CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-441
Name of drug:	Advil Multi-symptom Allergy Sinus (Ibuprofen 200 mg/ Pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg)
Applicant:	Whitehall-Robins Healthcare
Indication:	Allergic Rhinitis
Documents reviewed:	Sponsor's electronic submission, can be found from: \\CDSESUB1\N21441\N_000
Project manager:	Jane Dean
Clinical reviewer:	Christina Fang, M.D.
Dates:	Received February 28, 2002
Statistical reviewer:	Suktae Choi, Ph.D.
Statistics acting team leader:	Atiar Rahman, Ph.D.
Biometrics division director:	Mo Huque, Ph.D.

Keywords: NDA review, clinical studies, analysis of variance

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

This NDA showed evidence of contribution of ibuprofen 400 mg for efficacy in relief of allergy-associated pain when they were added to a combination of pseudoephedrine hydrochloride 60 mg/ chlorpheniramine maleate 4 mg – two caplets. One caplet contained 200 mg of ibuprofen, 30 mg of pseudoephedrine hydrochloride and 2 mg of chlorpheniramine maleate (I/P/C). Also, this three combination drug showed evidence of efficacy in relief of over all allergy symptoms and relief of allergy-associated pain for both doses – one caplet and two caplets. However, a significant dose-response was not detected for any efficacy parameters between one caplet and two caplets of I/P/C treated groups.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

This NDA contains one study (AD-99-02), with a title of "Advil Multi-Symptom Allergy Sinus Efficacy and Safety Study." The primary objective of this study was to demonstrate the contribution of ibuprofen to the overall and/or analgesic effectiveness of ibuprofen/pseudoephedrine/chlorpheniramine in relieving the symptoms of seasonal allergic rhinitis (SAR). It was a multicenter, outpatient, multiple-dose, placebo controlled, double-blind, parallel group, randomized trial with a duration of 7 days of treatment. After receiving the first dose of study medication at the site, subjects continued to dose every 6 hours, 3 doses per day (morning midday, evening) for 7 days. There were four treatment groups as follow:

Group A: ibuprofen 400 mg/ pseudoephedrine hydrochloride 60 mg/ chlorpheniramine maleate 4 mg (I/P/C 2-cap)
Group B: ibuprofen 200 mg/ pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg (I/P/C 1-cap)
Group C: pseudoephedrine hydrochloride 30 mg/ chlorpheniramine maleate 2 mg (P/C 1-tab)
Group D: Placebo

Key efficacy endpoints were as follow:

- Change from baseline in the 7-day, overall average reflective total symptom score (OATSS).
- The time-weighted sum of the pain intensity difference scores at two and three hours after the first dose of study medication (SPID3)
- Change from baseline in the overall average reflective total antihistamine symptoms score (OATASS)

A total of 1070 subjects were enrolled and included in the safety analysis. Of these, sponsor included only 1044 subjects (97.5%) on their intent-to-treat (ITT) analysis, and included only 1032 subjects (96.4%) for modified intent-to-treat analysis (for SPID3). ITT should include

all the patients who were randomized and took at least one medication. However, based on this reviewer's sensitivity analysis, the exclusion of 2-4% was ignorable for efficacy results in this study. All efficacy variables based on change from baseline were analyzed via an ANOVA model including effects for treatment, corresponding baseline, and center. Comparisons were tested in sequential order. Each step had to be significant for the subsequent steps to be eligible for significance. The sequential order used was as follow:

1. a. The 2-caplet I/P/C combination vs. Placebo for SPID3 and OATSS
   b. The 2-caplet I/P/C combination vs. 1-tablet P/C for SPID3
2. The 1-caplet I/P/C vs. Placebo for SPID3, OATSS and OATASS
3. The 2-caplet I/P/C vs. 1-caplet I/P/C for SPID3, OATSS and OATASS

Step 1 a is for contribution of ibuprofen to the combination P/C for two caplets in pain, and step 1 b is for efficacy of two caplet I/P/C in over all allergy symptom. Step 2 is for efficacy of one caplet of I/P/C in over all allergy symptom. Step 3 is for dose response. In results as shown in the following table, statistical significant results were shown at step 1 and step 2, but failed at step 3.

Summary of efficacy analysis results three steps (sponsor's ITT)

Step	Efficacy Variable	Treatment Group	Mean (std)	P-value	Result	Interpretation
Step 1 a	SPID3	I/P/C 2-cap	2.80 (2.23)	<0.001	Signif diff	I/P/C 2-cap showed efficacy in pain
		Placebo	2.01 (2.09)			
	OATSS	I/P/C 2-cap	5.59 (3.47)	<0.001	Signif diff	I/P/C 2-cap showed efficacy in allergic rhinitis
		Placebo	3.80 (3.45)			
Step 1 b	SPID3	I/P/C 2-cap	2.80 (2.23)	<0.001	Signif diff	Ibuprofen showed contribution of efficacy in pain for I/P/C 2-cap
		P/C 1-tab	2.10 (1.99)			
Step 2	SPID3	I/P/C 1-cap	2.81 (2.49)	<0.001	Signif diff	I/P/C 1-cap showed efficacy in pain
		Placebo	2.01 (2.09)			
	OATSS	I/P/C 1-cap	5.43 (3.54)	<0.001	Signif diff	I/P/C 1-cap showed efficacy in allergic rhinitis
		Placebo	3.80 (3.45)			
	OATASS	I/P/C 1-cap	2.80 (1.87)	<0.001	Signif diff	
		Placebo	1.92 (1.83)			
Step 3	SPID3	I/P/C 2-cap	2.80 (2.23)	0.553	Failed	I/P/C 2-cap and I/P/C 1-cap didn't show any difference of efficacy in either pain nor allergic rhinitis
		I/P/C 1-cap	2.81 (2.49)			
	OATSS	I/P/C 2-cap	5.59 (3.47)	0.376	Failed	
		I/P/C 1-cap	5.43 (3.54)			
	OATASS	I/P/C 2-cap	2.87 (1.85)	0.390	Failed	
		I/P/C 1-cap	2.80 (1.87)			

P-values are from ANOVA with effects for treatment, baseline, and site

1.3 PRINCIPAL FINDINGS

1. Among 1070 randomized subjects, sponsor's ITT population excluded 26 subjects. This restricted ITT was used for analyses of OATSS, OATASS. Sponsor's "modified ITT" excluded 38 subjects, which was used for analyses of SPID3. However, this reviewer's additional analyses with all randomized patients (without excluding any patients) showed almost same results with sponsor's restricted ITT analyses.

2. Sponsor planned 3 steps of statistical comparisons. First step was to show the contribution of ibuprofen in allergy-associated pain by comparing two caplets of I/P/C and one tablet of P/C. In addition, this step was to show the efficacy of two caplets of I/P/C for relief of over all allergy symptoms and relief of allergy-associated pain by comparing two caplets of I/P/C and placebo. Second step was to show the efficacy of one caplet of I/P/C for relief of over all allergy symptoms and relief of allergy-associated pain by comparing two caplets of I/P/C and placebo. These first two steps were successively showed significant differences for all efficacy variables. The third step was to show the dose response by comparing 2 caplets of I/P/C and 1 caplet of I/P/C, but this step was failed. Therefore, this NDA showed evidence of contribution of ibuprofen 400 mg for efficacy in relief of allergy-associated pain when they were added to a combination of pseudoephedrine hydrochloride 60 mg/ chlorpheniramine maleate 4 mg - two caplets. Also, this three combination drug showed evidence of efficacy in relief of over all allergy symptoms and relief of allergy-associated pain for two different doses – one caplet and two caplets. However, comparison between one caplet of I/P/C and one tablet of P/C was not included in the primary analysis sequence. A significant dose-response was not detected for any efficacy parameters between one caplet and two caplets of I/P/C treated groups.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

For those who suffer painful symptoms associated with their allergies, there are numerous three-ingredient combination products currently available OTC that contain an analgesic in addition to a decongestant and antihistamine. Acetaminophen is the analgesic component for most of these combinations. The sponsor submitted this NDA for analgesic efficacy as well as the overall efficacy of the new three-ingredient combination containing ibuprofen as an analgesic. In this NDA, one study (AD-99-02) was submitted as a pivotal for efficacy and safety.

2.2 DATA ANALYZED AND SOURCES

Only electronic copy were reviewed, and sources and data are listed as following table.

Summary of sources and data reviewed

Source	Type	Descripuon
General		
\\Cdsesub1\n21441\N_000\2002-02-28\ndatoc.pdf	PDF File	Labeling, Summary of efficacy, etc.
Study AD-99-02: Advil multi-symptom allergy sinus efficacy and safety study.		
\\Cdsesub1\n21441\N_000\2002-02-28\clinstat\allergicrhinitis\ad9902\ad9902.pdf	PDF File	Final report for the study – main part
\\Cdsesub1\n21441\N_000\2002-02-28\clinstat\allergicrhinitis\ad9902\ad9902a.pdf	PDF File	Final report for the study – appendix A
\\Cdsesub1\n21441\N_000\2002-02-28\clinstat\allergicrhinitis\ad9902\ad9902b.pdf	PDF File	Final report for the study – appendix B
\\Cdsesub1\n21441\N_000\2002-02-28\crt\datasets\ad9902\efftran2.xpt	SAS Transport File	Efficacy data used in reviewer's analyses

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Following is sponsor's conclusions of efficacy quoted from sponsor's final report.

- The analgesic/decongestant/antihistaminic efficacy of ibuprofen/pseudoephedrine/ chlorpheniramine (200/30/2 – 400/60/4 mg) in the treatment of seasonal allergic rhinitis;
- Ibuprofen contributes to the overall effectiveness of the combination by not only relieving allergy-associated pain but also by reducing the severity of other seasonal allergic rhinitis symptoms, as I/P/C 1-Cap was more effective than P/C 1-Tab for most assessments;
- A 2 mg dose of chlorpheniramine is effective as an antihistamine, as both I/P/C 1-Cap and P/C 1-Tab were more effective than placebo in relieving the histamine-related symptoms of seasonal allergic rhinitis;
- Both doses of I/P/C were equally efficacious;

2.3.2 STATISTICAL METHODOLOGIES

All variables based on changes from baseline were analyzed via an ANOVA model including effects for treatment, corresponding baseline, and center. In addition, the treatment-by-baseline and treatment-by-center interaction effects were assessed, one at a time by adding the interactions to the initial ANOVA model.

Comments: Factors for primary efficacy analysis are recommended to be pre-specified. In this review, additional analysis results with interactions is considered as sensitivity analysis.

Multiple efficacy analyses with different variables were performed, comparisons were tested in sequential order to protect against Type I error. Three steps are listed in the following section.

2.3.3 DETAILED REVIEW OF STUDY AD-99-02

Following summary of the study is quoted from sponsor's submission.

Objectives:
Objective of this study was to evaluate and compare the analgesic/ decongestant/ antihistaminic efficacy of ibuprofen/ pseudoephedrine hydrochloride/ chlorpheniramine maleate (total dose 400/60/4 mg or 200/30/2 mg), pseudoephedrine/chlorpheniramine 30 mg/2 mg and placebo in relieving the symptoms of seasonal allergic rhinitis (SAR).

The primary objective of this study was to demonstrate the contribution of ibuprofen to the overall and/or analgesic effectiveness of ibuprofen/ pseudoephedrine/ chlorpheniramine in relieving the symptoms of SAR. This study also determined: a) the minimum effective dose of the combination and b) the minimum effective dose of the antihistamine component of the combination.

Methodology:
This study was a multicenter, outpatient, multiple-dose, placebo controlled, double-blind, double-dummy, parallel group, randomized trial. Study participants were required to have: a) at least a two year history of seasonal allergic rhinitis, and b) a history of experiencing at least moderate headache, and/or facial pain/ pressure/ discomfort which worsened during the allergy season and responded to over-the-counter (OTC) analgesics (based on self report).

After receiving the first dose of study medication at the site, subjects then continued to dose with drug on an outpatient basis, approximately every 6 hours, 3 doses per day (morning, midday, evening) up to a total of 19- 21 doses over 7 days, regardless of the presence/absence of allergy symptoms. Two and three hours after taking the first dose, subjects assessed the severity of their allergy-associated pain. Prior to each subsequent dose of study medication, subjects indicated whether or not they were experiencing any allergy-associated headache and/or facial pain/ pressure/ discomfort. On the evening of Day 1 (prior to bedtime) and on each morning (upon awakening) and evening of Days 2-7, subjects provided a reflective assessment of the severity of the following allergy symptoms: nasal congestion, sneezing, rhinorrhea, itchy nose/throat/palate, itchy/watery/red eyes, and allergy-associated headache and/or facial pain/pressure/discomfort. On the evening of Day

7, after completing the reflective allergy symptom assessment, subjects provided an overall assessment of the study medication.

Efficacy evaluation

Primary Efficacy Parameter

- Change from baseline in the 7-day, overall average reflective total symptoms score (OATSS)

Key Secondary Efficacy Parameters

- The time-weighted sum of the pain intensity difference scores at two and three hours after the first dose of study medication (SPID3);
- Change from baseline (CFB) in the overall average reflective total antihistamine symptoms score (sneezing, itchy/watery/red eyes, itchy nose/throat/palate) – OATASS;

In order to protect against Type I error, comparisons were tested in sequential order. Each step had to be significant for the subsequent steps to be eligible for significance. The sequential order used was as follows:

1. a. The 2-caplet I/P/C combination vs. Placebo for SPID3 and OATSS
   b. The 2-caplet I/P/C combination vs. 1-tablet P/C for SPID3
2. The 1-caplet I/P/C vs. Placebo for SPID3, OATSS and OATASS
3. The 2-caplet I/P/C vs. 1-caplet I/P/C for SPID3, OATSS and OATASS

Comments: All quoted parts in this section are from synopsis of the sponsor's final report, but above sequence is from main contents of final report summarized by this reviewer because the sequence in the synopsis was different from the contents and specified in the protocol.

Efficacy Results:

A total of 1631 subjects were screened. Among those, 1070 subjects were enrolled and took at least one dose of study medication. A total of 957 subjects completed the study. One thousand forty four (1044) subjects were included in the ITT analysis of all efficacy variables (except SPID3). For the analysis of SPID3, a modified ITT population was used and consisted of 1032 subjects. All 1070 subjects were included in the safety analysis.

Comments: ITT analyses of efficacy variables are recommended to include all the 1070 subjects who were enrolled and took at least one dose of study medication. Sponsor also submitted the analysis results including all 1070 randomized subjects, and summarized in Table 1 of appendix. The analysis results based on all randomized subjects were verified by this reviewer's analyses with sponsor's submitted data, and the statistical comparison results (significant or not) agree with the results based on sponsor's restricted ITT.

The results for the primary efficacy parameter, key secondary parameters and other selected secondary variables are briefly summarized below:

- The 1-Caplet I/P/C and 2-Caplet I/P/C groups were each significantly better than placebo and the 1-Tablet P/C group for CFB OATSS, SPID3 and CFB OATASS. These results demonstrate the contribution of ibuprofen to the overall as well as the pain-relieving effects of the I/P/C combination;

- For the composite scores of all allergy symptoms and histamine-mediated symptoms, the 2-Caplet I/P/C group had numerically better scores than the 1-Caplet I/P/C group although a statistical trend was not established;
- Both doses of I/P/C yielded almost the same SPID3 scores;
- The P/C group was significantly better than the placebo group for both histamine-mediated and overall symptom composite scores. These data indicate that 2 mg chlorpheniramine is an effective antihistamine dose;

Comments:The last bullet does not have to be true, because the analysis result only shows that P/C 1-tablet treated group was significantly better than the placebo. To show the effectiveness of 2 mg of chlorpheniramine, P/C 1-table treated group need to show the significant difference from pseudoephedrine 30 mg treated group, which does not exist in this study.

Comments:Sponsor's efficacy results are based on sponsor's restricted ITT.

The detail results for efficacy parameters based on sponsor's restricted ITT are summarized in Table 3 and 4 of appendix, and based on real ITT (all randomized) are summarized in Table 5 and 6 of appendix. As shown, the statistical results (significant differences) are identical. Consistent results are also shown for the efficacy analysis based on evaluable groups, which is summarized in Table 7 and 8 of appendix.

2 3.4 STATISTICAL REVIEWER'S FINDINGS

1. Analysis results in sequential order

Sponsor defined the efficacy analysis in sequential order. Each step had to be significant for the subsequent steps to be eligible for significance. The statistical analysis results by steps are summarized in Table 2 of appendix. As shown in the table, I/P/C 2-caplet showed efficacy in pain and in allergic rhinitis comparing placebo, and also showed contribution of ibuprofen in pain. I/P/C 1-caplet showed efficacy in pain and in allergic rhinitis comparing placebo, however, analysis for contribution of ibuprofen was not included in the sequence of primary analyses.

2. Sensitivity of efficacy analysis for restricted ITT population

As mentioned in the comments of the above section, sponsor excluded some subjects from their ITT, and sponsor's primary analyses are based on this restricted ITT. However, ITT is expected to include all the patients who were randomized and took at least one study medication. Patient disposition is summarized in Table 1 of appendix, as shown, the proportion of exclusion are less than 4% which is pretty small. Table 3 and 4 of appendix is all the possible pairwise comparisons between treatment groups for SPID3, OATSS, and OATASS, based on sponsor's restricted ITT, and the table 5 and 6 of appendix is the same analyses based on true ITT (with all randomized and took medication) It is not surprise that the analysis results with true ITT (all randomized patients) are almost same as with sponsor's restricted ITT.

3. Key secondary analysis results

Table 3 and 4 of appendix shows all the possible pairwise comparisons between treatment groups for SPID3, OATSS, and OATASS. As shown, I/P/C 1-caplet treated group showed significantly better than P/C 1-tablet treated group for SPID3, and P/C 1-tablet showed significantly better than placebo treated group for OATSS and OATASS, but failed for SPID3. All these results support the contribution of ibuprofen in combined drug for two caplet.

For overall evaluation of study medication, Cochran-Mantel-Haenszel (CMH) test was used for pairwise comparison of the distribution of five categories from poor to Excellent between treatment groups. All the pairs among two I/P/C treated groups and one P/C treated group didn't show significant difference, but all these three groups showed significant different from placebo treated group.

2.4 CONCLUSIONS AND RECOMMENDATIONS

This NDA showed evidence of contribution of ibuprofen 400 mg for efficacy in relief of allergy-associated pain when they were added to a combination of pseudoephedrine hydrochloride 60 mg/ chlorpheniramine maleate 4 mg - two caplets. Note that one caplet contained 200 mg of ibuprofen, 30 mg of pseudoephedrine hydrochloride and 2 mg of chlorpheniramine maleate (I/P/C). Also, this three combination drug showed evidence of efficacy in relief of over all allergy symptoms and relief of allergy-associated pain for two different doses – one caplet and two caplets. However, a significant dose-response was not detected for any efficacy parameters between one caplet and two caplets of I/P/C treated groups.

Sponsor planned 3 steps of statistical comparisons. First step was to show the contribution of ibuprofen in allergy-associated pain by comparing two caplets of I/P/C and one tablet of P/C, and to show the efficacy of two caplets of I/P/C for relief of over all allergy symptoms and relief of allergy-associated pain by comparing two caplets of I/P/C and placebo. Second step was to show the efficacy of one caplet of I/P/C for relief of over all allergy symptoms and relief of allergy-associated pain by comparing one caplets of I/P/C and placebo. These first two steps were successively showed efficacy. The third step was to show the dose response by comparing 2 caplets of I/P/C and 1 caplet of I/P/C, but this step was failed.

2.5 APPENDIX

Table 1 Summary of subject disposition and completion

	Total	Placebo	I/P/C 1-cap	I/P/C 2-cap	P/C 1-tab
Randomized and received medication	1,070	265	263	269	273
Discontinued	113 (10.6%)	28 (10.6%)	27 (10.3%)	30 (11.2%)	28 (10.3%)
Reason for discontinuation					
Lost to follow-up	2 (0.2%)	0 (0%)	2 (0.8%)	0 (0%)	0 (0%)
Adverse event	18 (1.7%)	4 (1.5%)	3 (1.1%)	6 (2.2%)	5 (1.8%)
Treatment failure	5 (0.5%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)
Withdrew consent	1 (0.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Ineligible	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol violation	84 (7.9%)	22 (8.3%)	20 (7.6%)	21 (7.8%)	21 (7.7%)
Administrative/Other	3 (0.3%)	0 (0%)	1 (0.4%)	2 (0.7%)	0 (0%)
ITT[a]	1,044 (97.6%)	257 (97.0%)	256 (97.3%)	265 (98.5%)	266 (97.4%)
Modified ITT	1,032 (96.4%)	253 (95.5%)	254 (96.6%)	262 (97.4%)	263 (96.3%)
Evaluable subjects	989 (92.4%)	242 (91.3%)	244 (92.8%)	250 (92.9%)	253 (92.7%)
Modified evaluable subjects	999 (93.4%)	250 (94.3%)	244 (92.8%)	248 (92.2%)	257 (94.1%)

a. Sponsor's restricted ITT
Source: Table A.1 of ABC Tables of sponsor's submission

Table 2 Summary of efficacy analysis results by three steps (sponsor's restricted ITT)

Step	Efficacy Variable	Treatment Group	Mean (std)	P-value	Result	Interpretation
Step 1 a	SPID3	I/P/C 2-cap	2.80 (2.23)	<0.001	Signif diff	I/P/C 2-cap showed efficacy in pain
		Placebo	2.01 (2.09)			
	OATSS	I/P/C 2-cap	5.59 (3.47)	<0.001	Signif diff	I/P/C 2-cap showed efficacy in allergic rhinitis
		Placebo	3.80 (3.45)			
Step 1 b	SPID3	I/P/C 2-cap	2.80 (2.23)	<0.001	Signif diff	Ibuprofen showed contribution of efficacy in pain for I/P/C 2-cap
		P/C 1-tab	2.10 (1.99)			
Step 2	SPID3	I/P/C 1-cap	2.81 (2.49)	<0.001	Signif diff	I/P/C 1-cap showed efficacy in pain
		Placebo	2.01 (2.09)			
	OATSS	I/P/C 1-cap	5.43 (3.54)	<0.001	Signif diff	I/P/C 1-cap showed efficacy in allergic rhinitis
		Placebo	3.80 (3.45)			
	OATASS	I/P/C 1-cap	2.80 (1.87)	<0.001	Signif diff	
		Placebo	1.92 (1.83)			
Step 3	SPID3	I/P/C 2-cap	2.80 (2.23)	0.553	Failed	I/P/C 2-cap and I/P/C 1-cap didn't show any difference of efficacy in either pain nor allergic rhinitis
		I/P/C 1-cap	2.01 (2.09)			
	OATSS	I/P/C 2-cap	5.59 (3.47)	0.376	Failed	
		I/P/C 1-cap	5.43 (3.54)			
	OATASS	I/P/C 2-cap	2.87 (1.85)	0.390	Failed	
		I/P/C 1-cap	2.80 (1.87)			

P-values are from ANOVA with effects for treatment, baseline, and site
Source: Table B.2a, Table B.2b of ABC Tables of sponsor's submission

Table 3 Mean and Standard Deviation of Change from baseline of efficacy variables (sponsor's restricted ITT)

	PLB	I/P/C 1-cap	I/P/C 2-cap	P/C 1-tab
SPID3	(N=253) 2.01 (2.09)	(N=254) 2.81 (2.49)	(N=262) 2.80 (2.23)	(N=263) 2.10 (1.99)
OATSS	(N=257) 3.80 (3.45)	(N=256) 5.43 (3.54)	(N=265) 5.59 (3.47)	(N=266) 4.57 (3.29)
OATASS	(N=257) 1.92 (1.83)	(N=256) 2.80 (1.87)	(N=265) 2.87 (1.85)	(N=266) 2.39 (1.74)

Source: Table B 2a of ABC Tables of sponsor's submission

Table 4 P-Values of pairwise comparison between treatment groups (sponsor's restricted ITT)

	I/P/C 2-cap vs. PLB	I/P/C 1-cap vs. P/C 1-tab	I/P/C 1-cap vs. PLB	I/P/C 2-cap vs. I/P/C 1-cap	P/C 1-tab vs. PBO	I/P/C 2-cap vs. P/C 1-tab
SPID3	**<0.001[1a]**	<0.001	**<0.001[2]**	**0.553[3]**	0.583	**<0.001[1b]**
OATSS	**<0.001[1a]**	0.007	**<0.001[2]**	**0.376[3]**	0.009	<0.001
OATASS	<0.001	0.012	**<0.001[2]**	**0.390[3]**	0.003	<0.001

P-values are from ANOVA with effects for treatment, baseline, and site
1a, 1b, 2, and 3: Steps of sequential order of pairwise analyses
Source: Table B.2b of ABC Tables of sponsor's submission

Table 5 Mean and Standard Deviation of Change from baseline of efficacy variables (All randomized)

	PLB	I/P/C 1-cap	I/P/C 2-cap	P/C 1-tab
SPID3	(N=265) 2.01 (2.06)	(N=263) 2.80 (2.49)	(N=269) 2.78 (2.25)	(N=273) 2.09 (2.02)
OATSS	(N=265) 3.74 (3.43)	(N=263) 5.39 (3.60)	(N=269) 5.55 (3.48)	(N=273) 4.51 (3.32)
OATASS	(N=265) 1.88 (1.83)	(N=263) 2.78 (1.91)	(N=269) 2.84 (1.85)	(N=273) 2.36 (1.75)

Source: Table B.2a of Appendix X of sponsor's submission

Table 6 P-Values of pairwise comparison between treatment groups (All randomized)

	I/P/C 2-cap vs. PLB	I/P/C 1-cap vs. P/C 1-tab	I/P/C 1-cap vs. PLB	I/P/C 2-cap vs. I/P/C 1-cap	P/C 1-tab vs. PBO	I/P/C 2-cap vs. P/C 1-tab
SPID3	**<0.001[1a]**	<0.001	**<0.001[2]**	**0.499[3]**	0.601	**<0.001[1b]**
OATSS	**<0.001[1a]**	0.005	**<0.001[2]**	**0.371[3]**	0.014	<0.001
OATASS	<0.001	0.007	**<0.001[2]**	**0.372[3]**	0.006	<0.001

P-values are from ANOVA with effects for treatment, baseline, and site
1a, 1b, 2, and 3: Steps of sequential order of pairwise analyses
Source: Table B.2b of Appendix X of sponsor's submission

Table 7 Mean and Standard Deviation of Change from baseline of efficacy variables (evaluable group)

	PLB	I/P/C 1-cap	I/P/C 2-cap	P/C 1-tab
SPID3	(N=250) 1.99 (2.07)	(N=244) 2.83 (2.47)	(N=248) 2.81 (2.23)	(N=257) 2.12 (1.98)
OATSS	(N=242) 3.90 (3.43)	(N=244) 5.45 (3.54)	(N=250) 5.54 (3.43)	(N=253) 4.65 (3.23)
OATASS	(N=242) 1.97 (1.82)	(N=244) 2.80 (1.87)	(N=250) 2.84 (2.84)	(N=253) 2.42 (1.71)

Source: Table B 2a of Appendix IX of sponsor's submission

Table 8 P-Values of pairwise comparison between treatment groups (evaluable group)

	I/P/C 2-cap vs. PLB	I/P/C 1-cap vs. P/C 1-tab	I/P/C 1-cap vs. PLB	I/P/C 2-cap vs. I/P/C 1-cap	P/C 1-tab vs. PBO	I/P/C 2-cap vs. P/C 1-tab
SPID3	**<0.001[1a]**	<0.001	**<0.001[2]**	**0.565[3]**	0.523	**<0.001[1b]**
OATSS	**<0.001[1a]**	0.009	**<0.001[2]**	**0.633[3]**	0.016	<0.001
OATASS	<0.001	0.012	**<0.001[2]**	**0.632[3]**	0.009	<0.001

P-values are from ANOVA with effects for treatment, baseline, and site
1a, 1b, 2, and 3. Steps of sequential order of pairwise analyses
Source: Table B 2b of Appendix IX of sponsor's submission

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/s/

Suktae Choi
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Atiar Rahman
12/16/02 10:03:07 AM
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