3)	5(3)		7(4)	7(3)	
Phonophobia, n(%)									
None	6(3)	7(3)	0.496	10(5)	9(5)	0.615	15(8)	16(8)	0.770
Mild	40(20)	49(24)		58(29)	46(25)		61(32)	70(34)	
Moderate	115(56)	103(51)		98(50)	98(54)		91(48)	95(46)	
Severe	43(21)	43(21)		31(16)	28(15)		24(13)	24(12)	
Photophobia, n(%)									
None	8(4)	8(4)	0.587	4(2)	5(3)	0.420	6(3)	7(3)	0.991
Mild	40(20)	35(17)		44(22)	43(24)		61(32)	62(30)	
Moderate	112(55)	128(63)		114(58)	106(59)		97(51)	110(54)	
Severe	44(22)	31(15)		35(18)	27(15)		27(14)	26(13)	

Source: Sponsor Table 2.1.1 study reports S98-072, S98-073, S98-074.
[1]Total for each symptom may differ from each treatment arm total due to nonreporting by the subject.

Table 6 outlines the distributions of subjects reporting their typical migraine treatment history for each treatment arm in each study. As Table 6 demonstrates, there appears to be a fairly even distribution of subjects using the various migraine treatment options between each treatment arm within each study however the distribution is not even between studies. In study S98-074 the subjects more often tended to treat their migraine headaches with a combination of prescription medication plus over-the-counter medications than in the other two studies that had more patients treating their migraines with over-the-counter preparations alone. This finding is especially interesting since subjects in study S98-074 tended to treat less severe headaches than seen in the other two studies. It is difficult to determine why this difference exists but one possibility is that subjects in study S98-074 may have greater access to medical care or they treat earlier and more aggressively compared to subjects in the other two studies.

Table 6: Usual Migraine Treatment by Treatment Group and Study. (ITT_{ALL})

	S98-072		S98-073		S98-074	
	ESBA (N=205)	**Placebo (N=204)**	**ESBA (N=199)**	**Placebo (N=183)**	**ESBA (N=192)**	**Placebo (N=208)**
None	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
OTC only	170(83%)	160(78%)	120(60%)	121(66%)	61(32%)	66(32%)
RX only	17(8%)	23(11%)	42(21%)	36(20%)	56(29%)	61(29%)
OTC and Rx	18(9%)	21(10%)	37(19%)	26(14%)	75(39%)	81(39%)

Source: Sponsor Table 2.3.1 study reports S98-072, S98-073, S98-074.

3.3 Endpoints and Analysis Methods

The sponsor's NDA application contains two efficacy analyses. The primary analyses presented in the NDA application consists of those subjects that took the study medication, have a confirmed migraine, and followed up (ITT_{CM}). The secondary analysis is the sponsor defined intent-to-treat (ITT_{ALL}) population and can be found at the end of each study report with minimal commentary. As previously discussed, the sponsor defines ITT_{ALL} as all subjects that took study medication whether the subject followed up or not. From a review of the individual data listings, it was determined that eleven patients took study medication but failed to keep their follow-up appointment or failed to return their dairy. Since these subjects scheduled a follow up appointment but failed to show the sponsor assumed these subjects took their study medication and were included in the ITT_{ALL} analyses as treatment failures. Given that the difference between the analyses is minor and results in no changes in conclussions, my comments in this section will be limited to the sponsor's confirmed migraine intent-to-treat population (ITT_{CM}).

In previous migraine NDAs, the Division of Neuropharmacological Drug Products has defined ITT as all subjects that take at least one dose of the study medication plus there is at least one valid post-dosing observation. In my review of the datasets (section 3.5), I will evaluate the efficacy endpoints using the ITT population preferred by this division (ITT_{AGENCY}).

The primary efficacy endpoint for each study is percent responders. Percent responders is defined as the proportion of subjects who experience a change in pain intensity from a baseline evaluation of moderate (2) or severe (3), to mild (1) or none (0), at two hours post-dosing without the use of rescue medication. Subjects that used rescue medication before the two hour evaluation are considered non-responders and included two subjects in study S98-072 (#356-ESBA, #460-placebo), no subjects in study S98-073, and three subjects from study S98-074 (#165-plascebo, #377 and #490-ESBA).

Secondary efficacy endpoints include:

1. Pain intensity difference (PID).
2. Six-hour sum of pain intensity difference (SPID).
3. Headache recurrence followed out to 24 hours.
4. Time to headache recurrence.
5. Severity of migraine associated symptoms of nausea, phonophobia, and photophobia.

6. Assessment of functional ability at various times.
7. The presence or absence of vomiting at various times.

Pain is rated on a 4-point scale with 0 for no pain, 1 for mild pain, 2 for moderate pain, and 3 for severe pain. Pain severity is assessed by the patient at baseline then 30 minutes and one, two, three, four, five, and six hours after taking study medication. Pain intensity difference is calculated by subtracting each post-dosing pain score from the baseline pain score. Six-hour sum of pain intensity differences is calculated by the total of the pain intensity differences between hour two and hour six plus one-half of the sum of the pain intensity differences at 30 minutes and one hour. Headache recurrence is calculated as the percent of subjects who initially respond at two hours after taking study medication but go on to have a recurrent headache of grade 2 or 3, up to hour 24, whether they took rescue medication or not.

The associated migraine symptoms of nausea, phonophobia, and photophobia are rated on a 4-point scale with 0 for none, 1 for mild, 2 for moderate, and 3 for severe. Vomiting is rated as being present or absent. Functional ability is rated on a 5-point scale with 0 for "able to perform all activities as usual", 1 for "daily activities require little additional effort", 2 for " daily activities require some additional effort", 3 for "daily activities require a great deal of additional effort", and 4 for "unable to perform daily activities".

Pairwise comparisons are made between ESBA 1000 mg and placebo. The primary efficacy endpoint of percent responders is analyzed using the Cochran-Mantel-Haenszel test stratified by investigator. Subgroup analyses of the primary endpoint are evaluated for the different races, gender, baseline migraine severity, and the age of the subjects enrolled in the study. Variables such as age, weight, and height are considered continuous and are analyzed using two-way analysis of variance (ANOVA). Categorical variables such as gender and race are analyzed using Cochran-Mantel-Haenzel test.

The secondary variables of nausea, photophobia, and phonophobia are analyzed using a repeated measure analysis of variance with factors of treatment, investigator, time, and treatment-by-time interaction. A significant treatment-by-time interaction or between subjects effects provided evidence of a treatment effect that was subsequently analyzed by an analysis of covariance at each post-dosing time point during the six-hour study. Nausea, photophobia and phonophobia are also analyzed for the proportion of subjects reporting resolution at the various time points during the study.

The secondary variables of vomiting and improvement in functional ability are analyzed using repeated measures ANOVA with factors of treatment, time, and treatment-by-time interaction. Pain intensity difference and six-hour summed pain intensity difference scores are analyzed using ANOVA with factor of treatment group. The percent of subjects with headache recurrence over 24 hours are analyzed using a Log-Rank test.

The sample size was calculated to detect a 15% difference between Extra Strength Bayer® Aspirin and Placebo with a two-sided alpha of 0.05 and a power of 0.85. The sponsor states that a 15% difference between ESBA and placebo for the primary endpoint would be considered clinically significant. The sponsor did not recalculate the power of the studies

using an expected treatment effect of 25-30 percentage points above placebo as requested by the Department of Neuropharmacologic Drug Products after the review of the original protocol.

Dropouts and missing data are handled using the following rules:

1. If the subject used rescue medication before the end of the study, the subsequent efficacy variables are set equal to the baseline measure or the score immediately prior to rescue medication, which ever is more severe.
2. Efficacy variable scores missing after the application of the first rule were replaced by carrying forward the preceding non-missing score.
3. Any missing efficacy variable score for a subject who medicated a recurrent headache was set equal to baseline score or the most recent non-missing score recorded prior to medication, whichever score was more severe.
4. The two-hour score was interpolated in the event that the two-hour evaluation was off schedule by more than 15 minutes. Linear interpolation was used if there was observed data that preceded and followed the 2-hour clock time.

3.4 Sponsor's Efficacy Results

The sponsor analyzed confirmed migraine subjects (ITT_{CM}) as their primary efficacy analysis and presents ITT_{ALL} analysis at the end of each study report with minimum commentary. The difference between the two groups is 21 subjects. Ten subjects[2] are excluded from ITT_{CM} because they treated a headache other than a migraine. Eleven subjects[3] are excluded from the ITT_{CM} because it was determined they took the study medication but either failed to follow up or did not return the diary. All eleven of these subjects are included in the ITT_{ALL} analysis but are considered treatment failures. The differences between the two analyses are minor and do not change the my final conclusions. I will present the sponsor's analysis of ITT_{CM} in this section of my review.

The sponsor does not provide any subgroup analysis for subjects with menstrual associated migraines or for any other known triggers. The sponsor does not provide an analysis of time to rescue or remedication. The sponsor does not provide an analysis of cumulative headache response rates over the six-hour study.

3.4.1 Two-hour Headache Response Rate

The two-hour headache response rates for study S98-072, S98-073, and S98-074 are shown in Table 7. In study S98-072 and S98-074 ESBA was significantly better than placebo for two-hour response rate for the ITT_{CM} population. In study S98-072, 52% of ESBA treated subjects reported headache relief at two hours compared to only 34% of the placebo treated subjects ($p<0.001$). In study S99-074, 38% for ESBA treated subjects reported headache relief at two hours compared to 27% of the placebo treated subjects ($p=0.020$). However, in study S98-074 the difference between placebo response rate and ESBA response rate is only 11%, which is less than the 15% the sponsor stated would be considered clinically relevant.

[2] **S98-072**: PID # 369, 507, 47, 135, 222. **S98-073**: PID # 394. **S98-074**: PID # 242, 177, 189, 456.
[3] **S98-072**: PID # 171, 178, 161. **S98-073**: PID # 75, 146, 99, 181. **S98-074**: PID # 279, 295, 403, 142.

Study S98-073 fails to demonstrate a significant difference between ESBA and placebo in the treatment of moderate and severe migraine with only 49% of the ESBA treated subjects reporting relief at two hours compared to 42% for placebo (p=0.206).

The sponsor's subset analysis for percent responders by gender and race fails to demonstrate any significant difference for the analysis of ITT_{CM} in all three studies. Subset analysis by age has too few subjects in the ≥65-year old age group to make a comparison valid. Study S98-072 and S98-073 has no subjects in the ITT_{CM} population ≥65 years of age and study S98-074 has only nine subjects in this age group.

Table 7: Percent Responders at 2 hours (ITT_{CM})

S98-072		S98-073		S98-074	
Placebo (N=200)	ESBA (N=201)	Placebo (N=183)	ESBA (N=199)	Placebo (N=204)	ESBA (N=188)
68 (34%)	105 (52%)	76 (42%)	96 (49%)	55 (27%)	72 (38%)
p<0.001		p=0.206		p=0.020	

Source: Sponsor Table 3.2.2, study reports S98-072, S98-073, and S98-074.

Sponsor subset analysis for percent responders by baseline severity is demonstrated in Table 8. As demonstrated, the primary efficacy endpoint of percent responders was significant for ESBA treated group in all three studies for those subjects documenting a baseline migraine severity of moderate intensity (p≤0.026). However for those subject with a baseline migraine severity of severe, study S98-073 and S98-074 failed to demonstrate a significant difference in treatment (p≥0.415) and surprisingly it appears subjects reporting a migraine of severe intensity grossly did better with placebo than ESBA.

Table 8: Percent Responders by Baseline Severity (ITT_{CM})

		Baseline Moderate	Baseline Severe
S98-072	Placebo	49 (39%)	19 (26%)
	ESBA	67 (56%)	38 (48%)
	p-value	0.008	0.005
S98-073	Placebo	55 (47%)	21 (33%)
	ESBA	77 (62%)	19 (26%)
	p-value	0.026	0.415
S98-074	Placebo	44 (28%)	11 (25%)
	ESBA	62 (43%)	10 (22%)
	p-value	0.004	0.761

Source: Sponsor Table SD 3.2.8, study reports S98-072, S98-073, and S98-074.

3.4.2 Migraine Associated Symptoms

The sponsor analyzes the associated symptoms of nausea, phonophobia, and photophobia using two approaches. Both analyses include only those subjects reporting the associated

symptoms at baseline. The first analysis compares the mean difference from baseline in the severity of these symptoms at various time points using the least square means. The second analysis compares the proportion of patients reporting resolution of their symptom at various time points using Cochran-Mantel-Haenszel test for row mean scores.

3.4.2.1 Nausea

Table 9 demonstrates the results of the sponsor's ITT_{CM} analysis of nausea for each trial and treatment arm. As seen in table 9, study S98-072 fails to demonstrate a significant difference between placebo and ESBA in the treatment of migraine associated nausea in most analyses. There is no statistical difference between treatment arms for overall treatment effect (p=0.090) and for the mean reduction of nausea at two-hours (p=0.753). However, difference in the mean reduction of nausea is significant, favoring ESBA, at hour four through six ($p \leq 0.031$)[4]. There is no significant difference in the proportion of patients reporting resolution of their baseline nausea at two hours, with 40% of placebo treated patients reporting resolution compared to 37% of ESBA treated patients (p=0.704). In fact, the difference in the proportion of subjects between treatment groups reporting resolution of nausea did not reach significance at any time during the six hours ($p \geq 0.153$)[5]. Treatment-by-time interaction for mean reduction in nausea severity is significant (p=0.018).

Study S98-073 fails to demonstrate a significant difference between placebo and ESBA in the treatment of migraine associated nausea in all analyses. There is no statistical difference between treatment arms for overall treatment effect (p=0.264), treatment-by-time interaction (p=0.725), and for the mean reduction in nausea severity at any time point ($p \geq 0.131$)[6] during the six hours post-dosing. There is no significant difference in the proportion of patients reporting resolution of their baseline nausea at two hours, with 32% of placebo treated patients reporting resolution of nausea compared to 40% of ESBA treated patients (p=0.213). The difference between treatment groups in the proportion of subjects reporting resolution of nausea did not reach significance at any time during the six hours ($p \geq 0.126$)[7].

Study S98-074 also fails to demonstrate a significant difference between placebo and ESBA in the treatment of migraine associated nausea in most analyses. There is no statistical difference between treatment arms for overall treatment effect (p=0.166) or treatment-by-time interaction (p=0.283). The mean reduction in nausea severity at two hours is not significant (p=0.151). The mean reduction of nausea was significant, favoring ESBA, at hour three through six ($p \leq 0.050$)[8]. There is no significant difference in the proportion of patients reporting resolution of their baseline nausea at two hours, with 26% for placebo treated patients reporting resolution compared to 32% for ESBA treated patients (p=0.366). The difference in the proportion of subjects reporting resolution of nausea did reach significance, favoring ESBA, at hour three through six during the six hours ($p \leq 0.044$)[9].

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[4] Source: Sponsor's Table 3.3.2, page 52, study report S98-072.
[5] Source: Sponsor's Table 3.3.2.1, page 54, study report S98-073.
[6] Source: Sponsor's Table 3.3.2, page 51, study report S98-073.
[7] Source Sponsor's Table 3.3.2A, page 53, study report S98-073.
[8] Source: Sponsor's Table 3.3.2, page 55, study report S98-074.
[9] Source: Sponsor's Table 3.3.2.1, page 57, study report S98-074.

Table 9: Efficacy results for Nausea (ITT_{CM})

		Least Square Means @ 2 hours	Treatment by time interaction	Overall Treatment effect	Proportion reporting resolution @ 2 hours	Proportion reporting resolution @ 6 hours
S98-072	**Placebo** (N=110)	0.83			44 (40%)	51 (46%)
	ESBA (N=115)	0.86			43 (37%)	63 (55%)
	p value	0.753	0.018	0.090	0.704	0.194
S98-073	**Placebo** (N= 108)	0.94			35 (32%)	59 (55%)
	ESBA (N=124)	0.79			50 (40%)	80 (64%)
	p value	0.144	0.725	0.264	0.213	0.126
S98-074	**Placebo** (N=137)	1.19			36 (26%)	26 (19%)
	ESBA (N=122)	1.02			39 (32%)	36 (30%)
	p value	0.151	0.283	0.166	0.366	0.044

Source: Sponsor's Table 3.3.2 and 3.3.2.1(A) study reports S98-072, S98-073, and S98-074.

3.4.2.2 Phonophobia.

Table 10 demonstrates the results of the sponsor's ITT_{CM} analysis of phonophobia for each trial and treatment arm.

Study S98-072 demonstrates a significant difference between placebo and ESBA in the treatment of migraine associated phonophobia in all analyses. There is a statistical difference between treatment arms, favoring ESBA, for overall treatment effect ($p<0.001$), treatment-by-time interaction ($p<0.001$), and for the mean reduction in nausea severity at two-hours ($p<0.001$). There is a significant difference in the proportion of patients at two hours reporting resolution of their baseline phonophobia, with 34% of ESBA treated patients reporting resolution compared to 17% of placebo treated patients ($p<0.001$).

Study S98-073 fails to demonstrate a significant difference between placebo and ESBA in the treatment of migraine associated phonophobia in most analyses. There is no statistical difference between treatment arms for overall treatment effect ($p=0.174$) and treatment-by-time interaction ($p=0.485$). The difference between treatment arms for mean reduction in phonophobia severity was slightly significant at two hours ($p=0.049$), favoring ESBA, but not at any other time point during the study ($p\geq0.112$)[10]. There is no statistical difference between treatment arms in the proportion of patients at two hours reporting resolution of their

[10] Source: Sponsor's Table 3.3.2, page 51, Study report S98-073.

baseline phonophobia, with 28% of ESBA treated patients reporting resolution compared to 21% of placebo treated patients (p=0.131).

Study S98-074 demonstrates a significant difference between placebo and ESBA in the treatment of migraine associated phonophobia in most analyses. There is a statistical difference between treatment arms, favoring ESBA, for treatment-by-time interaction (p=0.014) and the mean reduction in nausea severity at two hours (p=0.016). However the difference between treatment arms for overall treatment effect is not significant (p=0.087). There is a significant difference between treatment arms, favoring ESBA, in the proportion of patients reporting resolution of their baseline phonophobia at two hours, with 26% of ESBA treated patients reporting resolution compared to 14% of placebo treated patients (p=0.009).

Table 10: Efficacy results for Phonophobia (ITT_{CM})

		Least Square Means @ 2 hours	Treatment by time interaction	Overall Treatment effect	Proportion reporting resolution @ 2 hours	Proportion reporting resolution @ 6 hours
S98-072	**Placebo** (N=193)	1.45			33 (17%)	77 (40%)
	ESBA (N=195)	1.06			66 (34%)	115 (59%)
	p value	<0.001	<0.001	<0.001	<0.001	<0.001
S98-073	**Placebo** (N=172)	1.33			36 (21%)	86 (50%)
	ESBA (N=187)	1.14			52 (28%)	103 (55%)
	p value	0.049	0.485	0.174	0.131	0.336
S98-074	**Placebo** (N=188)	1.48			27 (14%)	43 (23%)
	ESBA (N=175)	1.25			45 (26%)	55 (31%)
	p value	0.016	0.014	0.087	0.009	0.084

Source: Sponsor's Table 3.3.2 and 3.3.2.1(A) study reports S98-072, S98-073, and S98-074.

3.4.2.3 Photophobia.

Table 11 demonstrates the results of the sponsor's ITT_{CM} analysis of photophobia for each trial and treatment arm.

Study S98-072 demonstrates a significant difference between placebo and ESBA in the treatment of migraine associated photophobia in all analyses. There was a statistical difference between treatment arms, favoring ESBA, for overall treatment effect (p<0.001), treatment-by-time interaction (p=0.002), and for the mean reduction in photophobia severity at two hours (p<0.001). There was a significant difference, favoring ESBA, in the proportion

of patients at two hours reporting resolution of their baseline photophobia, with 30% of ESBA treated patients reporting resolution compared to 14% of placebo treated patients ($p<0.001$).

Study S98-073 fails to demonstrate a significant difference between placebo and ESBA in the treatment of migraine associated photophobia in most analyses. There is no statistical difference between treatment arms for overall treatment effect ($p=0.179$) and treatment-by-time interaction ($p=0.114$). The mean reduction in photophobia severity was significant, favoring ESBA, at two hour ($p=0.045$) but failed to demonstrate significance between treatment groups at any other time point[11]. There is no significant difference between treatment groups in the proportion of patients reporting resolution of their baseline photophobia at two hours, with 21% of ESBA treated patients reporting resolution compared to 14% of placebo treated patients ($p=0.083$). In fact, the proportion of subjects reporting resolution of photophobia does not reach significance at any time during the six hours except at the first hour[12].

Study S98-074 demonstrates a significant difference between placebo and ESBA in the treatment of migraine associated photophobia in most analyses. There is a statistical difference between treatment arms, favoring ESBA, for overall treatment effect ($p=0.023$), treatment-by-time interaction ($p=0.012$), and for the mean reduction in photphobia severity at two hours ($p=0.019$). There is a significant difference in the proportion of patients reporting resolution of their baseline photophobia at two hours, with 23% of ESBA treated patients reporting resolution compared to 12% of placebo treated patients ($p=0.007$).

[11] Source: Sponsor's Table 3.3.2, page 51, study report S98-073.
[12] Source: Sponsor's Table 3.3.2A, page 53, study report S98-073.

Table 11: Efficacy results for Photophobia (ITT_{CM})

		Least Square Means @ 2 hours	Treatment by time interaction	Overall Treatment effect	Proportion reporting resolution @ 2 hours	Proportion reporting resolution @ 6 hours
S98-072	**Placebo** (N=194)	1.45			28 (14%)	75 (39%)
	ESBA (N=194)	1.11			59 (30%)	113 (58%)
	P value	<0.001	0.002	<0.001	<0.001	<0.001
S98-073	**Placebo** (N=175)	1.45			25 (14%)	83 (47%)
	ESBA (N=193)	1.27			41 (21%)	102 (53%)
	P value	0.045	0.114	0.179	0.083	0.300
S98-074	**Placebo** (N=197)	1.56			24 (12%)	36 (18%)
	ESBA (N=183)	1.34			42 (23%)	59 (32%)
	P value	0.019	0.012	0.023	0.007	0.002

Source: Sponsor's Table 3.3.2 and 3.3.2.1(A) study reports S98-072, S98-073, and S98-074.

3.4.2.4 Vomiting

The sponsor analyzes vomiting separately. In study S98-072, S98-073, and S98-074 there are too few subjects reporting vomiting (0, 3, 5 respectively) to form a statistical basis for comparison between treatment arms. Table 12 outlines the limited experience the sponsor had with efficacy in vomiting during the three clinical trials. The sponsor does not calculate incidence rates for vomiting in any of the three studies. In general it appears that there was no difference in vomiting reduction between placebo treated patients and ESBA treated patients however, the incidence of vomiting in all three studies was too low to make any meaningful conclusions about efficacy.

*Table 12: Efficacy on Vomiting (ITT_{CM})**

		Least Squares Means @ 2 hours	Treatment by time interaction	Overall Treatment effect
S98-072	**Placebo** (N=201)	0.01		
	ESBA (N=203)	0.01		
	p value	0.946	0.240	0.781
S98-073	**Placebo** (N=180)	0.00		
	ESBA (N=197)	0.00		
	p-value	NA	0.331	0.287
S98-074	**Placebo** (N=204)	0.03		
	ESBA (N=188)	0.02		
	p-value	0.428	0.807	0.743

Source: Sponsor's Table 3.3.4, study report S98-072, S98-073, and S98-074.
*The incidence of vomiting is too low in the three studies to make analyses meaningful.

3.4.3 Functional Ability

Functional ability is evaluated on a five-point scale as outlined in Section 3.3. The results of the sponsor's analyses can be found in Table 13.

Study S98-072 demonstrates a significant difference, favoring ESBA, in all analyses. The treatment-by-time interaction and overall treatment effect were significant at $p<0.001$. The mean improvement in functional ability score demonstrated significance from hour two through hour six ($p<0.001$)[13].

Study S98-073 fails to demonstrate any significant difference between ESBA and placebo in most analyses. The treatment-by-time interaction and the overall treatment effect fails to demonstrate any significant differences between ESBA and placebo($p=0.080$ and 0.264 respectively). Although the mean functional ability score difference was nearly significant at two hours ($p=0.052$), most other time points were not close to significance (p range 0.098-0.762)[14].

Study S98-074 demonstrates a significant difference between treatments, favoring ESBA, for treatment-by-time interaction ($p=0.004$) but not overall treatment effect ($p=0.214$). The difference between treatment arms for mean change in functional ability also fails to

[13] Source: Sponsor's Table 3.3.4, page 58, study report S98-072.
[14] Source: Sponsor's Table 3.3.4, page 57, study report S98-073.

demonstrate significance at two hours (p=0.087) but was significant from hour four through hour six (p≤0.010)[15].

Table 13: Efficacy Analyses for Functional Ability (ITT_{CM})

		Least Squares Means @ 2 hours	Treatment by time interaction	Overall Treatment effect
S98-072	**Placebo** (N=200)	1.86		
	ESBA (N=200)	1.38		
	p value	<0.001	<0.001	<0.001
S98-073	**Placebo** (N=180)	1.89		
	ESBA (N=197)	1.68		
	p-value	0.052	0.080	0.264
S98-074	**Placebo** (N=204)	2.06		
	ESBA (N=188)	1.864		
	p-value	0.087	0.004	0.214

Source: Sponsor's Table 3.3.4, study reports S98-072, S98-073, and S98-074.

3.4.4 Pain Intensity Difference

Table 14 demonstrates the results of the sponsor's analysis of pain intensity difference (PID) for all three studies. The calculation of PID is discussed in Section 3.3. All three studies demonstrate a significant difference favoring ESBA, in the mean pain intensity difference at two hours (p≤0.033). In study S98-072 and S98-074 the difference between treatment groups was significant from hour one through hour six (p≤0.038)[16]. Study S98-073 demonstrated significance between treatment arms, favoring ESBA, only at two and three hours post test drug administration (p≤0.033)[17].

3.4.5 Summed Pain Intensity Difference

Table 14 demonstrates the results of the sponsor's analysis of six hour summed pain intensity difference (SPID) for all three studies. The calculation of SPID is discussed in Section 3.3. Study S98-072 and S98-074 demonstrated a significant difference (p<0.001) between treatments, favoring ESBA, in the six hour summed pain intensity difference. Study S98-073 demonstrates an indication of significance between treatment arms, favoring ESBA, but failed to meet the preset alpha of 0.05 for SPID (p=0.062).

[15] Source: Sponsor's Table 3.3.4, page 61, study report S98-074.
[16] Source: Sponsor's Table 3.4.2, page 59 (study S98-072) and page 62 (study S98-074).
[17] Source: Sponsor's Table 3.4.1, page 94, study report S98-073.

Table 14: Efficacy evaluation for PID and SPID (ITT_{CMI})

		PID @ 2hours	SPID
S98-072	**Placebo** (N=200)	0.61	4.25
	ESBA (N=200)	1.03	6.94
	p-value	<0.001	<0.001
S98-073	**Placebo** (N=180)	0.66	4.81
	ESBA (N=197)	0.84	5.80
	p-value	0.033	0.062
S98-074	**Placebo** (N=204)	0.28	1.59
	ESBA (N=188)	0.53	3.360
	p-value	0.003	<0.001

Source: Sponsor's Table 3.4.2, study reports S98-072, S98-073, and S98-074.

3.4.6 Headache Recurrence through hour 24.

The sponsor analyzes the incidence of migraine recurrence at 24 hours in the three studies. The recurrence rates are similar between each treatment group within each study. The incidence of headache recurrence within 24 hours for study S98-072 was 10% for placebo treated subjects and 11% for ESBA treated subjects. Study S98-073 had a 24-hour recurrence incidence of 11% for placebo treated subjects and 12% for ESBA treated subjects. Study S98-074 had a 24-hour recurrence incidence of 17% for placebo treated subjects and 14% for ESBA treated subjects. None of the differences between treatment arms for each study was significant ($p \geq 0.532$)[18].

3.5 Reviewer's Efficacy Analyses

As previously discussed the two different group analyses presented by the sponsor are not the typical ITT analyses requested by the Division of Neuropharmacological Drug Products for migraine studies. The sponsor's ITT_{ALL} population contains 11 subjects that took study medication but did not follow-up or provide any valid post-dosing information. The sponsor's ITT_{CM} population excludes 10 subjects that took study medication but did not treat an IHS defined migraine headache. Although the outcome of the two analyses result in similar conclusions, I will present in this section an analyses of the ITT population as preferred by the Division, that being, all subjects that took study medication and recorded at least a single valid post-dosing evaluation. Efficacy endpoints will be analyzed using Cochran-Mantel-Haenzel test stratified by investigator. I will handle missing 2-hour efficacy data by the last observation carried forward (LOCF) method.

[18] Source: Sponsor's Table 3.5.2, page 61 (S98-072), page 60 (S98-073), and page 643 (S98-074)

The datasets for studies S98-072, S98-073, and S98-074 contains records for 485, 446 and 482 subjects respectively. Not all of these subjects took study medication. Study S98-072 has 409 subjects that took study medication. Of these subjects, five subjects (#323, 359, 436, 507, and 510) require LOCF for the 2-hour efficacy assessment and three subjects (#161, 171, 178) have no post-treatment readings. The three subjects without post-treatment efficacy readings were deleted from my ITT population, resulting in 406 subjects for the ITT_{AGENCY} population. Study S98-073 has 382 subjects that took study medication. Of these subjects, one requires LOCF (#015) for the 2-hour efficacy assessment and four subjects (#076, 099, 146, and 181) have no post-treatment readings resulting in 378 subjects for the ITT_{AGENCY} population. Study S98-074 has 400 subjects that took study medication. Of these subjects, three require LOCF (#165, 189, and 365) for the 2-hour assessment and four subjects (#142, 279, 295, and 403) did not record any post-treatment readings resulting in 396 subjects for the ITT_{AGENCY} population.

3.5.1.1 Migraine Characteristics

The sample Case Report Form and the Migraine Qualifying Form were reviewed. The sponsor failed to collect information detailing the characteristics of the auras experienced by subjects (reversibility, time between aura and headache onset, etc.); therefore, I could not apply the International Headache Society's strict migraine with aura criteria.

The electronic datasets for each study were evaluated to determine the percentage of subjects in each study reporting a headache that met the International Headache Society (HIS) diagnostic criteria for migraine headache. A modified IHS criterion for migraine was used. I assumed that if the patient had an aura with their headache, then the headache was a migraine. There were 157 subjects reporting an aura with their headache out of the 1180 subjects in the ITT_{AGENCY} population. Otherwise the reported non-aura headache had to meet the following two conditions. First the headache had to have two of the following characteristics: unilateral, throbbing, aggravated by activity, or baseline severity of moderate to severe intensity. Secondly, the headache had to have one of the following associated symptoms: nausea and/or vomiting, or photophobia plus phonophobia.

In the ITT_{AGENCY} population all three studies had a very high percentage of reported headaches meeting the above definition of migraine. Study S98-072 had 406 subjects reporting and treating a headache, of which 400 (98.5%) headaches met the above definition of migraine. Study S98-073 had 378 subjects reporting a headache, of which 376 (99.5%) headaches met the above definition of migraine. Study S98-074 had 396 subjects reporting a headache, of which 391 (98.7%) headaches met the above definition of migraine. The sponsor had slightly different results for subjects they defined as having a confirmed migraine, with 401 subjects in Study S98-072, 377 subjects in Study S98-073, and 392 subjects in Study S98-074. I am unable to account for the slight difference in numbers from reviewing the sponsor's datasets however, I conclude that most headaches treated in these studies were migraine.

The Patient Dairy was reviewed and found adequate. The patient's diary did not query for information such as the

3.5.1.2 Study Design

The study was adequately designed and powered to assess the primary efficacy variable for each study. The randomization scheme was reviewed for each trial and appears adequate. For all three clinical efficacy studies patients were selected using both population based recruiting and conventional recruiting methods. Patients screening criterion selected subjects with mild to moderate migraine history and excluded subjects with severe migraines that did not respond to traditional prescription or over-the-counter therapies and subjects that have vomiting ≥ 20% of the time during migraine attacks. Hence individuals that would be expected to respond to available therapies and not be suffering from severe migraine syndromes inhabit the study population in all three studies.

3.5.1.3 Headache Response at 2 hours

For my analyses, I chose to evaluate the ITT_{AGENCY} population. The primary endpoint of headache response at two hours was evaluated for each study. I first did a subset of the sponsor's dataset by those subjects reporting a headache. Secondly, I evaluated all subjects from the above subset without a completed two-hour assessment. Whenever possible missing post-treatment efficacy assessments where carried forward from the proceeding hours assessment. For Study S98-072, five subjects required efficacy assessment information to be carried forward to the two hour timepoint. For Study S98-073 one subject required efficacy assessments information to be carried forward. Finally Study S98-074 had three subjects requiring efficacy assessments to be carried forward. Eleven subjects were deleted from my combined study subset due to lack of post-treatment assessments.

Table 15 demonstrates the primary efficacy endpoint results at two hours for the ITT_{AGENCY} population. The 2-hour headache response rates were numerically higher for ESBA treated patients in all three studies, but reached statistical significance in only two studies (S98-072 and S98-074). Since the study design of all three studies did not allow for variable doses of ESBA, a dose effect can not be determined. I conclude that the result of these studies demonstrates that ESBA is effective in the treatment of headache pain associated with migraine at two hours.

Table 15 Headache Response at 2-Hours using ITT_{AGENCY}

Study	ESBA	Placebo	p-value*
S98-072	112/204 (54.9%)	72/202 (35.6%)	<0.001
S98-073	97/197 (49.2%)	76/181 (42.0%)	0.158
S98-074	76/191 (39.8%)	56/205 (27.2%)	0.007

*CMH, stratified by Investigator

Table 16 demonstrates the headache response at two hours stratified for baseline headache severity. ESBA was significantly better than placebo in patients treating a moderate headache in all three studies. For patients experiencing a migraine headache of severe intensity, only study S98-072 was able to demonstrate a significant difference (p=0.003) between treatment

groups, favoring ESBA, for the relief of headache at two hours. It may be important to note that study S98-074 had relatively fewer subjects treating a baseline severe headache than in either study S98-072 or S98-073 (22.5% for study S98-074 compared to 36.2% and 38.4% for studies S98-073 and S98-072 respectively). I conclude that ESBA is effective for the treatment of moderate headache pain associated with migraine but not for the treatment of severe headache pain associated with migraine.

Table 16 Headache Response at 2-Hours by Baseline Severity using ITT_{AGENCY}

Study	Baseline Severity	ESBA	Placebo	p-value
S98-072	Moderate	69/123 (56.1%)	50/127 (39.4%)	0.008
	Severe	43/81 (53.1%)	22/75 (29.3)	0.003
S98-073	Moderate	78/125 (62.4)	55/116 (47.4)	0.020
	Severe	19/72 (26.4%)	21/65 (32.3%)	0.448
S98-074	Moderate	65/146 (44.5%)	44/161 (27.3%)	0.002
	Severe	11/45 (24.4%)	11/44 (25.0)	0.927

*CMH, stratified by Investigator

3.5.1.4 Migraine Associated Symptoms

Using the ITT_{AGENCY} population previously defined, I evaluated the two hour efficacy results for the secondary symptoms of nausea, phonophobia, and photophobia associated with migraine. As had the sponsor, I choose not to evaluate the symptom of vomiting since so few patients reported vomiting at baseline. Study S98-072 has no subjects reporting vomiting at baseline and studies S98-073 and S98-074 have only three and five subjects respectively reporting vomiting at baseline.

For the post-treatment analyses the sponsor analyzed the mean changes from baseline in symptom severity in the subgroup of patients reporting an associated symptom at baseline, as well as the percentage of patients experiencing a resolution of symptoms to none at the various time points. Both analyses include only those patients who experienced symptoms at baseline.

For my analyses of associated symptoms, I chose to analyze the percentage of subjects reporting associated symptoms at baseline and at two hours. This method has the advantage over the sponsor's method since it may capture subjects not reporting an associated symptom at baseline but rather develops it after taking their assigned medication. I was particularly concerned that ESBA may cause nausea. This method will also allow a comparison of all subjects reporting an associated symptom at baseline to all subjects reporting the associated symptom at two hours. To accomplish my analyses the sponsor's dataset entries for nausea, photophobia, and phonophobia were converted from the sponsor's four-point severity scale to a two-point scale to reflect whether or not the subject had the symptom.

A review of the sponsor's datasets demonstrates that 60 subjects developed nausea within two hours after taking their test medication in the three studies combined (placebo 26, ESBA 34). An analysis of these 60 subjects failed to demonstrate a significant difference ($p \geq 0.170$)

between treatment arms in study S98-072 (ESBA 8 vs. PB 7) and S98-073 (ESBA 7 vs. PB 12). In study S98-074 19 subjects taking ESBA developed nausea within two hours compared to seven patient taking placebo (p=0.008). My conclusion is that there is little evidence that ESBA causes nausea to any great extent in subjects with migraine.

Table 17 demonstrates the distribution of patients reporting an associated symptom with their treated headache at baseline for each treatment group in all three studies. As can be seen from the table there does not appear to be any significant difference between the two treatments for any of the three associated symptoms at baseline in all three studies, although there were minor numerical imbalances noted. Nausea was present in about 55 to 67% of the subjects, phonophobia was present in about 92 to 97% of subjects, and photophobia was present in about 96 to 98% of the subjects. These results are typical for most migraine studies. I conclude that the distribution of subjects reporting nausea, phonophobia, or photophobia at baseline is not significantly different for ESBA and placebo in all three studies.

Table 17 Subjects reporting migraine associated symptoms at baseline using ITT_{AGENCY}

Study		Nausea	Phonophobia	Photophobia
S98-072	ESBA	116/204 (56.9%)	198/204 (97.1%)	196/204 (96.1%)
	Placebo	110/202 (54.5%)	195/202 (96.5%)	194/202 (96.0%)
	p-value*	0.654	0.734	0.959
S98-073	ESBA	124/197 (62.9%)	187/197 (94.9%)	193/197 (98.0%)
	Placebo	108/181 (59.7%)	172/181 (95.0%)	176/181 (97.2%)
	p-value*	0.514	0.963	0.641
S98-074	ESBA	122/191 (63.9%)	176/191 (92.2%)	185/191 (96.9%)
	Placebo	137/205 (66.8%)	189/205 (92.2%)	198/205 (96.6%)
	p-value*	0.593	0.917	0.925

*CMH, stratified by Investigator

Table 18 demonstrates the distribution of subjects reporting nausea, phonophobia, or photophobia in each treatment group for all three studies at two hours. These results demonstrate that there was an overall decline in the number of subjects reporting nausea, phonophobia, and photophobia at two hours for both ESBA and placebo in each study when compared to baseline. For phonophobia, two out of the three studies (S98-072 and S98-074) demonstrates a significant difference, favoring ESBA, in the proportion of subjects reporting phonophobia in ESBA treated subjects compared to placebo treated subjects ($p \leq 0.002$). For photophobia, two out of three studies (S98-072 and S98-074) demonstrates a significant difference, favoring ESBA, in the proportion of subjects reporting photophobia in ESBA treated subjects compared to placebo treated subjects ($p \leq 0.003$). Although there was an overall decline in subjects reported nausea at two hours compared to baseline for both ESBA and placebo treated subjects, there was no significant difference between treatment arms at two hours in all three studies ($p \geq 0.214$). I conclude from the analysis that ESBA is effective in the treatment of phonophobia and photophobia associated with migraine but is ineffective in the treatment of nausea associated with migraine.

Table 18 Subjects reporting migraine associated symptoms at 2 hours using ITT_{AGENCY}

Study		Nausea	Phonophobia	Photophobia
S98-072	ESBA	81/204 (39.7%)	130/204 (63.7%)	134/204 (65.7%)
	Placebo	70/202 (34.7%)	159/202 (78.7%)	164/202 (81.2%)
	p-value*	0.299	<0.001	<0.001
S98-073	ESBA	80/197 (40.6%)	136/197 (69.0%)	152/197 (77.2%)
	Placebo	85/181 (47.0%)	138/181 (76.2%)	151/181 (83.4%)
	p-value*	0.214	0.118	0.127
S98-074	ESBA	100/191 (52.4%)	130/191 (68.1%)	140/191 (73.3%)
	Placebo	107/205 (52.2%)	167/205 (81.5%)	175/205 (85.4%)
	p-value*	0.870	0.002	0.003

*CMH, stratified by Investigator

My findings for the proportion of subjects reporting an associated symptom at four hours and six hours are demonstrated in Table 19 and Table 20 respectively. Multiple data elements were blank and required last observation to be carried forward. Again, the results demonstrate that there is an overall decline in subjects reporting nausea, phonophobia, and photophobia at four hours and six hours for both treatment groups, in each study, compared to two hours and baseline however statistical significance was variable.

The proportion of subjects reporting nausea at four and six hours fails to demonstrate a difference between treatments in all three studies ($p \geq 0.058$, most much higher). The proportion of patients reporting photophobia at four hours was significantly different between treatment groups, favoring ESBA, in study S98-072 ($p=0.007$) and S98-074 ($p=0.040$) but not study S98-073 ($p=0.806$) however only study S98-072 was significant at six hours ($p=0.016$). The proportion of patients reporting phonophobia at four and six hours in ESBA treated patients is only significantly different from placebo in study S98-072 ($p=0.002$ and 0.004 respectively). I conclude from these results that ESBA is ineffective in the treatment of nausea associated with migraine at four hours and six hours. The efficacy of ESBA shown at two hours for phonophobia and photophobia has variable efficacy results at four and six hours.

Table 19 Subjects reporting migraine associated symptoms at 4 hours using ITT_{AGENCY}

Study		Nausea	Phonophobia	Photophobia
S98-072	ESBA	42/204 (20.6%)	77/204 (37.8%)	85/204 (41.7%)
	Placebo	47/202 (23.3%)	107/202 (53.0%)	111/202 (55.0%)
	p-value*	0.533	0.002	0.007
S98-073	ESBA	52/197 (26.4%)	97/197 (49.2%)	102/197 (51.8%)
	Placebo	52/181 (28.7%)	88/181 (48.6%)	96/181 (53.0%)
	p-value*	0.612	0.904	0.806
S98-074	ESBA	77/191 (40.3%)	110/191 (57.6%)	115/191 (60.2%)
	Placebo	91/205 (44.4%)	129/205 (63.0%)	144/205 (70.2%)
	p-value*	0.459	0.294	0.040

*CMH, stratified by Investigator

Table 20 Subjects reporting migraine associated symptoms at 6 hours using ITT_{AGENCY}

Study		Nausea	Phonophobia	Photophobia
S98-072	ESBA	33/204 (16.2%)	47/204 (23.0%)	51/204 (25.0%)
	Placebo	24/202 (11.9%)	72/202 (35.6%)	72/202 (35.6%)
	p-value*	0.221	0.004	0.016
S98-073	ESBA	25/197 (12.7%)	58/197 (29.4%)	62/197 (31.5%)
	Placebo	36/181 (19.9%)	57/181 (31.5%)	62/181 (34.3%)
	p-value*	0.058	0.666	0.566
S98-074	ESBA	55/191 (28.8%)	81/191 (42.4%)	89/191 (46.6%)
	Placebo	61/205 (29.8%)	91/205 (44.4%)	105/205 (51.2%)
	p-value*	0.860	0.724	0.381

*CMH, stratified by Investigator

3.6 Efficacy Conclusions

The following statements are the sponsor's conclusions found in the Integrated Summary of Efficacy.

- Relative to S98-072
  1. Study S98-072 demonstrates a significant treatment response ($p<0.001$) for percent responders at two hours. This is supported by a significant difference between treatment arms, favoring ESBA, for SPID ($p<0.001$) and PID ($p\leq0.001$ between hour one and hour six). The subset of gender and race did not demonstrate a difference in response as noted by the interaction effect (gender $p=0.573$, race $p=0.391$)[19]. There was not a significant interaction for the subgroup analysis of baseline severity ($p=0.644$).

[19] Source: Sponsor's ISE page 87.

2. Study S98-072 demonstrates a significant treatment effect on the primary variable for the subjects with a baseline headache severity of moderate (p=0.008) and severe (p=0.005).
3. Study S98-072 demonstrates a significant (treatment-by-time) interaction (p≤0.018) for the secondary variables of nausea, phonophobia, and photophobia. Also demonstrated was a significant treatment effect for nausea at hour four through hour six (p≤0.031), and for photophobia and phonophobia from hour one through hour six post-dosing (p≤0.027).
4. The analysis of the proportion of subjects reporting reduced nausea at all time intervals failed to demonstrate any significant difference between placebo and ESBA.
5. The analysis of the proportion of subjects reporting reduced phonophobia and photophobia demonstrated significance favoring ESBA at hour one through hour six post-dosing (p≤0.036)
6. The analysis of functional ability resulted in significant treatment-by-time interaction (p<0.001) with significance noted from hour one through hour six post-dosing (p<0.001).

- Relative to study S98-073
  7. Study S98-073 fails to demonstrate a significant difference between placebo and ESBA for percent responders (p≥0.206). However there was a significant difference, favoring ESBA, in the reduction of pain (PID) at hour two (p=0.033) and hour three. The treatment by gender interaction was not significant (p=0.718), the treatment by race interaction showed an indication of significance (p=0.081), and the treatment by baseline severity was significant (p=0.042).
  8. Study S98-073 demonstrated a significant treatment effect, favoring ESBA, on the primary variable for the subjects with a baseline headache severity of moderate (p=0.026) but not severe (p=0.415).
  9. The change in symptom severity of nausea, photophobia, and phonophobia did not reach a level of significance (p≥0.05).
  10. There was not a significant difference between ESBA and placebo in the proportion of subjects reporting a reduction in nausea at any time (p≥0.126).
  11. There was a favorable treatment effect for the proportion of subjects who had a reduction in photophobia at the hour one evaluation (p≤0.028), and an *indication* of significance at 30 minutes and hour two evaluations (p=0.098 and 0.083 respectively).
  12. There was an "*indication*" of significance for a reduction in phonophobia at hour one (p=0.070) and hour three (p=0.058) post dosing.
  13. There was an "*indication*" of significance in treatment effect (treatment-by-time) in the improvement in functional ability (p=0.080) with significance noted at the hour two and hour four evaluations (p≥0.052). [Reviewer's note: I believe the sponsor meant to say that the mean improvement in functional ability was nearly significant at hour two (p=0.052) and hour four (p=0.098)]

- Relative to S98-074
  1. Study S98-074 demonstrates a significant difference between placebo and ESBA for percent responders at two hours (p≤0.020). This is supported by a significant

treatment effect in reducing PID from hour one through hour six ($p \leq 0.038$) and a significant SPID ($p < 0.001$) compared to placebo. The treatment by gender interaction and treatment by race interaction does not demonstrate a significant difference in response ($p \geq 0.201$). The treatment by baseline severity interaction showed an indication of significance ($p = 0.078$).

2. Comparison of responders with a baseline severity of moderate demonstrated a significant treatment effect ($p = 0.004$) favoring ESBA but not for baseline severity of severe ($p = 0.761$).
3. In the analyses of the secondary variables, nausea, photophobia, and phonophobia, there was not a significant difference between treatments for the mean reduction in nausea ($p \geq 0.166$).
4. ESBA significantly reduced photophobia from hour two through hour six ($p \leq 0.019$).
5. ESBA significantly reduced phonophobia from hour two through hour five ($p \leq 0.026$) and *approaching significance* at hour six ($p = 0.083$).
6. There was a significant treatment effect for the proportion of subjects who experienced a reduction in nausea at hour three through hour six post-dosing ($p \leq 0.044$).
7. There was a significant treatment effect for the proportion of subjects who experienced a reduction in photophobia from hour two through hour six post-dose ($p \leq 0.007$). There was a significant treatment effect for the proportion of subjects who experienced a reduction in phonophobia from hour 2 through hour 5 post-dosing ($p \leq 0.013$) with an *indication of significance* at hour six ($p = 0.084$).
8. The ability to function was improved significantly for the ESBA treated group at hour four through hour six ($p \leq 0.010$).

The sponsor ends their summary of efficacy results with the findings obtained by the analyses of pooled efficacy data. The sponsor was specifically informed during the pre-NDA meeting that pooled efficacy results could not be used in support of an NDA and therefore I will not summarize their efficacy findings in this review.

The sponsor finishes their conclusion with the following statement:

> *"The weight of evidence presented in this integrated summary of the individual trials (S98-072, S98-073, and S98-074) and the pooled analysis, support the efficacy of Extra Strength Bayer® Aspirin in treating migraine headache pain, and in reducing the symptoms of phonophobia and photophobia. Studies S98-072 and S98-074 and the pooled analysis support a reduction for the symptom of nausea. Additionally, pain intensity difference throughout the study period as well as the 6-hour summed pain intensity difference significantly favored the Extra Strength Bayer® Aspirin treatment group."*

The sponsor's conclusions are based on the primary analysis of the confirmed migraine population (ITT_{CM}) but are consistent with the ITT_{ALL} analyses.

3.6.1 Reviewer's Comments

The following comments are based on the sponsor conclusions outlined in the previous section. For consistency my comments here will also cite statistical values derived from sponsor's ITT_{CM} analysis unless otherwise stated. Additionally results from my ITT_{AGENCY} analyses will also be included where appropriate. The conclusions are relatively consistent between all analyses.

- Relative to study S98-072, I concur with the sponsor's statements however I would like to include the following:
  1. Study S98-072 fails to demonstrate a significant difference between treatment arms in the mean reduction of nausea at hour two (p=0.753) or in the overall treatment effect for nausea (p=0.090).
  2. Study S98-072 fails to demonstrate a significant reduction in the proportion of subjects treated with ESBA reporting resolution of their baseline nausea at two hours (p=0.704). In fact, as a percentage it appears placebo did slightly better than ESBA with 44 (40%) of the placebo treated subjects reporting resolution of nausea compared to 43 (37%) of the ESBA treated subjects.
  3. Study S98-072 fails to demonstrate a significant difference between treatment arms in the proportion of subjects reporting nausea at two hours (ITT_{AGENCY}, p=0.299).
  4. Study S98-072 demonstrates a significant proportion of ESBA treated subjects compared to placebo reporting relief of their headache at two hours stratified by baseline severity for both moderate (ITT_{AGENCY}, p=0.008) and severe (ITT_{AGENCY}, p=0.003).
  5. Study S98-072 fails to demonstrate a difference between placebo and ESBA on headache recurrence at 24 hours (p=0.532).
  6. There are no subjects <18 years of age or ≥65 years of age in this study.

- Relative to study S98-073, I concur with the sponsor's statements however I would like to include the following:
  1. The PID was not significantly different between treatments for hour four through hour six (p≥0.074) and the SPID was not significant (p=0.062).
  2. There was not a significant difference between placebo and ESBA in the proportion of subjects reporting resolution of nausea at hour two (p=0.213) or any time thereafter (p≥0.126).
  3. There was not a significant difference between placebo and ESBA in the proportion of subjects reporting resolution of photophobia at hour two (p=0.083) or any time thereafter (p≥0.105).
  4. There was not a significant difference between placebo and ESBA in the proportion of subjects reporting resolution of phonophobia at hour two (p=0.131) or any time thereafter (p≥0.58).
  5. Study S98-073 fails to demonstrate a significance in the mean reduction of nausea at hour two (p=0.144), in the overall treatment effect for nausea (p=0.264), and in the treatment-by-time interaction for nausea (p=0.725).
  6. Significance was demonstrated for the mean reduction in photophobia and phonophobia at hour two (p≤0.049) but not at any other time point during the six-hour study for both symptoms. Additionally, the overall treatment effect and

treatment-by-time interaction were also not significant for photophobia and phonophobia ($p \geq 0.114$).

7. Study S98-073 fails to demonstrate a significant difference between treatment for subjects reporting nausea at two hours (ITT_{AGENCY}, $p=0.214$).
8. Study S98-073 fails to demonstrate a significant difference between treatments for subjects reporting photophobia at two hours (ITT_{AGENCY}, $p=0.127$).
9. Study S98-073 fails to demonstrate a significant difference between treatments for subjects reporting phonophobia at two hours (ITT_{AGENCY}, $p=0.118$).
10. Study S98-073 demonstrates a indication of significance in the improvement of functional ability at hour two ($p=0.052$) but not at any other time thereafter ($p \geq 0.098$) or in the overall treatment effect ($p=0.264$) and in treatment-by-time interaction ($p=0.080$).
11. Study S98-073 fails to demonstrate a difference between placebo and ESBA on headache recurrence at 24 hours ($p=0.770$).
12. There are no subjects <18 or ≥65 years of age in this study.

- Relative to study S98-074, I concur with the sponsor's statements however I would like to include the following:
  1. Despite the significance demonstrated between treatments in percent responders at hour two the actual whole number difference was small, 55 subjects (27%) for placebo and 72 subjects (38%) for ESBA, and less than the 15% the sponsor stated would be the threshold for clinical significance.
  2. Study S98-074 fails to demonstrate a significant difference between treatments for headache relief at two hours in subjects reporting a baseline headache of severe intensity (ITT_{AGENCY}, $p=0.927$).
  3. Study S98-074 fails to demonstrate a significant difference between treatments in the mean reduction of nausea at hour two ($p=0.151$), in the overall treatment effect for nausea ($p=0.166$), and in the treatment by time interaction for nausea ($p=0.283$).
  4. There was not a significant difference between placebo and ESBA in the proportion of subjects reporting resolution of nausea at hour two ($p=0.366$).
  5. Study S98-074 fails to demonstrate a significant difference between treatments in the overall treatment effect for the mean reduction of phonophobia ($p=0.087$).
  6. Study S98-074 fails to demonstrate a significant difference between treatments for the proportion of subjects reporting nausea at two hours ((ITT_{AGENCY}, $p=0.870$).
  7. There was no difference between treatment groups in their ability to function at hour two ($p=0.087$). Similarly, the overall treatment effect for functional ability was not significant ($p=0.214$).
  8. Study S98-074 fails to demonstrate a difference between placebo and ESBA for headache recurrence at 24 hours ($p=0.550$).

Table 21 summarizes each variable analyzed by the sponsor with the resulting statistical p values and the results of my analyses when appropriate. The last column provides a tally of the results between the three studies in regards to whether the results were significant or not. The last row following each variable provides an overview of my conclusions about that specific variable.

Table 21: Summary of efficacy variable analyses for each study (ITT_{CM})

Variable		S98-072	S98-073	S98-074	Sign:Nonsign
Headache response @ 2 hrs.	Overall	p<0.001	p=0.206	p=0.020	2:1
	Baseline Moderate	p=0.008	p=0.026	p=0.004	3:0
	Baseline Severe	p=0.005	p=0.415	p=0.761	1:2
	Reviewer Conclusions: Unable to claim efficacy in severe migraine. Able to claim efficacy at two hours overall.				
Nausea	Treatment by Time	p=0.018	p=0.725	p=0.283	1:2
	Overall Treatment Effect	p=0.090	p=0.264	p=0.166	0:3
	% reporting resolution @ 2 hours	p=0.704	p=0.213	p=0.366	0:3
	% reporting nausea @ 2 hours*	p=0.299	p=0.214	p=0.870	0:3
	Reviewer Conclusions: Unable to claim efficacy in Nausea				
Phonophobia	Treatment by Time	p<0.001	p=0.485	p=0.014	2:1
	Overall Treatment Effect	p<0.001	p=0.174	p=0.087	1:2
	% reporting resolution @ 2 hours	p<0.001	p=0.131	p=0.009	2:1
	% reporting phonophobia @ 2 hours*	p<0.001	p=0.118	p=0.002	2:1
	Reviewer Conclusions: Able to claim efficacy in phonophobia				
Photophobia	Treatment by Time	p=0.002	p=0.114	p=0.012	2:1
	Overall Treatment Effect	p<0.001	p=0.179	p=0.023	2:1
	% reporting resolution @ 2 hours	p<0.001	p=0.083	p=0.007	2:1
	% reporting photophobia @ 2 hours*	p<0.001	p=0.155	p=0.003	2:1
	Reviewer Conclusions: Able to claim efficacy in photophobia				
Functional Ability	Treatment by time	p<0.001	p=0.080	p=0.004	2:1
	Overall Treatment Effect	p<0.001	p=0.264	p=0.214	1:2
	LS means @ 2 hrs	p<0.001	p=0.052	p=0.087	2:1
	Reviewer Conclusions: Debatable efficacy claim for functional ability				
PID	Overall @ X hr.	p≤0.001 @1 thru 6 hrs	p≤0.037 @ hour 2 and 3	p≤0.038 @ 1 thru 6 hrs	Mostly significant
SPID	Overall @ 6 hrs.	p<0.001	p=0.062	p<0.001	2:1
Headache Recurrence	@ 24 hours	p=0.532	p=0.770	p=0.550	0:3
	Reviewer Conclusions: Unable to claim efficacy in headache recurrence at 24 hours				

*These values are from my analyses using ITT_{AGENCY} population.

3.7 Reviewer's Efficacy Conclusions

- ESBA is effective in the treatment of headache pain in migraine patients.
- There is little evidence that ESBA if effective against severe headache pain in migraine sufferers.
- There is little evidence that ESBA is effective against nausea associated with migraine.
- There is no evidence that ESBA is effective in resolving nausea at two hours post-dosing in migraine patients experiencing nausea at baseline with their migraine.
- There is no evidence that ESBA is effective in reducing the proportion of subjects reporting nausea at two hours compared to placebo.
- ESBA is effective in the resolution of photophobia and phonophobia at two hours post-dosing.
- ESBA is effective in reducing the proportion of subjects reporting photophobia and phonophobia at two hours.
- There is no evidence that ESBA is effective in relieving vomiting in migraine patients.
- There is some evidence that ESBA has an overall treatment effect in improving functional ability.
- There is some evidence that ESBA is effective in improving functional ability at two hours post-dosing.
- There is no evidence that ESBA is effective in preventing migraine recurrence at 24 hours post-dosing.
- The efficacy of ESBA in adolescents has not been established because adolescents were not studied in the clinical trials outlined in this review.
- The efficacy of ESBA in the geriatric patient can not be established since few subjects ≥65 years of age were enrolled in the three clinical trials outlined in this review.
- [redacted]
- The efficacy of multiple doses of ESBA in the treatment of migraine is not established since multiple dose regimens are not studied in the trials outlined in this review.

4. Review of Safety

4.1 Background and Methodology

In this section I will review the safety profile results derived from the three clinical safety and efficacy trials (S98-072, S98-073, and S98-074) plus the pharmacokinetic trial (S99-102). By mutual agreement, the safety data obtained from the global safety review and the AERS database search will be reviewed by the primary review division (OTC Drug Products). Each clinical trial are of similar design and monitored adverse events in a similar manner.

There are 1242 subjects available for the safety analyses, 1191 patient exposures to a single dose of placebo (595 subjects) or ESBA (596 subjects) from the three clinical trials, and 51 exposures to ESBA in 26 subjects from study S99-102. The sponsor's ITT_{ALL} population consisting of 595 subjects receiving placebo and 596 subjects receiving Extra Strength Bayer® Aspirin (1000 mg) from the three clinical trials (S98-072, S98-073 and S98-074) all

had a similar design with each patient receiving a single blinded treatment. Study S99-102 had a crossover design with 25 subjects dosed with Extra Strength Bayer® Aspirin (500 mg) and 26 subjects dosed with Extra Strength Bayer® Plus Buffered Aspirin (500 mg). In this bioequivalence study, each subject exposure to aspirin was counted as a unique event, therefore if a subject completed both phases of the study, the subject was counted twice. Subjects from study S99-102 are not included in the sponsor's primary analysis of safety due to a lack of adverse events reporting (a single subject developed a migraine after taking Extra Strength Bayer® Plus Buffered Aspirin).

The demographic profile of the subjects included in the ITT_{ALL} population is discussed in Section 3.2 for each trial and will not be repeated here. The demographic profile of study S99-102 is outlined in Table 22. The PK study had slightly younger subjects, a higher percentage of men, and no African-Americans compared to the clinical efficacy trials.

Table 22: Demographic Profile of Subjects in Study S99-102

	S99-102	
	ESBA (n=25)	**ESBA+ (n=26)**
Age		
Mean	34.24	34.35
Range	19-45	19-45
Gender		
Male	11(44%)	12(46%)
Female	14(56%)	14(54%)
Race		
White	21(84%)	22(85%)
Black	0(0%)	0(0%)
Hispanic	4(16%)	4(15%)
Asian	0(0%)	0(0%)
Other	0(0%)	0(0%)

Source: Sponsor's Tables 2.1.1 and 2.2.1, study report S99-102, page 34-35.

4.2 Deaths

There were no deaths reported in any study.

4.3 Serious Adverse Events

There were a total of three serious adverse events reported between study S98-072 and S98-074 (See Table 23). Study S98-073 and S99-102 reported no serious adverse events.

Study S98-072 had a single serious adverse event reported in subject #178. Subject #178 is a 36 year old Caucasian female that experienced a perforated appendix approximately two weeks after taking a single dose of placebo medication. Patient #178 was included in the sponsor's ITT_{ALL} analyses however no valid follow up information regarding the migraine treatment is available since the patient did not return for a follow-up visit or return the diary.

Study S98-074 had two subjects reporting a serious adverse event, subject #281 and subject #441. Subject #281 is a 44 year old female diagnosed with a brain tumor and was subsequently treated with chemotherapy. Although the subject was randomized to ESBA, the subject did not medicate with study medication. Subject #441 was a 64 year old female that experienced a gastrointestinal bleed that required surgery. Although the subject had been randomized to ESBA, the subject did not medicate with study medication. Since neither subject took study medication they are not included in the sponsor's ITT_{ALL} analysis.

Table 23: Serious Adverse Events for Study S98-072, S98-073, S98-074 and S99-102.

	Patient ID	Randomization	Took Study Medication	Event
S98-072	178	Placebo	Yes	Perforated Appendix, 2 weeks post-dosing.
S98-073	NA	NA	NA	NA
S98-074	281	ESBA	No	Brain Tumor, treated with Chemotherapy
	441	ESBA	No	GI bleed, required surgery
S99-102	NA	NA	NA	NA

Source: Adapted from individual study reports, section 12.3.

4.4 Adverse Dropouts and "Other Significant Adverse Events"

Other then the serious adverse events outlined above, there were no other significant adverse events reported in any of the four studies. The sponsor does not report any drop outs due to adverse events in any study report.

4.5 Adverse Events

The sponsor combines study S98-072, S98-073, and S98-074 in their primary analysis of adverse events in the Integrated Summary of Safety. The ITT_{ALL} population was used from each trial. For the integration of the three clinical efficacy trials, the sponsor used Fisher's Exact Test to compare the proportions of subjects reporting adverse events for ESBA (1000 mg) and placebo including subset analyses where applicable.

Study S99-102 was not included in the safety analysis of ITT_{ALL} due to a lack of adverse events reporting. For study S99-102 there was a single adverse event reported for all 51 treatment exposures; subject #10 complained of a migraine approximately 5 hours after Extra Strength Bayer® Plus Buffered Aspirin was administered.

Table 24 outlines the number of subjects in each treatment group reporting any adverse event in the three clinical trials. Although there are slightly more subjects treated with ESBA that reported an adverse event, there is no statistically significant difference between treatment groups (p=0.169).

Table 24: Summary of All Averse Events, Studies S98-072, S98-073, and S98-074.

	Placebo N=595	ESBA N=596	p-value*
Subjects with AE's	50 (8%)	65 (11%)	0.169
# of AE's	66	86	
Deaths	0	0	

*Fisher's Exact Method
Source: ISS, Section 7.1

Of the 596 subjects that took ESBA, 65(11%) subjects reported a total of 86 adverse events. The majority of the reported adverse events were related to the digestive system with 30 subjects reporting 33 adverse events related to the digestive system. In order of greatest frequency, these events included nausea, dyspepsia, diarrhea, vomiting, dry mouth, eructation, and tooth disorder. Twenty subjects (3%) reported adverse events related to the nervous system, 13 subjects (2%) reported adverse events related to the body as a whole, and 1% or less reported adverse events in the remaining systems.

Of the 595 subjects that took placebo, 50(8%) subjects reported 66 adverse events. As seen in the ESBA treatment arm, the majority of adverse events were related to the digestive system with 18 subjects reporting 21 adverse events. In order of greatest frequency, these events included nausea, dyspepsia, vomiting, diarrhea, and intestinal perforation. Fifteen subjects (3%) reported adverse events related to body as a whole, 11 subjects (2%) reported adverse events related to the nervous system, and 1% or less reported adverse events in the remaining systems.

Table 25 outlines the number of subjects reporting adverse events by body system and treatment groups. Using the Fischer's Exact Test, the sponsor demonstrates there are no statistical difference between placebo and ESBA treatment for patients reporting any adverse event (p=0.169). The subset of subjects reporting adverse events related to the digestive system also fails to demonstrate any difference between placebo and ESBA (p=0.104).

Table 25: Summary of Subjects Reporting Adverse Events by Body System*.

Body System	Placebo (N=595) n (%)	ESBA (N=596) n (%)	p-value+
Any adverse event	50 (8%)	65 (11%)	0.169
Body as a whole	15 (3%)	13 (2%)	
Cardiovascular	5 (1%)	2 (0%)	
Digestive	18 (3%)	30 (5%)	0.104
Nervous	11 (2%)	20 (3%)	
Respiratory	1 (0%)	0 (0%)	
Skin	3 (1%)	2 (0%)	
Special senses	6 (1%)	7 (1%)	

Source: Sponsor's Table ISS-4a, page 24 and 25
*Pooled ITT_{ALL} for study S99-072, S99-073, and S99-074
+Fisher's Exact Test

Table 26 outlines adverse events occurring in ≥1% of the subjects for either treatment group. Overall, nausea was the most common adverse event for subjects taking ESBA. Somnolence and asthenia is reported more frequently in ESBA treated subjects than placebo treated subjects. It is difficult to determine whether these adverse events are from treatment or to be expected as sequelae of migraine.

An analysis of adverse events by gender fails to demonstrate any difference between men and women reporting any adverse events. Approximately 9.6% of the males reported an adverse event (10% for placebo and 9% for ESBA) compared to 9.7% of women reporting an adverse event (8% for placebo and 11% for ESBA).

Stratification of adverse events by severity demonstrates the majority (approximately 90%) of adverse events for each treatment group was of mild to moderate severity and resolved without problems. For adverse events reported as mild intensity, 27 placebo treated subjects reported 38 adverse events compared to 43 ESBA treated subjects reporting 54 adverse events. There was no statistical difference between these two groups (p=0.563)[20]. For adverse events reported as moderate intensity, 17 placebo treated subjects report 21 adverse events compared to 16 ESBA treated subjects reporting 23 adverse events. For adverse events reported as severe intensity, 5 placebo treated subjects report 6 adverse events compared to 6 ESBA treated subjects reporting 9 adverse events. The incidences of adverse events of moderate and severe intensity were too low to permit analysis.

A complete listing of all adverse events reported is located in Appendix 1.

[20] Source: ISS, Section 7.5, page 12.

Table 26 Most commonly reported Adverse Event (≥1%)

Body system Event	**Placebo** (N=595) n (%)	**ESBA** (N=596) n (%)
Any adverse event	50 (8%)	65 (11%)
Body as a whole		
Abdominal Pain	6(1%)	8(1%)
Asthenia	1(0%)	4(1%)
Cardiovascular		
Tachycardia	3(1%)	1(0%)
Digestive		
Diarrhea	3(1%)	5(1%)
Dyspepsia	5(1%)	7(1%)
Nausea	8(1%)	14(2%)
Vomiting	4(1%)	3(1%)
Nervous		
Dizziness	4(1%)	5(1%)
Insomnia	0(0%)	3(1%)
Somnolence	4(1%)	10(2%)
Special senses		
Tinnitus	3(1%)	4(1%)

Source: Sponsor's Table ISS-4a, page 24 and 25.

4.5.1 Approach to Eliciting Adverse Events

For the three clinical trials, adverse events were recorded by the subject in the migraine diary and collected at the post-treatment follow-up visit (Visit 2). The subject recorded all adverse events for 24 hours after dosing with test medication. The subject's verbatim terms were then transcribed onto the Case Report Forms. Any adverse event occurring after 24 hours and reported by the subject at Visit 2 was recorded on the Adverse Event Case Report Form. The post-treatment follow-up visit was designed to occur preferably the next business day after treating a migraine but no later than 1 week after treatment.

Study S99-102 consisted of two 12-hour PK assessments separated by a seven-day washout period. Subjects were monitored in a clinic environment for any adverse event.

4.5.2 Adverse Events Categorization and Preferred Terms

Verbatim terms transcribed from the patient's diary to the Case Report Forms were linked to preferred terms and related body systems using the COSTART mapping systems.

4.5.3 Common and Drug-Related Side Effects

Aspirin has been used for a variety of conditions for over 100 years. The adverse event profile of aspirin is well known and in general is considered a safe medication when used appropriately. The most common adverse events seen in clinical practice relate to the digestive system and include stomach pain, heartburn, nausea, vomiting, and dyspepsia.

Other less common adverse events include melana, hematchezia, severe headache, tinnitus, and urticaria. Rarely, Reye's syndrome has been reported in children and hypersensitivity/allergy to aspirin is relatively common in clinical practice.

4.6 Other Safety Data

There were no additional safety data collected in the three clinical efficacy trials or the pharmacokinetic trial since the doses used are currently approved over-the-counter doses for aspirin. Specifically, there is no:

- Laboratory data.
- Vital signs data.
- ECG data.
- Withdrawal phenomena and abuse potential information.
- Human reproduction data.
- Overdose information.

4.7 Reviewers Safety Analysis

Using both the electronic and paper versions of the NDA, treatment emergent adverse events occurring with ESBA use were evaluated in the follow manner. To verify the accuracy of the primary data that was summarized in the NDA, any available CRF's and death narratives were crossed checked for accuracy. Each study safety dataset was reviewed to assess the accuracy of translating verbatim terms to Costart terms. Verbatim adverse event listings for all three studies were reviewed looking for vague terms that might suggest some other underlying pathology such as easy bruising might suggest underlying thrombocytopenia.

Study S98-072 had 48 adverse events reported. A few minor inconsistencies were noted in the translation of verbatim terms to COSTART terms. There is inconsistency in term translation where a "cold" was translated to "infection" but an "upper respiratory infection" was translated to "pharyngitis". Likewise "fatigue" and "slight fatigue" was translated to "asthenia" which in my opinion more likely should translate to lethargy. Finally, the verbatim term of "herniated disc" was translated to "hernia" which in my opinion is wrong. A better term might be low back pain or something similar. There are no verbatim terms that suggest some underlying pathology such as aplastic anemia, thrombocytopenia, or serious skin disorders. Study S98-072 had a single serious adverse dropout event experienced two weeks after taking the study medication. The sponsor does not provide the Case Report Form for review. Details regarding this case are outlined in Section 4.3.

Study S98-073 had 54 adverse events reported. Review of verbatim term translation to COSTART terms found no problems. There are no verbatim terms that suggest some underlying pathology such as aplastic anemia, thrombocytopenia, or serious skin disorders. There were no deaths or serious adverse events in this study therefore no Case Report Forms were submitted for review.

Study S98-074 had 73 adverse events reported. Again there was minor inconsistencies in how common colds were translated. For example, "cold" was translated to "infection", "upper respiratory infection" was translated to "pharyngitis", and "sinus cold" was translated

to "rhinitis". Likewise, the verbatim term of "tired" was translated to "asthenia" which in my opinion should translate to lethargy. There are no verbatim terms that suggest some underlying pathology such as aplastic anemia, thrombocytopenia, or serious skin disorders. Study S98-074 had two serious adverse event dropouts however neither subject dosed with study medication. Details regarding these cases are outlined in Section 4.3. The sponsor provided no case report forms for review.

Although verbatim term translation is important, the few inconsistencies and single error found in these studies do not change my opinion regarding the safety of ESBA 1000 mg in the treatment of migraine. Likewise, despite the inability to review the three missing Case Report Forms, I do not believe they would substantially change my opinion regarding the safety of ESBA 1000 mg for the treatment of migraine. This is true since two of the subjects that withdrew due to a serious adverse event were randomized to ESBA but never took the study medication and the third subject that withdrew was randomized to placebo.

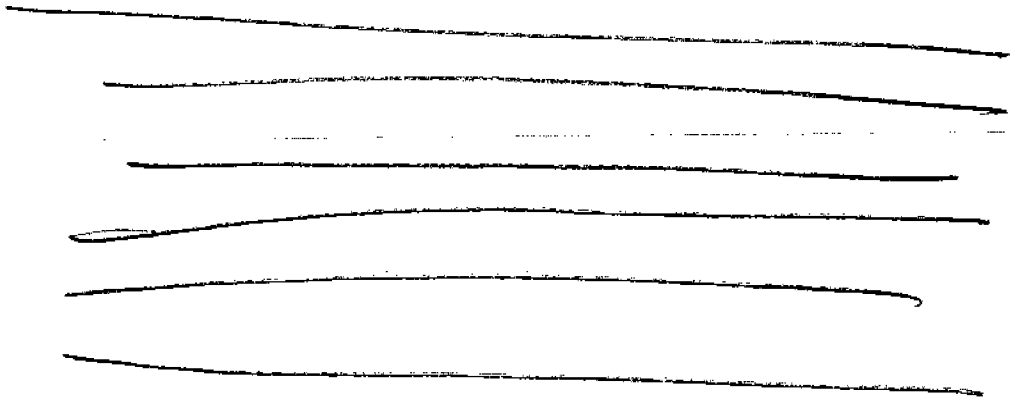
4.8 Sponsor's Safety Conclusion

- Gastrointestinal side effects of stomach pain, heartburn, nausea, vomiting, and dyspepsia are labeled adverse events for aspirin. The frequency for these adverse events in the three clinical trials was not significantly different for ESBA compared to placebo.
- The safety data from the three clinical efficacy trials does not suggest any unsuspected or serious adverse events resulting from ESBA 500 mg or 100 mg, to treat the pain of a migraine attack, with and without aura.

4.9 Reviewer's Safety Conclusions

- I concur with the sponsor's conclusions. The safety results from studies S98-072, S98-073, S98-074, and S99-102 do not disclose any significant clinical safety concerns with the use of ESBA 1000 mg for the treatment of acute migraine.

5. Labeling Review



[redacted]

6. Conclusions

I conclude:

- ESBA 1000 mg appears to be effective in the treatment of e headache pain associated with migraine.
- ESBA 1000 mg appears to be ineffective in treating nausea associated with migraine.
- ESBA 1000 mg appears to be effective in the treatment of phonophobia and photophobia associated with migraine.
- There is some evidence that ESBA 1000 mg improves functional disability associated with migraine.
- ESBA 1000 mg appears to be no different than placebo in preventing headache recurrence in the first 24 hours after treatment in migraine patients.
- The efficacy of ESBA 1000 mg in adolescents has not been established because adolescents are not studied in the clinical trials outlined in this review.
- The efficacy of ESBA in the geriatric patient can not be established since few subjects ≥65 years of age were enrolled in the three clinical trials outlined in this review.
- [redacted]
- The efficacy of multiple doses of ESBA in the treatment of migraine is not established since multiple dose regimens are not studied in the trials outlined in this review.
- The safety results from studies S98-072, S98-073, S98-074, and S99-102 do not disclose any significant clinical safety concerns with the use of ESBA 1000 mg in the treatment of acute migraine.
- The efficacy of ESBA for the treatment of the full migraine syndrome has not been proven.

7. Recommendations

I recommend that ESBA be approved for the treatment of headache pain associated with migraine.

Kevin Prohaska, D.O.
Medical Reviewer

A. Oliva, M.D. _____

cc: R. Katz M.D., Charley Ganley M.D., Rosemary Neuner M.D., Walter Ellenberg
HFD-120
NDA 21317

Appendix A - Analysis of Subjects Reporting Adverse Events by Body System (Pooled ITT_{ALL}), All Adverse Events

Analysis of Subjects Reporting Adverse Events by Body System (ITT_{ALL})*		
Adverse Events	**Placebo** (N=595) n (%)	**ESBA 1000 mg** (N=596) n (%)
Number of subjects reporting one or more adverse event	50 (8%)	65 (11%)
Number of Adverse Events Reported	66	86
Body as a Whole	**15 (3%)**	**13 (2%)**
Abdominal Pain	6 (1%)	8 (1%)
Asthenia	1 (0%)	4 (1%)
Back Pain	1 (0%)	0 (0%)
Chest Pain	1 (0%)	1 (0%)
Chills	2 (0%)	2 (0%)
Fever	1 (0%)	0 (0%)
Flu Syndrome	1 (0%)	0 (0%)
Infection	1 (0%)	0 (0%)
Neck Pain	1 (0%)	0 (0%)
Pain	1 (0%)	1 (0%)
Cardiovascular System	**5 (1%)**	**2 (0%)**
Palpitations	1 (0%)	0 (0%)
Tachycardia	3 (1%)	1 (0%)
Vasodilatation	1 (0%)	1 (0%)
Digestive System	**18 (3%)**	**30 (5%)**
Diarrhea	3 (1%)	5 (1%)
Dry Mouth	0 (0%)	2 (0%)
Dyspepsia	5 (1%)	7 (1%)
Eructation	0 (0%)	1 (0%)
Intestinal Perforation	1 (0%)	0 (0%)
Nausea	8 (1%)	14 (2%)
Tooth Disorder	0 (0%)	1 (0%)
Vomiting	4 (1%)	3 (1%)
Nervous system	**11 (2%)**	**20 (3%)**
CNS Stimulation	1 (0%)	0 (0%)
Dizziness	4 (1%)	5 (1%)
Euphoria	0 (0%)	1 (0%)
Insomnia	0 (0%)	3 (1%)
Nervousness	0 (0%)	2 (0%)
Parasthesia	1 (0%)	2 (0%)
Sleep Disorder	0 (0%)	1 (0%)
Somnolence	4 (1%)	10 (2%)
Tremor	1 (0%)	0 (0%)
Respiratory System	**1 (0%)**	**0 (0%)**
Pharyngitis	1 (0%)	0 (0%)
Skin	**3 (1%)**	**2 (0%)**
Pruritus	0 (0%)	1 (0%)
Rash	1 (0%)	1 (0%)
Sweating	2 (0%)	0 (0%)
Urticaria	0 (0%)	1 (0%)

Analysis of Subjects Reporting Adverse Events by Body System (ITT_{ALL})*		
Adverse Events	**Placebo** (N=595) n (%)	**ESBA 1000 mg** (N=596) n (%)
Special Senses	**6 (1%)**	**7 (1%)**
Abnormal Vision	1 (0%)	0 (0%)
Conjunctivitis	0 (0%)	1 (0%)
Eye Pain	1 (0%)	0 (0%)
Photophobia	1 (0%)	0 (0%)
Taste Perversion	0 (0%)	2 (0%)
Tinnitus	3 (1%)	4 (1%)

*Pooled safety data from studies S98-072, S98-073, and S98-074.
Source: Sponsor's Table ISS-4a, page 24.
At each level of body system and event subjects are only counted once.

Appendix B - Original Protocol Review and Important Amendments

1. Original Protocol Summary

The original protocol for all three clinical trials were submitted under IND [redacted] dated 12/15/98, and reviewed by Dr. Armando Oliva on 12/30/98.

Design:
These were to be double blind, randomized, parallel group, single dose, placebo controlled studies. The primary objective was to evaluate the analgesic effect of ESBA versus placebo in patients with moderate to severe migraines as defined by the International Headache Society.

Each study was expected to enroll approximately 200 patients per treatment arm. Additional patients were enrolled to compensate for the expected non-treatments that often occur in migraine studies.

Exclusion/Inclusion Criterion and Recruitment
The original key inclusion/exclusion criterion was typical for most migraine studies. The original plan was for potential candidates to be identified via a random telephone screening procedure, followed by a screening history and physical (population based recruiting).

Outcome Measures
The original protocol stated there would be two primary outcome measures, migraine Pain Intensity Difference at two hours and the proportion of headache responders at two hours. There were 15 secondary outcomes outlined in the original protocol many of which where eliminated in the final analysis.

Analysis Plan
The sample size was based on the ability to detect a 15 percentage point difference in the two-hour headache response rate between drug and placebo, using a two-tailed test with an alpha of 0.05% resulting in power of 0.85.

Efficacy analysis was to include ANOVA, Cochran-Mantel-Haenszel, and Wilcoxon Survival Tests. Safety analysis would be done using Fisher's Exact Test to compare incidence rates. Two efficacy analysis were planned, a primary analysis and the intent-to-treat analysis. The primary analysis would include only those subjects who meet the protocol requirement and provide a valid two-hour evaluation. Subjects who use rescue medication before the two hour evaluation would be considered invalid for primary efficacy analysis. The intent to treat population would include all patients that took study medication.

Comments sent to the Sponsor
The medical reviewer sent the following comments to the sponsor (paraphrased).

1. The primary outcome should be two-hour response rate.
2. Telephone screening of potential subjects is adequate however the division would also like to see a study consisting of subjects previously diagnosed with migraines.

3. The case report forms should also contain the information necessary to confirm the diagnosis of migraine.
4. You should consider adding a sumatriptan arm to one of these studies.
5. You should recalculate the power of the studies using an expected treatment effect of 25-30 percentage points above placebo.

2. Protocol Amendments

On April 19, 1999 the sponsor submitted the following significant changes to the protocol.

1. Changed the primary efficacy variable to two-hour headache response rate only.
2. Added an additional secondary variable to evaluate the reduction in symptoms of nausea, photophobia, and phonophobia for those who experience any or all of these symptoms at baseline.
3. Redefined recurrence to anyone who initially responds at 2 hours then experiences a recurrent moderate or severe headache within 24 hours.
4. Redefined ITT to include subjects who take rescue medication prior to the 2-hour evaluation who will now be considered as non-responders.
5. Deleted: patients must provide a valid two-hour evaluation to be included in the primary efficacy analysis.
6. The following secondary efficacy endpoints were deleted:
   - Subject's global evaluation of treatment effectiveness.
   - Time to remedication.
   - MAXPID.
   - Duration of pain reduction over the six hour treatment period.
   - Percent of subjects who take rescue medication.
   - Time to headache response.

Comments sent to the Sponsor

The medical reviewer sent the following comments to the sponsor (paraphrased).

1. Please provide the time to remedication or rescue.
2. Please provide an analysis of the proportion of patients experiencing nausea, photophobia, and phonophobia at various time points.

3. Issues regarding data analysis discussed at the Pre-NDA meeting

The following items were discussed:

- Cross study pooling of efficacy data is not permitted.
- It was recommended the associated symptoms of nausea, photophobia, and phonophobia also be evaluated as dichotomous variables.
- Secondary endpoints should be evaluated at the two-hour timepoint as well as other timepoints.
- The datasets are to be provided in SAS transport format.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Prohaska
6/22/01 10:08:47 AM
MEDICAL OFFICER

Armando Oliva
6/22/01 11:34:25 AM
MEDICAL OFFICER
please see my separate team leader memo.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

CLINICAL REVIEW (ADDENDUM) OF NDA 21317

Brand Name:	**Bayer Migraine**
Generic Name:	**Acetylsalicylic Acid**
Sponsor:	**Bayer Corporation**
Indication:	**Acute Migraine**
NDA Number:	**21-317**
Original Receipt Date:	**12/19/00**
Clinical Reviewers:	**Kevin A. Prohaska, D.O**
Addendum Review Completed:	**10/11/01**

This is an addendum review of submission NDA21-317 dated December 18, 2000. The purpose of this review is to comment on the financial disclosure statement contained in the original submission.

1. Financial Disclosure Review

The financial disclosure statements (Form FDA 3455) for the following investigators are contained in Volume 1 of the submission.

Jeffrey S. Baggish, M.D.
Alberto Yataco, M.D.
Stephen E. Daniels, D.O.
Roger Cady, M.D.
Mareh J. Gawel, M.D.
Jerome Goldstein, M.D.
Egilius L. H. Spierings, M.D.

None of the investigators report any financial arrangements entered between the sponsor and themselves whereby the value of the compensation to the clinical investigator for the study could be influenced by the outcome of the study.

None of the investigators report any significant payments of other sorts made on or after February 2, 1999 from the sponsor such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

None of the investigators report any proprietary interest in the product tested.

None of the investigators report any significant equity interest in the sponsor as defined in 21 CFR 54.2(b).

2. Conclusions

None of the investigators appear to have a financial stake in the outcome of these trials.

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HFD-120
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