CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-830

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA #: 20-829 and 20-830

AUG 16 1997

Applicant: Merck

Name of Drug: Singulair (Montelukast Sodium) 10mg Tablets and 5mg Chewable Tablets

Indication: Treatment of Symptoms of Asthma

Documents Reviewed: Volumes 1.1,1.2,1.96-1.114 of NDA 20-830 dated February 21, 1997

This review pertains to 3 studies in the treatment of asthma, two in adults (Studies 20 and 31) and the other in children 6 to 14 years old (Study 49); 2 studies in exercise induced asthma, one in adults (Study 42) and the other in children (Study 40) ; and one corticosteroid sparing trial in adults (Study 46). The 5mg montelukast chewable tablets were used in the studies in children. The study reports were presented in both submissions and, therefore, only the jackets of one submission were reviewed.

The medical officer of this submission is P. Honig, M.D. (HFD-570), with whom this review was discussed.

This review will mainly focus on the primary efficacy variables. The results of the secondary efficacy variables will be mentioned briefly to highlight the consistency of efficacy.

Methods of analyses were discussed in the sponsor's data analysis plans. The sponsor followed these plans in their study reports.

I. Study 20

A. Study Description and Method of Analysis

This study was an international multi-center, randomized, double blind, parallel group study in nonsmoking asthmatic patients 15 years of age or over with a FEV_1 between 50 and 85% of predicted normal and demonstrating reversibility of at least 15% with beta-agonist. Up to 25% of the patients were allowed concomitant use of theophylline.

There was a 2-week placebo run-in period, a 12-week treatment period and, for a subset of the patients, a 3-week placebo wash-out period. (Other non-placebo patients could go into a 9-month double-blind extension.) The purpose of the placebo washout period was to see how Montelukast patients responded when taken off drug. Patients during the placebo run-in period had to have a predetermined level of daytime symptoms (biweekly total score of at least 64) and daytime and nighttime beta-agonist use (weekly

average of at least one puff per day).

Clinic visits were every three weeks during the 12 week treatment period. An additional clinic visit was scheduled after three weeks for those patients who went into the placebo washout period. Spirometry measurements were obtained between 6 and 9 AM of each visit, approximately 8 to 10 hours after the previous bedtime dose.

Four daytime asthma symptom scores were assessed, at bedtime and before taking medication, on 7 point scales:

- How often did you experience asthma symptoms today?

0	1	2	3	4	5	6
None of the time						All of the time

- How much did your asthma symptoms bother you today?

0	1	2	3	4	5	6
Not at all bothered						Severely bothered

- How much activity could you do today?

0	1	2	3	4	5	6
More than usual activity						Less than usual activity

- How often did your asthma affect your activity today?

0	1	2	3	4	5	6
None of the time						All of the time

The daily daytime symptom score was determined by averaging the daily scores for the four questions. The average daytime symptom score for the visit was determined by averaging the daily symptom scores over all days between two consecutive visits.

Randomization was done by stratified randomization in each center. The two strata were theophylline users and non-users. Blocked randomization was used with a block size of 7 (three montelukast patients and two of both placebo and beclomethasone.) Patients without concurrent theophylline use were assigned the smallest patient numbers, while patients with concurrent theophylline were assigned the largest patient number available.

The primary efficacy variables were daytime asthma symptom scores and FEV$_1$ both averaged over the whole treatment period. Both efficacy variables had to be significant to declare efficacy. The primary efficacy variables were analyzed by an analysis of

variance with factors: treatments, centers and strata (theophylline users or non-users). Treatment-by-center and treatment-by-stratum interaction were tested by supplementary analyses.

B. Results

Eight hundred and ninety-five patients (257 placebo, 387 montelukast, and 251 beclomethasone) were randomized at 38 centers in 19 countries. About 10% of the patients were taking theophylline.

The 15 patients of study center 020-030 were not included in the intent-to-treat analyses because of Good Clinical Practice compliance issues. [This reviewer reran the primary analyses including this center. The exclusion of this center had negligible effect on the results of the study.] A further 10 patients were excluded from the intent-to-treat analysis of FEV_1 and 19 patients from the intent-to-treat analysis of daytime asthma symptom score because they either did not have baseline scores or on-treatment data.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Table 1 contains the percent changes from baseline for FEV_1 and p-values comparing treatments (average over the treatment period). Table 2 contains the mean average changes in daytime asthma symptom scores and the p-values comparing treatments. Montelukast was significantly better than placebo but less effective than beclomethasone for these parameters.

Significant results for both efficacy variables, not shown here, were also seen at the last on-treatment clinic visit.

Significance of montelukast over placebo and beclomethasone over montelukast were seen in most secondary efficacy variables, global evaluations and quality of life assessments.

The treatment-by-center and treatment-by-stratum interactions were not significant ($P>0.05$) for both primary efficacy variables. The treatment-by-gender interaction was also not-significant for ~~these variables~~.

C. Reviewer's Comments

This study showed efficacy of Montelukast in adults.

II. Study Protocol 31

A. Study Description and Method of Analysis

This study was similar to study 20 with the following exceptions. It did not contain Beclomethasone. Up to 25% of the patients were allowed concomitant use of inhaled corticosteroids rather than theophylline. Randomization was by blocked randomization in each center with a block size of ten (6 montelukast patients and 4 placebo patients).

B. Results

There were 681 randomized patients (273 placebo and 408 montelukast) at 52 U.S. centers who entered the study. About 23% of the patients were taking inhaled corticosteroids.

All randomized patients (N=2, one in each group) from center 031-028 were excluded from the intent-to-treat analyses because case report forms could not be verified (the center lost their copies and all source documents). These patients are not included in the 681 patients listed above. A further 5 patients were excluded from the intent-to-treat analysis of FEV_1 and 8 patients from the intent-to-treat analysis of daytime asthma symptom score because they either did not have baseline scores or on-treatment data.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Table 3 contains the average percent changes from baseline for FEV_1 over the whole treatment period and p-values comparing treatments. Table 4 contains the mean changes in daytime asthma symptom scores over the whole treatment period and the p-values comparing treatments. Montelukast was significantly better than placebo for these primary efficacy parameters.

Significant results for both efficacy variables, not shown here, were also seen at the last on-treatment clinic visit.

Significance of montelukast over placebo were seen in most secondary efficacy variables, global evaluations and quality of life assessments.

The treatment-by-center interaction was not significant ($P>0.05$) for both primary efficacy variables. The treatment-by stratum interaction was significant for daytime symptom score. The patients on corticosteroids showed only a small difference between treatments with a change of -0.24 for placebo and -0.29 for montelukast. Both users of corticosteroids and non-users showed comparable increases in FEV_1, however. The treatment-by-gender interaction was significant for FEV_1. Here the interaction

was a quantitative interaction with more increase over placebo in males 9.5% than females 7.2%.

C. Reviewer's Comments

This study showed efficacy in adults. If a patient is taking corticosteroid, efficacy might be limited to FEV_1, no effect in daytime asthma systems was demonstrated.

III. Study Protocol 49

A. Study Description and Method of Analysis

This study was similar to study 20 with the following exceptions. It was in children 6- to 14- years of age rather than adults. It was only 8 weeks rather than 12 weeks. This study used the 5-mg chewable tablets rather than the 10-mg tablets used with adults. Up to 40% of the children were allowed to continue on inhaled corticosteroids. The stratification factor was therefore corticosteroids use or non-use. The primary efficacy variable was defined to be FEV_1 only rather than both FEV_1 and daytime asthma score.

The daytime asthma score was defined differently also. The patient answered each of the following questions (based on symptoms since arising) by circling the most appropriate number:

- How much of the time did you have trouble breathing today?

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
0	1	2	3	4	5

- How much did your asthma bother you today?

Did not bother me	Bothered me a little	Bothered me somewhat	Bothered me a good deal	Bothered me very much	Bothered me as much as possible
0	1	2	3	4	5

- How much of the time did your asthma limit your activity today?

None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
0	1	2	3	4	5

B. Results

There were 336 patients (135 placebo and 201 montelukast) randomized into the trial. About 37% of the patients were on inhaled corticosteroids.

The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Five patients (2 placebo and 3 Montelukast) from center 049-032 were excluded because of significant deviations from good clinical practice. An additional 4 patients were excluded from the analysis of FEV_1 and an additional two patients from the analysis of asthma symptom scores because they either did not have baseline scores or on-treatment data.

Table 5 contains the percent changes from baseline for average FEV_1 and p-values comparing treatments. Montelukast was significantly better than placebo for this primary efficacy parameters. Table 6 contains the mean changes in average daytime asthma symptom scores and the p-values comparing treatments for this analysis. This difference was not significant. It should be emphasized that this was not a primary efficacy parameter in this study.

C. Reviewer's Comments

The evidence for efficacy is weaker here than in the adult studies. Since the FEV_1 measurements are at about 8 to 10 hours after dosing while the daytime asthma scores are at near the end of dosing interval, no end of dosing interval efficacy is demonstrated here. Less efficacy was seen in daytime asthma score in inhaled corticosteroid users (placebo mean change -0.11, Montelukast mean change -0.14) than in nonusers (placebo mean change -0.13, Montelukast mean change -0.22). Since the proportion of inhaled corticosteroid users was higher in this study than in the adult study (Study 31), this also may have caused the lack of overall efficacy in this parameter. [The daytime asthma scores are not equivalently defined, however.]

Some efficacy was seen in secondary measures: total daily b-agonist use and clinic assessed AM PEFR but not in nocturnal assessments and patient assessed AM PEFR.

IV. Study 42 - Exercise Induced Asthma

A. Study Design and Method of Analysis

This was a multi-center, placebo controlled, randomized, double blind, parallel group exercise challenge study with a one week

placebo run-in period, a 12 week treatment period, and a two week placebo washout period.

Two exercise challenges were held during the placebo run-in period. The patient had to demonstrate a post-exercise fall of at least 20% at both challenges. Exercise challenges were also done at weeks 4, 8 and 12 of treatment and after 2 weeks of placebo washout. The exercise challenge after two weeks of placebo washout was to test for persistence of effect.

The exercise challenge had a two minute or more warm up to obtain a targeted heart rate of 80 to 90% of age predicted maximum. This targeted heart rate was maintained for 6 minutes.

Spirometry was performed immediately after exercise and at 5, 10, 15,30, 45 and 60 minutes. If by 60 minutes the patient had not returned to within 5% of the pre-exercise level, an FEV_1 measurement was obtained at 75 minutes, and, if necessary, at 90 minutes. If the patient had still not returned to within 5% of the pre-exercise FEV_1, then rescue beta-agonist was given.

The primary efficacy variables in this study were $AUC_{0\text{-}60min}$ and Maximum Percent Fall in FEV_1. The sponsor considered $AUC_{0\text{-}60min}$ primary, while the medical officer considered Maximum Percent Fall in FEV_1 most important.

The primary analyses was endpoint changes from baseline with last value carried forward. To calculate $AUC_{0\text{-}60min}$ the last spirometry value at the clinic assessment was also carried forward.

The $AUC_{0\text{-}60min}$ was calculated as area below the pre-exercise FEV_1. If the FEV_1 went above pre-exercise FEV_1, no positive area was added.

The primary endpoints were analyzed by an analysis of variance with factors treatment and center. Treatment-by-center interaction was assessed in supplementary analyses.

The sponsor also analyzed $AUC_{0\text{-}60min}$ and Maximum Percent Fall in FEV_1 with a repeated measures (Weeks 4,8 and 12) mixed model.

B. Results

There were 110 patients (56 placebo and 54 montelukast) who entered the trial. The treatment groups were comparable at baseline in demographic and baseline efficacy variables.

Four patients(two in each treatment group) were excluded from the intent-to-treat analysis of the primary efficacy variables because they either had no baseline values or no on-treatment values and hence no changes from baseline could be obtained.

The table below shows the mean changes from baseline for the week 12 endpoint analysis of $AUC_{0-60min}$ of FEV_1. Montelukast showed significantly less decrease than placebo in the hour after exercise.

Analysis of $AUC_{0-60min}$ of FEV_1 (week 12 endpoint)
(Intent-to-treat)

Treatment	N	Mean(%*min)	Change from baseline at week 12		
		Baseline	Mean	SD	P-value
Placebo	54	1540.0	-99.2	983.4	
Montelukast	52	1397.6	-630.0	783.1	0.001

The table below shows the mean changes from baseline for the week 12 endpoint analysis of maximum percent fall in FEV_1. Montelukast showed significantly less of a fall in FEV_1 than placebo after exercise.

Maximum Percent Fall in FEV_1 (Week 12 endpoint)
(Intent-to-treat)

Treatment	N	Mear (%)	Change from baseline at week 12		
		Baseline	Mean	SD	P-value
Placebo	54	38.3	-5.90	14.61	
Montelukast	52	36.45	-14.12	12.56	0.003

The repeated measures analysis found no difference between the slope of the two treatments but a difference in intercept for both primary endpoints. The slope for both treatments looked to be zero, which means that the treatment difference at weeks 4, 8 and 12 were effectively constant and significant.

Fifty percent (26/52) of Montelukast patients were protected against a 20% drop in FEV_1 compared to 37% (20/54) of the placebo patients. This difference is not significant (p=0.177, binomial test).

Two weeks after cessation of treatment the montelukast parameter values approached the placebo values but did not exceed them. The

protection has worn off by two weeks after treatment.

C. Reviewer's Comments

This study showed an effect on AUC FEV_1 and max percent fall in FEV_1 but only 50% of the patients were protected against a 20% fall in FEV_1 on Montelukast. Whether such a protection percentage is adequate must be left to clinical judgement.

V. Study 040 - Exercise Induced Asthma

A. Study Design and Method of Analysis

This was a two period, randomized, double-blind, crossover exercise challenge study comparing montelukast 5-mg chewable tablet with placebo in children 6 to 14 years of age. There was a three day treatment period with the exercise challenge at the end of the third day. The exercise challenge was done 20 to 24 hours post-dose. There was a 4-day washout period between treatments.

Children were exercised on a treadmill for 6 minutes at a workload calculated to increase the patient's heart rate to approximately 160 to 190 beats per minute. This workload was used on all exercise challenges for that patient.

$AUC_{0\text{-}60\ min}$ and Maximum FEV_1 percent fall from pre-exercise challenge FEV_1 were analyzed by an analysis of variance with factors for centers, sequence, subjects within center-by-sequence, period and treatment.

B. Results

There were 27 children who entered the study. Two patients on placebo during the second period dropped out and did not perform an exercise challenge. Therefore the primary efficacy analyses included only 25 patients who took both treatments.

The table below provides the treatment means and p-values comparing treatments for the primary efficacy variables. Montelukast provided more protection against fall in FEV_1 than placebo.

Variable	Placebo Mean(SD) n=25	Montelukast Mean(SD) n=25	P-value
$AUC_{0\text{-}60\ min}$ FEV_1 (%*min)	-589.72 (705.27)	-264.60 (271.56)	0.013
Maximum % Fall	-26.11 (13.93)	-18.27 (12.54)	0.009

Sixty percent of the children were protected against a 20% drop in FEV_1 on Montelukast compared to only 40% while on placebo. This difference is not significant using McNemar's test.

No period or carryover effects were detected ($P>0.05$).

C. Reviewer's Comments

This study showed an effect on AUC FEV_1 and max percent fall in FEV_1 but only 60% of the patients were protected against a 20% fall in FEV_1 on Montelukast. Whether such a protection percentage is adequate must be left to clinical judgement.

VI. Study 046 - Corticosteroid Sparing Study

A. Study Description and Method of Analysis.

This was a high-dose inhaled corticosteroid study to investigate the ability of Montelukast to allow tapering of inhaled corticosteroids in asthmatic patients. It was a multi-center, double-blind, randomized, parallel group study with a one month single-blind placebo period where patients were tapered once or twice (at two week intervals) while maintaining FEV_1 at 90% or greater of their run-in baseline value (pre-study visit and visit 1 average). If the FEV_1 fell below 90%, the inhaled cortico-steroid was increased. The purpose of this run-in period was to handle the situation that the dose of corticosteroids that the patient was using might be higher than the patient needed to control his asthma.

Patients entered a pre-randomization baseline period during which baseline values of FEV_1, daytime symptom score and total daily inhaled beta-agonist use were determined. These three parameters were used to determine whether the patient's inhaled cortico-steroid dose would be tapered during the double-blind period.

The patients who entered the study were stratified into high and low dose groups with separate randomizations in each group within a center.

The inhaled corticosteroid tapering criteria depended upon a composite clinical score determined over the clinic visit for FEV_1 or the last 7 days for the two diary components. If pre-beta-agonist $FEV_1 \geq 90\%$ of pre-randomized baseline then 1 point was scored. If daytime symptom score $\leq 120\%$ of pre-randomized baseline, another point was added. If beta-agonist use $\leq 135\%$ of pre-randomized baseline, another point was added. If the composite score was 3, inhaled corticosteroid was tapered. If the composite score was 2, the dose was maintained. If the composite score was 0 or 1, the dose of corticosteroid was increased. The taper dose or dose increase in puffs/day were proportional to the

dosage of the inhaled corticosteroids in puffs per day that the patient was currently taking.

The primary efficacy variable was last dose of inhaled corticosteroid as a percent change from pre-randomized baseline dose. Since the patients were using a variety of inhaled corticosteroids, this variable is independent of the dosage of corticosteroid. (It is also why the dose increase or dose taper were proportional to the current dose taken.) This percent was analyzed by an analysis with factors for treatment, stratum and center. The treatment-by-stratum and treatment-by-center interactions were assessed in supplementary analysis and found to be not significant.

B. Results

The table below provides the mean percent changes in last tolerated dose of inhaled corticosteroids and p-value comparing treatments. Montelukast was able to reduce the inhaled corticosteroid dosages significantly more than placebo.

Percent Change from baseline Last Tolerated dose of inhaled corticosteroids (Intent-to-treat)

Treatment	N	Mean (mcg/day)	Percent Change from pre-randomized baseline		
		Baseline	Mean	SD	P-value
Placebo	113	1078.8	30.27	67.37	
Montelukast	112	975.9	46.73	62.22	0.046

C. Reviewer's Comments

This study demonstrated that Montelukast would provide some steroid tapering.

The tapering criteria allowed a patient to be slightly worse and still have the dosage of inhaled corticosteroid reduced. This may partially explain why the placebo patients were able to further reduce their inhaled corticosteroid from their baseline level even with the run-in tapering period.

VII. Overall Conclusions

Studies 20 and 31 showed efficacy of Montelukast in adults in AUC FEV_1 and daytime asthma score averaged over the treatment period.

Study 49 showed efficacy for AUC FEV_1 in children 6- to 14-years of age.

Both studies 31 and 49 showed almost no efficacy in daytime symptom score if patients were taking corticosteroid. This difference was not seen in AUC FEV_1. Both corticosteroid users and non-users increased their AUC FEV_1.

Both exercise challenge studies (Studies 40 and 42) showed efficacy for AUC FEV_1 and Maximum percent fall in FEV_1. However, only 50 to 60% of the patients were protected against a fall of 20% in FEV_1.

Montelukast showed steroid sparing ability in Study 46 where the mean reduction from baseline of corticosteroid dosage was 47% for Montelukast and 30% for placebo.

/S/

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Concur: Dr. Wilson /S/ 8/8/97

Dr. Nevius /S/ 8/16/97

This review contains 12 pages of text and 6 pages of tables.

cc:
Orig NDA 20-829
NDA 20-830
HFD-570
HFD-570/Dr. Honig
HFD-570/Ms. Trout
HFD-715/Div. File
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

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ON ORIGINAL

Table 1

Analysis of FEV1

Study 20

(Intention-To-Treat Approach)

Treatment	N	Mean (L)		Percent Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	249	2.21	2.23	1.07	15.87	0.71	(-2.27, 3.69)
Montelukast	375	2.16	2.32	7.49	17.01	7.35	(4.61, 10.08)
Beclomethasone	246	2.10	2.38	13.30	19.72	13.12	(10.06, 16.18)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	<0.001	6.64	(3.89, 9.38)
Beclomethasone vs Placebo	<0.001	12.41	(9.39, 15.44)
Montelukast vs Beclomethasone	<0.001	-5.78	(-8.53, -3.02)

p-Value For Effect	
Treatment	<0.001
Study center	<0.001
Stratum	0.751

Root MSE of Percent Change = 17.02

Table 2

Analysis of Daytime Symptom Score
Study 20

(Intention-To-Treat Approach)

Treatment	N	Mean (Score)		Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	245	2.40	2.14	-0.26	0.74	-0.17	(-0.30, -0.05)
Montelukast	372	2.35	1.85	-0.49	0.81	-0.41	(-0.53, -0.29)
Beclomethasone	244	2.38	1.68	-0.70	0.80	-0.62	(-0.75, -0.49)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	<0.001	-0.24	(-0.35, -0.12)
Beclomethasone vs Placebo	<0.001	-0.44	(-0.57, -0.31)
Montelukast vs Beclomethasone	<0.001	0.21	(0.09, 0.33)

p-Value For Effect	
Treatment	<0.001
Study center	<0.001
Stratum	0.410

Root MSE of Change = 0.73

Table 3

Study 31

Analysis of FEV1

(Intention-To-Treat Approach)

Treatment	N	Mean (L)		Percent Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	270	2.54	2.64	4.22	12.67	3.21	(1.45, 4.96)
Montelukast	406	2.47	2.78	13.05	13.84	12.10	(10.60, 13.61)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	<0.001	8.90	(6.84, 10.96)

p-Value For Effect	
Treatment	<0.001
Study center	0.359
Stratum	0.012

Root MSE of Percent Change = 13.28

Table 4

Analysis of Daytime Symptom Score

Study 31

(Intention-To-Treat Approach)

Treatment	N	Mean (Score)		Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	269	2.49	2.32	-0.18	0.59	-0.17	(-0.25, -0.08)
Montelukast	404	2.51	2.10	-0.41	0.69	-0.39	(-0.47, -0.32)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	<0.001	-0.23	(-0.33, -0.13)

p-Value For Effect	
Treatment	<0.001
Study center	0.119
Stratum	0.357

Root MSE of Change = 0.65

Table 5

Analysis of FEV_1

Study 49

(Intention-To-Treat Approach)

Treatment	N	Mean (L)		% Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	131	1.85	1.93	4.16	10.74	3.58	(1.29, 5.87)
Montelukast	196	1.85	2.01	8.71	12.54	8.23	(6.33, 10.13)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	<0.001	4.65	(1.92, 7.38)

p-Value For Effect	
Treatment	<0.001
Study center	0.849
Stratum	0.370

Root MSE of % Change = 12.05

Table 6

Analysis of Daytime Symptom Score
Study 49
(Intention-To-Treat Approach)

		Mean (Score)		Change From Baseline			
Treatment	N	Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	132	1.26	1.14	-0.12	0.55	-0.09	(-0.19, 0.02)
Montelukast	197	1.28	1.09	-0.19	0.58	-0.16	(-0.25, -0.07)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	0.273	-0.07	(-0.20, 0.06)

p-Value For Effect	
Treatment	0.273
Study center	0.714
Stratum	0.265

Root MSE of Change = 0.57