CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-076

STATISTICAL REVIEW(S)

OCT 2 2 1999

Date: 10/22/99
To: Christina Fang, MD, HFD-550
From: Stan Lin. Team Leader, HFD-725
RE: Statistical Review for NDA#21-076 (Aleve Cold & Sinus)

This is a secondary review of the above referenced NDA and is based on the draft statistical review of Dr. Taneja. (See attached.)

My assessment of the induced cold study (S97-051) is that the data support the efficacy shown in the nasal obstruction endpoint. This conclusion is based on a statistically significant treatment difference on this endpoint using a repeated measures ANOVA analysis, which was specified in the protocol, for the intent-to-treat and primary efficacy subsets.

One problem I see in this trial, (as we have also discussed,) is the mild nature of cold symptoms exhibited by the subjects, who at screening were normal without suffering from common cold, but were induced with rhinovirus for the study. At baseline before medication started on day 2 following induction on day 1, 65 and 68 patients, representing 63% and 67% respectively in the placebo and treated group showed no symptom of nasal obstruction, and the overall baseline symptoms were heavily skewed towards absent or mild (with a baseline average of ≤ 0.5 on a 0-4 scale). Therefore, it's not clear whether the treatment difference shown from this study has useful clinical relevance to the efficacy evaluation of the combination product.

The second study (S97-052) is a common cold study. However, both the "primary efficacy analysis" and the intent-to-analysis showed a treatment by time interaction from the protocol specified repeated measures analysis. As a result, it appears that the sponsor did not produce an overall treatment difference evaluation. Instead an ANCOVA adjusting for baseline scores was produced for each time point, for each day. However, such an analysis is difficult to interpret statistically because of the multiplicity issues involved from the multiple p-values, and the post-hoc nature of the analysis.

Somewhat similar to the induced cold study, around 70% of the patients had mild or moderate cold symptoms at baseline (baseline nasal average about 2.1 on a 0-4 scale), which may not represent the population who will use the product.

The maximum average difference between treatment and placebo was ≤ 0.3 for the nasal score on a scale of 0-4, throughout different time points, for both studies. The protocol clearly stated that the study sample size was based on a treatment difference in nasal obstruction score of 0.316. This must have been an estimate and therefore must have a distribution around this number, which would then mean that a difference in average score higher than 0.316 may be expected from the current clinical trial. However, as mentioned, all difference scores were ≤ 0.3.

Additional comments:

1. Study S97-051 was stopped with n=245, short of the planned sample size of 266. Study S97-052 was stopped with n=439, more than the planned sample size of 362. The sponsor did not provide reasons for sample size adjustments.
2. The trial design may be deficient in that a fixed-dose combination should be compared to its components to validate their contributions.

In summary, the sponsor has not produced very strong evidence, from a statistical point of view, for a meaningful treatment effect from the two studies in a common cold population. Further evaluation of the trial results would need to incorporate clinical knowledge about the drug and the disease.

/S/

Stan Lin, Ph.D.

/S/

Concur: Dr. Huque 10/22/99

cc: HFD-550/Schmidt,
HFD-550/Fang
HFD-550/Hyde
HFD-550/Midthun
HFD-550/Division File
HFD-725/Taneja
HFD-725/LinSt
HFD-725/Huque
HFD-725/Division File
HFD-725/Chron.

This summary has two pages of text.

Attachment: Dr. Taneja's draft review.

STATISTICAL REVIEW AND EVALUATION
(Clinical)

NDA #: 21-076/Drug Class 4S

APPLICANT: Bayer Corporation

NAME OF DRUG: ALEVE COLD & SINUS
(naproxen/pseudoephedrine combination)

DOCUMENTS REVIEWED: Volumes 1.1, 1.31 through 1.41, Documents and Data Components on Floppy Diskettes.

REVIEWING MEDICAL OFFICER: Christina Fang, M.D. (HFD-550)

INDICATIONS: Non-prescription (OTC) use as a
pain reliever/fever reducer/nasal decongestant.

This review is arranged in four sections and an Appendix. Section I gives the summary findings of the NDA supported by the statistical analyses. Section II provides a brief summary of protocols, background information and sponsor's description of the trials. It also includes the sponsor's results and conclusions. Section III contains the results and conclusions of this reviewer's statistical analyses. It does not include all the analyses but only those that have bearing on the conclusions. Section IV summarizes the conclusions that may be conveyed to the sponsor.

I. Summary Findings

Bayer has submitted the following two studies as pivotal for the evaluation of ALEVE COLD & SINUS:

Induced Cold Trial: S97-051
Natural Cold Trial: S97-052

for the OTC use as a pain reliever/fever reducer/nasal decongestant.

Review Issues:

There are several review issues that need attention. These are listed below.

1. The sample size calculations in the protocols are not clear to this reviewer. Further, it is not clear whether these calculations (based on the data from other drugs) really apply to the combination (naproxen/pseudoephedrine) at hand.

2. It appears that the Study S97-051 (Induced Cold Trial) was stopped early whereas the Study S97-052 (Natural Cold Trial) went beyond its stopping point. It is evident from the number of subjects planned in the protocol and really enrolled in the study. For S97-051, there were 245 subjects enrolled and not 266 as planned in the protocol. For S97-052, there were 439 subjects enrolled and not 362 as planned in the protocol.

3. According to the protocols, the data on temperature was recorded, but it was not supplied to this reviewer for analysis. The temperature data does not appear to be included in the line listings in the NDA.

4. The contributions of naproxen and pseudoephedrine to the effect of the combination have not been shown in the pivotal trials as required by the combination drug policy (CFR 300.50).

Conclusions:

On the basis of the statistical analyses performed by this reviewer, both the trials demonstrated the efficacy of Aleve: Cold and Sinus for nasal obstruction, headache pain, malaise and total symptoms associated with common colds. ***But, these conclusions are only tentative in the presence of several review issues brought out in this review and are succinctly presented above.***

II. Brief Summary of Protocols, Background Information, and Sponsor's Description and Results of the Studies

Induced Cold Trial: S97-051

Title of Study: A Randomized, Double-Blind, Placebo-Controlled Comparative Study to Assess the Effectiveness of a Combination of Naproxen Sodium and Sustained Release (12-Hour) Pseudoephedrine on Symptoms and Clinical Outcome of an Induced Common Cold in Normal Subjects.

Objectives: To assess the efficacy and safety of a combination of naproxen sodium and sustained release (12-hour) pseudoephedrine HCl on symptoms and clinical outcome of a common cold in normal subjects who have been inoculated intranasally with a rhinovirus. The primary objective of the study was to assess the effectiveness of drug treatment in reducing the severity of nasal obstruction.

Methodology: Subjects who have been found to have a serum neutralizing antibody titer of 1:2 or less to the challenge rhinovirus were entered into the study. On day 1, subjects provided a baseline evaluation of cold symptoms, underwent a nasal wash for viral culture, and then received two intranasal inoculations with

rhinovirus at a dose of 10-100 TCID. Subjects took study medication for four days (starting on Day 2 and continuing through Day 5) on a BID (8:00 a.m. and 8:00 p.m.) dosage schedule. Additionally, on Days 2 through 6, subjects underwent: morning nasal blows for viral culture; complete morning evaluations of the severity of their cold symptoms (sneezing, runny nose, nasal obstruction, sore throat, cough, headache pain, malaise, and chilliness); and tissue collection for nasal mucus weights. Daily assessments of cold symptoms were made before dosing, using a 5-point categorical rating scale. The severity of each symptom was scored as: 0 = absent (less than mild), 1 = mild, 2 = moderate, 3 = severe, 4 = very severe.

In addition, on Day 2 and Day 3, subjects rated the severity of their nasal obstruction (stopped-up nose/stuffiness) at 4, 8, and 12 hours after the post morning dose. The 12-hour rating was made prior to the evening dose of study medication. Oral body temperature was recorded for subjects at approximately the same time each morning. Also, subjects underwent a physical examination in the evening of Day 5 or morning of Day 6. Subjects evaluated their cold symptoms on the mornings of Days 7 through 12 and returned to the study site for an end of study antibody titer on approximately Day 21. Information regarding adverse events were collected and recorded throughout the study.

Number of Subjects: Two hundred forty-five subjects were enrolled into the study. Two subjects were excluded from safety/intent-to-treat analyses, because they were not inoculated or randomized. An additional thirty-seven subjects were excluded from primary efficacy analyses, leaving 206 subjects eligible for the primary efficacy analyses.

Efficacy: The primary efficacy variable was the severity of nasal obstruction. The criterion for evaluation was the change in nasal obstruction scores, subsequent to baseline for each treatment. Other secondary efficacy variables of sneezing, runny nose, sore throat, cough, headache pain, malaise, and chilliness were also measured as well as the total symptom score.

Statistical Methods: All analyses were performed using PC SAS. Statistical significance was based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less, except for the pooling analyses where a result was considered statistically significant if the p-value was 0.10 or less. The treatment-by-site interaction was used to test the poolability of Investigators. Repeated measures analysis of variance (ANOVA) was used to assess the overall effects of treatment (active or placebo). Finally, to explore the differential treatment effect on various study days, the Student's t-test was applied independently to data obtained on Days 2 through 6 using baseline as a covariate. All reported adverse events were analyzed by treatment group and summarized by: the number of subjects reporting adverse events, severity, relationship to study drug, and body system.

Sponsor's Efficacy Results:

Primary Outcome Measure: The results of the study revealed that during Days 2 and 3 there was a favorable active treatment effect at 4 (p=0.014) and 8 hours (p=0.020) for Day 2 and on Day 3 upon rising (p=0.017) and at 4 hours (p=0.012) post dose. Nasal obstruction decreased in severity beyond Day 3, consistent with the natural resolution of a cold for both treatments.

Secondary Outcome Measures: Although the omnibus tests for both headache pain and malaise failed to control the experimental wide error rate to 5%, headache pain had favorable active treatment effect for the morning symptom evaluation on Day 3 (p=0.002) and Day 4 (p=0.038). Malaise had a weak indication of significance favoring the active treatment also for the morning symptom evaluation on Day 3 (p=0.046).

Sponsor's Summary Conclusions: The study succeeded in demonstrating the effectiveness of 220 mg of sodium naproxen (Aleve®) combined with a sustained release formulation (12-hour) of 120 mg pseudoephedrine HCl in reducing the cold symptoms of nasal obstruction and headache pain in an induced common cold trial.

Common Cold Trial: S97-052

Title of Study: A Prospective, Multi-Center, Randomized, Double-Blind, Placebo Controlled Study to Assess the Effectiveness of the Combination of Sodium Naproxen (Aleve®) and Sustained Release (12-Hour) Pseudoephedrine on Reducing Symptoms of a Natural Common Cold.

Objectives: To evaluate the effectiveness and safety of 220 mg of sodium naproxen (Aleve®) combined with a 12 hour sustained release formulation of 120 mg pseudoephedrine HCl in reducing the symptom of nasal obstruction (stopped-up nose/stuffiness). An important secondary objective is to evaluate the effectiveness of the active treatment and placebo in reducing the systemic cold symptoms of headache pain, maiaise and other cold symptoms.

Methodology: Subjects from a prospective symptom surveillance group were entered into the four (4) day treatment study if they had reported appropriate cold symptoms. Subjects received study medication on a BID (8:00 a.m. and 8:00 p.m.) dosage schedule. Daily assessments of cold symptoms were recorded prior to the first a.m. doses on each of Days 1-4. The symptoms rated using a 5-point categorical rating scale were: sneezing, runny nose, nasal obstruction (stopped-up nose/stuffiness), sore throat (dry/scratchy), cough, headache pain, malaise (blah feeling) and chilliness. The severity of each symptom over the last 24 hours was scored as: 0 = absent (less than mild), 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. In addition, subjects rated the severity of their nasal obstruction (stopped-up nose/ stuffiness) at 4 and 8 hours after the a.m. Day 1 dose. The 8-hour post-

dose evaluation was made prior to the p.m. dose of study medication. The subjects also rated their nasal obstruction (stopped-up nose/stuffiness) at 4, 8 and 12 hours after the a.m. Day 2 dose. The 12-hour post-dose evaluation was made prior to the p.m. dose of study medication. On the morning of Day 5, subjects who had dosed for the 4 day dosing period rated their Day 5 symptoms and returned to the study site. The subject also recorded adverse events and concomitant medications.

Number of Subjects: Four hundred thirty-nine (439) subjects were enrolled into the study. Eighteen (18) subjects were excluded from primary efficacy analyses, leaving 421 subjects eligible for the primary efficacy analyses.

Efficacy: The primary efficacy variable was the severity of nasal obstruction. The criterion for evaluation was the change in nasal obstruction scores, subsequent to baseline for each treatment. Other secondary efficacy variables of sneezing, runny nose, sore throat, cough, headache pain, malaise, and chilliness were also measured as well as the total symptom score. The analytical focus of the secondary variables was on a change from baseline in headache pain and malaise.

Statistical Methods: All analyses were performed using PC SAS. Statistical significance was based on two-tailed tests of the null hypothesis resulting in p-values of 0.05 or less, except for the pooling analyses where a result was considered statistically significant if the p-value was 0.10 or less. The treatment-by-Investigator interaction was used to test the poolability of Investigators. Repeated measures analysis of variance (ANOVA) was used to assess the overall effects of treatment (active or placebo). The analysis of covariance was used to analyze the differential treatment effect on various study days and times.

Sponsor's Efficacy Results:

Primary Outcome Measure: The results of the study revealed that during Days 1 and 2 there was a favorable active treatment effect at 4 ($p=0.001$) and 8 hours ($p=0.004$) for Day 1 and on Day 2 upon rising ($p=0.001$) and at 4 hours ($p=0.001$) post dose. Nasal obstruction decreased in severity beyond Day 2, consistent with the natural resolution of a cold for both treatments.

Secondary Outcome Measures: The omnibus test for headache pain was significant with a demonstrated favorable active treatment effect for headache pain at Days 2 through 4 ($p\leq0.001$). While malaise was not statistically significant, there was an indication of favorable active treatment effect at Day 2 ($p=0.071$).

Sponsor's Summary Conclusions: The study succeeded in demonstrating the effectiveness of 220 mg of sodium naproxen (Aleve®) combined with a sustained relief formulation (12-hour) of 120 mg pseudoephedrine HCl in reducing the cold symptoms of nasal obstruction and headache pain in a prospective natural cold trial.

III. Results and Conclusions of Statistical Reviewer's Analyses

This reviewer's primary concern is that neither of the two pivotal trials meet the evidentiary standards set in CFR 300.50 regarding fixed combination dosage forms. Specifically, this regulation requires, in part, that it be established that each component of a fixed combination makes a contribution to the claimed effects. However, CFR 300.50 refers to prescription drugs and Aleve is proposed for OTC use. Further, there may be additional information regarding this combination that is available to HFD-550 which is beyond the scope of this review.

Aleve (naproxen/pseudoephedrine) involves a sustained-release pseudoephedrine formulation which is different from immediate-release formulation. This makes evaluation of efficacy of nasal obstruction (an outcome more related to pseudoephedrine) extremely important.

Induced Cold Trial: S97-051

Number of Subjects

The sponsor took estimates of 20% treatment effect in nasal obstruction and estimates of standard deviations from the published literature (see the protocol for references) and pooled the information in some way (not clear to the reviewer) and recommended a sample size of 133 per treatment group to detect the treatment difference with 80% power. Thus, the protocol stated that a sufficient number of subjects would be enrolled to assure that at least 266 evaluable subjects (133 per treatment group) complete the study.

There were 245 subjects enrolled and randomized in the study. Two of these subjects were excluded from the safety/intent-to-treat analyses because they withdrew after inoculation but prior to receiving medication, leaving 243 subjects (Placebo=122. Aleve=121) in the safety/intent-to-treat analyses. Another thirty-seven subjects (Placebo=18, Aleve=19) were excluded from the primary efficacy analyses because of either voluntary withdrawal (1 subject), or of failing pre-titer challenge only (9 subjects), or having no evidence of infection only (25 subjects), or failing pre-titer challenge as well as having no evidence of infection (2 subjects) resulting in 206 subjects (Placebo=104, Aleve=102) in the primary efficacy analyses.

The primary endpoint, as identified in the protocol, was the severity of nasal obstruction. A study nurse recorded the severity of the subject's nasal obstruction on Day 1 and each morning before the administration of the study medication on Days 2 through 6. The subjects also rated their nasal obstruction at 4, 8 and 12 hours after the morning dose on Day 2 and Day 3. Further,

secondary endpoints of headache, malaise, and total symptoms were also evaluated.

As stated in the protocol, the sponsor planned for two efficacy analyses: a primary analysis and an intent-to-treat analysis. All subjects who took at least one dose of study medication were included in the intent-to-treat analysis. Only those subjects who met inclusion criteria, and who were not invalidated by exclusion criteria, and who yielded valid evaluations were included in the primary analysis.

This reviewer performed both the analyses on the datasets provided by the sponsor. Results are summarized below: first for the primary analysis and then for the intent-to-treat analysis.

Primary Efficacy Analysis: 206 subjects (Placebo=104, Aleve=102)

Baseline Comparisons

Subjects were given two intranasal inoculations with rhinovirus to induce cold on Day 1. So, Day 2 morning recording was treated as the baseline.

According to the protocol, variables such as age, weight and height were considered to be continuous and were analyzed with a two-way analysis of variance (ANOVA) model with factors of treatment and site. The Cochran-Mantel-Haenszel test stratified by site was used to analyze the differences between treatment groups for categorical variables such as gender and race. Likewise, the Cochran-Mantel-Haenszel test stratified by site was used to determine if differences existed between the treatment groups for the categorical baseline nasal obstruction (stopped-up nose/stuffiness) score, headache pain score, malaise score and total symptoms score.

The statistical methods proposed in the protocol were appropriate for baseline comparison. This reviewer's results match with those of the sponsor. These results are included in the Appendix as Table P-1 (Study 051).

There were no significant differences among treatment groups in any of the analyzed baseline demographic characteristics ($p \geq 0.196$).

Efficacy Analyses

Primary Efficacy Variable: Nasal Obstruction Score

The protocol specified that a repeated measures analysis of variance was to be used to test the treatment effect for the primary efficacy measure nasal obstruction on Days 2 and 3 following dosing with the study medications as well

as before morning dosing on Days 2 through 6. That is, three different repeated measures analyses were performed: first, the time was Days 2 through 6; second, the time was 0, 4, 8, and 12 hours on Day 2; and third, the time was 0, 4, 8, and 12 hours on Day 3.

In the context of repeated measures analyses, the treatment by time interaction is a global measure of the effectiveness of the treatments and was proposed to be used as an omnibus test to control the type I error. Prior to the initiation of the study it was anticipated that during the time course of the study the treatment difference would become larger as the cold developed (Days 2 and 3), peak, and decrease as Day 6 approached. The statistical significance of treatment by time interaction was used to determine if there was a non-parallel treatment effect. But, if a non-parallel treatment effect activity is not observed, an alternate omnibus test appropriate for this pattern of treatment effect is the "Repeated Measures Analysis of Variance Test of Hypotheses for Between Subjects Effects". This test is one of the components of a repeated measures analysis of variance and is also an effective method of controlling the type one error rate.

The first repeated measures ANOVA was used [redacted] to assess the effects of treatment on morning nasal obstruction measurements (stopped-up nose/stuffiness) for Days 2 through 6. The ANOVA included factors of treatment, time, and treatment-by-time interaction. The treatment-by-time interaction was non-significant (p=0.3297), whereas the factor of time was significant (p=0.0001).

An analysis of the nasal obstruction scores showed, Table P-2 (Study 051), that the active and placebo treatments separated following the first dose of medication and remained more or less parallel through the dosing period. The proposed omnibus test based on a time-by-treatment interaction is insensitive to detecting a treatment effect consisting of a generally uniform differential effect throughout the dosing period. Because this method is consistent with the characteristics of the data, the significant "Between Subjects Effects" omnibus test as applied to all the nasal obstruction scores was presented as justification for performing the within dosing period analyses while controlling for the type one error. Thus, specific aspects regarding the treatment effect were subsequently examined following a statistically significant between subjects effects p-value. Thus, the type I error was controlled by the statistical significance of the overall global measure of the effectiveness (Between Subjects Effects).

When all nasal obstruction scores from Day 2 through Day 6 were analyzed with the "Between Subjects Effects" test, there was a statistically significant (p=0.026) treatment effect for nasal obstruction in favor of Aleve, after adjusting for a significant time effect. The results are included in Table P-2 (Study 051) in the Appendix.

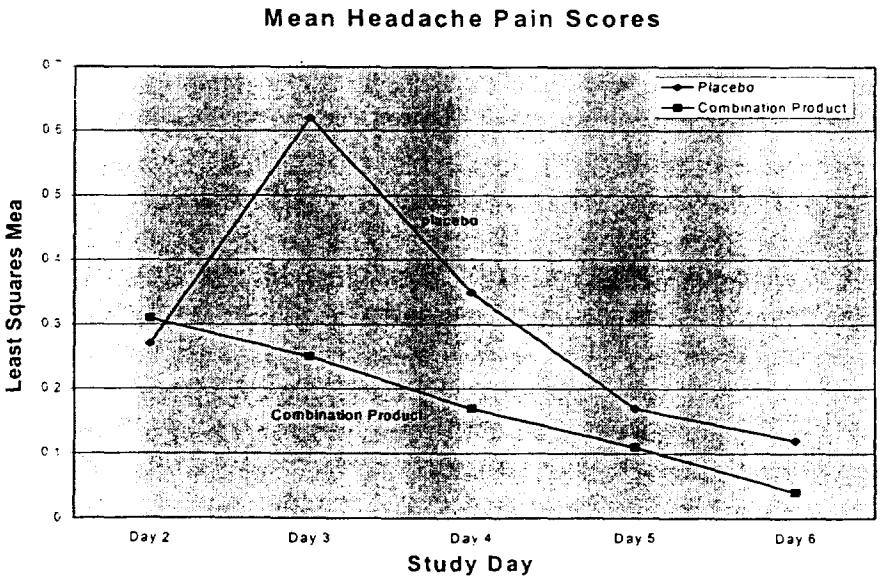
The second repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4, 8, and 12 hours on Day 2. The third repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4, 8, and 12 hours on Day 3.

These analyses showed a nominal statistical significance in favor of Aleve at 4 and 8 hours for Day 2, and at 4 hours for Day 3 with p-values of 0.014, 0.020 and 0.012 respectively. These results are included in Table P-3 (Study 051) in the Appendix.

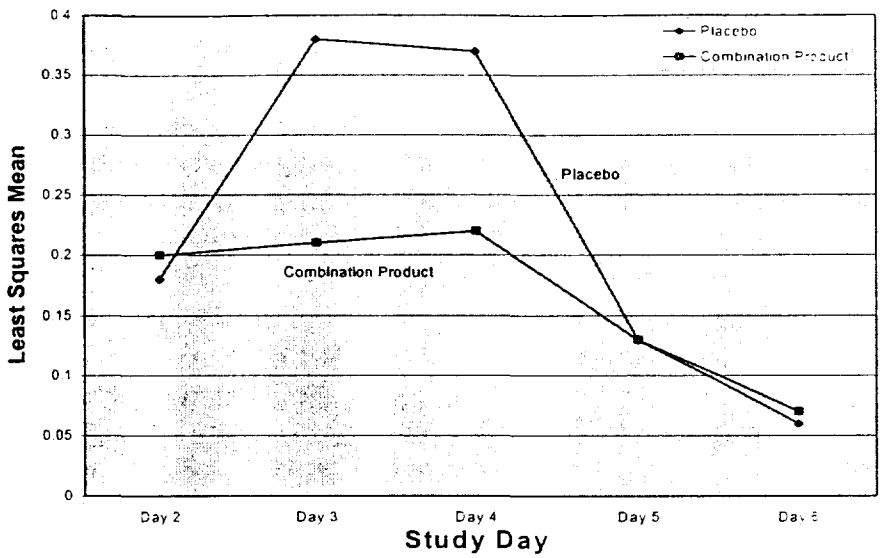
Secondary Efficacy Variables: Headache Pain Score, Malaise Score and Total Symptom Score

As stated in the protocol, a repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment for morning measurements of the secondary variables of headache pain, malaise and total symptom score from Day 2 through 6. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Though the treatment-by-time interaction was non-significant (p=0.0538 for headache pain, p=0.2410 for malaise, and p=0.0768 for total symptoms), the factor of time was significant (p=0.0001) for all three. All these results are included in Table P-4 (Study 051) in the Appendix.

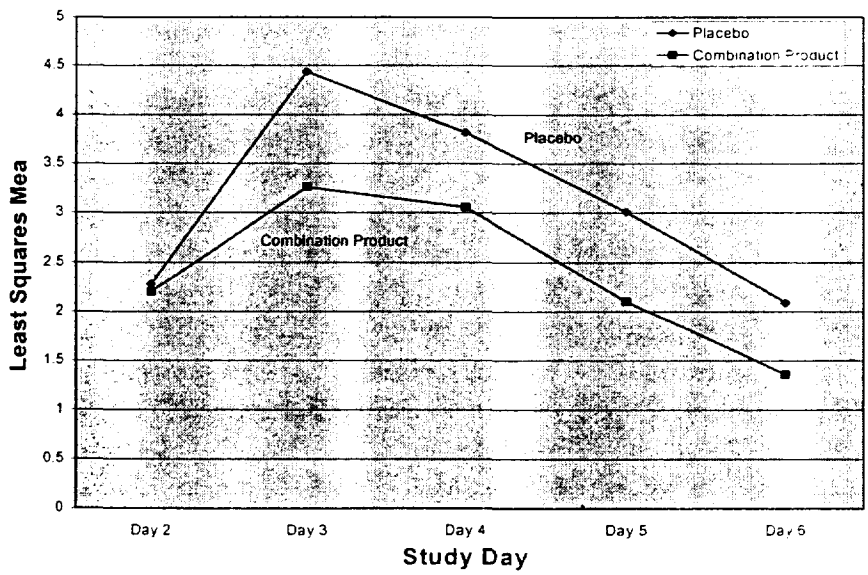
As stated in the protocol, these analyses were followed up by subsequent analyses (covariance analysis with baseline as covariate). Results are included in Table P-5 (Study 051) in the appendix. Plots showing trends are produced below for the three secondary efficacy variables.



Mean Malaise Scores



Mean Total Symptom Score



Intent-to-Treat Analysis: 243 subjects (Placebo=122, Aleve=121)

Baseline Comparisons

Subjects were given two intranasal inoculations with rhinovirus to induce cold on Day 1. So, Day 2 morning recording was treated as the baseline.

According to the protocol, variables such as age, weight and height were considered to be continuous and were analyzed with a two-way analysis of variance (ANOVA) model with factors of treatment and site. The Cochran-Mantel-Haenszel test stratified by site was used to analyze the differences between treatment groups for categorical variables such as gender and race. Likewise, the Cochran-Mantel-Haenszel test stratified by site was used to determine if differences existed between the treatment groups for the categorical baseline nasal obstruction (stopped-up nose/stuffiness) score, headache pain score, malaise score and total symptoms score.

The statistical methods proposed in the protocol were appropriate for baseline comparison. This reviewer's results match with those of the sponsor. These results are included in the Appendix as Table I-1 (Study 051).

There were no significant differences among treatment groups in any of the analyzed baseline demographic characteristics ($p \geq 0.327$).

Efficacy Analyses

Primary Efficacy Variable: Nasal Obstruction Score

The protocol specified that a repeated measures analysis of variance was to be used to test the treatment effect for the primary efficacy measure nasal obstruction on Days 2 and 3 following dosing with the study medications as well as before morning dosing on Days 2 through 6. That is, three different repeated measures analyses were performed: first, the time was Days 2 through 6; second, the time was 0, 4, 8, and 12 hours on Day 2; and third, the time was 0, 4, 8, and 12 hours on Day 3.

The first repeated measures ANOVA was used to assess the effects of treatment on morning nasal obstruction measurements (stopped-up nose/stuffiness) for Days 2 through 6. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Though the treatment-by-time interaction was non-significant (p=0.1836), the factor of time was significant (p=0.0001).

When all nasal obstruction scores from Day 2 through Day 6 were analyzed with the "Between Subjects Effects" test, there was a statistically significant (p=0.020)

treatment effect for nasal obstruction in favor of Aleve. The results are included in Table I-2 (Study 051) in the Appendix.

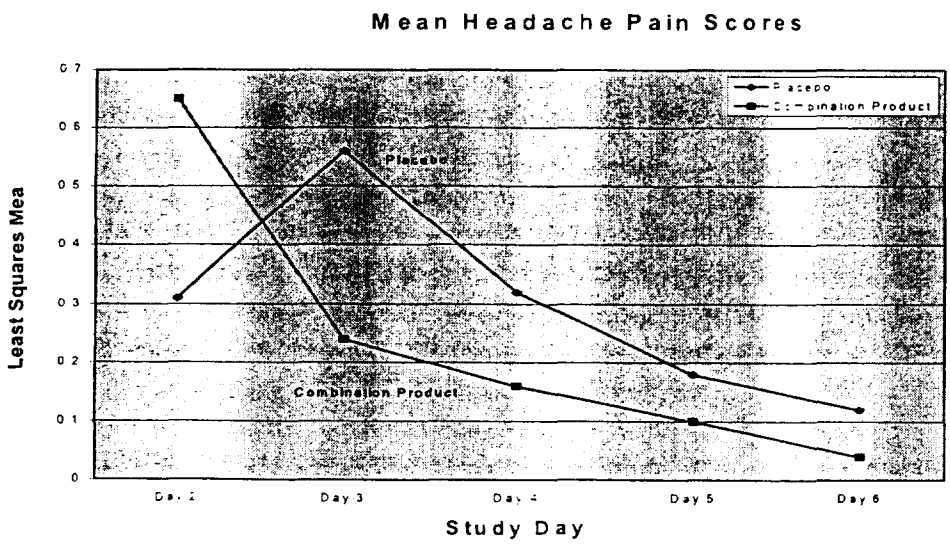
The second repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4, 8, and 12 hours on Day 2. The third repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4, 8, and 12 hours on Day 3.

These analyses showed statistical significance in favor of Aleve at 4 and 8 hours for Day 2, and at 4 hours for Day 3 with p-values of 0.003, 0.003 and 0.004 respectively. These results are included in Table I-3 (Study 051) in the Appendix.

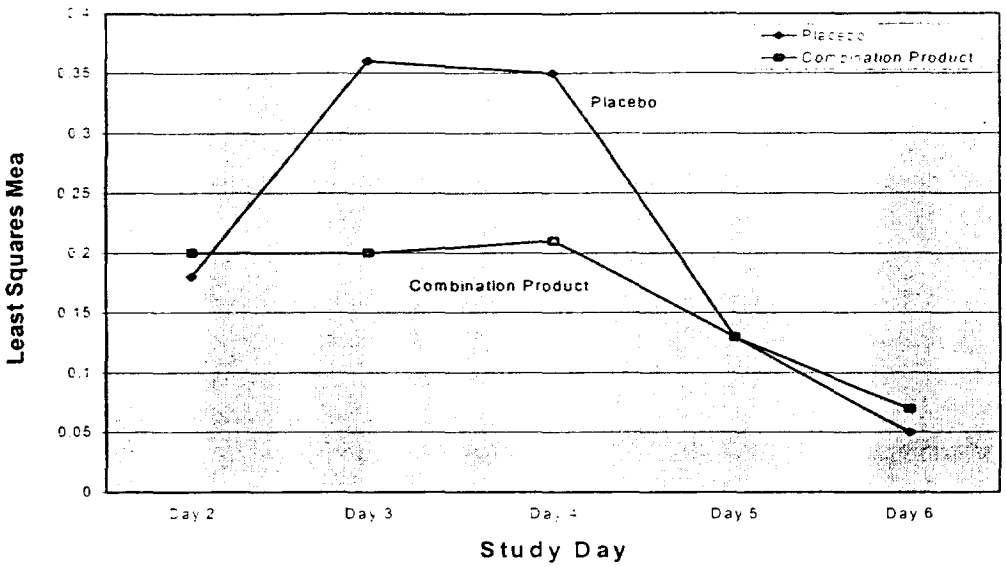
Secondary Efficacy Variables: Headache Pain Score, Malaise Score and Total Symptom Score

As stated in the protocol, a repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment for morning measurements of the secondary variables of headache pain, malaise and total symptom score from Day 2 through 6. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Though the treatment-by-time interaction was non-significant (p=0.1514 for headache pain, p=0.1869 for malaise, and p=0.0760 for total symptoms), the factor of time was significant (p=0.0001) for all three. All these results are included in Table I-4 (Study 051) in the Appendix.

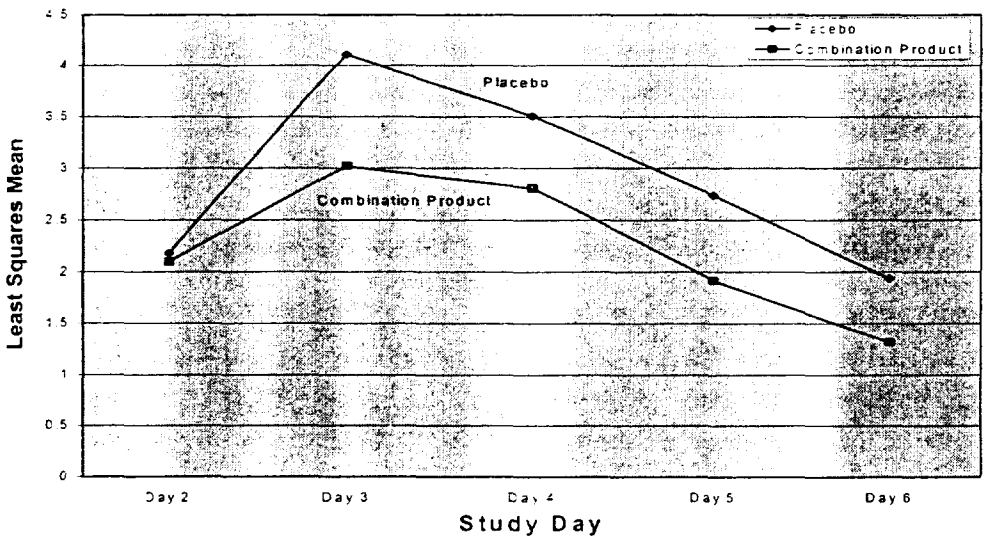
As stated in the protocol, these analyses were followed up by subsequent analyses (covariance analysis with baseline as covariate). Results are included in Table I-5 (Study 051) in the appendix. Plots showing trends are produced below for the three secondary efficacy variables.



Mean Malaise Scores



Mean Total Symptom Score



Statistical Reviewer's Conclusions

Two efficacy analyses were conducted and both yield similar results. On the basis of these analyses, this trial demonstrated the efficacy of Aleve for nasal obstruction, headache, malaise and total symptoms associated with the rhinovirus common colds.

Natural Cold Trial: S97-052

Number of Subjects

The sponsor took estimates of 20% treatment effect in nasal obstruction and estimates of standard deviations from the published literature regarding Clemastine Fumarate (see the protocol for references) and recommended a sample size of 181 per treatment group to detect the treatment difference with 80% power. Thus, the protocol stated that a sufficient number of subjects would be enrolled to assure that at least 362 evaluable subjects (181 per treatment group) complete the study. It is not clear to this reviewer if these sample calculations based on Clemastine Fumarate apply to the combination (naproxen/pseudoephedrine) at hand.

There were 439 subjects enrolled and randomized in the study. Two of these subjects were excluded from the intent-to-treat analyses as they were lost to follow-up prior to submitting any efficacy data. So, there were 437 subjects in the intent-to-treat analyses. Another sixteen were excluded from the primary efficacy analyses, resulting in 421 subjects in the primary efficacy analyses. These 16 subjects were excluded because of these reasons: termination due to adverse event (2 subjects), termination due to an intercurrent illness (4 subjects), inappropriately enrolled (1 subject), more than one off-schedule evaluation (2 subjects), non-compliant to the protocol (2 subjects), requiring back-up medication (4 subjects), and illegibility of diary times (1 subject).

The primary endpoint, as identified in the protocol, was the severity of nasal obstruction. A study nurse recorded the severity of the subject's nasal obstruction on Day 1 and each morning before the administration of the study medication on Days 2 through 5. The subjects also rated their nasal obstruction at 4, 8 and 12 hours after the morning dose on Day 1 and Day 2. Further, secondary endpoints of headache, malaise, and total symptoms were also evaluated.

As stated in the protocol, the sponsor planned for two efficacy analyses: a primary analysis and an intent-to-treat analysis. All subjects who took at least one dose of study medication were included in the intent-to-treat analysis. Only those subjects who met inclusion criteria, and who were not invalidated by exclusion criteria, and who yielded valid evaluations were included in the primary analysis.

This reviewer performed both the analyses on the datasets provided by the sponsor. Results are summarized below: first for the primary analysis and then for the intent-to-treat analysis.

Primary Efficacy Analysis: 421 subjects (Placebo=211, Aleve=210)

Baseline Comparisons

According to the protocol, variables such as age, weight and height were considered to be continuous and were analyzed with a two-way analysis of variance (ANOVA) model with factors of treatment and site. The Cochran-Mantel-Haenszel test stratified by site was used to analyze the differences between treatment groups for categorical variables such as gender and race. Likewise, the Cochran-Mantel-Haenszel test stratified by site was used to determine if differences existed between the treatment groups for the categorical baseline nasal obstruction (stopped-up nose/stuffiness) score, headache pain score, malaise score and total symptoms score.

The statistical methods proposed in the protocol were appropriate for baseline comparison. This reviewer's results match with those of the sponsor. These results are included in the Appendix as Table P-6 (Study 052).

There were no significant differences among treatment groups in any of the analyzed baseline demographic characteristics ($p \geq 0.183$).

Efficacy Analysis

Primary Efficacy Variable: Nasal Obstruction Score

The protocol specified that a repeated measures analysis of variance was to be used to test the treatment effect for the primary efficacy measure nasal obstruction on Days 1 and 2 following dosing with the study medications as well as before morning dosing on Days 1 through 5. That is, three different repeated measures analyses were performed: first, the time was Days 1 through Day 5 ; second, the time was 0, 4, and 8 hours on Day 1; and third, the time was 0, 4, 8, and 12 hours on Day 2.

The first repeated measures ANOVA was used to assess the effects of treatment on morning nasal obstruction measurements (stopped-up nose/stuffiness) for Days 1 through 5. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Statistical significance of the treatment-by-time interaction demonstrated differential treatment activity for the primary variable nasal obstruction ($p=0.0076$, Table P-7 (Study 052)) in favor of Aleve. However, the factor of time was also significant ($p=0.0001$). The results are included in Table P-7 (Study 052) in the Appendix.

The second repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4, and 8 hours on Day 1. The

third repeated measures ANOVA was used to assess the effects of treatment on nasal obstruction measurements at 0, 4. 8, and 12 hours on Day 2. These analyses showed statistical significance in favor of Aleve at 4 and 8 hours for Day 1, and at 4 hours for Day 2 with p-values of 0.001, 0.004 and 0.001 respectively. These results are included in Table P-8 (Study 052) in the Appendix.

Secondary Efficacy Variables: Headache Pain Score, Malaise Score and Total Symptom Score

As stated in the protocol, a repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment for morning measurements of the secondary variables of headache pain, malaise and total symptom score from Day 1 through 5. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Statistical significance or marginal significance of the treatment-by-time interaction demonstrated differential treatment activity for the secondary efficacy variables of headache pain (p=0.0206, Table P-9 (Study 052)), malaise (p=0.0509, Table P-9 (Study 052)) and total symptom score (p=0.0053, Table P-9 (Study 052)). However, the factor of time was also significant (p=0.0001).

Headache pain demonstrated a statistically significant overall treatment effect (p=0.0206). Further, the Day 2 (p=0.001, Table P-10 (Study 052)), the Day 3 (p=0.001, Table P-10 (Study 052)) and Day 4 (p=0.001, Table P-10 (Study 052)) morning observations indicate a statistically significant active treatment effect, which supports the likelihood of a treatment effect in favor of Aleve.

Further, malaise demonstrated a statistically marginally significant overall treatment effect (p=0.0509), however, the Day 2 morning observation indicated statistical significance (p=0.013, Table P-10 (Study 052)) in favor of Aleve.

Furthermore, total symptom score demonstrated a statistically significant overall treatment effect (p=0.0053). But, only the Day 2 (p=0.002, Table P-10 (Study 052)) morning observation indicated statistical significance in favor of Aleve.

Intent-to-Treat Analysis: 439 subjects (Placebo=220, Aleve=219)

Baseline Comparisons

According to the protocol, variables such as age, weight and height were considered to be continuous and were analyzed with a two-way analysis of variance (ANOVA) model with factors of treatment and site. The Cochran-Mantel-Haenszel test stratified by site was used to analyze the differences between treatment groups for categorical variables such as gender and race. Likewise, the Cochran-Mantel-Haenszel test stratified by site was

used to determine if differences existed between the treatment groups for the categorical baseline nasal obstruction (stopped-up nose/stuffiness) score, headache pain score, malaise score and total symptoms score.

The statistical methods proposed in the protocol were appropriate for baseline comparison. This reviewer's results match with those of the sponsor. These results are included in the Appendix as Table I-6 (Study 052).

There were no significant differences among treatment groups in any of the analyzed baseline demographic characteristics ($p \geq 0.114$).

Efficacy Analyses

Please note that two subjects (#35 and #526) in the Aleve group did not submit any efficacy data. And so, sample size was reduced to 217 from 219 in the analyses.

Primary Efficacy Variable: Nasal Obstruction Score

As stated in the protocol, a repeated measures ANOVA was used to assess the effects of treatment on morning nasal obstruction measurements (stopped-up nose/stuffiness). The ANOVA included factors of treatment, time, and treatment-by-time interaction. Results are included in Table I-7 (Study 052) in the Appendix.

Statistical significance of the treatment-by-time interaction demonstrated differential treatment activity for the primary variable nasal obstruction (p=0.0026, Table I-7 (Study 052)) in favor of Aleve.

As stated in the protocol, subsequent analyses (Covariance Analysis with baseline as covariate) of the within day nasal obstruction measurements also showed statistical significance in favor of Aleve at 4 and 8 hours for Day 1, and at 4 hours for Day 2 with p-values of 0.001, 0.002 and 0.001 respectively. These results are included in Table I-8 (Study 052) in the Appendix.

Secondary Efficacy Variables: Headache Pain Score, Malaise Score and Total Symptom Score

As stated in the protocol, a repeated measures analysis of variance (ANOVA) was used to assess the effects of treatment for morning measurements of the secondary variables of headache pain, malaise and total symptom score from Day 1 through 5. The ANOVA included factors of treatment, time, and treatment-by-time interaction. Statistical significance or marginal significance of the treatment-by-time interaction demonstrated differential treatment activity for the secondary efficacy variables of headache pain (p=0.0161, Table I-9 (Study

052)), malaise (p=0.0509, Table I-9 (Study 052)) and total symptom score (p=0.0024, Table I-9 (Study 052)). However, the factor of time was also significant (p=0.0001).

Headache pain demonstrated a statistically significant overall treatment effect (p=0.0161). Further, the Day 2 (p<0.001, Table I-10 (Study 052)), the Day 3 (p=0.001, Table I-10 (Study 052)) and Day 4 (p<0.001, Table I-10 (Study 052)) morning observations indicate a statistically significant active treatment effect, which supports the likelihood of a treatment effect in favor of Aleve.

Further, malaise demonstrated a statistically marginally significant overall treatment effect (p=0.0509), however, the Day 2 morning observation indicated statistical significance (p=0.005, Table I-10 (Study 052)) in favor of Aleve.

Furthermore, total symptom score demonstrated a statistically significant overall treatment effect (p=0.0024). But, only the Day 2 (p<0.001, Table I-10 (Study 052)) and the Day 4 (p=0.048, Table I-10 (Study 052)) morning observation indicated statistical significance in favor of Aleve.

Statistical Reviewer's Conclusions

Two efficacy analyses were conducted and both yield similar results. On the basis of these analyses, this trial demonstrated the efficacy of Aleve for nasal obstruction, headache, malaise and total symptoms associated with the common colds.

IV. Statistical Reviewer's Conclusions That May Be Conveyed To The Sponsor

Bayer has submitted the following two clinical trials as pivotal for the evaluation of ALEVE COLD & SINUS (naproxen/pseudoephedrine combination):

Induced Cold Trial: S97-051
Natural Cold Trial: S97-052.

There are some review issues:

1. The sample size calculations in the protocols are not clear to this reviewer. Further, it is not clear whether these calculations (based on other drugs) really apply to the combination (naproxen/pseudoephedrine) at hand.

2. It appears that the Study S97-051 (Induced Cold Trial) was stopped early whereas the Study S97-052 (Natural Cold Trial) went beyond its stopping point. It is evident from the number of subjects planned in the protocol and really enrolled in the study. For S97-051, there were 245 subjects enrolled and not 266 as planned in the protocol. For S97-052, there were 439 subjects enrolled and not 362 as planned in the protocol.

3. According to the protocols, the data on temperature was recorded, but it was not supplied to this reviewer for analysis. The temperature data does not appear to be included in the line listings in the NDA.

4. The contributions of naproxen and pseudoephedrine to the effect of the combination have not been shown in the pivotal trials as required by the combination drug policy (CFR 300.50).

However, on the basis of two efficacy analyses (primary analysis and intent-to-treat analysis), this reviewer's conclusions for the two trials are given below. ***In the light of the above review issues, these conclusions are only tentative.***

Induced Cold Trial: **S97-051**

This trial demonstrated the efficacy of Aleve for nasal obstruction, headache, malaise and total symptoms associated with the rhinovirus common colds.

Natural Cold Trial: **S97-052**

This trial demonstrated the efficacy of Aleve for nasal obstruction, headache, malaise and total symptoms associated with the natural common colds.

Baldeo K. Taneja, Ph.D.
Mathematical Statistician (Biomed)

Concur: Dr. Lin

Dr. Huque

cc: Archival NDA 21-076
HFD-550/Schmidt
HFD-550/Fang
HFD-550/Hyde
HFD-550/Midthun
HFD-550/Division File
HFD-725/Taneja
HFD-725/Lin
HFD-725/Huque
HFD-725/Division File
HFD-725/Chron.

There are total 41 pages (20 pages of text and 21 pages of Appendix) in this review.

APPENDIX

Table P-1 (Study 051)
Baseline Comparisons

Variable		Placebo	Aleve	p-Value
Number of Subjects		104	102	
Age (in years)				0.907
	Mean	26.85	26.54	
	SD	9.55	8.34	
Race				0.762
	Caucasian	78 (75%)	78 (76%)	
	Black	10 (10%)	15 (15%)	
	Hispanic	6 (6%)	1 (1%)	
	Asian	7 (7%)	5 (5%)	
	Other	3 (3%)	3 (3%)	
Gender				0.196
	Male	48 (46%)	38 (37%)	
	Female	56 (54%)	64 (63%)	
Height (in inches)				0.274
	Mean	67.63	67.07	
	SD	3.92	3.51	
Weight (in lbs.)				0.669
	Mean	157.32	159.01	
	SD	34.83	35.65	
Nasal Obstruction				0.568
	Absent	65 (63%)	68 (67%)	
	Mild	28 (27%)	23 (23%)	
	Moderate	9 (9%)	11 (11%)	
	Severe	2 (2%)	0 (0%)	
	Very Severe	0 (0%)	0 (0%)	
Headache Pain				0.685
	Absent	81 (78%)	80 (78%)	
	Mild	18 (17%)	14 (14%)	
	Moderate	5 (5%)	7 (7%)	
	Severe	0 (0%)	1 (1%)	
	Very Severe	0 (0%)	0 (0%)	
Malaise				0.744
	Absent	90 (87%)	87 (85%)	
	Mild	10 (10%)	10 (10%)	
	Moderate	3 (3%)	4 (4%)	
	Severe	1 (1%)	1 (1%)	
	Very Severe	0 (0%)	0 (0%)	

Table P-2 (Study 051)
Repeated Measures Analysis of Nasal Obstruction

	Placebo (N=104)		Aleve (N=102)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 2 (Baseline)	0.50	0.71	0.44	0.71	
Post Dose Hour 4	0.48	0.62	0.28	0.62	
Post Dose Hour 8	0.55	0.70	0.32	0.70	
Post Dose Hour 12	0.61	0.75	0.44	0.75	
Day 3 Pre-Treatment	1.04	0.88	0.75	0.88	
Post Dose Hour 4	0.81	0.80	0.52	0.80	
Post Dose Hour 8	0.70	0.81	0.54	0.81	
Post Dose Hour 12	0.71	0.85	0.60	0.85	
Day 4 Pre-Treatment	1.01	0.99	0.84	0.99	
Day 5 Pre-Treatment	0.79	0.85	0.63	0.85	
Day 6 Pre-Treatment	0.58	0.67	0.46	0.67	
Between Subjects Effect Over All Time Periods					0.026

APPEARS THIS WAY
ON ORIGINAL

Table P-3 (Study 051)
Covariance Analysis of Nasal Obstruction
With Baseline as Covariate

	Placebo (N=104)		Aleve (N=102)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 2 (Baseline)	0.50	0.71	0.44	0.71	0.569
Post Dose Hour 4	0.47	0.52	0.29	0.52	0.014
Post Dose Hour 8	0.54	0.63	0.33	0.63	0.020
Post Dose Hour 12	0.60	0.67	0.45	0.67	0.125
Day 3 Pre-Treatment	1.03	0.78	0.77	0.78	0.017
Post Dose Hour 4	0.80	0.77	0.53	0.77	0.012
Post Dose Hour 8	0.69	0.76	0.55	0.76	0.208
Post Dose Hour 12	0.70	0.82	0.61	0.82	0.444
Day 4 Pre-Treatment	1.00	0.94	0.85	0.94	0.260
Day 5 Pre-Treatment	0.78	0.84	0.64	0.84	0.215
Day 6 Pre-Treatment	0.58	0.67	0.46	0.67	0.213

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Table P-4 (Study 051)
Repeated Measures Analysis of Secondary Efficacy Variables

	Placebo (N=104)		Aleve (N=102)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 2 (Baseline)	0.27	0.60	0.31	0.60	
Day 3	0.61	0.90	0.26	0.90	
Day 4	0.34	0.64	0.17	0.64	
Day 5	0.17	0.46	0.12	0.46	
Day 6	0.11	0.34	0.05	0.34	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0538
Malaise					
Day 2 (Baseline)	0.18	0.54	0.20	0.54	
Day 3	0.37	0.68	0.22	0.68	
Day 4	0.36	0.68	0.23	0.68	
Day 5	0.13	0.42	0.14	0.42	
Day 6	0.05	0.26	0.07	0.26	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.2410
Total Symptom Score					
Day 2 (Baseline)	2.28	2.52	2.20	2.52	
Day 3	4.47	3.98	3.21	3.98	
Day 4	3.84	3.88	3.02	3.88	
Day 5	3.02	3.16	2.08	3.16	
Day 6	2.10	2.55	1.35	2.55	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0768

Table P-5 (Study 051)
Covariance Analysis of Secondary Efficacy Variables
With Baseline as Covariate

	Placebo (N=104)		Aleve (N=102)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 3	0.62	0.86	0.25	0.86	0.002
Day 4	0.35	0.62	0.17	0.62	0.038
Day 5	0.17	0.44	0.11	0.44	0.321
Day 6	0.12	0.32	0.04	0.32	0.110
Malaise					
Day 3	0.38	0.60	0.21	0.60	0.046
Day 4	0.37	0.57	0.22	0.57	0.073
Day 5	0.13	0.42	0.13	0.42	0.985
Day 6	0.06	0.26	0.07	0.26	0.760
Total Symptom Score					
Day 3	4.44	3.26	3.26	3.26	0.009
Day 4	3.82	3.39	3.06	3.39	0.109
Day 5	3.01	2.99	2.1	2.99	0.029
Day 6	2.09	2.44	1.36	2.44	0.033

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ON ORIGINAL

Table I-1 (Study 051)
Baseline Comparisons

Variable		Placebo	Aleve	p-Value
Number of Subjects		122	121	
Age (in years)				0.720
	Mean	26.62	27.01	
	SD	9.33	8.82	
Race				0.570
	Caucasian	92 (75%)	95 (79%)	
	Black	13 (11%)	16 (13%)	
	Hispanic	7 (6%)	1 (1%)	
	Asian	7 (6%)	5 (4%)	
	Other	3 (2%)	4 (3%)	
Gender				0.327
	Male	55 (45%)	47 (39%)	
	Female	67 (55%)	74 (61%)	
Height (in inches)				0.442
	Mean	67.63	67.26	
	SD	3.85	3.72	
Weight (in lbs.)				0.784
	Mean	156.92	158.21	
	SD	34.81	35.93	
Nasal Obstruction				0.743
	Absent	78 (64%)	79 (65%)	
	Mild	31 (25%)	29 (24%)	
	Moderate	11 (9%)	13 (11%)	
	Severe	2 (2%)	0 (0%)	
	Very Severe	0 (0%)	0 (0%)	
Headache Pain				0.947
	Absent	94 (77%)	97 (80%)	
	Mild	19 (16%)	15 (12%)	
	Moderate	9 (7%)	7 (6%)	
	Severe	0 (0%)	1 (1%)	
	Very Severe	0 (0%)	1 (1%)	
Malaise				0.796
	Absent	105 (86%)	105 (87%)	
	Mild	13 (11%)	10 (8%)	
	Moderate	3 (2%)	4 (3%)	
	Severe	1 (1%)	2 (2%)	
	Very Severe	0 (0%)	0 (0%)	

Table I-2 (Study 051)
Repeated Measures Analysis of Nasal Obstruction

	Placebo (N=122)		Aleve (N=121)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 2 (Baseline)	0.48	0.71	0.45	0.71	
Post Dose Hour 4	0.48	0.60	0.27	0.60	
Post Dose Hour 8	0.54	0.68	0.30	0.68	
Post Dose Hour 12	0.58	0.74	0.42	0.74	
Day 3 Pre-Treatment	0.98	0.88	0.70	0.88	
Post Dose Hour 4	0.78	0.78	0.49	0.78	
Post Dose Hour 8	0.65	0.79	0.52	0.79	
Post Dose Hour 12	0.65	0.83	0.56	0.83	
Day 4 Pre-Treatment	0.95	0.96	0.79	0.96	
Day 5 Pre-Treatment	0.73	0.82	0.57	0.82	
Day 6 Pre-Treatment	0.55	0.67	0.44	0.67	
Between Subjects Effect Over All Time Periods					0.020

Table I-3 (Study 051)
Covariance Analysis of Nasal Obstruction
With Baseline as Covariate

	Placebo (N=122)		Aleve (N=121)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 2 (Baseline)	0.48	0.71	0.45	0.71	0.743
Post Dose Hour 4	0.47	0.52	0.28	0.52	0.003
Post Dose Hour 8	0.54	0.61	0.31	0.61	0.003
Post Dose Hour 12	0.57	0.66	0.43	0.66	0.103
Day 3 Pre-Treatment	0.98	0.78	0.71	0.78	0.008
Post Dose Hour 4	0.78	0.75	0.50	0.75	0.004
Post Dose Hour 8	0.65	0.74	0.53	0.74	0.221
Post Dose Hour 12	0.65	0.79	0.56	0.79	0.407
Day 4 Pre-Treatment	0.95	0.90	0.80	0.90	0.213
Day 5 Pre-Treatment	0.73	0.81	0.57	0.81	0.139
Day 6 Pre-Treatment	0.55	0.66	0.44	0.66	0.208

APPEARS THIS WAY
ON ORIGINAL

Table I-4 (Study 051)
Repeated Measures Analysis of Secondary Efficacy Variables

	Placebo (N=122)		Aleve (N=121)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 2 (Baseline)	0.31	0.65	0.30	0.65	
Day 3	0.56	0.86	0.24	0.86	
Day 4	0.33	0.62	0.16	0.62	
Day 5	0.18	0.45	0.10	0.45	
Day 6	0.12	0.34	0.04	0.34	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.1514
Malaise					
Day 2 (Baseline)	0.18	0.54	0.20	0.54	
Day 3	0.35	0.66	0.21	0.66	
Day 4	0.35	0.65	0.22	0.65	
Day 5	0.13	0.41	0.13	0.41	
Day 6	0.05	0.26	0.07	0.26	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.1869
Total Symptom Score					
Day 2 (Baseline)	2.18	2.48	2.10	2.48	
Day 3	4.14	3.93	2.98	3.93	
Day 4	3.53	3.77	2.77	3.77	
Day 5	2.75	3.01	1.90	3.01	
Day 6	1.95	2.43	1.31	2.43	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0760

Table I-5 (Study 051)
Covariance Analysis of Secondary Efficacy Variables
With Baseline as Covariate

	Placebo (N=122)		Aleve (N=121)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 3	0.56	0.84	0.24	0.84	0.003
Day 4	0.32	0.60	0.16	0.60	0.036
Day 5	0.18	0.44	0.10	0.44	0.154
Day 6	0.12	0.33	0.04	0.33	0.054
Malaise					
Day 3	0.36	0.60	0.20	0.60	0.042
Day 4	0.35	0.57	0.21	0.57	0.054
Day 5	0.13	0.40	0.13	0.40	0.983
Day 6	0.05	0.26	0.07	0.26	0.636
Total Symptom Score					
Day 3	4.11	3.19	3.02	3.19	0.008
Day 4	3.51	3.25	2.81	3.25	0.096
Day 5	2.74	2.87	1.92	2.87	0.027
Day 6	1.94	2.33	1.32	2.33	0.038

APPEARS THIS WAY
ON ORIGINAL

Table P-6 (Study 052)
Baseline Comparisons

Variable		Placebo	Aleve	p-Value
Number of Subjects		211	210	
Age (in years)				0.439
	Mean	26.20	26.61	
	SD	8.73	8.88	
Race				0.606
	Caucasian	159 (75%)	163 (78%)	
	Black	25 (12%)	25 (12%)	
	Hispanic	5 (2%)	5 (2%)	
	Asian	15 (7%)	13 (6%)	
	Other	7 (3%)	4 (2%)	
Gender				0.686
	Male	66 (31%)	62 (30%)	
	Female	145 (69%)	148 (70%)	
Height (in inches)				0.438
	Mean	67.03	66.76	
	SD	3.76	3.67	
Weight (in lbs.)				0.215
	Mean	149.89	146.19	
	SD	30.55	29.17	
Nasal Obstruction				0.483
	Absent	0 (0%)	0 (0%)	
	Mild	43 (20%)	35 (17%)	
	Moderate	110 (52%)	112 (53%)	
	Severe	47 (22%)	54 (26%)	
	Very Severe	11 (5%)	9 (4%)	
Headache Pain				0.183
	Absent	92 (44%0	101 (48%)	
	Mild	46 (22%)	39 (19%)	
	Moderate	38 (18%)	48 (23%)	
	Severe	25 (12%)	19 (9%)	
	Very Severe	10 (5%)	3 (1%)	
Malaise				0.491
	Absent	51 (24%)	57 (27%)	
	Mild	57 (27%)	53 (25%)	
	Moderate	66 (31%)	69 (33%)	
	Severe	28 (13%)	23 (11%)	
	Very Severe	9 (4%)	8 (4%)	

Table P-7 (Study 052)
Repeated Measures Analysis of Nasal Obstruction

	Placebo (N=211)		Aleve (N=210)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 1 (Baseline)	2.12	0.94	2.17	0.95	
Day 2	1.99	1.10	1.78	1.11	
Day 3	1.59	1.13	1.52	1.13	
Day 4	1.29	1.13	1.12	1.14	
Day 5	0.96	1.06	0.94	1.07	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0076

APPEARS THIS WAY
ON ORIGINAL

Table P-8 (Study 052)
Covariance Analysis of Nasal Obstruction
With Baseline as Covariate
By Hour Analysis

	Placebo (N=211)		Aleve (N=210)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction Day 1					
Hour 4	1.70	0.93	1.45	0.94	0.001
Hour 8	1.82	1.03	1.58	1.03	0.004
Nasal Obstruction Day 2					
Hour 4	1.62	1.04	1.33	1.05	0.001
Hour 8	1.58	1.09	1.43	1.10	0.092
Hour 12	1.67	1.13	1.63	1.13	0.702

Table P-9 (Study 052)
Repeated Measures Analysis of Secondary Efficacy Variables

	Placebo (N=211)		Aleve (N=210)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 1 (Baseline)	1.10	1.40	0.95	1.41	
Day 2	0.88	1.24	0.53	1.25	
Day 3	0.59	1.04	0.30	1.04	
Day 4	0.43	0.84	0.18	0.84	
Day 5	0.27	0.76	0.18	0.76	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0206
Malaise					
Day 1 (Baseline)	1.37	1.35	1.29	1.36	
Day 2	1.17	1.28	0.93	1.29	
Day 3	0.72	1.12	0.61	1.13	
Day 4	0.44	0.94	0.36	0.94	
Day 5	0.24	0.77	0.25	0.78	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0509
Total Symptom Score					
Day 1 (Baseline)	10.78	5.79	10.43	5.79	
Day 2	9.21	5.51	7.92	5.51	
Day 3	6.65	5.51	6.16	5.51	
Day 4	5.03	5.07	4.26	5.07	
Day 5	3.62	4.63	3.37	4.63	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0053

Table P-10 (Study 052)
Covariance Analysis of Secondary Efficacy Variables
With Baseline as Covariate

	Placebo (N=211)		Aleve (N=210)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 2	0.85	0.99	0.58	1.00	0.001
Day 3	0.57	0.95	0.33	0.96	0.001
Day 4	0.42	0.81	0.20	0.82	0.001
Day 5	0.27	0.75	0.19	0.75	0.188
Malaise					
Day 2	1.21	0.95	1.02	0.96	0.013
Day 3	0.75	0.99	0.66	1.00	0.263
Day 4	0.46	0.88	0.40	0.89	0.384
Day 5	0.25	0.75	0.27	0.75	0.737
Total Symptom Score					
Day 2	9.17	4.21	8.10	4.24	0.002
Day 3	6.62	4.95	6.28	4.99	0.394
Day 4	5.02	4.84	4.32	4.88	0.071
Day 5	3.61	4.42	3.41	4.46	0.580

Table I-6 (Study 052)
Baseline Comparisons

Variable		Placebo	Aleve	p-Value
Number of Subjects		220	219	
Age (in years)				0.424
	Mean	26.29	26.81	
	SD	8.71	8.9	
Race				0.675
	Caucasian	167 (76%)	170 (78%)	
	Black	25 (11%)	27 (12%)	
	Hispanic	5 (2%)	5 (2%)	
	Asian	15 (7%)	13 (6%)	
	Other	8 (4%)	4 (2%)	
Gender				0.485
	Male	69 (31%)	62 (28%)	
	Female	151 (69%)	157 (72%)	
Height (in inches)				0.194
	Mean	67.08	66.62	
	SD	3.77	3.70	
Weight (in lbs.)				0.114
	Mean	150.32	145.74	
	SD	31.73	29.03	
Nasal Obstruction				0.454
	Absent	0 (0%)	0 (0%)	
	Mild	45 (20%)	37 (17%)	
	Moderate	115 (52%)	117 (53%)	
	Severe	49 (22%)	55 (25%)	
	Very Severe	11 (5%)	10 (5%)	
Headache Pain				0.308
	Absent	98 (45%)	105 (48%)	
	Mild	48 (22%)	40 (18%)	
	Moderate	38 (17%)	50 (23%)	
	Severe	26 (12%)	20 (9%)	
	Very Severe	10 (5%)	4 (2%)	
Malaise				0.569
	Absent	148 (67%)	166 (76%)	
	Mild	38 (17%)	24 (11%)	
	Moderate	71 (32%)	71 (32%)	
	Severe	30 (14%)	25 (11%)	
	Very Severe	9 (4%)	10 (5%)	

Table I-7 (Study 052)
Repeated Measures Analysis of Nasal Obstruction

	Placebo (N=220)		Aleve (N=217*)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction					
Day 1 (Baseline)	2.10	0.94	2.15	0.94	
Day 2	1.99	1.09	1.76	1.10	
Day 3	1.61	1.12	1.52	1.12	
Day 4	1.33	1.13	1.13	1.13	
Day 5	1.00	1.07	0.97	1.07	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0026

*: The number differs from the ITT dataset because two subjects did not submit efficacy data.

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Table I-8 (Study 052)
Covariance Analysis of Nasal Obstruction
With Baseline as Covariate
By Hour Analysis

	Placebo (N=220)		Aleve (N=217*)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Nasal Obstruction Day 1					
Hour 4	1.70	0.95	1.44	0.96	0.001
Hour 8	1.80	1.03	1.55	1.04	0.002
Nasal Obstruction Day 2					
Hour 4	1.65	1.04	1.35	1.04	0.001
Hour 8	1.63	1.10	1.46	1.10	0.052
Hour 12	1.70	1.12	1.65	1.13	0.566

*: The number differs from the ITT dataset because two subjects did not submit efficacy data.

Table I-9 (Study 052)
Repeated Measures Analysis of Secondary Efficacy Variables

	Placebo (N=220)		Aleve (N=217*)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 1 (Baseline)	1.09	1.40	0.97	1.41	
Day 2	0.89	1.23	0.54	1.24	
Day 3	0.62	1.05	0.34	1.06	
Day 4	0.47	0.87	0.21	0.87	
Day 5	0.32	0.80	0.21	0.80	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0161
Malaise					
Day 1 (Baseline)	1.41	1.36	1.33	1.36	
Day 2	1.21	1.27	0.95	1.27	
Day 3	0.80	1.15	0.67	1.15	
Day 4	0.53	0.99	0.44	0.99	
Day 5	0.33	0.85	0.32	0.85	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0509
Total Symptom Score					
Day 1 (Baseline)	10.86	5.70	10.47	5.72	
Day 2	9.38	5.52	7.94	5.53	
Day 3	6.97	5.63	6.36	5.64	
Day 4	5.39	5.23	4.51	5.25	
Day 5	4.03	4.89	3.62	4.90	
Overall Time Effect					0.0001
Time by Treatment Interaction Over All Time Periods					0.0024

*: The number differs from the ITT dataset because two subjects did not submit efficacy da

Table I-10 (Study 052)
Covariance Analysis of Secondary Efficacy Variables
With Baseline as Covariate

	Placebo (N=220)		Aleve (N=217*)		p-Value
	LS Mean	LS SD	LS Mean	LS SD	
Headache Pain					
Day 2	0.87	0.99	0.58	0.99	< 0.001
Day 3	0.60	0.96	0.36	0.96	0.001
Day 4	0.46	0.83	0.23	0.84	< 0.001
Day 5	0.32	0.78	0.22	0.78	0.099
Malaise					
Day 2	1.23	0.94	1.02	0.95	0.005
Day 3	0.82	1.00	0.72	1.00	0.208
Day 4	0.54	0.92	0.47	0.92	0.362
Day 5	0.34	0.81	0.34	0.81	0.936
Total Symptom Score					
Day 2	9.30	4.24	8.10	4.25	< 0.001
Day 3	6.92	5.07	6.48	5.09	0.272
Day 4	5.36	5.08	4.57	5.10	0.048
Day 5	4.00	4.78	3.67	4.80	0.376

*: The number differs from the ITT set as 2 subjects did not submit efficacy data.

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