CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-829

MEDICAL REVIEW(S)

JAN 12 1998

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #:	20829	APPLICATION TYPE:	NDA
SPONSOR:	Merck	PROPRIETARY NAME:	Singulair®
CATEGORY OF DRUG:	LTD4 Antagonist	USAN / Established Name:	montelukast
		ROUTE:	oral
MEDICAL REVIEWER:	Honig	REVIEW DATE:	January 9, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
November 14, 1997	*November 17, 1997*	*Labeling*	*Proposed PPI*

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
February 21, 1997	NDA 20-830	Singulair Pediatric Indication

Overview of Application: see accompanying review

Outstanding Issues: Labeling

Recommended Regulatory Action: Recommended revisions to be forwarded to sponsor

New Clinical Studies: na Clinical Hold na Study May Proceed

NDAs:

Efficacy / Label Supp.: x Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 1/9/98

Medical Team Leader _____ Date: 1/12/98

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

7 pages

JAN 5 1998

MEDICAL OFFICER REVIEW

DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

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MEDICAL REVIEWER:	Honig	**REVIEW DATE:**	January 5, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
January 2, 1998	January 5, 1998	Response to IR	Infectious gastroenteritis

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
February 21, 1997	NDA 20-830	Singulair Pediatric Indication

Overview of Application: see accompanying review

Outstanding Issues: Labeling

Recommended Regulatory Action: Approval

New Clinical Studies: na Clinical Hold na Study May Proceed

NDAs:

Efficacy / Label Supp.: x Approvable Not Approvable

Signed: Medical Reviewer: /S/ **Date:** 1/5/98

Medical Team Leader: **Date:** 1/5/98

The fourteen (14) case report forms from the patients who reported to have 'infectious gastroenteritis' in Study 031 were requested and submitted by the sponsor. All fourteen of these patients received montelukast during the time period they reported the event. The sponsor was also asked to analyze these for any possible common denominator which may link the events to montelukast therapy.

The sponsor provided a table (attachment) describing the demographics of each patient, the location of the study site, the duration of the infectious gastroenteritis as well as other temporally associated adverse experiences. Of note it the fact that none of the diagnoses of infectious gastroenteritis were confirmed by laboratory data (e.g. stool cultures). In fact, all were self-diagnoses of mild to moderate events that were, by and large, self-limited while montelukast therapy continued. In no case did the event require the patient discontinue medication or participation in the study. The events were equally distributed by sex (7 men/7 women) and there was no clustering with regard to geographical region or center. There was also no report of associated nausea or vomiting.

A detailed review of the case report forms confirmed the sponsor's analysis. The events were generally mild to moderate, self-limited and were treated with over-the-counter medications (e.g. immodium A-D, pepto-bismol, alka-seltzer, etc.). Several of the patients had multiple episodes during the treatment period indicating that the event may not have been due to an infectious agent but rather to montelukast or concomitant medications. One patient (a 68 year old male: AN4586) had multiple exacerbations of gout requiring frequent treatment with probenecid which may have contributed to the gastrointestinal complaints of loose stools. Another patient (a 23 year old male: AN3985) had a severe enough case of gastroenteritis to require IV rehydration. None of the cases had remarkably abnormal clinical laboratories and all remained afebrile during the adverse events.

Reviewer comment: The overwhelming preponderance of infectious gastroenteritis reported by the montelukast treatment group in Study 031 is not easily explained. Although some of the cases may be due to viral agents or undiagnosed bacterial infection, some may also represent montelukast-induced gastrointestinal toxicity. It is reassuring that this appears to be a self-limited and mild event which is not associated with laboratory or vital sign abnormalities.

Reviewer recommendation: This adverse event should be discussed in the product label.

cc;
HFD-570 NDA20-829/Division file

HFD 570 /Honig
HFD 570 /Trontell
HFD-570/Chen
HFD 570/Williams
HFD 570/Kuzmik

Table 1

Review of Adverse Experiences of Infectious Gastroenteritis (Primary Study Protocol 031)

AN Number	Study Center	Age	Gender	City, State	Study Day Onset[1]	Duration (Days)	Date of Diagnosis	Method of Diagnosis	Stool Culture Performed	Case Report Form Entry	Nausea, Vomiting, Diarrhea, or Blood in Stool[2]	Other Temporally Associated Adverse Experiences
3952	031-005	34	F	San Diego, CA	7	16 hrs	April 23	Patient Reported	No	Stomach Flu	No	None
3956	031-005	60	F	San Diego, CA	43	10 hrs	May 18	Patient Reported	No	Stomach Flu	No	None
3980	031-009	39	F	North Dartmouth, MA	40	4	December 27	Patient Reported	No	Stomach Flu	No	Flu 12/17 to 12/22
3985	031-009	23	M	North Dartmouth, MA	84	2	March 7	Patient Reported	No	Flu, intestinal	No	None
4712	031-014	31	F	Albany, NY	26	6	April 14	Patient Reported	No	Acute Gastroenteritis	No	Headache 4/13 to 4/14 Face Rash 4/4 to 4/12
4051	031-017	20	F	Philadelphia, PA	83	2	January 29	Patient Reported	No	Stomach Virus	No	None
4110	031-022	18	M	San Diego, CA	49	2	February 22	Patient Reported	No	Stomach Flu	No	None
4137	031-024	50	F	Spokane, WA	66	8	March 10	Patient Reported	No	Flu (GI)	No	Sinus infection 3/10 to 3/22
4239	031-036	25	F	Aurora, CO	15	8	March 16	Patient Reported	No	Gastrointestinal Virus	No	URI 2/28 to 3/7
4266	031-038	16	M	San Diego, CA	68	2	June 12	Patient Reported	No	Stomach Flu	No	None
4363	031-048	31	M	Englewood, CO	13	2	December 25	Patient Reported	No	Stomach Flu	No	Sinusitis 12/6 to 12/13
4586	031-050	49	M	Sacramento, CA	16	3	April 6	Patient Reported	No	Stomach Flu	No	None
4668	031-054	35	M	Riverdale, GA	19	2	April 9	Patient Reported	No	Stomach Virus	No	Headache 4/11
4668	031-054	35	M	Riverdale, GA	38	2	April 28	Patient Reported	No	Stomach Virus	No	Headache 4/28 to 4/29
4367	031-049	15	M	Minneapolis, MN	6	2	December 12	Patient Reported	No	Stomach Flu	No	None

[1] Post-randomization

[2] Temporally associated adverse experiences reported on case report forms

JAN 5 1998

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DIVISION OF PULMONARY DRUG PRODUCTS (HFD-570)

APPLICATION #: 20829
APPLICATION TYPE: NDA
SPONSOR: Merck
PROPRIETARY NAME: Singulair®
CATEGORY OF DRUG: LTD4 Antagonist
USAN / Established Name: montelukast
ROUTE: oral
MEDICAL REVIEWER: Honig
REVIEW DATE: December 31, 1997

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
~~December 21, 1996~~ February 21, 1997	~~December 21, 1997~~ February	Original NDA application	
April 4, 1997	April 11, 1997	Information request response	
June 19, 1997	June 24, 1997	Four month safety update (SU-1)	
July 15, 1997	July 16, 1997	Information request response	
August 8, 11 and 29, 1997	—	DSI audit reports	
September 4, 1997	September 5, 1997	LTEUR (long term efficacy update report)	
September 29, 1997	September 30, 1997	Safety Update (SU-2)	
November 13, 1997	November 14, 1997	Information request response	
December 8, 1997	December 9, 1997	Information request response	
December 9, 1997	December 10, 1997	Information request response	
April 11, 1997	April 14, 1997	information request response	
May 1, 1997	May 2, 1997	information request response	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
February 21, 1997	NDA ~~20-830~~	Singulair Pediatric Indication

Overview of Application: see accompanying review

Outstanding Issues: Labeling

Recommended Regulatory Action: Approval

New Clinical Studies: na Clinical Hold na Study May Proceed

NDAs:

Efficacy / Label Supp.: x Approvable _____ Not Approvable

Signed: Medical Reviewer: /S/ Date: 12/31/97

Medical Team Leader: Date: 1/5/98

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Executive Summary of Safety and Efficacy

Montelukast is a selective LTD4 leukotriene antagonist developed by Merck for the maintenance treatment of asthma and proposed to be marketed under the tradename Singulair®. In support of approval, Merck has conducted an extensive clinical pharmacology and Phase 2b/3 efficacy and safety evaluation program. Adequate dose-ranging studies have been conducted allowing selection of a dose of 10 mg once daily in the evening to be evaluated in Phase 3. Double-blind studies versus placebo support the proposed dose and dosing interval and confirm the efficacy of montelukast as maintenance therapy in chronic asthma. Onset of action occurs within one day of treatment for the clinical endpoints of daytime symptoms, rescue beta-agonist requirements, morning peak expiratory flow rates, and nocturnal asthma scores. First dose bronchodilatory effects (i.e. FEV1) were not evaluated in Phase 3 studies; however, data from earlier studies indicate that the first dose effect on FEV1 is not clinically meaningful. No rebound phenomenon exists and patients generally return to pretreatment baselines within 2 weeks after withdrawal of montelukast therapy. Importantly, montelukast does not significantly impact on adult asthma-specific quality of life (QOL) evaluations. Data from a study involving an active comparator as well as placebo indicate that inhaled beclomethasone dosed at 400 mcg per day is statistically superior to montelukast and placebo for the endpoints of FEV1 and daytime symptoms. Clinically significant improvements over placebo as measured quantitatively by a minimal important difference indicates that beclomethasone, but not montelukast, is superior to placebo for overall quality of life and the individual QOL domains of activity, symptoms, and emotions.

Montelukast is effective in asthmatic patients with demonstrated aspirin sensitivity; however, it has not been shown to be of more value (i.e. enhanced efficacy) in these patients than in the population of general asthmatics. Importantly, montelukast has not been demonstrated to truncate the response to aspirin challenge in these patients and, consequently, allow such patients to receive aspirin or other non-steroidal antiinflammatory agents. As such the EIB trials serve as additional evidence of the efficacy of montelukast in the control of asthma and the proposed dosing interval for montelukast but do not provide adequate support for a labeled EIB indication.

Montelukast is not effective as monotherapy in truncating exercise-induced exacerbations of asthma. Montelukast was effective in shifting the population response to exercise; however, it did not truncate a significant decrement in maximal FEV1 in response to exercise in the majority of patients.

An inhaled corticosteroid-sparing trial was conducted and had serious design flaws which make the quantitative treatment differences in the primary endpoint difficult to interpret from a clinical perspective. The study does, however, serve as a bioassay demonstrating the effect of montelukast in allowing the taper of inhaled corticosteroids. Whether the results of this study are generalizeable to the population of asthma on high dose inhaled or systemic corticosteroids who may be the real beneficiaries of an agent that allow steroid tapering is not known. Another trial evaluated the effects of adding montelukast to or substituting montelukast for low-dose inhaled beclomethasone dosed at 400 micrograms per day. The findings of this study indicate that adding montelukast to the regimen significantly improved FEV1 and morning peak expiratory flow rates. The combination, however, was not statistically superior to beclomethasone alone as represented by daytime asthma symptoms, rescue beta-agonist requirements and nocturnal asthma scores. The study also demonstrated that is better to leave patients on beclomethasone than to switch them to montelukast. The results of this study confirm the finding that low dose beclomethasone dosed at 400 micrograms per day is more effective than montelukast in the treatment of mild to moderate asthma.

The safety of montelukast has been supported in extensive short and long-term clinical evaluations. Two thousand six hundred and six subjects or patients received montelukast, some for periods as long as two years or more. As predicted by preclinical studies, the clinical toxicity profile of montelukast focuses on the gastrointestinal system. Clinical adverse events including gastritis, diarrhea, vomiting, nausea, abdominal pain, and dyspepsia are reported at a higher frequency in montelukast treatment groups. The frequency of infectious gastroenteritis is statistically significantly higher in the montelukast treatment group than in the placebo or beclomethasone treated patients. Most of the reports of this finding are from one clinical trial and a satisfactory explanation of this phenomenon is not apparent from the data provided. It might be considered that modulation of leukotrienes may alter patient's resistance to infection; however, the frequency of infection in other organ system is not higher in the montelukast treated population. Extensive laboratory evaluation in double-blind and open-label extension periods again reveals the montelukast treated patients to have a higher frequency of elevated serum transaminases. Sensitivity analyses indicate that these elevations are, for the most part mild (less than three times the upper limit of normal) and normalize with continued therapy. There was no evidence of drug-induced hepatitis in any patient receiving montelukast. Importantly, available data from the long-term extension studies demonstrate that the frequencies of montelukast associated toxicities decrease with time providing some reassurance that the toxicity profile of montelukast is not related to the cumulative dose received. Montelukast does not appear to have an effect on cardiac electrophysiology. No evidence of Churg-Strauss syndrome or eosinophilic variants were noted. Given the rarity of the event in the population and the experience with another marketed LTD4 antagonist, this is not surprising. The phenomenon appears to manifest in the context of systemic steroid tapering in more severe asthmatics. This was not the population studied in the NDA. In conclusion, montelukast appears to be safe at the proposed dose for marketing.

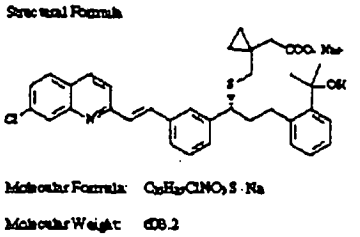
1.0 Introduction

Merck Laboratories has developed montelukast under the tradename Singulair® as a selective leukotriene antagonist for use in the treatment of asthma.

1.1 Proposed Indication

Singulair is indicated in adult and pediatric patients 6 years of age and older for the prophylaxis and chronic treatment of asthma.

1.2 Molecular Structure



Montelukast is administered only as the R-enantiomer.

1.3 How Supplied

10 mg film coated tablets (beige) and 5 mg (pink, cherry-flavored) chewable tablets.

1.4 Proposed Dose

For adults and children older than 15 years of age: 10 mg once daily at bedtime without regard to meal.

For children 6 to 14 years of age: 5 mg chewable tablet once daily at bedtime without regard to meals.

2.0 Reviewer Approach and Notations Used in Review

The medical officer NDA review started with an overall appraisal of the content and format of the application and sponsor-proposed labeling. This allowed targeting of specific studies for detailed review as well as DSI auditing sites. The following studies were reviewed in detail and categorized in the review document as follows.

Placebo-controlled studies in chronic asthma: Studies 020 and 031.

Placebo-controlled study in aspirin-sensitive asthmatics: Study 015.

Inhaled corticosteroid trials in chronic asthma: Studies 046 and 029.

Exercise-induced bronchospasm study: Study 042.

In addition to the review of the efficacy data for the aforementioned 'pivotal' studies, selected data from the NDA was cross-referenced to available case report forms (CRFs) and is documented within each study review. Additional supportive studies supporting the dose in

Phase 3 and investigating the effect of montelukast on cellular markers of inflammation and exercise induced bronchospasm were reviewed in less detail and include Studies 009, 013, 025, 028, 056, and 059. The reviews of the pediatric efficacy trials were performed by another medical officer and are contained in a separate review. On completion of the efficacy review of the individual studies, a review of the integrated summary of safety was conducted. Throughout the review, data presentations are referenced to the corresponding source by the notation [Volume:Page].

3.0 Clinical Pharmacokinetics [57:46-129]

Montelukast is administered as the R-enantiomer and does not appear to undergo chiral inversion. Montelukast is rapidly absorbed with an absolute bioavailability (F) in the range of 0.7 (70%). Mean maximum plasma concentrations for the 10 mg tablet range from 0.33 to 0.54 mcg/mL at 3-4 hours (Tmax) after oral administration. Pharmacokinetics appear to be linear in the range of doses studied (up to 200 mg). No difference in pharmacokinetics was noted between dosing in the morning or the evening. Co-administration with food (high-fat breakfast or evening snack) do not appear to alter the exposures over a dosing interval ($AUC_{0\text{-}24hrs}$); however, they do prolong the Tmax and decrease the maximum concentrations (Cmax). Montelukast pharmacokinetics did not appear to be affected by gender; however, in healthy elderly, the plasma clearance of montelukast was slower (31 mL/min) compared to healthy young adults (45 mL/min). Montelukast is extensively protein bound (99.5%) and the steady state volume of distribution ranges from 8 to 11 liters. Montelukast is extensively metabolized with all identified metabolites being excreted in the bile. Following a radiolabeled oral dose of montelukast, 86% of the radioactivity was recovered in the 5 day fecal collections and <0.2% was recovered in urine. In vitro metabolism studies indicate that montelukast is oxidized by the P450 system. Cytochrome P450 3A4 is involved in the 21-OH metabolite while cytochrome P450 2C9 contributes to the formation of the 36-OH metabolite. These are the predominant metabolites found in vivo and the only metabolites found circulating in plasma. In patients with mild-to-moderate hepatic insufficiency, the montelukast clearance is decreased (27 mL/min). The pharmacokinetics of montelukast in patients with renal insufficiency was not studied. In vitro interaction studies also indicate that therapeutic concentrations of montelukast would not be expected to inhibit the metabolism of other drugs biotransformed by isoenzymes 3A4 (e.g. terfenadine), 2C9 (e.g. losartan), 1A2 (e.g. theophylline), 2C19 (e.g. omeprazole) or 2D6 (e.g. tricyclic antidepressants). In vivo interaction studies conducted with montelukast doses to steady-state indicated that no clinically significant interactions exist with oral contraceptives, oral/IV corticosteroids, theophylline, warfarin, digoxin, terfenadine or carboxyterfenadine.

4.0 Clinical Pharmacology and Rationale for dose-selection in Phase 3 studies

Clinical pharmacology proof-of-principle LTD4 challenge trials (Studies 005 and 011) suggested montelukast could be dosed once daily [61:1555 and 63:2793]. The selection of the specific montelukast dosage for use in the Phase 3 clinical program was primarily based on two Dose-Ranging studies and the Low–Dose-Ranging Exercise Study (Studies 028, 009, and 025). These studies identified a minimal dose which provided statistically significant improvement in both measures of airway obstruction and patient-reported outcomes in chronic asthma, as well as attenuation of EIB at the end of the dosing interval. Bedtime dosing strategy was used to provide near maximal montelukast plasma levels (4 to 7 hours after dosing in an attempt to address the diurnal variability in asthma although no studies comparing morning and evening dosing were conducted. The pediatric (6 to 14 year olds) dose was selected by identifying the chewable tablet dose yielding a comparable single-dose pharmacokinetic (AUC) profile to the adult dose. The studies supporting the dose, dose interval, and time of dose administration for montelukast in the adult and pediatric programs are summarized below.

4.1 Pharmacodynamic Studies (Inhaled LTD4 Challenge Studies)

Two inhaled LTD4 challenge trials (Studies 005 and 011) demonstrated the action of montelukast in the airways of asthmatic patients. In one study (Protocol 005), a 5-mg capsule dose of montelukast, with the challenge performed at peak plasma concentrations (4 to 7 hours after dosing), caused a >85-fold median shift in the concentration of LTD4 required to cause a 50% fall in specific airway conductance versus placebo [61:1707]. In a second study (Protocol 011), a >56-fold median shift versus placebo was observed 20 to 24 hours after a 40-mg dose (capsule formulation) [62:2636]. These mechanism of action trials served as 'proof-of-principle' and indicated there was prolonged (24 hour) activity with montelukast and suggested the potential for clinical effect with a once-daily dosing interval.

4.2 Dose-Ranging Studies:

The first dose-ranging trial (Study 009) was a 6-week, double-blind, placebo-controlled, parallel-group study in mild to moderate asthmatics in which montelukast was evaluated over several doses and dosing intervals (10, 100, 200 mg once daily in the evening; 10 and 50 mg twice daily). Compared with placebo, montelukast at doses as low as 10 mg once daily demonstrated statistically significant improvements in measures of airway obstruction and patient-reported endpoints [73:9066]. In spite of a 5-fold difference between treatment groups in mean plasma concentrations (measured 12 hours after dosing), all dosing regimens appeared to be comparably effective on the key endpoints (AM FEV1, AM PEFR, b-agonist use, and daytime symptom score)

The results of this trial are summarized in the table below [73:9132].

Treatment	*n*	*AM FEV1 (% change)*	*AM PEFR (L/min)*	*Beta-agonist use (puffs/day)*	*Daytime Symptom Score (0-6 scale)*
Placebo	58	3.26	0.18	-0.18	-0.20
10 mg once daily	57	11.18	12.35	-1.22	-0.39
100 mg once daily	56	11.60	25.59	-1.25	-0.46
200 mg once daily	61	10.98	23.77	-1.13	-0.26
10 mg twice daily	54	12.05	15.74	-0.93	-0.31
50 mg twice daily	57	9.41	13.57	-1.16	-0.32

Based on these data, once-daily dosing was considered appropriate; however, a dose-response relationship was not established. Of note, Study 009 was the only study that evaluated the first dose bronchodilatory effect of the to-be-marketed dose (i.e. 10 mg once daily) and formulation of montelukast. FEV1 was measured 60 and 120 minutes after dosing. No statistically significant difference from placebo was noted at either timepoint. After two hours the mean FEV1 percent change from baseline was 14.04 for montelukast and 7.55 for placebo (p=NS). There was no dose response for magnitude of FEV1 response in this study. Two additional studies (Protocols 025 and 028) were conducted to evaluate the effect of lower doses of montelukast. These simultaneous dose-ranging studies were undertaken to verify that improvement in both chronic asthma (Protocol 025) and exercise-induced bronchospasm (Protocol 028) occurred throughout and persisted to the end of the proposed dosing interval. Study 025 compared the effects of montelukast (2, 10, and 50 mg once daily at bedtime) with placebo in mild to moderate asthmatics over a 3-week treatment period in a parallel-group design. Significant effects on measurements of airway obstruction (i.e., AM and PM PEFR and AM FEV1) were observed throughout the dosing interval. No dose-response relationship was observed for this endpoint. However, on parameters of daytime symptoms, beta-agonist use, asthma exacerbation rates, and asthma-specific quality of life, 2 mg was not significantly different from placebo while 10 and 50 mg were statistically significant compared with placebo and numerically similar to each other. The results of this study are summarized in the table below [77:11884]. Data are analyzed as the average over the treatment period.

Treatment	n	AM FEV1 (%)	AM PEFR (L/min)	Daytime Symptoms	Beta-agonist use (puffs/day)
Placebo	69	4.9	3.5	-0.10	-0.24
2 mg once daily	72	13.6*	21.6*	-0.31	-0.82
10 mg once daily	68	12.3*	22.8*	-0.38*	-1.10*
50 mg once daily	72	12.0*	18.0*	-0.42*	-0.93*

*Indicates p<0.05 compared to placebo.

Study 028 examined the ability of montelukast (0.4, 2, 10, and 50 mg once daily at bedtime), compared with placebo, to inhibit EIB in mild to moderate asthmatics, at the end of the dosing interval, after two doses in an incomplete block crossover design. The table below shows both the 10- and 50-mg doses produced a similar response ($AUC_{0\text{-}60\ min}$ and time to recovery), while the 0.4- and 2-mg doses had less effect [65:4524].

Treatment	n	AUC0-60 min (%-min)	Maximal FEV1 Fall (%)	Time to Recovery (min)
Placebo	22	-1193.1	-29.2	48.3
0.4 mg once daily	23	-927.0	-25.2*	44.7
2 mg once daily	20	-987.5	-24.4*	43.6
10 mg once daily	21	-714.7*	-20.9*	34.2*
50 mg once daily	22	-637.0	-21.6*	27.4*

*indicates p<0.001 versus placebo.

The end of dosing interval response to the 10-mg dose in Study 028 was similar to that observed in Study 013 which was a placebo-controlled, three-period, crossover EIB study that investigated montelukast doses of 50 and 100 mg administered twice daily [63:3177]. The results are summarized in the table below.

Treatment	n	AUC0-60min (%-min)	Max FEV1 Fall (%)	Time to Recovery (min)
100 mg BID	14	-368.3*	-14.0*	25.7*
50 mg BID	14	-386.7*	-17.1*	20.7*
Placebo	14	-1166.3	-29.6	67.1

*indicates p<0.001 versus placebo.

In summary, the 10-mg once-daily bedtime dose of montelukast was identified from the dose-ranging studies as the lowest dose producing clinical and statistical significant improvement in both measures of airway obstruction and patient-reported endpoints in chronic asthma as well as attenuation of EIB. The 10-mg dose had a significant effect at the end of the dosing interval in both chronic asthma (PM PEFR) and EIB (inhibition of EIB). There were no dose-limiting toxicities detected (see ISS review). Therefore, the 10-mg once-daily bedtime dose was selected for the adult Phase 3 studies.

5.0 Efficacy

5.1 Placebo-controlled studies in chronic asthma:

Two primary Phase 3 studies were conducted (Studies 020 and 031). The were identical in design, patient selection, and analysis except that Study 020 contained an inhaled beclomethasone treatment arm in addition to placebo. The protocols for both studies are summarized below.

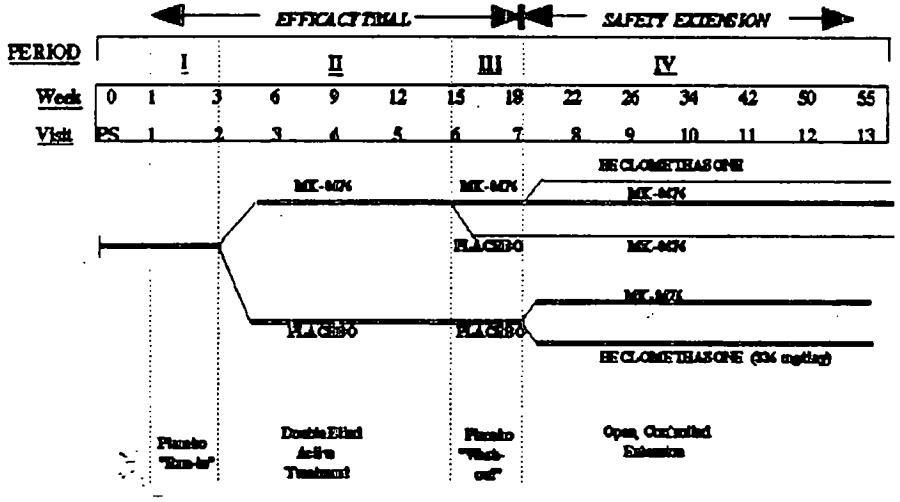
5.1.1 Protocol Summaries

5.1.1.A Study 031 [81:14303]: A Multicenter, Double-Blind, Randomized, Parallel-Group Study Comparing the Clinical Effect of Montelukast to Placebo in Patients with Chronic Asthma.

This study had several objectives including the safety assessment of montelukast over a one year treatment period as well as determining the efficacy of the drug compared to placebo over a 12 week double blind period. Additionally, the clinical effects after the withdrawal of therapy was assessed in a subset of patients.

In order to achieve these objectives non-smoking male and non-pregnant female asthmatics between the ages of 15 and 85 were eligible to enter into a single-blind 2-week placebo run-in period. In order to qualify for the study, each patient must have had a one year history of asthma, have a percent predicted FEV1 between 50 and 85% and demonstrate reversible airway obstruction (i.e., 15% increase or greater after inhaled albuterol). Furthermore, in order to qualify for randomization at the end of the run-in period, the patients must have demonstrated minimal daytime asthma symptoms (weekly score of 32 (see symptom scoring below) or above and a daily mean beta-agonist use of one puff per day or greater. Up to 25% of study patients were allowed to be maintained on stable daily inhaled corticosteroid regimens. Usual exclusion criteria were employed. Pulmonary disease or asthma requiring ER visit (one month or less prior to study) or hospitalization (three months prior to study) as well as URI within three weeks and clinically significant sinus disease were grounds for exclusion. Patients with other clinically significant medical or psychiatric condition were similarly excluded. Patients taking oral, IV or IM corticosteroids, cromolyn/nedocromil, theophylline, oral or long acting inhaled beta-agonists or anticholinergics within acceptably defined washout periods were ineligible. Other specifically prohibited concomitant medications included warfarin, digoxin, antibiotics, terfenadine/astemizole/loratadine and OTC products containing caffeine, theophylline or beta-agonists. Inhaled albuterol (90ug/puff) was provided and was used as-needed throughout all periods of the study.
The study is divided into four periods and is summarized in the figure below.

Study Design Schematic



Data Source: [3.2]

Period I is the aforementioned 2-week single-blind, placebo run-in. Period II is the twelve-week, double-blind, period in which eligible patients were randomized to montelukast 10 mg per day or placebo. During this period, patients were scheduled to return to clinic every three weeks after randomization for efficacy and safety evaluations. Upon completion of this period, a prespecified, random subset of patients (~40) from the montelukast-treatment group entered a three week double-blind washout period. The other patients who received montelukast and those patients who received placebo during Period II entered a 37 week open-label extension period

(Period IV). Patients were not to be told that he/she was entering the treatment period at this time. All patients receiving montelukast in Period II received montelukast in Period IV. Those patients who received placebo in Phase II were divided into two equal groups and received either montelukast or inhaled beclomethasone (eight puffs per day). Those patients who used inhaled CS during Period II continued on their usual dose if allocated to the beclomethasone treatment group. Visits during this period occurred at 28-60 day intervals.

The schedule of activities that occur at each visit are summarized in the table below.

Schedule of Clinical Observations and Laboratory Measurements

	Blinded Efficacy Trial								Open, Controlled Safety Extension[1]						
Periods →		I	II					III	IV						
Weeks →	0	1	3	6	9	12	15	18	22	26	34	42	50	55	
Visits →	Pre-study	1	2	3	4	5	6	7	8	9	10	11	12	13	D
Informed consent	X						X[2]								
Inclusion/exclusion review	X	X	X												
Baseline clinical history	X														
Patient demonstrates competence on study procedures		X	X												
Quality-of-life questionnaire (HRQL)			X	X			X								X
Review concomitant therapy and adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (sitting BP, HR, RR, and oral temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety tests (blood, urine)[3]	X		X	X	X		X	X		X		X		X	X
Serum β-hCG pregnancy test (all females)	X						X	X[4]		X				X[4]	X[4]
Urine β-hCG pregnancy test (all females)			X	X	X	X			X		X	X	X		
Plasma for archive			X	X			X					X			
Complete physical examination	X							X						X	X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
β-agonist reversibility	X	X	X		X		X				X			X	X
ECG (12-lead)	X							X						X	X
Tablets/inhalers: Dispensed[5]		X	X	X	X	X	X	X[6]	X	X	X	X	X		
Returned/counted			X	X	X	X	X	X	X	X	X	X	X	X	X
New diary card: Dispensed	X	X	X	X	X	X	X	X[6]	X	X	X	X	X		
Collected/reviewed		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray or report reviewed (required if entering Period II and x-ray not performed within the past 12 months)		X													
Patient Global Evaluation							X								X
Investigator Global Evaluation							X								X

[1] Patient did not exercise vigorously (brisk walk) for at least 3 days prior to visits.
[2] Beclomethasone inhaler, instead of montelukast tablets, was dispensed from Visit 7 through Visit 12 only to patients allocated to this treatment in Period IV.
[3] For patients participating in the extension period.
[4] Serum β-hCG was tested 14 days after Visit 7 (if not entering the extension), Visit 13, or Visit D.
[5] For entry into extension study.
[6] The open, controlled safety extension (Period IV) is not addressed in this report.

Data Source: [32]

In addition to data collection at scheduled visits, patients were asked to keep a daily diary in which they recorded and scored daytime asthma symptoms. The following questions were answered on a 0 to 6 scale.

-How often did you experience asthma symptoms today? (0= none, 6= all)
-How much did your asthma symptoms bother you today? (0=not at all, 6= severely)
-How much activity could you do today? (0=more than usual, 6= less than usual)
-How often did your asthma affect your activities today? (0=none, 6=all the time).

Patients were also asked to record the total number of puffs of albuterol used during the day, the AM PEFR, the pre-bedtime PEFR and the overnight asthma symptom score. In order to address this last parameter the patient answered the question "Did you wake up with asthma?" and quantify the number of puffs of albuterol used since going to bed. PEFRs were recorded as the best of three efforts.

Reviewer note: The aforementioned questions that comprise the Daytime Symptom Score are not independent of one another. In essence, they are asking the same question four different ways. This is not a particular problem because they were analyzed as a composite averaged score on a 0-6 scale. This methodology was used in all montelukast trials. It may be important, however, to define the Daytime Symptom Score components in labeling and promotional materials.

Two primary endpoints were designated in the protocol: a) FEV1 assessed at each clinic visit and b) daytime asthma symptom scores, as recorded on the daily asthma diaries. Secondary endpoints were: c) daily PEFR, d) daily inhaled beta-agonist use, and e) nighttime awakenings, all as recorded on daily diary card. Other endpoints included: physician's global assessment,

self-administered asthma-specific quality of life (Juniper et al, Thorax 1992;47:76 and Am Rev Resp Dis 1993;147:832), number of asthma attacks, exacerbations and patient discontinuations due to asthma, and the amount/need for rescue medication. An "exacerbation of asthma" was explicitly defined as one occurrence of any one of the following:

-decrease from baseline in bedtime PEFR of more than 20%
-AM PEFR less than 180 L/min
-Increase in beta-agonist use of more than 70% (or at least 2 puffs)
-Increase in baseline symptom score of more than 50%
-Awake all night
-Asthma attack resulting in an unscheduled visit to the doctor's office, ER or hospital, or treatment with oral corticosteroids.

An intent-to-treat analysis (all patients as randomized with post-baseline data) and a 'per protocol' approach which excludes patients with important protocol deviations were predefined. For the primary endpoints, the average response over the entire treatment period will be compared to placebo and tested at the p=0.05 level for both endpoints (FEV1 and Daytime Symptom Scores). Secondary endpoints were to be analyzed in the same manner.

The data analysis plan (protocol addendum, [81:14403]) contained ground rules for analysis and data point definitions, for this study and all Phase 3 trials described in this review, which deserve mention. As stated before, the ITT analysis includes all patients who have a baseline value and at least one post-treatment measurement. All measurements are used including data collected at discontinuation and unscheduled visits. For the endpoint of daily beta-agonist use, the patient needs to have both the daytime and evening time beta-agonist use recorded in order to have a total daily beta-agonist use. Only those patients whose baseline values of at least 0.5 puffs/day will be included in the percent change from baseline analyses.

The following rules apply to data point definitions for daily symptom scores. For Daytime Symptom scores, patients should have at least 2 (of 4) individual questions scores on a given day to register a score for that day. Patients should have at least 7 (of 21) to have a visit average for the following visit or 5 daily scores between the two biweekly visits or 3 daily scores between the two weekly visits.

For total daily beta-agonist use, patients should have both the daytime and the evening use recorded as above to have a total daily total and should have the same number of total daily recordings as required above to have a valid average interval assessment. The same rules apply for AM and PM PEFRs

If unallowed steroid, cromolyn or nedocromil rescue occurred; efficacy data collected during and within 21 days of the last day of rescue will be excluded. Other unallowed rescue medication will exclude the subsequent 7 days of efficacy data.

For all efficacy endpoints, the average Period I value will be defined as the baseline. Week 12 endpoints will be calculated using a Last Observation Carried Forward (LOCF) approach. The 'overall' result is defined as the average of all available data obtained throughout the trial. For laboratory parameters, the last value during Period I prior to randomization will be defined as baseline.

For Study 031, prospectively performed power and sample size analyses predicted that a sample size of 500 (300 montelukast/200 placebo) patients would be required to demonstrate statistically significant differences. For FEV1, this represented 95% power to detect a difference of 5.4 L/min between study groups assuming a variability of 16.5% (SD). To that end, the sponsor planned to enroll approximately 900 patients at 45 centers in Phase I of the study. This will allow for approximately 630 patients to enter into Phase II (15 patients/center). Randomization was performed centrally and patients were randomized into one of four groups in blocks of 25 (Appendix 3.8, [81:14764]) as shown in the table below. [81:14333]).

Group	Period I	Period II	Period III	Period IV	# Patients
1	Placebo	Montelukast	Montelukast	Montelukast	240
		—		Beclomethasone	20
2	Placebo	Montelukast	Placebo	Montelukast	40
3	Placebo	Placebo	Placebo	Beclomethasone	100
4	Placebo	Placebo	Placebo	Montelukast	100

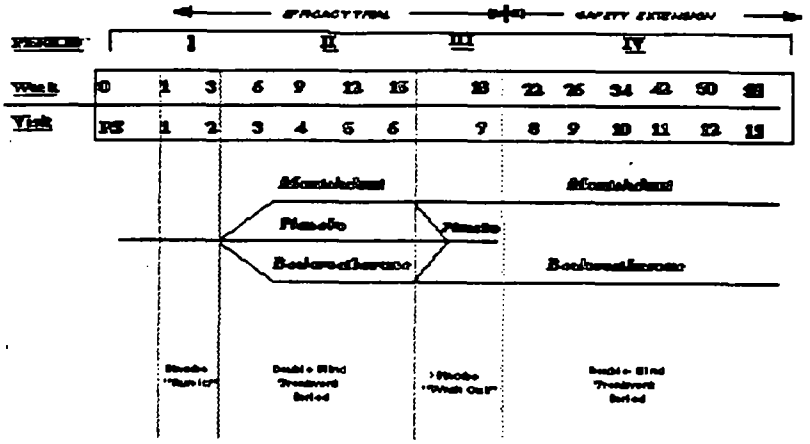
5.1.1.B Study 020 [76:11002]: A Multicenter, Double-Blind, Randomized, Parallel-Group Study Comparing the Clinical Effects of Montelukast to Placebo and Inhaled Beclomethasone in Patients with Chronic Asthma.

This study shared most of the design features and patient eligibility criteria as Study 031. The major difference between this study and the previously summarized protocol was the addition of a beclomethasone treatment arm. In this study, eligible patients were randomized to montelukast, beclomethasone at 400 ug/day (two puffs of beclomethasone 100 ug/actuation twice daily with spacer) or placebo employing a double-dummy design element. Stable theophylline use in this study was acceptable. The timing of visits in the double-blind and open-label periods, efficacy endpoints, montelukast/placebo-comparison data analysis methodologies were identical as well. This study also contained a "washout" evaluation in which a certain number of patients from each treatment arm entered a three-week, placebo washout period. All patients who received placebo in Period II continued to receive placebo and were dropped from the study after completion of the washout. A prespecified subset of patients (n= 40) who receive montelukast or beclomethasone in Period II received placebo for three weeks and were then dropped from further participation in the study.

Several distinguishing characteristics of this trial focus on the beclomethasone treatment arms. At the time of randomization, in addition to double-blinding, the patient as well as the on-site investigators were not informed that he/she was entering the treatment period. This was done, presumably, to limit the placebo effect that may obscure onset-of-action differences between montelukast and beclomethasone. The design of this study is summarized in the figure below. Furthermore, since the full clinical effect of belcomethasone treatment may not be achieved within 2-4 weeks after initiation of therapy, a secondary analysis compared the effects of montelukast and beclomethasone over the last nine weeks of the double-blind treatment period. Since onset of action is considered by the sponsor to be a potentially important distinguishing feature of montelukast and beclomethasone, provisions were made to examine this parameter. FEV1 was compared at the first post-randomization visit in Period II (3 weeks post-randomization) and Daytime Symptoms were compared as the average values of all the daily measurements prior to this visit. Similar analyses were performed for AM PEFR, total daily beta-agonist use and nocturnal asthma scoring.

Figure 1

Study Design



[1] The patients receiving placebo in Period III did not have the option to continue into Period IV.

The procedures to be performed at each visit are also similar. The schedule of activities that occur at each visit are summarized in the table below.

Schedule of Clinical Observations and Laboratory Measurements

Periods→		Blinded Efficacy Trial							Blind, Controlled Safety Extension						
		I		II				III	IV						
Weeks→	0	1	3	6	9	12	15	18	22	26	34	42	50	58	
Visits→	Prestudy	1	2	3	4	5	6	7	8	9	10	11	12	13	[5]
Informed consent	X						X'	X'							
Inclusion/exclusion review	X	X	X												
Baseline clinical history	X														
Patient demonstrates competence on study procedures		X	X												
Patient Global Evaluation							X								X
Quality-of-life questionnaire			X	X			X								X
Review concomitant therapy and adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (sitting BP, HR, RR, and oral temperature)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety tests (blood, urine)'	X		X	X	X		X	X		X		X		X	X
Serum βhCG pregnancy test (all females)	X						X	X		X				X	X
Urine βhCG pregnancy test (all females)			X	X	X	X			X		X	X	X		
Plasma for theophylline levels				X			X			X					
Plasma for archive			X	X			X					X			
Complete physical examination	X							X						X	X
Spirometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnostic reversibility	X	X	X		X		X		X		X		X	X	X
ECG (12-lead)	X							X						X	X
Study medication: Dispensed		X	X	X	X	X	X	X"	X	X	X	X	X		
Returned/destroyed			X	X	X	X	X	X	X	X	X	X	X	X	X
Take-home diary card: Dispensed	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collected/reviewed		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray or equivalent (taken during Period II and x-ray not performed within the past 12 months)		X													
Investigator Global Evaluation								X							X

* D = Dose titration Visit.
' Patient was asked not to exercise vigorously at least 3 days prior to visits.
" Serum βhCG was tested 14 days after Visit 7, Visit D, or Visit D on all females who completed or discontinued from the study.
' For entry into extension study.
" The patient's last contact in the extension signed a new informed consent either at Visit 6 or 7.
' The blinded, controlled safety extension (Period IV) is not addressed in this report.

Table Source: [p.2]

Since this trial employed an active-control treatment arm, there were predefined statistical provisions made for comparisons between beclomethasone and montelukast. In cases where both primary endpoints were significant (at the 0.05 level), the two treatment groups were to be declared significantly different by the sponsor. This is the same decision rule for declaring an active treatment group better than placebo. In cases where both primary endpoints are not

significant, the two treatment groups were to be declared to be comparable by the sponsor. The situation is less clearly defined for the case where one primary is and the other is not significantly different. According to the sponsor, this will require subjective assessments using analyses and integration of secondary endpoints.

Reviewer note: The sponsor's definition and rules for declaring comparability between treatment groups are not necessarily valid since the trial is not designed and powered as a comparability trial.

In this trial, the sponsor planned to enroll approximately 1100 patients at 40 centers in Phase I of the study. The sample size calculations used the same expected differences, anticipated variability around those differences and desired power as the previous study. This allowed for approximately 850 patients to enter into Phase II (20 patients/center). Randomization was performed centrally and patients were randomized into one of five groups in blocks of 7 in Phase II of the trial (Appendix 3.8, [77:11376]). The five groups are summarized in the table below:

Group	Period I	Period II	Period III	Period IV	n
1	Placebo	Montelukast	Montelukast	Montelukast	300
2	Placebo	Montelukast	Placebo		40
3	Placebo	Beclomethasone	Beclomethasone	Beclomethasone	200
4	Placebo	Beclomethasone	Placebo		40
5	Placebo	Placebo	Placebo		200

Patients receiving Phase II treatments were randomized in a (montelukast: beclomethasone: placebo) ratio of 3:2:2.

Reviewer comments: These trials, as designed, are proposing to study patients with very mild asthma (i.e. requiring a minimum average of one puff of albuterol per day). In this light, observed differences between drug and placebo are not likely to be very large. The protocol and data analysis plan are otherwise very detailed and explicit. For Study 020, a non-US formulation of beclomethasone was used with a spacer at a dosing schedule that will not allow direct comparisons to US formulations and labeled dosing. First dose effects on the endpoint of FEV1 are not evaluated and end-of-dosing interval FEV1 is not assessed. In fact, in these trials the only true end-of-dosing interval efficacy assessment if evening PEFR which was obtained prior to the evening dosing with montelukast. Although Daytime Symptom Scores were recorded before PM dosing, these represent reflective and not point-in-time assessments of efficacy. In these, and the other Phase 3 studies, quality of life was assessed using patient-recorded, asthma-specific quality of life instrument which was developed and published by No minimal important difference (MID) for the total or individual domains was specified in the protocol. More importantly, no prespecification of which domain or domains which would serve as the basis of comparison between montelukast and placebo was contained in the protocol.

5.1.2. Results of Study 031

This study was conducted at 52 centers in the United States. A complete list of investigators and study sites may be found in Appendix 3.5 [81:14499].

Patient Characteristics: 681 patients were randomized (408 montelukast/273 placebo) of which 55.2% were females and 89% were Caucasians. 22.8% were using concurrent inhaled corticosteroids as allowed by the protocol. The vast majority of the patients were between the ages of 18 and 65. Only 12 patients (1.8%) were older than 65 years of age [81:14101]. The baseline values for clinical efficacy endpoints are shown in the table below [81:14106].

Variable	Montelukast (n=408)	Placebo (n=273)
FEV1 (L)	2.47	2.54
FEV1 (% predicted)	66.32	67.62
Daytime Symptom Score (0-6)	2.50	2.72
Beta agonist use (puffs/day)	5.38	5.33
AM PEFR (L/min)	381.37	391.15
Nighttime awakening with asthma/week	4.04	3.96

Of the 681 patients 676 (99.3%) had at least one secondary diagnosis. The vast majority of these involved respiratory system disorders, predominantly allergic rhinitis (92% placebo, 89% montelukast patients)[82:15072]. There were no significant differences in the frequency or type of secondary diagnoses. Similar findings were noted for medications taken prior to randomization. Comparable numbers of montelukast and placebo patients (90% versus 89%) took such medications [82:15088]. By and large, the most common prior therapies included oral contraceptives/hormone replacements, antihistamines, ibuprofen, pseudoephedrine and acetaminophen which was, curiously, categorized as a 'central nervous system' drug by the sponsor in this study and all other trial reports in the application. Concomitant medication use during the study was also comparably distributed across treatment groups [81:15097]. Beclomethasone was used by 12.3% of montelukast and 13.2% of placebo patients. Prednisone, a potential indicator of 'on-study' asthma exacerbation, was used by 9.3% of montelukast and 11% of placebo patients.

Dropouts:

Of the 681 patients randomized, 615 (90.3%) completed Period II and 607 (89.1%) completed Period III. The overall proportion of patients who prematurely discontinued the study was 14.3% in the placebo group and 8.6% in the montelukast patients (p=0.023). The reasons for dropout are summarized in the table below [81:14119].

	Total	Placebo	Montelukast
RANDOMIZED: Total	681	273	408
DISCONTINUED: Total	74 (10.9%)	39 (14.3%)	35 (8.6%)
Clinical adverse experience	21 (3.1%)	12 (4.4%)	9 (2.2%)
Laboratory adverse experience	2 (0.3%)	1 (0.4%)	1 (0.2%)
Patient withdrew consent	25 (3.7%)	12 (4.4%)	13 (3.2%)
Protocol deviation	15 (2.2%)	9 (3.3%)	6 (1.5%)
Lost to follow-up	11 (1.6%)	5 (1.8%)	6 (1.5%)
COMPLETED Period III*	607 (89.1%)	234 (85.7%)	373 (91.4%)
* Of the 607 completed patients, 374 (138--placebo, 236--montelukast) entered the open extension (Period IV)			

Data Source: [4.29]

Auditing and Checking:

The following case report forms (CRFs) accompanied the study report in electronic format and were available through the CANDA as PDF graphic images. This is the list of dropouts due to adverse events. There were no deaths in this study.

031-002	3917	Bensch, G.	Anxiety	24633
031-003	3931	Berger, W. E.	Bronchitis	24829
031-003	3940	Berger, W. E.	Asthma,worsening	24925
031-003	3942	Berger, W. E.	Bronchitis,acute	25161
031-005	3949	Brandon, Milan	Serum Pregnancy Test Positive	25327
031-005	3959	Brandon, Milan	Depression	25557
031-007	4551	Brown, C.	Serum Pregnancy Test Positive	25669
031-010	4003	Condemi, John J.	Serum Pregnancy Test Positive	25843
031-012	4018	Daniel, D. L.	Serum Pregnancy Test Positive	25963
031-017	4062	Goldstein, Marc F.	Asthma,exacerbation	26193
031-019	4082	Harris, William O.	Anxiety	26445
031-020	4100	Hendeles,L.	Fatigue	26597
031-022	4114	Kemp,James P	Asthma,exacerbation	26839
031-023	4466	Korenblat, Phillip E	Right Bundle Branch Block	26977
031-031	4524	Nelson,Harold	Respiratory Arrest	27171
031-032	4216	Noonan, Michael J.	Serum Pregnancy Test Positive	27305
031-032	4229	Noonan, Michael J.	Depression	27615
031-034	4597	Owens, Gregory R.	Pain,back	27853
031-036	4231	Pearlman, David S.	Asthma,worsening	27961
031-036	4235	Pearlman, David S.	Asthma,exacerbation	28095
031-036	4236	Pearlman, David S.	Edema,facial	28261
031-037	4246	Pedinoff, Andrew	Asthma,worsening	28373
031-037	4249	Pedinoff, Andrew	Endometriosis,probable	28605
031-037	4255	Pedinoff, Andrew	Asthma,exacerbation	28771
031-038	4272	Prenner, Bruce	Asthma,exacerbation	28897
031-040	4285	Segal, Allen	Depression	29025
031-041	4411	Seltzer,James	Asthma,exacerbation	29131
031-041	4414	Seltzer,James	Asthma,exacerbation	29313
031-041	4423	Seltzer,James	Asthma,exacerbation	29551
031-042	4295	Storms, William	Serum Pregnancy Test Positive	29741
031-044	4316	Stricker, W.	Asthma,exacerbation	29879
031-045	4323	Sveum, R. J.	Asthma,exacerbation	30105
031-045	4327	Sveum, R. J.	Asthma,exacerbation	30255
031-047	4342	Taylor, J. R.	Asthma,exacerbation	30437
031-049	4369	Weinberg, Stephen	Asthma,exacerbation	30565
031-050	4376	White, Richard	Asthma,worsening	30835
031-051	4387	Wolfe, J. D.	Nausea	31023
031-052	4648	Finn, Albert F.	Headache	31223
031-052	4649	Finn, Albert F.	Gastritis	31307
031-054	4678	Tinkelman,David G	Difficulty Breathing	31481

Data from the first ten (10) CRFs were cross-referenced to the electronically submitted case report tabulations (i.e. line listings) and randomization code [Appendix 3.8, [81:14764]. No discrepancies were noted for selected laboratory and efficacy values.

A total of 21 patients discontinued due to a clinical adverse experience. Of these, 12 patients (4.4%) were receiving montelukast and 9 (2.2%) were receiving placebo. An additional two patients (one per treatment group) discontinued due to laboratory abnormalities (positive pregnancy test). All CRFs were reviewed, compared to the line-listings, and no discrepancies with regard to reasons for dropout were noted.

The remainder of the safety as well as a qualitative review of the CRFs associated with these patients is contained in the safety section of this review.

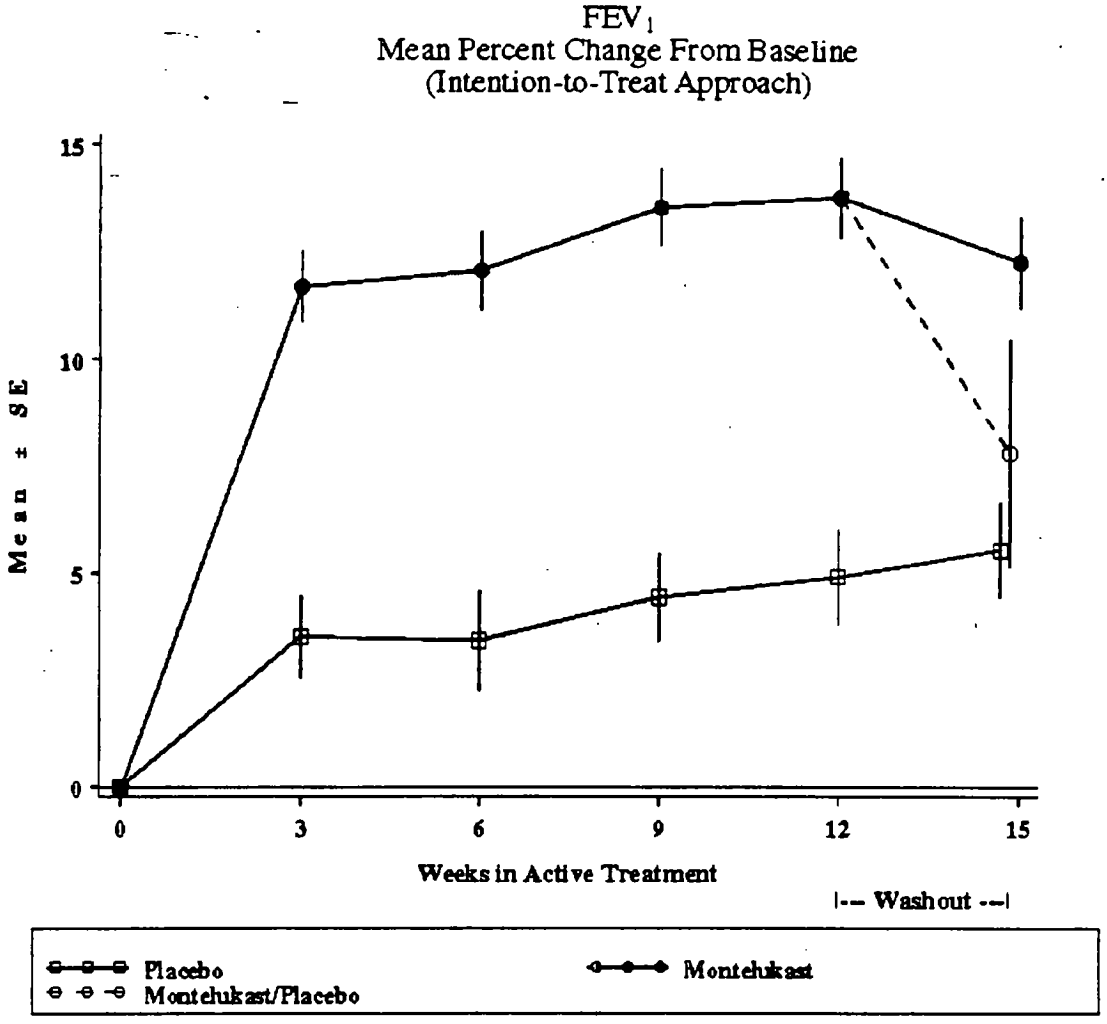
For the primary ITT analysis, patients were excluded if they had no baseline or post-randomization data. For the primary endpoints, a total of 5 patients (3 montelukast and 2 placebo) were excluded from the ITT analysis of FEV1. For Daytime Symptom Score, a total of 8 (1.2%) patients (4 in each treatment arm) were excluded.

Efficacy

FEV1

The mean percent change in FEV1 was 4.22% and 13.05% for placebo and montelukast, respectively, averaged over the 12-week treatment period. At the end of Period III (Week 15), the mean percent changes from baseline were 7.71% and 5.64% for the M/P and the P/P groups. In contrast, the M/M group demonstrated a continuing effect with a mean percent change from baseline of 12.44% (p=0.58 versus M/P) [81:14122]. These findings are graphically illustrated in the figure below [81:14124].

Reviewer Note: In this and all studies, percent change from baseline in FEV1 was calculated as (Patient/Visit-Specific FEV1 Value - Patient-Specific Baseline FEV1/Patient-Specific Baseline FEV1) x 100. [Merck correspondence of December 9, 1997.



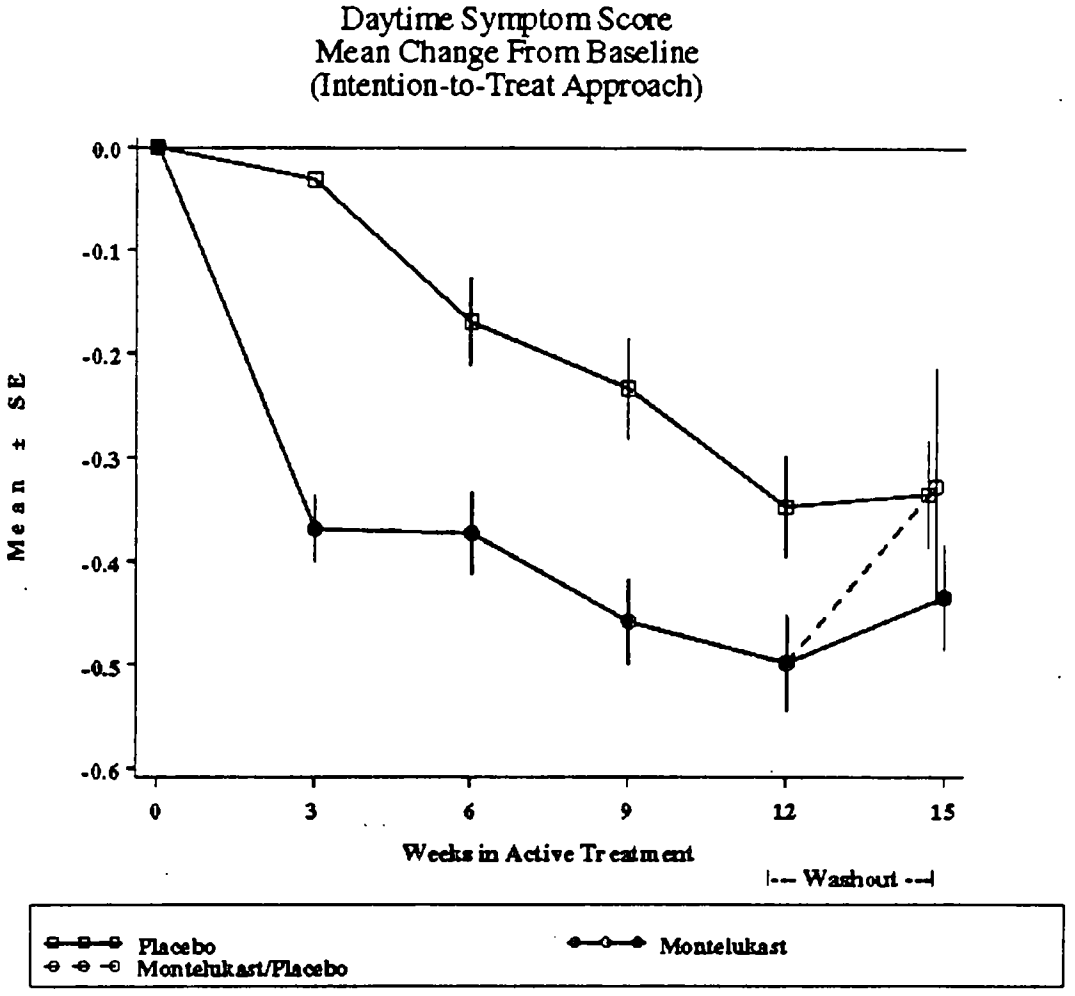
The curves are similar for the endpoint of change from baseline in percent predicted FEV1 shown in the figure below. Over the 12-week treatment period, the mean change from baseline for montelukast patients was 8.34 versus 2.61 for those patients randomized to placebo ($p<0.001$). In terms of liters, these changes from baseline represent a mean change of 0.32 versus 0.10 for montelukast and placebo groups, respectively [82:14887].

For the endpoint of percent change from baseline in FEV1, a cumulative proportion analysis was conducted and summarized in the table below [82:14898]. Note: patients are represented more than once as this table is constructed from all FEV1 recordings obtained throughout the treatment period.

Rx	Count and Percent of Patients with % Change in FEV1 greater than or equal to:								
	0	5	10	15	20	25	30	35	40
Placebo	169	123	79	49	22	14	11	4	3
n=270	(63%)	(46%)	(29%)	(18%)	(8%)	(5%)	(4%)	(1.5%)	(1%)
Monteluk	345	287	219	150	110	68	45	33	19
n=406	(85%)	(71%)	(54%)	(37%)	(27%)	(17%)	(11%)	(8%)	(5%)

Daytime Symptom Score (DSS):

Compared with placebo, montelukast demonstrated a significant improvement in DSS change from baseline. Averaged over the 12-week treatment period, mean change from baseline was -0.18 and -0.41 for placebo and montelukast, respectively ($p<0.001$)[81:14125]. The findings are shown in the figure below. Baseline equals 2.49 for placebo and 2.51 for montelukast of a possible maximum of six.



As can be seen, removal of montelukast in Period III resulted in deterioration of those patients who were taking montelukast during the double-blind, 12-week, treatment period. The mean changes for P/P and M/P patients was -0.33. The M/M group demonstrated a continuing but not statistically significant effect of -0.43 mean change from baseline versus the M/P group ($p=0.41$).

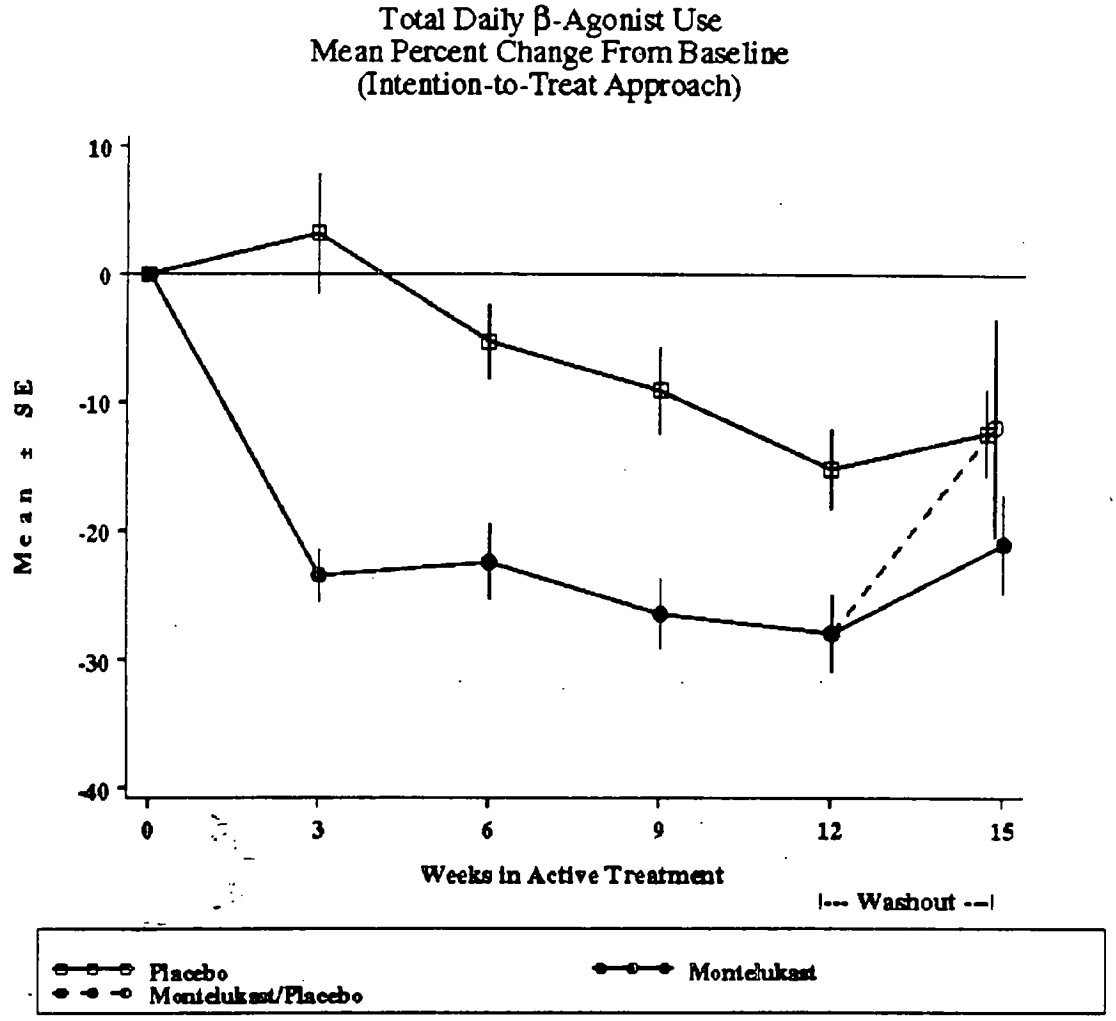
For the two co-primary endpoints, visit-by-visit analyses were conducted and are summarized in the table below [82:14907].

Visit (baseline)	FEV1 (mean percent change from baseline) Placebo	Montelukast	p value	Daytime Symptom Scores (change from baseline) Placebo	Montelukast	p value
	2.55L	2.46L		2.50	2.52	
3 (3 weeks)	3.52	11.68	<0.001	-0.03	-0.37	<0.001
4 (6 weeks)	3.42	12.07	<0.001	-0.17	-0.37	<0.001
5 (9 weeks)	4.43	13.52	<0.001	-0.23	-0.46	<0.001
6 (12 weeks)	4.91	13.76	<0.001	-0.35	-0.50	0.038

Secondary Endpoints

Rescue beta-agonist use

The results of this analysis are summarized in the figure below. The mean baseline beta-agonist requirement was 5.33 and 5.42 puffs per day for the placebo and montelukast treatment groups, respectively [81:14128].

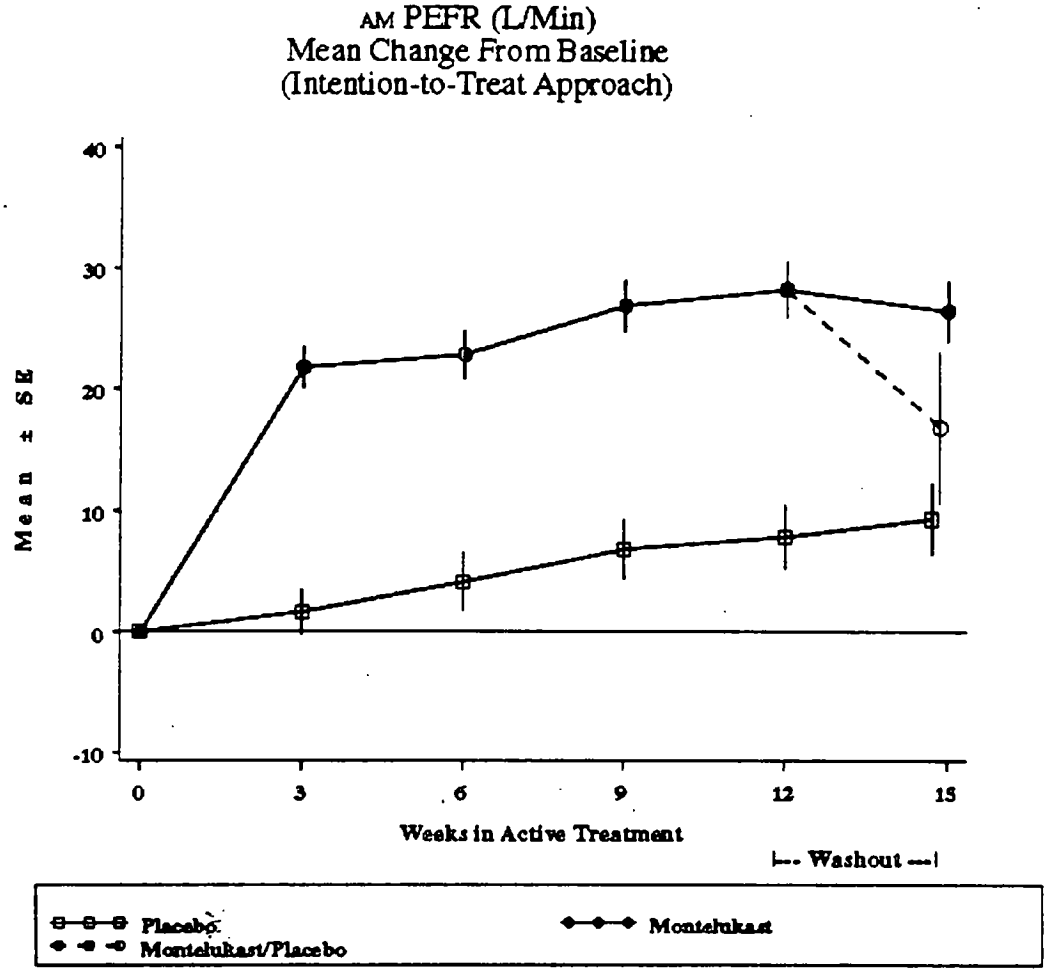


Statistically significant differences were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.003) [82:14908]. Significant differences between the M/M and M/P treatment groups were not demonstrated at the end of the washout period for this endpoint [82:14880].

Reviewer comment: In all studies, the sponsor-presented analysis is percent change from baseline. This should, of course, be interpreted in the context of the baseline beta-agonist requirements. For this study, the mean daily beta-agonist requirement was approximately 5.3 puffs. In that light, a 10% difference between groups represents a difference of approximately ½ puff per day.

AM PEFR:

The results of this analysis are summarized in the figure below. The mean AM PEFR was 392 and 381 L/min for the placebo and montelukast treatment groups, respectively.



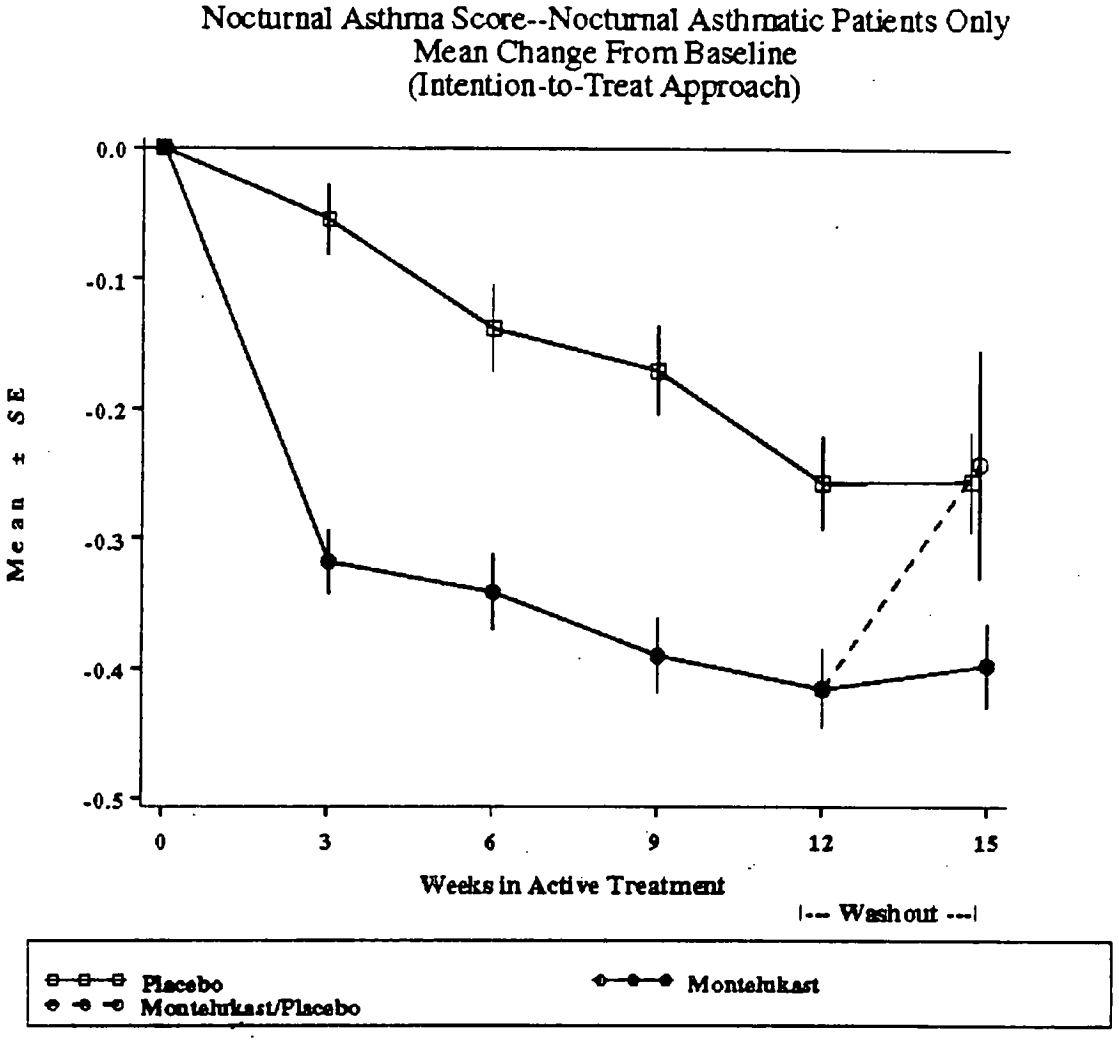
Statistically significant differences were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.001) [82:14908]. Significant differences between the M/M and M/P treatment groups were not demonstrated at the end of the washout period for this endpoint [82:14881].

PM PEFR: Montelukast demonstrated a significant improvement versus placebo over the 12-week treatment period (4.18 L/min for placebo, 15.90 L/min for montelukast, p<0.001).

Reviewer note: It is reassuring to note that the once-daily dosing interval is supported by this endpoint.

Nocturnal Asthma Score:

There were 488 patients in the prespecified subgroup of asthmatics with nocturnal awakenings greater than or equal to 2 nights per week (194 and 294 in the placebo and montelukast groups, respectively). The mean baseline score was 0.97 for both treatment groups. The mean change over the entire treatment period was -0.15 and -0.35 for the placebo and montelukast groups, respectively. The effect over the 12-week treatment period is shown in the figure below.

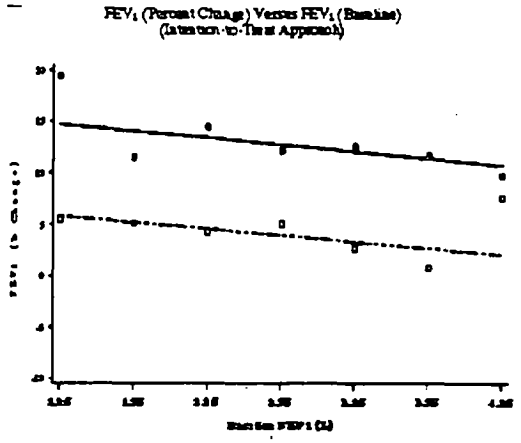


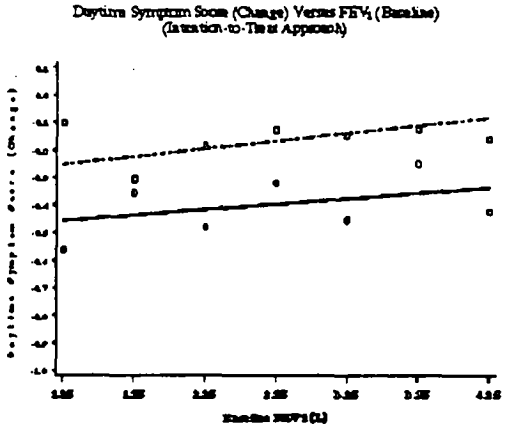
Statistically significant differences were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.003) [82:14908]. Significant differences between the M/M and M/P treatment groups were not demonstrated at the end of the washout period for this endpoint [82:14882].

Subgroup Analyses:

Treatment effects were fairly consistent across the following subgroups: age, sex, race, study center, stratum of inhaled corticosteroid use and history of EIB [81;14137]. Three significant interactions were noted: FEV1 for treatment by sex, DSS for treatment by ICS stratum, and DSS for treatment by ethnic group. Treatment effects were also consistent across baseline

disease severity for the primary endpoints as well as shown in the following figures [82:14944]. Montelukast is represented as the dark line connecting the filled squares.





Onset of Action:

The sponsor modeled the response over the first 21 days of treatment and calculated slopes and intercepts for the efficacy variables for each treatment group. Using this methodology, the differences in mean values for montelukast versus placebo for the endpoints of DSS, beta-agonist use, AM PEFR and nocturnal asthma was significant at $p<0.001$ after the first dose in the randomized 12-week study period [82:14792]. For day-by-day comparisons of montelukast, only summary statistics were provided [82:14802]. No inferential statistics were applied to these analyses which are summarized in the table below.

Day 1 (n of M/P)	*DSS (401/269)*	*% Δ in B-agonist (396/262)*	*AM PEFR (398/264)*	*Nocturnal Asthma (291/192)*
Montelukast	-0.30	-21.14	20.11	-0.29
Placebo	-0.01	4.86	-0.33	-0.09

Reviewer note: There are problems with the sponsor-proposed modeling of onset of action. A reviewer-requested reanalysis of diary data was submitted by the sponsor and is reviewed later in the document.

Quality of Life: Montelukast demonstrated statistically significant differences from placebo in all domains (activity, symptoms, emotions, environment) of the As

mentioned, no minimally important difference was prespecified in the protocol and no 'categorical' analysis based on an MID was performed. The mean change from baseline (LS mean) for the montelukast and placebo groups are shown in the table below.

Treatment	*Activity Domain*	*Symptoms Domain*	*Emotions Domain*	*Environment Domain*	*Total (average of four domains)*
Montelukast	0.50	0.70	0.58	0.48	0.57
Placebo	0.27	0.23	0.23	0.26	0.25

Reviewer note: Based on . published validation of 0.5 units being the minimal important difference for the individual and total score, it can be seen that montelukast does not achieve an MID over placebo (i.e. mean difference ≥ 0.5) for any of the individual or total domain endpoints.

Other endpoints: Montelukast was superior to placebo for the following secondary endpoints: asthma exacerbations and asthma-free days (sponsor definition), as well as the patient and physician global assessments.

Montelukast was not superior to placebo for the endpoints of asthma attacks, need for corticosteroid rescue and frequency of patients discontinuing due to worsening asthma.

5.1.3. Results of Study 020

This study was conducted at 40 centers in Europe, Central/South America, Africa and Australia using non-US formulations of beclomethasone administered with a spacer device as an active comparator. A complete list of investigators and study sites may be found in Appendix 3.5 [76:11195].

Patient Characteristics: 895 patients were randomized (387 montelukast/257 placebo/251 beclomethasone) of which 60.4% were females and 51.6% were Caucasians. 10.2% were using concurrent theophylline preparations as allowed by the protocol. The vast majority of the patients were between the ages of 18 and 65. Only 45 patients (5%) were older than 65 years of age [76:10715]. The baseline values for clinical efficacy endpoints are shown in the table below [76:10717].

Variable	*Montelukast n=379*	*Beclomethasone n=248*	*Placebo n=253*
FEV1 (L)	2.15	2.10	2.21
FEV1 (% predicted)	64.93	64.83	65.99
Daytime Sx Score (0-6)	2.35	2.39	2.40
Beta agonist use (puffs/day)	5.37	5.46	5.82
AM PEFR (L/min)	338.99	330.64	333.07
Nighttime awakening with asthma/week	4.36	4.50	4.63

Of the 895 patients 778 (86.9%) had at least one secondary diagnosis. The vast majority of these involved respiratory system disorders predominantly allergic rhinitis (65% placebo, 62% montelukast, 61% beclomethasone patients) [77:11764]. There were no significant differences in the frequency or type of secondary diagnoses. Similar findings were noted for medications taken prior to randomization. Comparable numbers of montelukast, beclomethasone, and placebo patients (59%, 55% and 56%, respectively) took such medications [76:10720]. By and large, the most common prior therapies included oral contraceptives/hormone replacements, antihistamines, ibuprofen, pseudoephedrine and acetaminophen. Concomitant medication use during the study was also balanced across treatment groups [76:10724]. Theophylline was used by 10.3% of montelukast, 10.8 of beclomethasone, and 10.5% of placebo patients. Prednisone, a potential indicator of asthma exacerbation was used by 10.9% of montelukast, 10.0% of beclomethasone, and 19.5% of placebo patients.

Dropouts

Of the 895 patients randomized, 802 (89.6%) completed Period II and 783 (87.5%) completed Period III. The overall proportion of patients who prematurely discontinued the study was 18.3% in the placebo group and 10.6% in the montelukast and 9.6% in the beclomethasone patients (both pairwise comparisons yielded p=0.007). The reasons for dropout are summarized in the table below
[76:10728].

Patient Accounting

	Total	Placebo	Montelukast	Beclomethasone
RANDOMIZED: Total	895	257	387	251
DISCONTINUED: Total	112 (12.5%)	47 (18.3%)	41 (10.6%)	24 (9.6%)
Clinical adverse experience	24 (2.7%)	11 (4.3%)	8 (2.1%)	5 (2.0%)
Laboratory adverse experience	4 (0.4%)	1 (0.4%)	2 (0.5%)	1 (0.4%)
Patient withdrew consent	25 (2.8%)	10 (3.9%)	11 (2.8%)	4 (1.6%)
Protocol deviation	34 (3.8%)	14 (5.4%)	12 (3.1%)	8 (3.2%)
Lost to follow-up	17 (1.9%)	9 (3.5%)	4 (1.0%)	4 (1.6%)
Other[2]	8 (0.9%)	2 (0.8%)	4 (1.0%)	2 (0.8%)
COMPLETED Period III[1]	783 (87.5%)	210 (81.7%)	346 (89.4%)	227 (90.4%)

[1] Of the 783 completed patients, 436 (270 montelukast, 166 beclomethasone) entered the double-blind extension (Period IV).

[2] Eight patients discontinued due to study closure (Site 020030). The other 7 patients at this study center had already been discontinued due to "protocol deviation."

Auditing and Checking

The following case report forms accompanied the study report in electronic format and were available through the CANDA as PDF graphic images. The table below contains a list of dropouts due to adverse events. There was one death in this study and it involved a 50 year old man who was involved in a fatal automobile accident after eight days of montelukast treatment. The patient died from severe head trauma.

020-001	5422	Ortega, Hector J	Serum Pregnancy Test Positive	5579
020-003	5917	Pineiro, Andres	Asthma Attack	5733
020-003	5919	Pineiro, Andres	Suicide Attempt	6037
020-003	5930	Pineiro, Andres	Asthma Attack	6327
020-003	5955	Pineiro, Andres	Hypotension,arterial	6611
020-005	5106	Jardim, Jose R	Thromboembolism,pulmonary	6757
020-006	5176	Quagliato, Reynaldo	Papules,abdomen	6953
020-008	6029	Bateman, Eric D	Asthma Attack	7031
020-008	6031	Bateman, Eric D	Asthma,worsening	7153
020-008	6042	Bateman, Eric D	Asthma,worsening	7341
020-010	5997	Bernstein, Manuel	Asthma Attack	7491
020-012	5886	Villaran Ferreyros,	Serum Pregnancy Test Positive	7823
020-013	5369	Torres, Carlos Artur	Asthma,worsening	8079
020-015	5233	Galleguillos, Fabian	Asthma Attack	8209
020-018	5800	Prieto, Fernando H	Asthma Attack	8459
020-019	5727	Perez-Padilla, Jose	Asthma,exacerbation	8671
020-019	5740	Perez-Padilla, Jose	Asthma,worsening	8923
020-021	5499	Rodriguez-Gomez, G	Serum Pregnancy Test Positive	9101
020-022	5982	Olaguibel-Rivera, Jo	Dyspepsia	9293

020-024	5308	Iordanoglou, John	Asthma,worsening	9417
020-024	5312	Iordanoglou, John	Gastritis	9729
020-025	5293	Siafakas, Nikolaos	Asthma Attack	10025
020-025	5296	Siafakas, Nikolaos	Epididymo-Orchitis	10253
020-026	5646	Bonifazi, Floriano	Menstrual Flow,dec	10407
020-026	5649	Bonifazi, Floriano	Diarrhea	10523
020-026	5650	Bonifazi, Floriano	Urticaria	10711
020-028	5703	Guerra, Jeremias	Serum Pregnancy Test Positive	10887
020-028	7027	Guerra, Jeremias	Serum Pregnancy Test Positive	11055
020-029	5654	Todisco, Tommaso	Asthma Attack	11219
020-029	5678	Todisco, Tommaso	Asthma Attack	11357
020-029	5684	Todisco, Tommaso	Syncope,vasovagal	11451
020-029	5686	Todisco, Tommaso	Neoplasm	11625
020-032	5039	Boehming, W.	Asthma,worsening	11811
020-033	5964	Picado-Valles, Cesar	Edema,eyelid	12079
020-034	5670	De Benedetto, Fernan	Asthma Attack	12195
020-036	5594	Kramer, Mordechai R	Asthma,worsening	12421
020-036	5598	Kramer, Mordechai R	ALT Increased	12607
020-037	5621	Weiler Ravell, Danie	Fatigue	12897
020-037	5625	Weiler Ravell, Danie	Asthma,worsening	13073
020-037	5627	Weiler Ravell, Danie	Asthma,worsening	13259
020-037	5631	Weiler Ravell, Danie	Asthma,worsening	13549
020-037	5633	Weiler Ravell, Danie	Asthma,worsening	13787
020-038	5017	Ben-Dov, Issachar	Serum Pregnancy Test Positive	14023
020-038	5612	Ben-Dov, Issachar	Irritation,throat	14251
020-039	5695	Vagliasindi, Mario	Serum Pregnancy Test Positive	14489

Data from the first ten (10) CRFs were cross-referenced to the electronically submitted case report tabulations (i.e. line listings) and randomization code [Appendix 3.8, 77:11376]. No discrepancies were noted for selected laboratory, efficacy values or designated treatment allocation.

A total of 24 patients discontinued due to a clinical adverse experience. Of these, 1 patient (4.3%) was receiving montelukast, 8 (2.1%) were receiving beclomethasone and 5 (2.0%) were receiving placebo. An additional four patients (two montelukast, one beclomethasone and one placebo) discontinued due to laboratory abnormalities (positive pregnancy tests). All CRFs were reviewed and no discrepancies were noted between selected data contained in the CRF and in the corresponding patient line listing.

The remainder of the safety as well as a qualitative review of the CRFs associated with these patients is contained in the Integrated Summary of Safety review.

For the primary ITT analysis, patients were excluded if they had no baseline or post-randomization data. The number of patients excluded for each endpoint in the ITT analyses is summarized below.

Endpoint	Placebo (N = 253)	Montelukast (N = 379)	Beclomethasone (N = 248)	Total(%) (N = 880)
FEV_1	4 (1.6%)	4 (1.1%)	2 (0.8%)	10 (1.1%)
Daytime Symptom Score	8 (3.2%)	7 (1.8%)	4 (1.6%)	19 (2.2%)
Total Daily β Agonist Use	12 (4.7%)	8 (2.1%)	6 (2.4%)	26 (3.0%)
AM PEFR	9 (3.6%)	7 (1.8%)	4 (1.6%)	20 (2.3%)
Nocturnal Asthma Score[1]	8 (3.2%)	7 (1.8%)	4 (1.6%)	19 (2.2%)

[1] There were 700 (79.5%) nocturnal asthmatic patients as defined in the protocol; 203 in the placebo group, 290 in the montelukast group, and 207 in the beclomethasone group.

Data Source: (4.2.3 to 4.2.6)

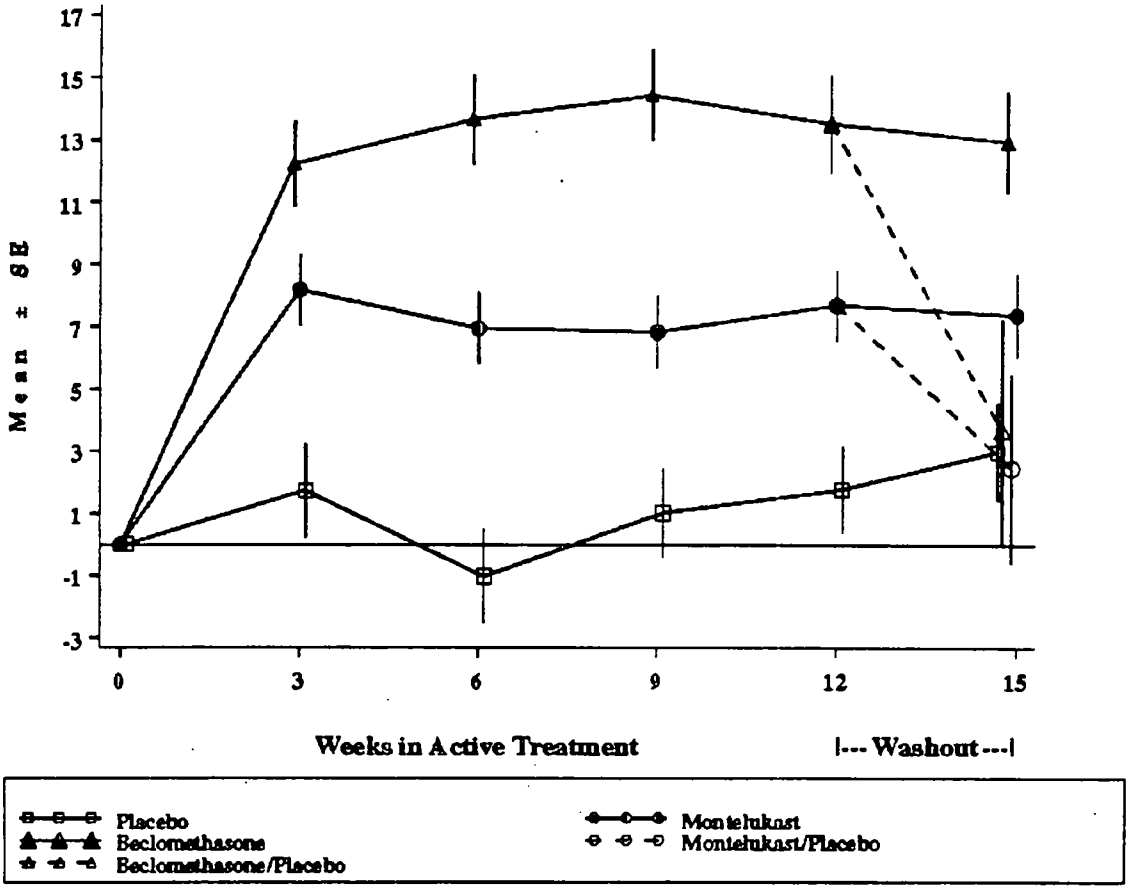
Efficacy

FEV1

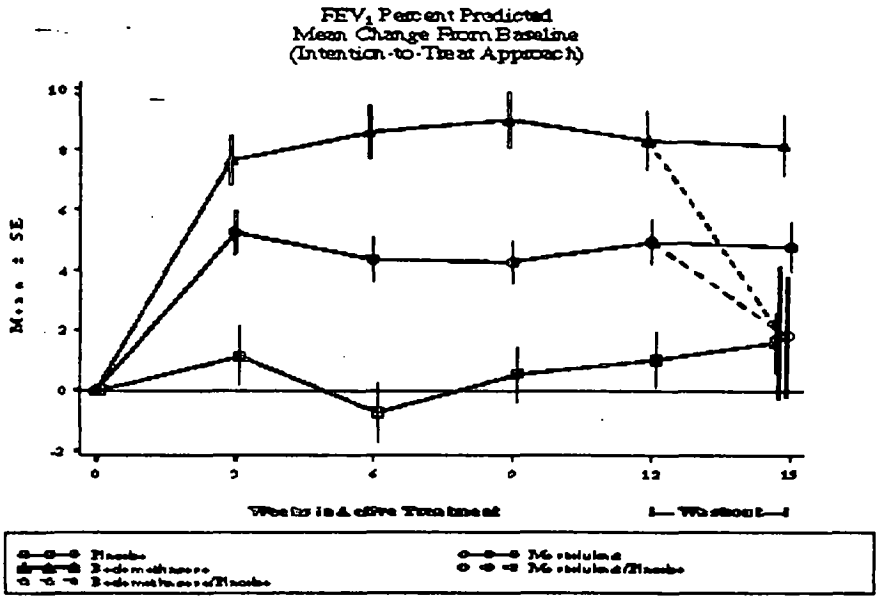
The mean percent change in FEV1 was 1.07% , 7.49% and 13.30 for the placebo, montelukast, and beclomethasone treatment groups, respectively, averaged over the 12-week treatment

period. At the end of Period III (Week 15), the mean percent changes from baseline were 2.90%, 2.46% and 1.95% for the P/P, M/P and B/P groups, respectively. In contrast, the M/M and B/B groups demonstrated a continuing effect with a mean percent change from baseline of 7.42% and 12.83% (p=0.007 for the pairwise comparison of B/B to B/P; no other comparisons were statistically significant) [76:10733]. These findings are graphically illustrated in the figure below.

FEV_1
Mean Percent Change From Baseline
(Intention-to-Treat Approach)



The curves are similar for the endpoint of change from baseline in percent predicted FEV1 shown in the figure below. Over the 12-week treatment period, the mean change from baseline for montelukast patients was 4.68 versus 0.61 for those patients randomized to placebo ($p<0.001$). The beclomethasone group had a mean change of 8.23 ($p<0.001$ versus placebo) In terms of liters, these changes from baseline represent a mean change of 0.16, 0.27 and 0.02 for montelukast, beclomethasone, and placebo, respectively (both M and B > P at $p<0.001$) [77:11547].



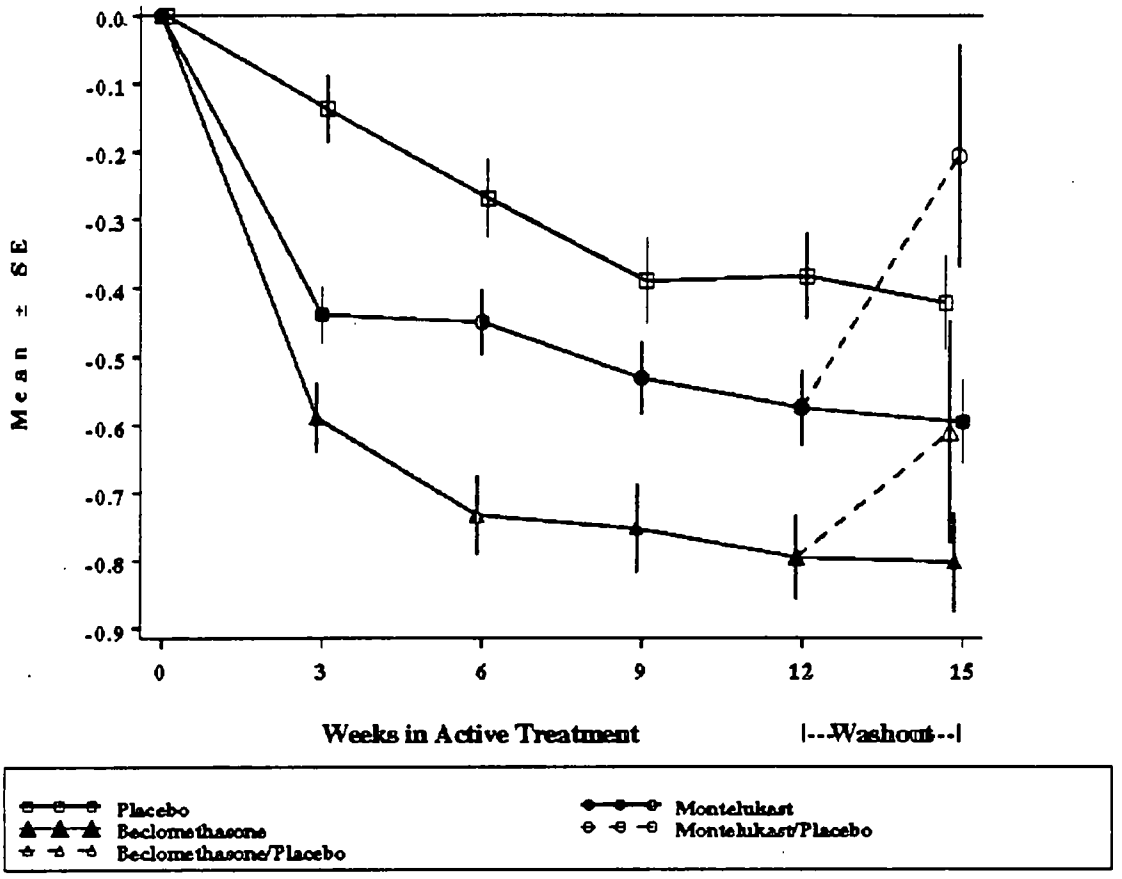
For the endpoint of percent change from baseline in FEV1, a cumulative proportion analysis was conducted and summarized in the table below [76:11556]. Note: Patients are represented more than once as this table is constructed from all FEV1 recordings obtained throughout the treatment period.

Rx	Count and Percent of Patients with % Change in FEV1 greater than or equal to:								
	0	5	10	15	20	25	30	35	40
Placebo	131	93	64	39	20	14	12	11	7
n=249	(53%)	(37%)	(26%)	(16%)	(8%)	(6%)	(5%)	(4%)	(3%)
Monteluk	246	203	159	110	83	47	32	19	12
n=375	(66%)	(54%)	(42%)	(29%)	(22%)	(13%)	(8%)	(5%)	(3%)
Beclo	191	166	125	96	69	54	41	32	24
n=246	(78%)	(68%)	(51%)	(39%)	(28%)	(22%)	(17%)	(13%)	(10%)

Daytime Symptom Score (DSS)

Compared with placebo, montelukast demonstrated a significant improvement in DSS change from baseline. Averaged over the 12-week treatment period, mean change from baseline was -0.26, -0.49, and -0.70 for placebo, montelukast and beclomethasone, respectively ($p<0.001$)[76:10736]. The findings are shown in the figure below. Baseline values were 2.40, 2.35 and 2.38 for placebo, montelukast, and beclomethasone, respectively, of a possible maximum of six.

Daytime Symptom Score
Mean Change From Baseline
(Intention-to-Treat Approach)



As can be seen, removal of montelukast or beclomethasone in Period III resulted in deterioration of those patients who were taking montelukast or beclomethasone during the double-blind, 12-week, treatment period. The mean changes for P/P, M/P, and B/P patients were -0.43, -0.21 and -0.52, respectively. The M/M and B/B groups demonstrated a continuing effect of -0.61 and -0.80, respectively. Both of these comparisons were significantly different from their placebo control groups at $p<0.006$.

For the two co-primary endpoints, visit-by-visit analyses were conducted and are summarized in the table below [77:11564].

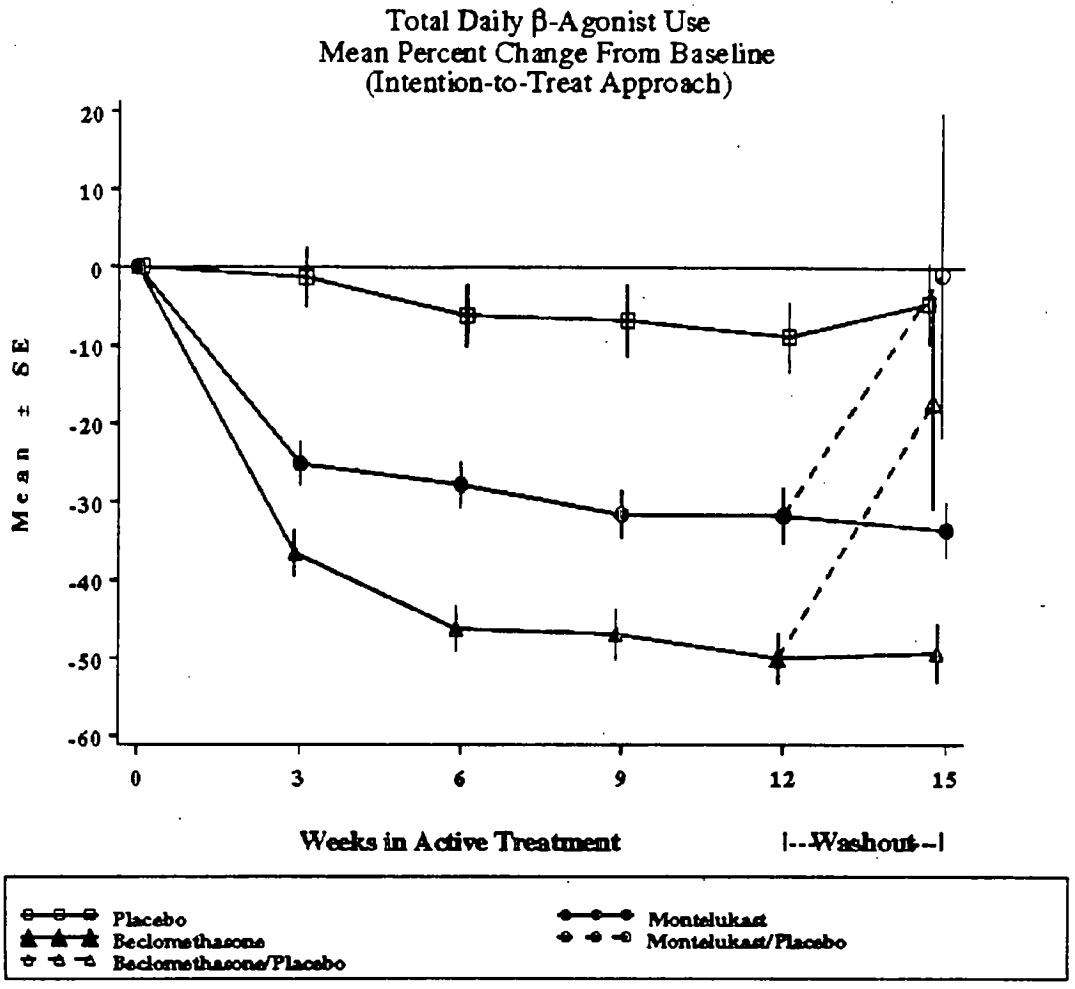
	FEV1 (mean percent change from baseline)			Daytime Symptom Scores (change from baseline)		
Visit (baseline)	Placebo	Montelukast	Beclometh	Placebo	Montelukast	Beclometh
	2.21L	2.16L	2.10	2.40	2.34	2.36
3 (3 weeks)	1.73	8.19*	12.23*,#	-0.14	-0.44*	-0.59*,#
4 (6 weeks)	1.03	6.94*	13.69*,#	-0.27	-0.45*	-0.73*,#
5 (9 weeks)	1.01	6.83*	14.46*,#	-0.39	-0.53	-0.75*,#
6 (12 weeks)	1.77	7.71*	13..58*,#	-0.38	-0.57*	-0.80*,#

*Indicates $p<0.05$ versus placebo, # indicates $p<0.05$ versus montelukast.

Secondary Endpoints:

Rescue beta-agonist use:

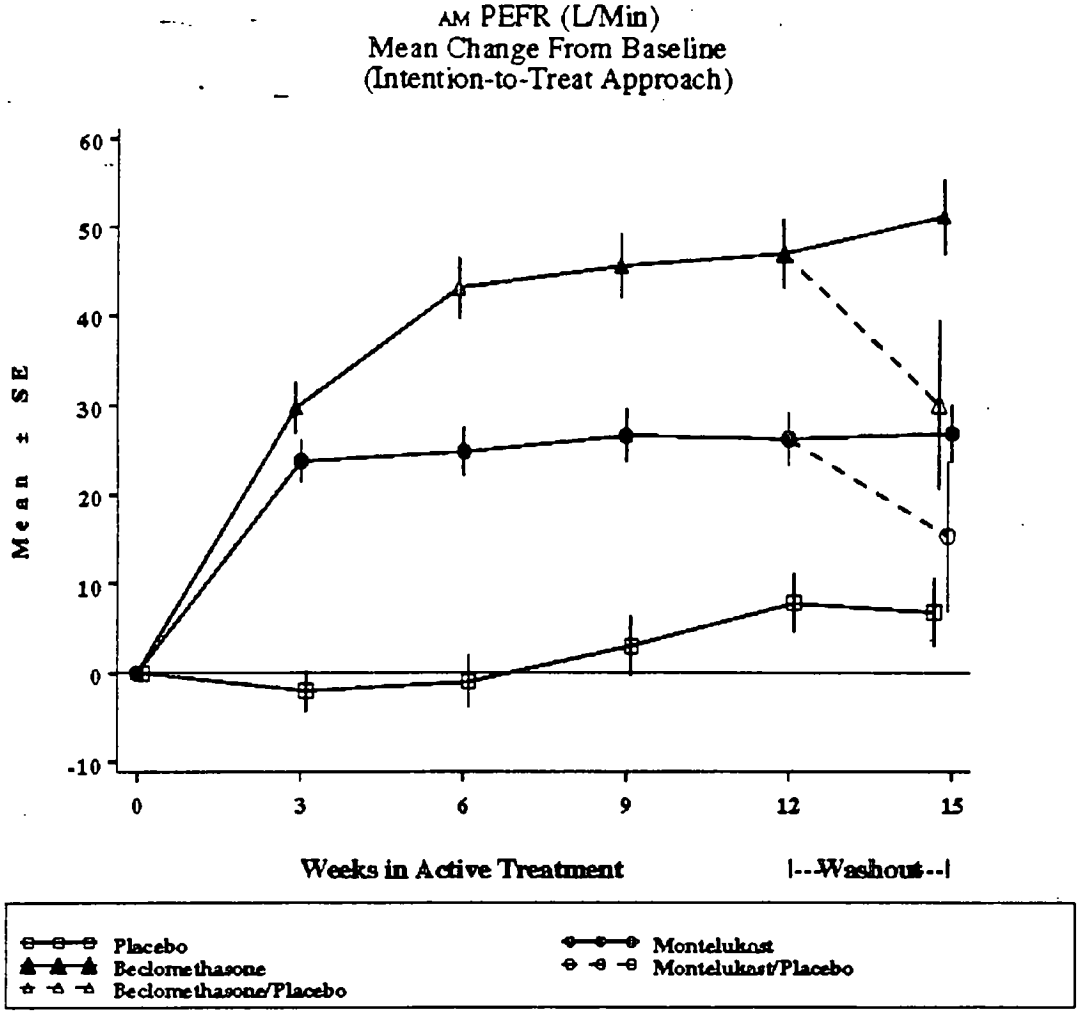
The results of this analysis are summarized in the figure below. The mean baseline beta-agonist requirement was 5.78, 5.35, and 5.43 puffs per day for the placebo, montelukast, and beclomethasone treatment groups, respectively.



Statistically significant differences favoring montelukast over placebo were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.001). Beclomethasone was superior to montelukast at each timepoint at $p<0.001$ [77:11575]].

AM PEFR:

The results of this analysis are summarized in the figure below. The mean AM PEFR was 335, 340 and 331 for the placebo, montelukast and beclomethasone treatment groups, respectively [76:10743].



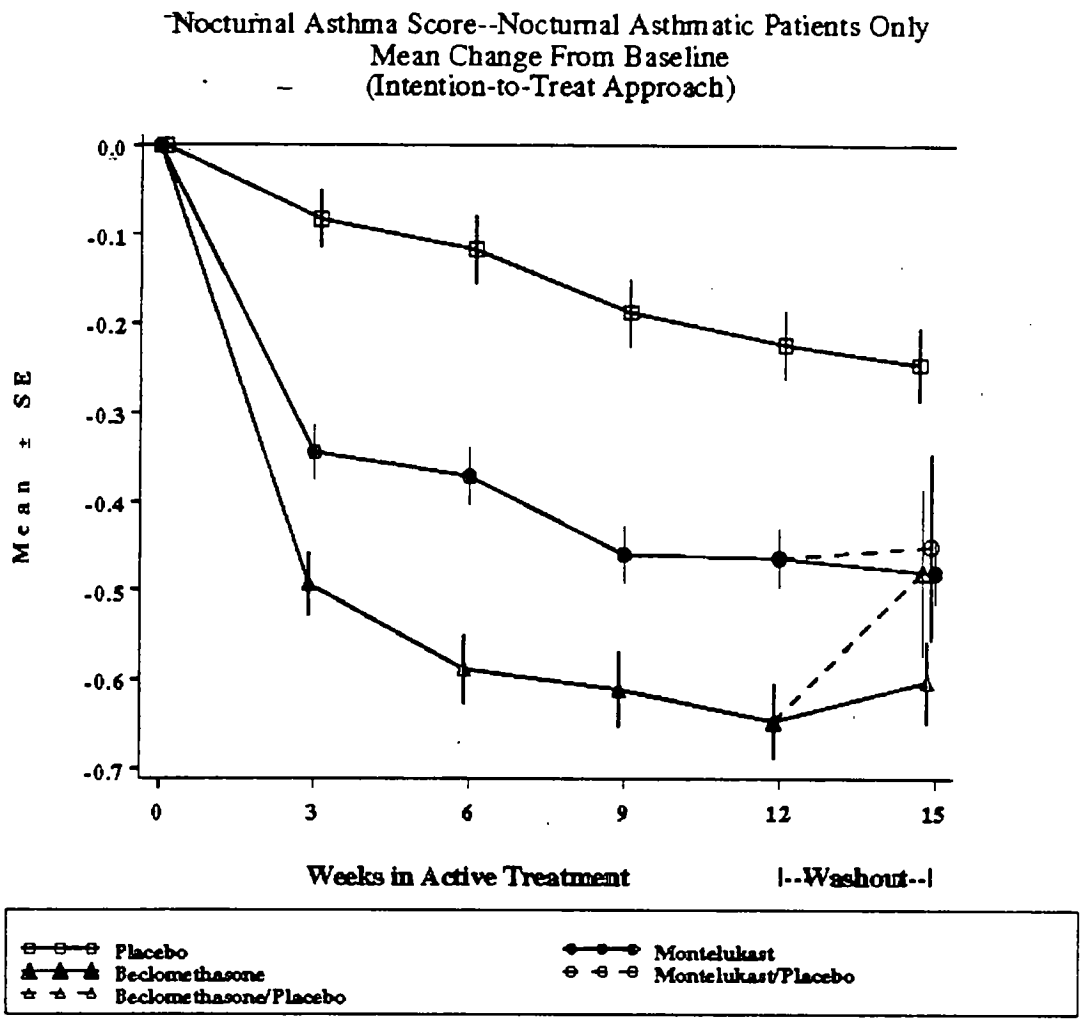
Statistically significant differences were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.001) [77:11567]. Beclomethasone was also statistically superior to placebo at Weeks 6, 9, and 12.

PM PEFR: Montelukast demonstrated a significant improvement versus placebo over the 12-week treatment period (-0.49 for placebo, 20.13 for montelukast, 31.10 for beclomethasone). Montelukast and beclomethasone were statistically superior to placebo and beclomethasone was superior to montelukast all at $p<0.001$.

Reviewer note: As mentioned before, this is the only end-of-dosing interval efficacy evaluated in these trials.

Nocturnal Asthma Score:

There were 700 patients in the prespecified subgroup of asthmatics with nocturnal awakenings greater than or equal to 2 nights per week (203, 290 and 207 in the placebo, montelukast, and beclomethasone groups, respectively). The mean baseline score were comparable for all treatment groups. The mean change over the entire treatment period was -0.15, -0.40, and -0.57 for the placebo, montelukast, and beclomethasone groups, respectively. The effect over the 12-week treatment period is shown in the figure below.



Statistically significant differences were noted at Weeks 3, 6, 9, and 12 (all p values less than 0.003) [77:11565]. Beclomethasone was statistically superior to montelukast at all visits.

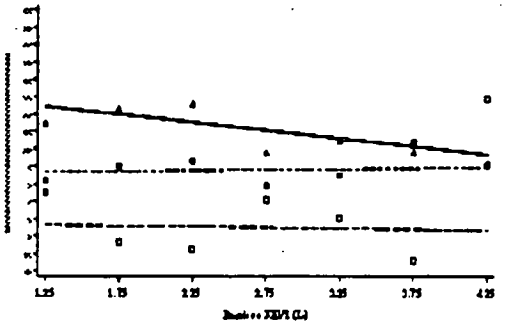
Subgroup Analyses

Treatment effects were consistent across the following subgroups: age, sex, race, study center, theophylline use and history of EIB [76:10747]. Treatment effects were also consistent across baseline disease severity for the primary endpoints as well as shown in the following figures [77:11601]. In these figures, beclomethasone is represented by filled triangles and montelukast by filled squares. Placebo is shown as open squares.

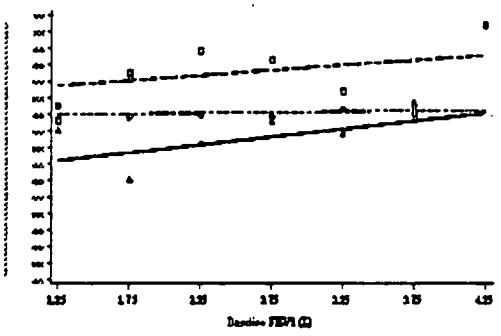
4.12.11: Average Treatment Period Response Versus Baseline Value (Intention-to-Treat Approach) (Cont.)

Figure 1

FEV_1 (Percent Change) Versus FEV_1 (Baseline) (Intention-to-Treat Approach)



Daytime Symptom Score (Change) Versus FEV_1 (Baseline) (Intention-to-Treat Approach)



Onset of Action

The sponsor modeled the response over the first 21 days of treatment and calculated slopes and intercepts for the efficacy variables for each treatment group. Using this methodology, the differences in mean values for montelukast versus placebo for the endpoints of DSS, beta-agonist use, AM PEFR and nocturnal asthma was significant at $p<0.001$ after the first dose in the randomized 12-week study period [76:10749]. For DSS, beta-agonist use, and AM PEFR, the effect of beclomethasone reached its maximal effect gradually and numerically surpassed the effect of montelukast before Day 8. Beclomethasone was numerically superior to montelukast after the first dose for nocturnal asthma score. For day-by-day comparisons of montelukast, only summary statistics were provided [77:11439]. No inferential statistics were applied to these analyses which are summarized in the table below.

Day 1 (n of M/B/P)	*DSS (370/243/245)*	*% ↓ in B-agonist (361/240/237)*	*AM PEFR (366/242/240)*	*Nocturnal Asthma (279/202/190)*
Montelukast	-0.39	-20.93	19.88	-0.29
Beclomethasone	-0.28	-23.92	8.77	-0.40
Placebo	-0.06	-3.09	-3.23	-0.07

Reviewer note: Please see reviewer requested reanalysis of daily diary scores for the first week of treatment at end of this section.

Quality of Life: Montelukast demonstrated statistically significant differences from placebo in all domains (activity, symptoms, emotions, environment) of the As mentioned, no minimally important difference was prespecified in the protocol and no

'categorical' analysis based on an MID was performed. The mean change from baseline (LS mean) for the montelukast and placebo groups are shown in the table below.

Treatment	*Activity Domain*	*Symptoms Domain*	*Emotions Domain*	*Environment Domain*	*Total (average of four domains)*
Montelukast	0.66	0.72	0.58	0.54	0.62
Beclomethasone	0.89	1.02	0.78	0.63	0.83
Placebo	0.25	0.33	0.22	0.20	0.25

Reviewer note: Based on published validation of 0.5 units being the minimal important difference for the individual and total score, it can be seen that montelukast does not achieve an MID over placebo (i.e. mean difference ≥ 0.5) for any of the individual or total domain endpoints. Beclomethasone was statistically superior to montelukast in these analyses and achieved a MID for the activity, symptoms emotions and total domains.

Other endpoints: Montelukast was superior to placebo for the following secondary endpoints: asthma exacerbations and asthma-free days (sponsor definition), as well as the patient and physician global assessments. Again, beclomethasone was superior to montelukast in these endpoints.

Montelukast was also superior to placebo for the endpoints of asthma attacks, need for corticosteroid rescue and frequency of patients discontinuing due to worsening asthma. For these endpoints, montelukast and beclomethasone were not statistically significantly different although beclomethasone was numerically favored for all endpoints.

Reviewer comment: The sponsor should be asked to perform inferential (pairwise of montelukast versus placebo) statistical analyses on the daily data for the first seven days for DSS, beta-agonist use, AM PEFR and nocturnal asthma scores to support the onset of efficacy claim for both Studies (020 and 031). This request was Faxed to the sponsor on October 27, 1997. The sponsor response is reviewed at the end of this section.

5.2 Placebo-controlled Trial in Aspirin-Sensitive Asthmatics

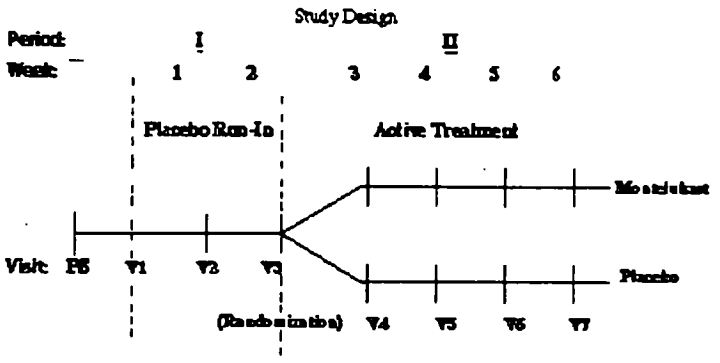
5.2.1 Protocol Review

Study 015 [75:10053]: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, 2-Period Parallel-Group Study to Assess the Clinical Effect of Montelukast in Aspirin-Sensitive Patients.

The primary objective of this study was to determine the clinical effect of montelukast in aspirin-sensitive asthmatics over a four week treatment period.

In order to achieve these objectives, non-smoking, male and non-pregnant female asthmatics between the ages of 15 and 75 with a history of aspirin-sensitivity were randomized to receive montelukast (10 mg) or placebo daily for four weeks. Aspirin-sensitivity was defined as documentation of a 20% decrease in FEV1 after oral/inhaled/nasal challenge or significant increase in nasal symptoms or decrease in nasal peak flow after nasal challenge using aspirin or lysine-aspirin. Additionally, the patients must have an FEV1 between 50% and 90% of predicted on at least two occasions during the Prestudy visit, Visit 1, 2, or 3. Reversible airway obstruction as demonstrated by 12-15% response to inhaled albuterol was also required. Other inclusion/exclusion criteria and acceptable medication washout and concomitant medication criteria are the same as in the previously described chronic asthma studies. The use of stable doses of theophylline and oral (up to 20 mg prednisone/day) or inhaled corticosteroids was permitted.

The study was divided into two periods as shown in the figure below [74:9828].



Period I of the study is a single-blind, placebo run-in period lasting two weeks during which time baseline quantification of Daytime Symptom Scores and inhaled beta-agonist requirements was made. Patients were then randomized to montelukast or placebo at Visit 3. Standard rescue albuterol was provided. Test medications were to be taken at bedtime without regard to meals. Compliance was assessed by pill counts at each visit and correlation of beta-agonist canister weights with the diary recording of beta-agonist use. The double-blind treatment period was 4 weeks in duration with clinic visits at weekly intervals.

The schedule of study procedures followed during Periods I and II are summarized in the table below [74:9835]. Data collection during Visits was standardized as described in the reviews of other chronic asthma studies. Similarly, procedures for handling asthma exacerbation were previously described.

Clinical Observations and Laboratory Measurements

Order of Procedures / Weeks: / Visit/Booklet:		Period I			Period II				
		0	1	2	3	4	5	6	
	PS	1	2	3	4	5	6	7	D
Informed consent	X								
Patient's global evaluation								X	X
Asthma-specific Quality-of-Life Questionnaire				X				X	X
Screening number provided	X								
Urine samples for LTE_4/creatinine				X				X	
Inclusion/exclusion criteria reviewed	X			X					
Clinical and asthma history	X								
Documentation of oral, inhaled, or nasal aspirin challenge	X								
Patient demonstrates competence in study procedures		X	X	X					
Review of concomitant therapy	X	X	X	X	X	X	X	X	X
Adverse experiences reviewed		X	X	X	X	X	X	X	X
Diary card collected and reviewed *with patient*[1]		X	X	X	X	X	X	X	X
Montelukast/placebo tablets returned/counted			X	X	X	X	X	X	X
Chest X-ray or report reviewed			X						
ECG (12-lead)	X							X	X
Physical examination	X							X	X
Vital signs (sitting BP, HR, RR, and oral temperature)	X	X	X	X	X	X	X	X	X
Spirometry[2]					X	X	X		X
Spirometry with β-agonist reversibility[2]	X	X	X	X				X	
Serum β-hCG pregnancy test (females only)[3]	X							X	X
Urine β-hCG pregnancy test (females only)				X	X	X	X		
Allocation number provided				X					
Laboratory safety tests[4]	X			X				X	X
Plasma samples for archiving				X				X	X
Physician's global evaluation								X	X
Tablets (montelukast/placebo) dispensed		X	X	X	X	X	X		
Albuterol dispensed as needed	X	X	X	X	X	X	X		
Practice diary card/diary card dispensed	X	X	X	X	X	X	X		

[1] The study coordinator reviewed the diary card in order to determine if patient achieved the inclusion criteria and could be randomized.
[2] In order to have premed spirometry testing performed between 0600 and 0900 AM, spirometry was done as the first procedure, after the Quality-of-Life Questionnaire.
[3] The last pregnancy test was done 14 days after Visit 7 or a Visit D.
[4] Patient was asked not to perform strenuous exercise 3 days before a visit with laboratory safety tests.
D = Discontinuation Visit.
PS = Prestudy Visit.

In addition to data collection at scheduled visits, patients were asked to keep a daily diary in which they will record and score daytime asthma symptoms. The following questions were answered on a 0 to 6 scale.

-How often did you experience asthma symptoms today? (0= none, 6= all)
-How much did your asthma symptoms bother you today? (0=not at all, 6= severely)
-How much activity could you do today? (0=more than usual, 6= less than usual)
-How often did your asthma affect your activities today? (0=none, 6=all the time).

Patients were also asked to record the total number of puffs of albuterol used during the day, the AM PEFR, the pre-bedtime PEFR and the overnight asthma symptom score. In order to address this last parameter the patient answered the question "Did you wake up with asthma?" and quantify the number of puffs of albuterol used since going to bed. PEFRs were to be recorded as the best of three efforts.

Two primary endpoints were designated in the protocol: a) FEV1 assessed at each clinic visit and b) daytime asthma symptom scores, as recorded on the daily asthma diaries. Secondary endpoints are: c) daily PEFR, d) daily inhaled beta-agonist use, and e) nighttime awakenings, all as recorded on daily diary card. Other endpoints include: physician's global assessment, self-administered asthma-specific quality of life, number of asthma attacks, exacerbation and patient discontinuations due to asthma, and the amount/need for rescue medication. An "exacerbation of asthma" was explicitly defined as one occurrence of any one of the following:

-decrease from baseline in bedtime PEFR of more than 20%
-AM PEFR less than 180 L/min
-Increase in beta-agonist use of more than 70% (or at least 2 puffs)
-Increase in baseline symptom score of more than 50%
-Awake all night
-Asthma attack resulting in an unscheduled visit to the doctor's office, ER or hospital, or treatment with oral corticosteroids.

An intent-to-treat analysis (all patients as randomized with post-baseline data) and a 'per protocol' approach which excludes patients with important protocol deviations were prespecified. For the primary endpoints, the average response over the entire treatment period was to be compared to placebo and tested at the p=0.05 level for both endpoints (FEV1 and Daytime Symptom Scores). Secondary endpoints will be analyzed in the same manner.

5.2.2. Results of Study 015

This study was conducted at 13 sites (3 US/10 Europe) in nine countries. A complete list of investigators may be found in Appendix 3.5 [75:10355].

Patient Characteristics: 80 patients were randomized at Visit 3 (40 to each treatment) of which 67.5% were females and 97.5% were Caucasians. Overall, 11.3% of the patients were older than 65 years of age [74:9861]. The mean baseline values of clinical endpoints for each treatment group are shown in the table below [74:9865].

Variable	*Montelukast n=40*	*Placebo n=40*
FEV1 (L)	2.19	2.19
FEV1 (% predicted)	69.71	69.57
Daytime Sx Scores (0-6)	2.37	2.27
Beta-agonist use (puffs/day)	3.84	4.43
AM PEFR (L/min)	343.57	343.25

The diagnosis of aspirin-sensitivity was made in 64 of the patients (80%) within 4 years of the study. The remaining patients were diagnosed within 8 years (n=12 or 15%) or within 10-20 years (n=4 or 5%). The manner in which the diagnosis was established is shown in the table below [74:9863].

Treatment	Total	Oral Aspirin Challenge[1]	Inhaled Lysine-Aspirin Challenge[2]	Nasal Aspirin Challenge[2]
Placebo	40	16 (40%)	19 (47.5%)	5 (12.5%)
Montelukast	40	12 (30%)	27 (67.5%)	1 (2.5%)

[1] Decrease in FEV_1
[2] Nasal symptoms and/or decrease in nasal peak flow

Prior and Concomitant Therapies: The qualitative and quantitative use of prior and concomitant therapies was similar to that described in the previous chronic asthma trials [74:9867].

Dropouts

Of the 80 patients randomized, 79 completed the study [74:9875].

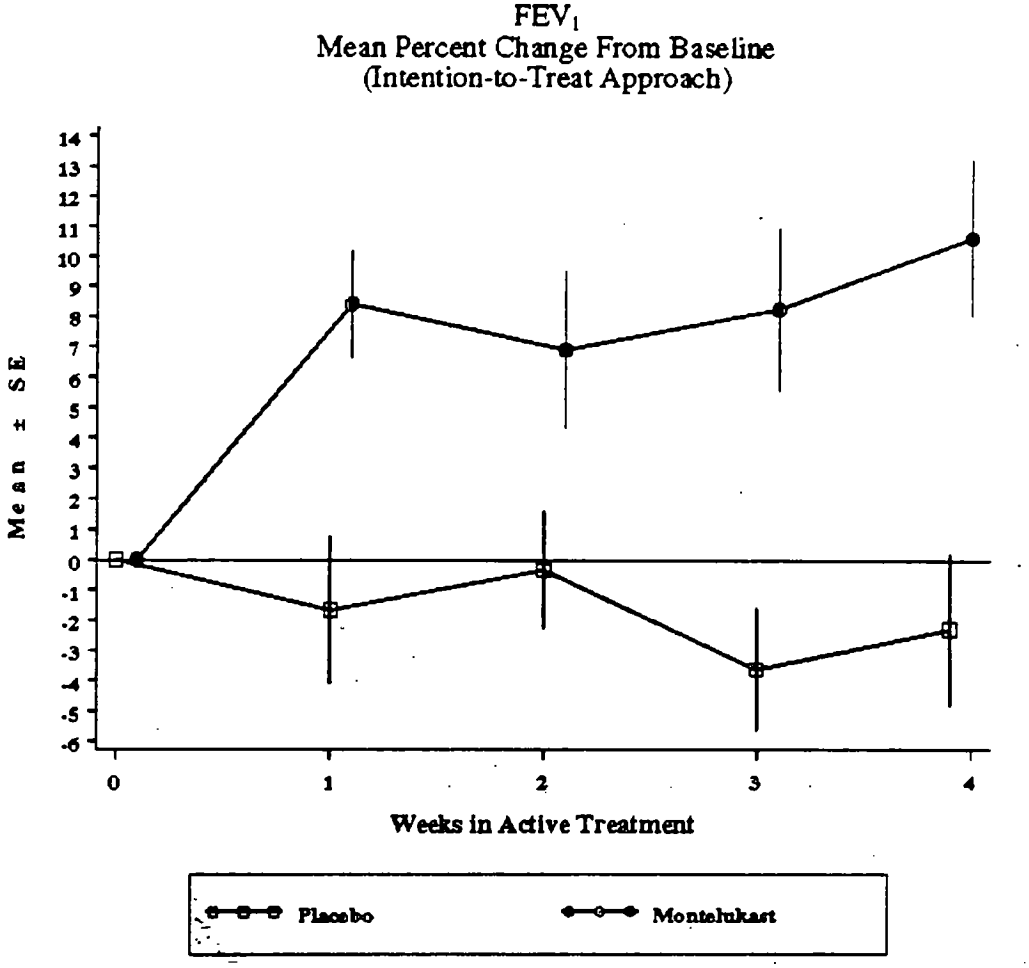
Auditing and Checking: Only one case report form was provided for this study. This CRF was for a 22 year old female (#1867) who discontinued from the trial after 13 days of treatment with placebo. The headache was present at the time of randomization (Visit 3) and worsened prior the second post-randomization visit (Visit 6). The data from this CRF was cross-referenced to the corresponding line-listings and allocation code [75:10415]. No discrepancies were noted.

Efficacy

Note: No patients were excluded from the ITT analyses for the primary efficacy variables. Only one placebo patient was excluded from the ITT analysis of the secondary endpoint of beta-agonist use.

FEV1

The mean percent change from baseline in FEV1 over the four week treatment period was +8.55% for montelukast and -1.74% for placebo ($p<0.001$). The results are summarized in the figure below [74:9877].



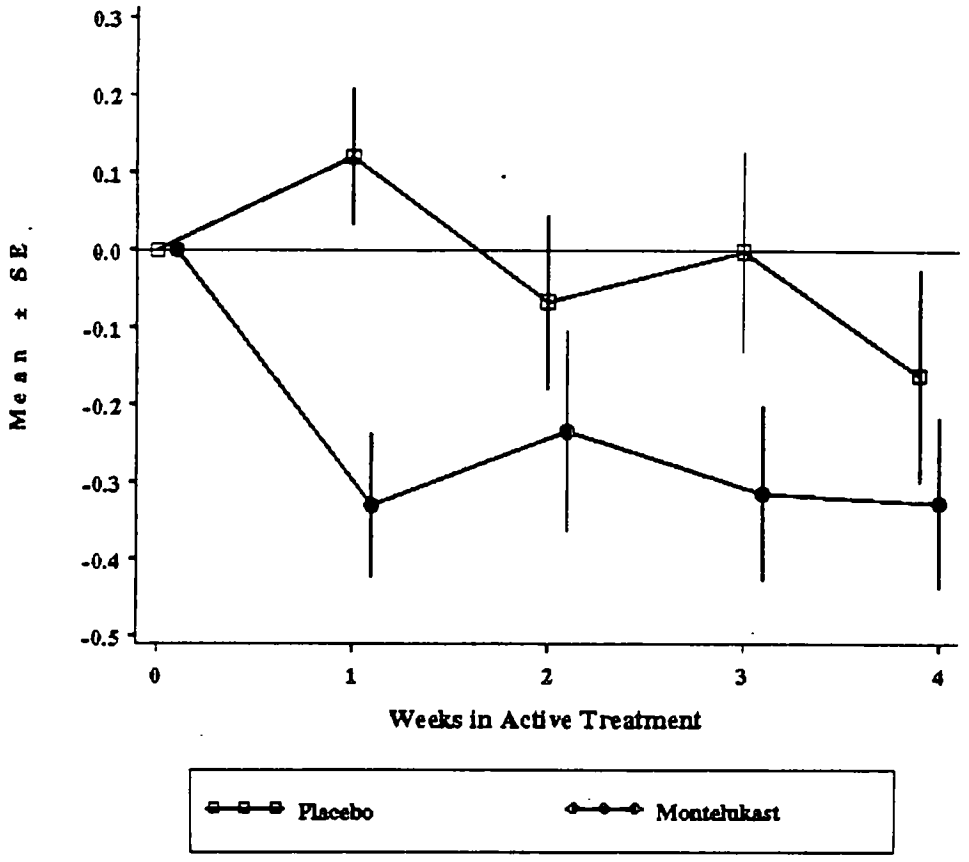
Analyses based on change from baseline in FEV1 percent predicted or FEV1 yielded similar results [75:10506]. The visit-by-visit analyses of the percent change from FEV1 baseline over the double-blind treatment period are contained in the table below [75:10523].

Visit	*Montelukast*	*Placebo*	*p Value*
Baseline (L)	2.19	2.19	NS
Visit 4 (% Change)	8.41	-1.67	0.002
Visit 5	6.88	-0.34	0.048
Visit 6	8.25	-3.63	<0.001
Visit 7	10.65	-2.31	<0.001
Last Available Visit	10.65	-1.76	0.001

Daytime Symptom Scores (DSS)

The mean percent change from baseline in DSS over the four week treatment period was -0.30 montelukast and -0.03 for placebo (p= 0.069). The results are summarized in the figure below [74:9880].

Daytime Symptom Score
Mean Change From Baseline
(Intention-to-Treat Approach)



The 'per-protocol' analysis showed smaller between-group differences. The ITT visit-by-visit analyses of the change from DSS baseline over the double-blind treatment period are contained in the table below [75:10524].

Visit	*Montelukast*	*Placebo*	*p Value*
Baseline (Score)	2.37	2.27	NS
Visit 4 (Change)	-0.33	0.12	0.001
Visit 5	-0.24	-0.07	0.512
Visit 6	-0.32	0.00	0.178
Visit 7	-0.33	-0.16	0.262
Last Available Visit	-0.33	-0.15	0.250

Secondary Endpoints

Compared with placebo, montelukast demonstrated a statistically significant decrease in beta-agonist use when percent-change from baseline was analyzed over the four week treatment period. The mean reduction was 27.65% for montelukast while treatment with placebo resulted in a 2.09% increase (p=0.002). The results of the analysis of change from baseline was also significant (p-0.013). The difference in LS means between the two treatment groups was 0.83 puffs per day [74:9884].

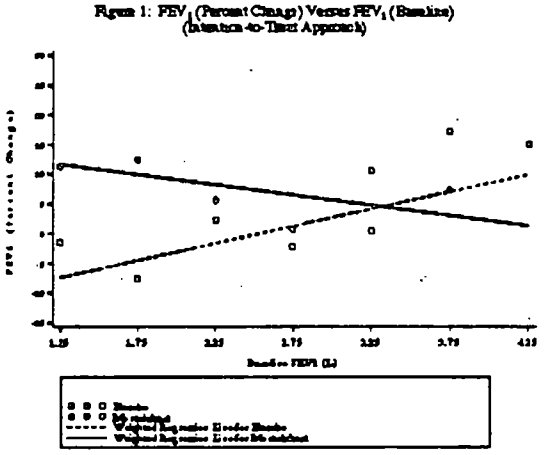
Other endpoints: Statistically significant differences between montelukast and placebo were noted for the overall 4 week ITT analyses for: AM PEFR [74:9885], PM PEFR [74:9895], nocturnal asthma score [74:9891], patient global [74:9900], and asthma exacerbation [74:9916].

Statistically significant differences were not demonstrated for the following endpoints: physician's global [74:9902], overall quality of life or the domain-specific quality of life (activity, symptoms, environment) [74:9906], and asthma-free days [74:9918].

Onset of Action:

Summary statistics for the daily scores for the first seven days for the endpoints of Daytime Symptom Scores, total daily beta-agonist use, AM PEFR and nocturnal asthma score were provided [75:10466]. No inferential statistical analyses on these data were performed. It appears that the favorable effect of montelukast was evident as early as the first day.

Subgroup Analyses: Subgroup analyses were conducted investigating potential interactions by sex, race, age, allergic rhinitis, and exercise-induced bronchospasm. In general, treatment effects were consistent across subgroups [75:10480]. Treatment effects were also consistent across patients and baseline values as demonstrated in the figure below [75:10554].



Reviewer Conclusions: This trial supports the efficacy of montelukast in a population that has been demonstrated to have aspirin sensitivity. It does not support any claims that this population may derive an enhanced benefit from treatment with montelukast. The differences between montelukast and placebo for FEV1 and DSS in this study were not greater than those observed in Studies 020 and 031. Furthermore, it does not support a claim that montelukast attenuates the response to aspirin in these patients and, consequently, that aspirin or NSAIDs may be used in these patients if they are treated with montelukast.

The sponsor should be asked to perform inferential (pairwise of montelukast versus placebo) statistical analyses on the daily data for the first seven days for DSS, beta-agonist use, AM

PEFR and nocturnal asthma scores to support the onset of efficacy claim. This request was Faxed to the sponsor on October 27, 1997.

Sponsor's Response to Reviewer Questions for Placebo Controlled Trials: The sponsor was asked to perform inferential analyses of the diary obtained endpoints of Daytime Symptom Scores, daily beta-agonist use, AM PEFR and nocturnal asthma scores in Studies 020, 031 and 015. These were submitted on November 13, 1997 and summarized in the table below. The data are represented as the LS mean treatment difference between montelukast and placebo. All pairwise comparisons for Studies 020 and 031 are significant at less than 0.001. As can be seen the numerical differences seen in Study 015 are comparable; however statistical significance was not consistently achieved for all endpoints. For the co-primary endpoint of Daytime Symptoms, statistical significance was achieved for Days 1 through 6 in this study.

	Daytime Symptoms			Daily Beta-agonist use (%)			AM PEFR (L/min)			Nocturnal Asthma Score		
Day	Study 020	Study 031	Study 015	Study 020	Study 031	Study 015	Study 020	Study 031	Study 015	Study 020	Study 031	Study 015
1	-0.33	-0.29	-0.32	-17.09	-25.84	-18.51	22.95	20.11	28.95	-0.23	-0.20	-0.41
2	-0.46	-0.32	-0.50	-27.79	-25.44	-31.61	28.83	19.64	25.55	-0.28	-0.27	-0.23
3	-0.43	-0.37	-0.39	-27.31	-23.99	-10.59	22.40	12.46	45.51	-0.30	-0.28	-0.37
4	-0.44	-0.27	-0.40	-34.91	-26.69	-29.23	28.24	19.84	31.02	-0.37	-0.27	-0.93
5	-0.45	-0.29	-0.55	-31.61	-23.37	-39.97	28.85	19.57	29.86	-0.33	-0.25	-0.08
6	-0.40	-0.35	-0.44	-31.95	-29.77	-34.88	28.10	22.67	31.05	-0.22	-0.26	-0.13
7	-0.35	-0.45	-0.28	-26.12	-25.57	-28.23	31.22	25.52	38.85	-0.23	-0.23	-0.27

Overall Reviewer Conclusion on Placebo-Controlled Studies:

Montelukast has been shown to be effective in the treatment of mild to moderate asthma in adequate and well-controlled trials. Onset of action has been shown to occur within one day of treatment for the endpoints of Daytime Symptoms, beta-agonist use, AM PEFR and nocturnal asthma scores. First-dose bronchodilatory effects (i.e. FEV1) were not evaluated in these trials; however, previous data indicate that the first dose effect on FEV1 is not significant (Study 009). Post-treatment observations indicate that no rebound phenomenon exists after withdrawal of montelukast in this patient population. Montelukast is effective in asthmatic patients with demonstrated aspirin sensitivity; however, it has not been shown to be of more value in these patients than in the population of general asthmatics. Importantly, montelukast has not been demonstrated to truncate the response to aspirin in these patients and, consequently, allow such patients to be treated with aspirin or NSAIDs. The data do not demonstrate that montelukast impacts significantly on asthma-specific quality of life evaluations. The data further indicate that inhaled beclomethasone dosed at 400 mcg/day is statistically superior to montelukast and placebo for the co-primary endpoints of Daytime Symptoms and FEV1 and superior to placebo for overall QOL and the individual QOL domains of activity, symptoms, and emotions.

5.3 Chronic Exercise Study

5.3.1 Protocol Review

Study 042 [83:15400]: A Randomized, Double-Blind, Placebo-Controlled, 3-Period, Parallel-Group Study to Investigate the Effects of 12 Weeks of Montelukast Therapy on Exercise and Methacholine-Induced Bronchoconstriction in Asthmatics.

The principal objective of this study was to determine the effect of chronic administration of montelukast therapy on exercise-induced bronchoconstriction (as measured by the post-exercise fall in FEV1 and $AUC_{0\text{-}60min}$, and time to recovery of FEV1) in asthmatics measured 20 to 24 hours after oral dosing. A second objective was to determine the effect of montelukast on airway hyperresponsiveness as measured by methacholine inhalational challenge testing.

In order to achieve these objectives, non-smoking male and nonpregnant female asthmatics with an average pre-exercise FEV1 of ≥65% of predicted were eligible to enroll. In addition, these patients had to demonstrate evidence of exercise-induced bronchospasm (EIB) defined as a minimum 20% decrease following standardized exercise challenge at the two pre-randomization visits. The patients must also have demonstrated evidence of airway hyperresponsiveness as defined by a PC20 FEV1 to methacholine of ≤4 mg/mL at the prestudy visit. The other inclusion/exclusion, medication washout, and prohibited/allowable concomitant medication criteria were similar to those used for studies 020 and 031. Specifically, any corticosteroid was prohibited within one month of study start. Inhaled cromolyn/nedocromil was prohibited within 2 weeks and oral theophylline/oral or long acting inhaled beta-agonists were prohibited within one week of study start. Inhaled short-acting albuterol was allowed throughout the study.

The study was divided into three Periods. Period I was a one-week, single-blind, run-in period during which time exercise and methacholine responsiveness were determined. Patients meeting the inclusion criteria were randomized to either montelukast or placebo each dosed at bedtime without regard to food intake. Patients were seen in clinic at 4-week intervals. Methacholine challenges are performed at Weeks 4 and 12 of the double-blind period. Exercise challenges were performed at Weeks 4, 8, and 12. This 12-week, double-blind, treatment period was followed by a two week, single-blind, placebo "washout" period. Repeat methacholine and exercise challenges were performed and after two weeks of "washout". On visits where both challenges are scheduled, the exercise challenge followed the methacholine challenge by a minimum of one day.

Exercise Challenge [83:15428]

For each challenge, the patient exercised for 6 minutes on a treadmill while inhaling compressed dry air at room temperature through a face mask at a workload that increased the heart rate to 80-90% of the individual's age predicted maximum. Once the workload to achieve this target heart rate was determined, it was used I all subsequent challenges. Pre-exercise spirometry was performed before each challenge (best of two efforts). Pre-exercise FEV1 had to be ≥65% of predicted for the exercise challenge to proceed. Spirometry was measured immediately after exercise and then at 5, 10, 15, 30, 45, and 60 minutes. If patient had not returned to within 5% of baseline, additional spirometry was performed at 75 and 90 minutes.

Methacholine Inhalation Challenge [83:15464]

Methacholine was administered using a . Output was measured from each and the same was used for a given patient throughout the study. Each challenge was preceded by a diluent challenge to ensure that PFT deterioration did not occur. FEV1 was recorded as the best of three efforts and had to be ≥65% of predicted for the challenge to be performed. The first methacholine concentration was inhaled 5 minutes after the end of the fifth diluent exhalation. Doubling concentrations (starting 0.156 mg/mL) of

methacholine were administered as tolerated. Spirometry (one maneuver) was measured 3 minutes after the end of the fifth exhalation of each methacholine concentration until a 20% fall in FEV1 occurred. Methacholine chloride was obtained from

Diary Cards: At the Prestudy Visit and at each post-randomization visit, patients were given a diary card to be completed at bedtime. Patients were asked to record beta-agonist use, compliance with medication, and any new/worsening symptoms.

The primary endpoint for exercise challenge was the post-exercise AUC for the FEV1 percent change from the pre-exercise FEV1 over the first hour. Secondary endpoints include the 1) maximum percent fall in FEV1 after exercise, 2) time to recovery to within 5% of pre-exercise FEV1, and 3) methacholine PC_{20}. The primary comparisons for these endpoints will be the change from the prerandomization baseline values for each endpoint [83:15427].

An intent-to-treat (ITT) principle was employed. All patients with baseline and, at least, one post-baseline measurement were evaluated. The study was designed to have 80 patients (40/group) to have 90% power to detect a 50% difference in the change from pre-randomization baseline between the two treatment groups in $AUC_{0\text{-}60min}$ [83:15443].

5.3.2. Results

This study was conducted at six centers in the United States. A complete list of investigators and study sites may be found in Appendix 3.5 [83:15547].

Patient Characteristics: 110 patients were randomized (54 montelukast/54 placebo) of which 51.8% were female and 87.3% were Caucasian. The majority of patients (85.5%) were between the ages of 18 and 45 (median 23.5 years). The baseline values for clinical endpoints are summarized in the table below [82:15235].

Parameter	*Montelukast (n=54) ± SD*	*Placebo (n=56) ± SD*
Pre-exercise FEV1 (L)	3.35 ± 0.66	3.33 ± 0.69
Pre-exercise FEV1 (% predicted)	83.21 ± 10.92	83.49 ± 10.98
$AUC_{0\text{-}60min}$ (%-min)	1386.7 ± 830.7	1526.2 ± 949.0
Maximum % FEV1 Fall post-exercise	36.65 ± 11.18	37.95 ± 12.79
Time to recovery (within 5% baseline)	63.85 ± 31.91	63.16 ± 33.43
Methacholine PC_{20}	0.46 ± 0.41	0.44 ± 0.34

Prior and Concomitant Drug Therapies [82:15237]: These were qualitatively and quantitatively comparable to those seen in previously reviewed placebo-controlled trials.

Dropouts

Of the 110 patients randomized, 97 (88.2%) completed the study. Six montelukast and seven placebo patients prematurely discontinued. Of these, seven (3 montelukast/4 placebo) discontinued secondary to adverse events [82:15243].

Auditing and Checking: Seven CRFs were provided in electronic format. Selected data from three patient CRFs (one from each study site) was cross-referenced to the electronic case report tabulations and allocation code [83:15587]. The CRFs were: Busse patient #4850, Hendeles patient #4831, and Pearlman patient #4912. No data discrepancies were noted for selected laboratory and efficacy values.

The remainder of the safety as well as a qualitative review of the CRFs is contained in the safety section of this review.

Efficacy

Two patients from each treatment group were excluded from the ITT analysis of the primary endpoint due to lack of treatment period data (patients 4844, 4852, 4913, and 4932).

$AUC_{0\text{-}60min}$

Compared with placebo, montelukast demonstrated a significant improvement in the Week 12 change from baseline (p=0.001). The visit-by-visit analyses of response is shown in the table below [83:15646].

Timepoint	*Montelukast*	*Placebo*	*p Value*
Baseline	1397.6	1540.0	NS
Week 4 (change)	-743.7	-20.0	<0.001
Week 8	-782.8	-264.5	<0.001
Week 12	-662.2	-90.6	<0.001
Washout	-187.0	-222.4	0.899

Maximum Percent Fall after Exercise

The results of this endpoint in the visit-by-visit analyses are shown in the table below [83:15649].

Timepoint	*Montelukast*	*Placebo*	*p Value*
Baseline	36.45%	38.30%	NS
Week 4	22.26%	35.43%	<0.001
Week 8	20.33%	30.85%	0.005
Week 12	20.91%	32.55%	0.001
Washout	28.31%	30.26%	0.806

Time to Recovery to Within 5% of Pre-exercise FEV1

The results of this endpoint in the visit-by-visit analyses are shown in the table below [83:15649].

Timepoint	*Montelukast*	*Placebo*	*p Value*
Baseline	64.33 minutes	63.75 minutes	NS
Week 4 (change)	-29.96 minutes	-0.44 minutes	<0.001
Week 8	-29.91 minutes	-4.29 minutes	<0.001
Week 12	-23.23 minutes	-0.61 minutes	0.003
Washout	-11.14 minutes	-4.21 minutes	0.283

Methacholine PC_{20} (mg/mL)

The results of this endpoint in the visit-by-visit analyses are shown in the table below [83:15649].

Timepoint	*Montelukast*	*Placebo*	*p Value*
Baseline	0.45	0.45	NS
Week 4 (ratio to baseline)	1.49	1.14	0.153
Week 8	not done	not done	–
Week 12	1.32	1.16	0.483
Washout	1.32	1.35	0.845

Other Endpoints:

Beta-agonist rescue during exercise challenge visit: There was a significant difference between montelukast and placebo in the proportion of patients requiring rescue during the exercise visit. These data are summarized in the table below.

Visit	Montelukast n/%	Placebo n/%	p Value
Week 4	4/51 or 7.8%	15/53 or 28.3%	0.01
Week 8	4/50 or 8.0%	13/53 or 24.5%	0.033
Week 12	7/49 or 14.3%	18/50 or 36.0%	0.02
Washout	14/48 or 29.2%	16/49 or 32.7%	0.827

There was no difference between montelukast and placebo for the mean use of beta-agonist over the 12-week treatment period (1.65 versus 1.85 puffs/day). Furthermore, compared to placebo, there was no significant difference in the percent of days beta-agonist was used before and/or after exercise with montelukast (22.76 days versus 26.82 days for montelukast and placebo, respectively).

The patient's global evaluation favored montelukast over placebo in a statistically significant fashion (p=<0.001).

Subgroup Analyses: Test of interaction by sex, age, and race were performed. In general, results were consistent across all groups of interest [83:15618].

Reviewer request for information: The sponsor should conduct a categorical analysis of the endpoint of maximum percent fall in FEV1 after exercise for montelukast versus placebo for the following response categories: patients with <5%, <10%, <15%, <20% from pre-exercise baseline for the overall 12-week and for Weeks 4, 8, and 12. This request was faxed to the sponsor on October 27, 1997.

Sponsor Response to Information Request: The requested data analyses are summarized in the tables below. The CMH p values are significant at p<0.05 at Weeks 4, 12, and Overall.

Maximum Percent Fall in FEV1 (Week 4)

	Number of Patients (%)				
	≤5	>5 and ≤10	>10 and ≤ 15	>15 and ≤ 20	>20
Montelukast	5 (10)	8 (16)	4 (8)	9 (18)	25 (49)
Placebo	0 (0)	4 (7)	4 (7)	3 (6)	43 (80)

Maximum Percent Fall in FEV1 (Week 8)

	Number of Patients (%)				
	≤5	>5 and ≤10	>10 and ≤ 15	>15 and ≤ 20	>20
Montelukast	2 (4)	10 (20)	8 (16)	7 (14)	24 (47)
Placebo	1 (2)	7 (13)	4 (8)	5 (9)	36 (68)

Maximum Percent Fall in FEV1 (Week 12)

	Number of Patients (%)				
	≤5	>5 and ≤10	>10 and ≤ 15	>15 and ≤ 20	>20
Montelukast	7 (13)	5 (10)	5 (10)	10 (19)	25 (48)
Placebo	2 (4)	1 (2)	10 (19)	7 (13)	34 (63)

Maximum Percent Fall in FEV1 (Overall)

	Number of Patients (%)				
	≤5	>5 and ≤10	>10 and ≤ 15	>15 and ≤ 20	>20
Montelukast	3 (6)	7 (13)	5 (10)	10 (19)	27 (52)
Placebo	1 (2)	1 (2)	7 (13)	6 (11)	39 (72)

Reviewer Comment on the role of montelukast in exercise induced exacerbations of asthma: This study provides weak support for the efficacy of chronically-dosed montelukast in the management of exercise-induced exacerbation of asthma. First, the minimum treatment period required to provide maximum benefit has not been determined from this study. Although information obtained from Study 013 (see Section 4.2 of this review) indicates that benefit may occur as early as after two doses, this effect was not replicated in Study 042. Second and more importantly, although montelukast

demonstrated statistically significant superiority over placebo for the mean effects on the AUC and Maximum Percent Fall endpoints, the categorical analyses clearly indicate that the majority of patients randomized to either montelukast or placebo had significant (i.e, >20%) maximum decrements in FEV1 with exercise. Montelukast shifted the population response to exercise; however, it did not truncate a significant effect in the majority of patients. This observation is confirmed by the secondary endpoint of rescue beta-agonist use. This endpoint indicated that although montelukast significantly decreased the need for rescue, there were patients that, nevertheless, required rescue with an inhaled beta-agonist during the exercise challenge. As such, this trial does not support an independent claim for efficacy in EIB as it does to demonstrate that montelukast improves asthma control as measured by a alternative measure of efficacy (i.e., challenge model).

5.4 Inhaled Corticosteroid Trials in Chronic Asthma

Two Phase 3 studies were conducted in patients receiving inhaled corticosteroids (Studies 046 and 029). Both studies were designed to address the role of montelukast as a therapy that might allow the inhaled corticosteroid dose to be reduced while maintaining asthma control as well as the benefit of adding montelukast to an existing regimen of inhaled corticosteroids. The designs of the studies are different and the protocols will be reviewed separately.

5.4.1 Study 046 [84:16214]: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to Investigate the Ability of Montelukast to Allow Tapering of Inhaled Corticosteroids in Asthmatic Patients.

5.4.1.1. Protocol Review

This study had several objectives including the safety assessment of montelukast in asthmatic patients on inhaled corticosteroids as well as determining the ability of montelukast to allow tapering of inhaled corticosteroids (ICS) in those patients.

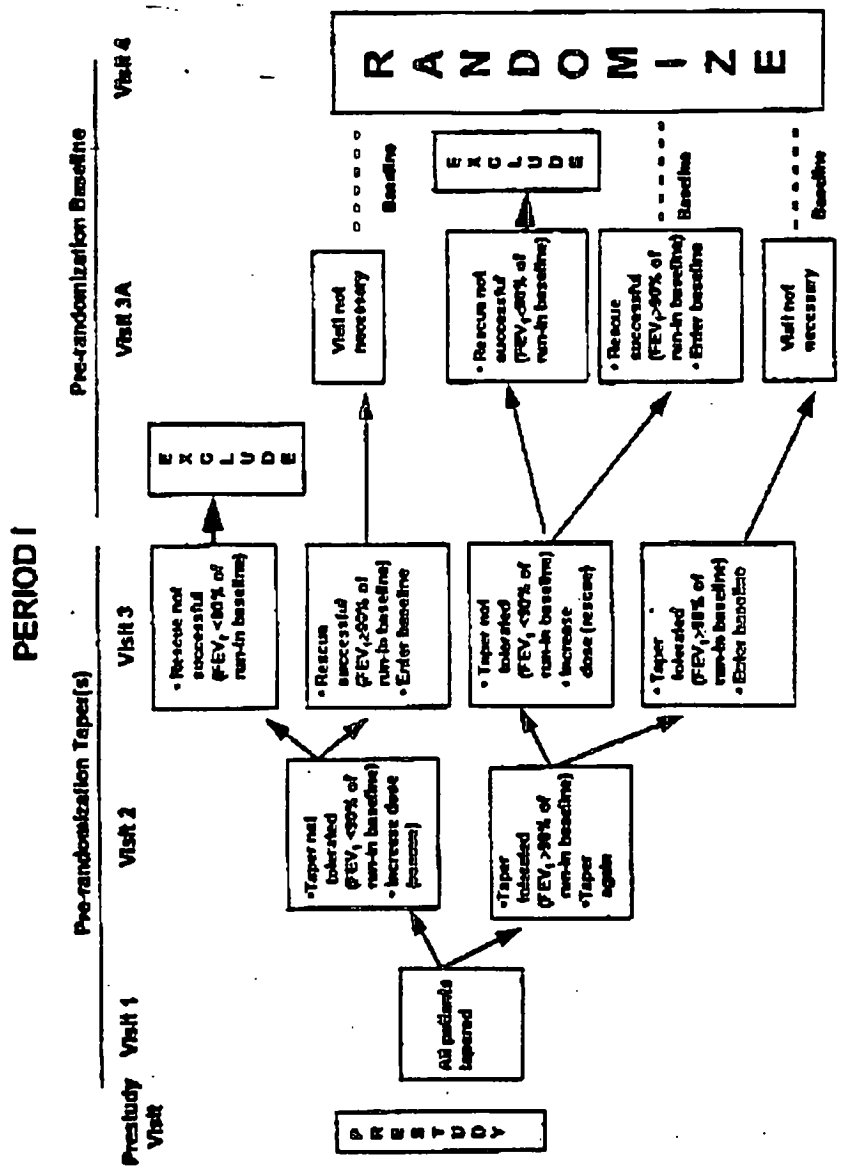
In order to achieve these objectives non-smoking male and non-pregnant female asthmatics between the ages of 15 and 70 were eligible to enter Period I of the study provided they met the following criteria: FEV1 greater than or equal to 70% of the predicted value at the Prestudy visit and Visit 1 (see study schematic below), FEV1 ≥90% of the run-in baseline FEV1 and Visit 1 FEV1 at Visit 4 (randomization visit) and evidence of reversible airway obstruction (15% FEV1 response to albuterol). Additionally, the patient must have been taking one of the following inhaled corticosteroids at stable doses (in micrograms) listed in the table below for 21 days prior to the prestudy visit (doses are ex-actuator).

Inhaled Corticosteroid	*Prestudy*	*Randomization (Visit 4)*
Fluticasone	300-1600	≥300
Beclomethasone	800-3000	≥500
Budesonide	800-3000	≥500
Flunisolide	1000-3000	≥500
TCA	1200-3200	≥800

Patients continued to take their usual ICS during the study as provided by the investigator. If a spacer device was used or not used at the Prestudy visit, the same use practice was to have been maintained throughout the duration of the trial.

Eligible patients were required to use a mean of 6 or less puffs of 'as-needed' beta-agonist daily during the pre-randomization period (i.e. between visits 3 and 4) and have a minimum PEFR that is 65% of the maximum PEFR recorded during this period. The patient was to be free of other significant pulmonary or other medical conditions. Patients taking oral, IV or IM corticosteroids, inhaled cromolyn/nedocromil, ketotifen oral or long acting inhaled beta-agonists or inhaled anticholinergics within acceptably defined washout periods were ineligible. Other specifically prohibited concomitant medications included warfarin, digoxin, antibiotics, terfenadine/astemizole/loratadine and OTC products containing caffeine, or beta-agonists. Inhaled albuterol, stable doses of theophylline and nasal corticosteroids/cromolyn are permitted throughout the study.

The study was divided into two periods. Period I of the study was a single-blind, placebo, run-in period lasting 5 to 7 weeks which was devoted to achieving the minimal dose of ICS needed to maintain clinical stability. Period I is summarized in the schematic below.



During Period I, patients on single-blind placebo were tapered once or twice (at 2 week intervals) maintaining the FEV1 at 90% of the run-in baseline FEV1. If their FEV1 fell below the allowable 90%, the patients were to be re-stabilized by increasing their ICS dose. Patients who fail to re-stabilize were excluded from further participation. A composite clinical score was used to guide further tapering. This composite consisted of FEV1, PEFRs, symptom scores and beta-agonist use. During Period I, patients entered a 7-10 day prerandomization baseline period during which time baseline for these variables was determined. To qualify for randomization, the patient must have had an FEV value from prestudy visit and Visit 1 of ≥ 70% of predicted and FEV1 at Visit 4 ≥ 90% of the run-in 'baseline' FEV1 value. Additionally, the patient must have had a daily symptom score of ≤7 and a mean daily beta-agonist use of ≤ 6 during the last seven days of the pre-randomization period. Randomization was done centrally and stratified by the dose of ICS at Visit 4. The stratification criteria are shown in the table below.

Inhaled Corticosteroid	*"Low" Dose Group (mcg/day)*	*"High" Dose Group (mcg/day)*
Fluticasone	<500	≥500
Beclomethasone	<1200	≥1200
Budesonide	<1200	≥1200
Flunisolide	<1000	≥1000
TCA	<1200	≥1200

The schedule of study procedures to be followed during Periods I and II is shown below.

Period →		I					II							
Week →	0	1	3	5	7	8	10	12	14	16	18	20	22	
Visit →	Prestudy	1	2	3	3A[a]	4	5	6	7	8	9	10	11	D[d]
Informed consent	X													
Inclusion/exclusion review	X	X				X								
Assign screening number	X													
Baseline clinical history	X													
Patient demonstrates competence with study procedures		X	X	X	X	X								
Review concomitant medications and adverse experiences	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (sitting BP, HR, RR, and oral temperature)	X												X	X
ECG	X													
Complete physical examination	X												X	X
Blood/urine safety tests[b]	X					X		X		X		X		
Serum β-hCG	X												X	X[e]
Urine β-hCG						X		X		X		X		
Tablets dispensed		X		X		X		X		X				
Tablets returned				X		X		X		X		X		
Spirometry with reversibility	X	X	X											
Spirometry				X	X	X	X	X	X	X	X	X		
Dispense diary cards		X	X	X	X	X	X	X	X	X	X			
Review diary cards			X	X	X	X	X	X	X	X	X	X		
Dispense peak flow meter		X												
Chest x-ray[b]				X										
Randomize patient						X								
Calculate average FEV_1 value (run-in baseline)		X												
Calculate prerandomization baseline values (spirometry, peak flow, β-agonist use, symptom score)						X								
Determine composite clinical score							X	X	X	X	X	X		
Taper decision (if tested corticosteroids)		Taper[f]	X				X	X	X	X	X			

[a] Patients did not exercise vigorously for at least 3 days prior to visits.
[b] Not necessary if chest x-ray performed in the past year with a normal report received.
[c] Needed only for patients who did not meet criteria for the prerandomization baseline at Visit 3 (repeated a maneuver at Visit 3).
[d] Discontinuation Visit.
[e] Serum pregnancy test was performed 14 days after the Discontinuation Visit.
[f] All patients tapered.

As implied, in addition to data collection at scheduled visits, patients were asked to keep a daily diary in which they recorded and scored daytime asthma symptoms during both Periods of the trial. The following questions were to be answered on a 0 to 6 scale.

-How often did you experience asthma symptoms today? (0= none, 6= all)
-How much did your asthma symptoms bother you today? (0=not at all, 6= severely)
-How much activity could you do today? (0=more than usual, 6= less than usual)
-How often did your asthma affect your activities today? (0=none, 6=all the time).

Patients were also asked to record the total number of puffs of albuterol used during the day, the AM PEFR, the pre-bedtime PEFR and the overnight asthma symptom score. In order to address this last parameter the patient answered the question "Did you wake up with asthma?" and quantify the number of puffs of albuterol used since going to bed. PEFRs were recorded as the best of three efforts

At each post-randomization visit, the investigator evaluated FEV1 obtained at that visit as well the diary to determine whether to taper the patient or maintain/increase the ICS dose. The decision algorithm is described below.

1. Pre beta-agonist ≥90% of prerandomized baseline. If yes, 1 point; if no, 0 points.
2. Daytime symptom score ≤120% of prerandomized baseline. If yes, 1 point; if no, 0 points.
3. Beta-agonist use ≤135% of prerandomized baseline. If yes, 1 point; if no, 0 points.

If patient has 3 points, tapering is performed as per schedule below.
If patient has 2 points, no tapering is performed at that time.
If patient has less than 2 points, patient is deemed unstable and dose of ICS is increased as per description below.

If a decision to change the ICS dosing is made, the investigator is directed to change the dosing according the tables shown below.

Taper Schedule

Inhaled* Corticosteroid Dose (Puffs/Day)	Taper (Puffs/Day)
2 to 10	2 (1 in AM, 1 in PM)
12 to 18	4 (2 in AM, 2 in PM)
20 to 26	6 (3 in AM, 3 in PM)
28 to 32	8 (4 in AM, 4 in PM)
34 to 40	10 (5 in AM, 5 in PM)
* Patients may have switched from one dose range to another during subsequent tapers	

Rescue Schedule

Inhaled Corticosteroid Dose (Puffs/Day)	Increase (Puffs/Day)
0 to 6	2 (1 in AM, 1 in PM)
8 to 12	4 (2 in AM, 2 in PM)
14 to 18	6 (3 in AM, 3 in PM)
20 to 22	8 (4 in AM, 4 in PM)
≥24	10 (5 in AM, 5 in PM)

The protocol contains provisions for telephone contact between the patient and the investigator if the patient feels that their asthma is worsening. The patient may request an unscheduled visit during Period I and, if the FEV1 obtained at that visit is <90% of the run-in baseline, the patient will be excluded from the study. If, during Period II, the patient telephones the investigator, a clinical assessment will be made on the basis of the following algorithm.

1. Patient reports lowest AM or PM PEFR on day of call and prior two days.
2. This result is compared to lowest PEFR (AM or PM) during Period I (prerandomization period).
3. If ≥95%, then award one point. If <95% of baseline, award 0 points.
4. Assess DSS (average of prior two days excluding day of call).
5. Compare to prerandomization DSS baseline. If ≤120% of baseline, then award one point. If >120%, award 0 points.
6. Assess beta-agonist use of prior two days (excluding day of call).
7. If ≤135% of baseline, award one point. If >135%, award 0 points.
8. If total points <2, increase dose of ICS. If greater than or equal to two points, maintain current dose.

Patients were never to be tapered as a result of a telephone contact.

The primary endpoint is the last tolerated ICS dose (as a percent change from baseline). The last tolerated dose was defined as the last dose at which a composite clinical score of 2 or 3 was achieved at a visit. Patients who were not successfully rescued (i.e. do not achieve a 2 or 3) after the dose increase of ICS were discontinued. The final ICS dose for these patients was defined as two dose increases above the dose at which the patient destabilized. Secondary endpoints included the number of patients discontinued due to instability, and the number of tapers minus the number of rescues.

Two approaches to the data analysis will be used. The primary approach will employ an ITT principle in which all individuals with efficacy measurements both at baseline and post-randomization will be evaluated.

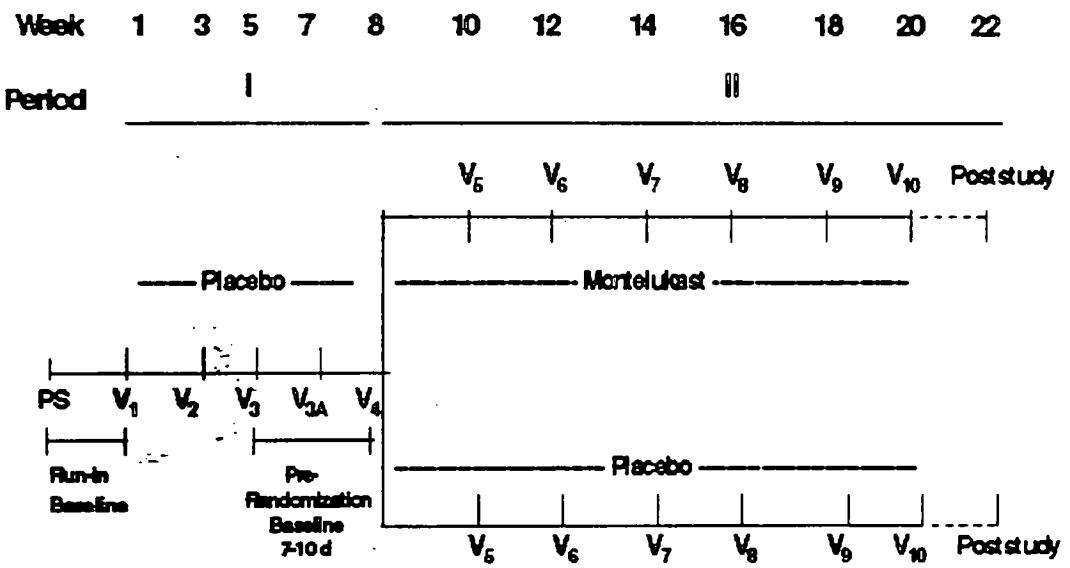
It was planned that approximately 230 patients were to be randomized into the two treatment groups and that 100 patients in each group would complete the study. The sample size was calculated to allow 90% power to detect a 30% difference between treatment groups. Randomization was performed centrally and no formal stratification (by ICS dose) variable was included, although there are requirements for each study center to use the smallest available number for patients with ICS doses in the 'low' group and use the largest available number for patients using 'high' ICS doses.

Reviewer comment on protocol and study design: Although this is a very detailed protocol, the study design suffers from a significant flaw which is the assumption that the nominal doses of the ICS are equi-effective. This brings the clinical interpretability of any 'numerical' decrease in ICS requirement into question since the numerical average is a composite of micrograms requirements of different ICS which are not equipotent/effective at the same nominal doses. Thus, assuming that randomization will allow for qualitative and quantitative distribution of the baseline ICS requirements across treatment arms, this study may be a reasonable instrument to assess the ICS-sparing effects; however, it does not allow for a clinical interpretation of the quantitatively measured differences in ICS requirements which is the primary endpoint.

5.4.1.3 Results of Study 046

This study was conducted at 24 sites (12 US/12 International) in seven countries including the United States, Canada, Finland, France, Germany, the Netherlands, and Sweden. A complete list of investigators may be found in Appendix 3.4 of the study report [85:17049].

The overall study design is recapitulated in the schematic below [84:16033].



Patient Characteristics: 226 patients were randomized at Visit 4 (113 montelukast/113 placebo) of which 52.2% were females and 92% were Caucasians. The vast majority of patients (96.9%) were between the ages of 18 and 65. Only 1.8% (4 patients) were older than 65 years of age [84:16064]. Stratification by amount of ICS use was balanced between 'low' and 'high' usage (53.5% and 46.5%, respectively) and across treatment groups. The plurality of patients were using inhaled triamcinolone (40.3%) followed by budesonide (22.1%),

beclomethasone/flunisolide (15.5% each), and fluticasone (6.6%) [84:16065]. Qualitative use was also balanced across montelukast and placebo arms. The mean baseline values for each treatment group of clinical endpoints are shown in the table below [84:16066].

Variable	*Montelukast n=113*	*Placebo n=113*
FEV1 (L)	2.96	2.95
FEV1 (% predicted)	84.83	82.34
Daytime Sx Score (0-6)	1.29	1.38
Beta-agonist use (puffs/day)	2.35	2.83
Prestudy ICS use (mcg/day)	1588.5	1680.53
Visit 4 ICS dose (mcg/day)	970.80	1078.76

Of the 226 randomized patients, 219 (96.9%) had at least one secondary diagnosis. The vast majority of these involved respiratory system disorders predominantly allergic rhinitis (75% and 88% for the placebo and montelukast groups, respectively) [84:16700]. There were no significant differences in the frequency or type of secondary diagnoses. Similar findings were noted for medications taken prior to randomization. Comparable numbers of montelukast (90.3%) and placebo patients (85.8%) took such medications the most common of which were OTC analgesics, terbutaline and theophylline [84:16070]. Concurrent (on-study) medication use was also comparably distributed across treatment groups [84:16074]. The most commonly used concomitant medications included antihistamines/cold remedies, theophylline, acetaminophen/ibuprofen, and terbutaline. Salmeterol use was permitted and used by 6 montelukast and 5 placebo patients.

Dropouts

Of the 226 patients randomized, 178 (78.8%) completed the study. Of the patients discontinued, 23 (16 placebo, 7 montelukast) prematurely withdrew due to protocol-specified clinical instability. The reasons for dropout are summarized in the table below [84:16079].

	Placebo	Montelukast	Total
RANDOMIZED: Total	113	113	226
DISCONTINUED: Total	31 (27.4%)	17 (15.0%)	48 (21.2%)
Clinical adverse experience	9 (8.0%)	4 (3.5%)	13 (5.8%)
Laboratory adverse experience	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patient withdrew consent	3 (2.7%)	1 (0.9%)	4 (1.8%)
Protocol deviation	3 (2.7%)	4 (3.5%)	7 (3.1%)
Lost to follow-up	0 (0.0%)	1 (0.9%)	1 (0.4%)
Other#	16 (14.2%)	7 (6.2%)	23 (10.2%)
COMPLETED	82 (72.6%)	96 (85.0%)	178 (78.8%)
# Discontinued due to clinical instability (investigator specified "failed rescues")			

Auditing and Checking

The following case report forms accompanied the study report in electronic format and were available through the CANDA as PDF graphic images.

046-001	7223	Edwards, Thomas B.	Asthma,exacerbation	32315
046-007	7297	Pearlman, David S.	Asthma,exacerbation	32493
046-007	7298	Pearlman, David S.	Bronchitis	32629
046-007	7300	Pearlman, David S.	Asthmatic Bronchitis	32767
046-009	7324	White, Richard	Asthma,exacerbation	32965
046-011	7455	Godard, Philippe	Asthma Attack	33101
046-013	7340	Israel,Elliott	Asthma,exacerbation	33251
046-013	7348	Israel,Elliott	Asthma,exacerbation	33377
046-013	7395	Israel,Elliott	Asthma,exacerbation	33561
046-019	7490	Fitzgerald, Mark J	Asthma,worsening	33727
046-019	7494	Fitzgerald, Mark J	Asthma,worsening	33907
046-019	7495	Fitzgerald, Mark J	Asthma,worsening	34053
046-024	7361	Scardella, Anthony T	Reaction,anaphylactic	34229

Data from the last (5) CRFs were cross-referenced to the electronically submitted case report tabulations (i.e. line listings) and randomization code [Appendix 3.8, 84:16581]. No discrepancies were noted for selected laboratory, efficacy values or designated treatment allocation.

A total of 13 patients discontinued due to a clinical adverse experience (shown above). Of these, 4 patients (3.5%) were receiving montelukast and 9 (8.0%) were receiving placebo. There were no deaths in this trial. No patients discontinued due to laboratory abnormalities. All CRFs were reviewed and no discrepancies were noted between selected data contained in the CRF and in the corresponding patient line listing.

The remainder of the safety information as well as a qualitative review of the CRFs associated with these patients is contained in the Integrated Summary of Safety review.

A qualitative review of the CRFs associated with these patients is contained in the safety section of this review. For the ITT analysis, only one patient (montelukast patient #7593) was excluded because no treatment period data were available. A spot-check of this patient's data indicated that this patient was a 42 year old male who was indeed randomized to and received montelukast. He only appeared for one post-randomization visit (visit 5) and was non-compliant with study procedures (e.g., using inhaled beta-agonist within 4 hours of PEFRs).

Efficacy

Last Tolerated Inhaled Corticosteroid Dose (Primary Endpoint)

The mean prerandomization baseline ICS requirements were comparable across treatment groups at 1078.8 and 975.9 ug/day for the placebo and montelukast groups, respectively [84:16080]. Compared with placebo, treatment with montelukast resulted in statistically significant decrease (p=0.046) in the last tolerated dose expressed as a percent change from baseline (30.27% versus 46.73% for placebo and montelukast, respectively). The table below summarizes the finding for the primary efficacy endpoint. A plot of cumulative proportion of patients (by treatment group) with percent changes in ICS in threshold percent changes from baseline is shown in the figure [84:16083].

Analysis of Last Tolerated Inhaled Corticosteroid Dose
(Intention-to-Treat Approach)

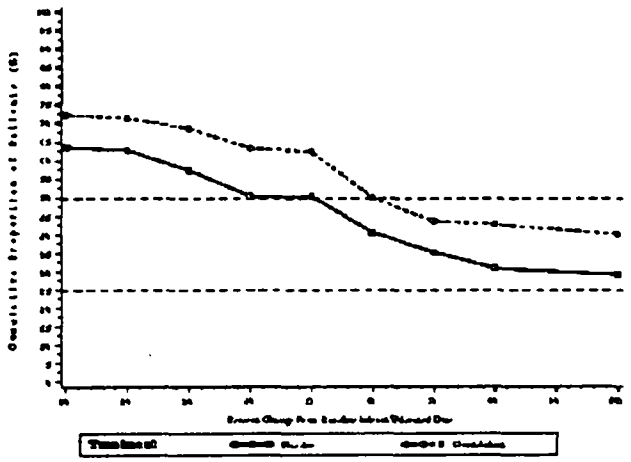
Treatment	N	Mean (µg/day)		Percent Change From Prerandomization Baseline			
		Baseline	Treatment	Mean	SD	LS Mean	95% CI for Mean
Placebo	113	1078.8	726.5	30.27	67.37	25.90	(12.63, 39.17)
Montelukast	112	975.9	525.9	46.73	62.22	43.48	(29.64, 57.32)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast vs Placebo	0.046	17.58	(0.32, 34.84)

p-Value for Effect	
Treatment	0.046
Study center	0.439
Stratum	0.072

Root MSE of Percent Change = 64.68

Last Tolerated Dose (Percent Change From Baseline)
Cumulative Proportion of Patients Equaling or Exceeding
Than or Equal to a Given Value



The sponsor also presented the data from the figure above in tabular format as shown below [84:16084].

Percent Change from Prerandomization Baseline in Last Tolerated Dose
Number (%) of Patients and CMH Test Results
(Intention-to-Treat Approach)

Treatment	Number (%) of Patients				
	Percent Change From Baseline in Last Tolerated Dose (Range)				Total
	≤0	>0 and <50	≥50 and <100	100	
Placebo	41 (36.3)	15 (13.3)	24 (21.2)	33 (29.2)	113
Montelukast	31 (27.7)	11 (9.8)	25 (22.3)	45 (40.2)	112
p-Value for CMH test controlling for stratum = 0.055					

There was a discrepancy between the ITT and the 'per-protocol' analysis for the primary endpoint. In the 'per-protocol' analysis, 15 patients from each treatment arm were excluded and no statistically significant difference between montelukast and placebo was noted. The mean baseline ICS requirements were 1137.8 ug/day and 1051 ug/day for the placebo and montelukast arms, respectively. The mean percent change from baseline in ICS requirement was comparable to the ITT for montelukast patients at 46.59%. However, the 'per-protocol' reduction for placebo patients was 35.49%.

An important consideration is the quantification of the number of patients who were able to be completely tapered off ICS. 67 montelukast versus 49 placebo patients were tapered off ICS at some point during the twelve week double blind treatment period (59.3% versus 43.4%, respectively; p=NS). Of these, 45 of the montelukast patients (40.2%) and 33 of the placebo patients (29.2%) remained off ICS at the end of the study. 28% of the montelukast and 36% of the placebo patients were not able to taper at all (p=NS) [84:16081].

An analysis of the primary endpoint by baseline ICS use (stratum) was also conducted. Summary statistics for this analysis are presented below [84:16638]. No inferential statistics were employed.

Treatment	N	Mean	SD	Median
Low Group				
Baseline				
Placebo	36	673.21	180.39	800.00
Montelukast	65	644.62	177.69	600.00
Treatment Period Value				
Placebo	36	312.50	465.07	400.00
Montelukast	64	364.06	455.08	200.00
Treatment Period Percent Change				
Placebo	36	20.89	77.37	22.50
Montelukast	64	44.95	66.48	50.00
High Group				
Baseline				
Placebo	37	1477.2	313.05	1300.0
Montelukast	48	1412.5	342.96	1200.0
Treatment Period Value				
Placebo	37	936.84	885.32	800.00
Montelukast	48	741.67	921.45	325.00
Treatment Period Percent Change				
Placebo	37	39.47	54.50	50.00
Montelukast	48	49.15	36.65	63.33

An analysis of the numbers of patients in each treatment group who were successfully weaned off ICS by strata was not included in the study report.

Secondary Endpoints:

Number of Successful Tapers (Number of tapers minus number of rescues) [84:16085]:

The number of successful tapers for each patient was classified into one of the three categories: less than zero (i.e. more rescues than tapers), zero (e.g. same number of rescues and tapers), and more than zero (e.g. more tapers than rescues). The results of this analysis is contained in the table below.

Treatment	Number (%) of Patients			
	No. of Successful Tapers			Total
	Less than zero (More rescues than tapers)	Zero (Same number of tapers and rescues)	More than zero (More tapers than rescues)	
Placebo	22 (19.5)	19 (16.8)	72 (63.7)	113
Montelukast	12 (10.7)	19 (17.0)	81 (72.3)	112
p-Value for CMH test controlling for stratum = 0.061				

Number of Patients with Failed Rescues: Compared to placebo, montelukast demonstrated a statistically significant ability (p=0.010) to reduce the number of patients with failed rescues (18 patients (16.1%) for montelukast and 34 (30.1%) for placebo).

Number of Tapers and Rescues Required: There was no statistically significant difference in the numbers of tapers per patient between the two groups

Spirometry, Symptoms and Beta-agonist use during treatment were, as per protocol, stable with tapering. The table below provides summary statistics for those clinical endpoints at the last tolerated dose visit.

Parameter	Treatment	Randomization Visit	Last Tolerated Dose Visit		
		Mean	N	Mean Value	Mean Change
FEV_1(L)	Placebo	2.95	113	2.78	-5.41#
	Montelukast	2.96	113	2.88	-2.73#
	All	2.95	226	2.83	-4.07#
Symptoms (score)	Placebo	1.38	113	1.49	0.12
	Montelukast	1.29	113	1.36	0.07
	All	1.33	226	1.43	0.09
β-Agonist Use (puffs/day)	Placebo	2.83	113	3.19	0.36
	Montelukast	2.35	113	2.64	0.29
	All	2.59	226	2.92	0.33
#: Percent Change					

Subgroup analyses were also conducted investigating potential interactions by sex, age, and race. There was no significant interaction between treatment and any of the subgroups.

Reviewer comment: The following comments regarding Study 046 were communicated to the sponsor by facsimile on October 24, 1997.

Sponsor Response:

1. *Please provide the Case Report Form for Patient 7593.*

This was the only patient excluded from the ITT analysis in Study 046. The case report form was requested so that a spot-check of the rules for exclusion from ITT were followed. In this instance, the patient violated decision rule #8 ("If an AE which was not asthma worsening occurred which may have contributed to a score of 0 or 1 then the last tolerated dose was as defined per protocol i.e. the last dose at which a score of 2 or 3 was obtained." This patient developed a URI between the randomized visit (4) and first post-randomization visit (5) at which time the patient had a clinical score of zero (0). The patient was, therefore, excluded from the

ITT analysis since no valid treatment period data were available. The CRF review confirmed the data handling in this patient.

2. *Please perform and submit inferential statistical analyses of the data presented in Volume 84: page 16638 (appendix 4.8).*

This question attempted to discern if the 'steroid-tapering' effect on the endpoint of Last Tolerated Dose was greater in one of the ICS strata. Interestingly enough, montelukast was statistically superior to placebo for the low ICS stratum (p=0.047); however, this statistical significance was not seen in the high ICS stratum (p=0.439). The sponsor explained this by pointing out that the high dose group had a larger placebo response than the low dose group (39.47% decrease in ICS in the high dose stratum versus 20.89 for the low ICS dose stratum). The percentage decrease in both montelukast groups were comparable (49.13% and 44.93% for high and low ICS strata, respectively). The sponsor stated that this was probably due to the fact that patients in the high dose stratum only had two 'run-in' tapers and may not have made it to their 'minimal' effective dose prior to randomization. This does not explain, however, why the montelukast-treated patients in the high dose stratum did not have a larger response than those in the low dose stratum.

3. *Please submit the data provided in Volume 84: page 16630 broken out by ICS dose strata with inferential statistical comparisons of mean change differences for both all and by strata.*

This question attempted to discern whether there was any difference in FEV1, Daytime Symptom Score, and beta-agonist sparing effects by starting ICS dose. The analysis provided by the sponsor indicated that the effect for both endpoints was consistent across strata.

4. Please perform categorical statistical analyses of the numbers of patients to be successfully completely weaned off inhaled corticosteroids. Total and by strata.

These data are summarized in the table below.

		Successfully Weaned		
Stratum	Treatment	Yes n/%	No n/%	p Value (Fishers)
Low	Montelukast	26 (41%)	38 (59%)	0.707
	Placebo	20 (36%)	36 (64%)	
High	Montelukast	19 (40%)	29 (60%)	0.088
	Placebo	13 (23%)	44 (77%)	
Combined	Montelukast	45 (40%)	67 (60%)	0.094
	Placebo	33 (29%)	80 (71%)	

These data are surprising. Given that the study was not designed or powered to address complete removal of inhaled corticosteroids, the difference between montelukast and placebo in the ability to completely withdraw ICS is remarkable. It is surprising that the effect of montelukast is most pronounced in the high dose ICS stratum. Nevetheless, these data support the ICS steroid sparing effects of montelukast.

5 Please clarify whether and which inhaled corticosteroids used in these trials are US formulations.

Patients were treated with ICS as determined by the local standard of practice for each country. Given that the primary endpoint was the percent change from baseline in ICS requirements, the issue of US versus non-US formulation of ICS is less critical.

Reviewer Conclusion on ICS Steroid Sparing Claim: This study demonstrates that treatment with montelukast allows patients to taper their ICS requirements or, in a minority of cases, even have there inhaled corticosteroids discontinued without serious

deterioration in asthma control over a twelve week treatment period. The fundamental problem with the study design (i.e. allowing different ICS in the treatment period), attaching clinical relevance to the numerical differences seen in the primary endpoint is not possible. Furthermore, given the favorable risk-benefit profile of ICS it remains to be seen whether such a strategy would be in the best interests of all patients who might benefit from therapy in addition to as-needed inhaled beta-agonists (i.e. chronic persistent asthmatics). Nevertheless, this is a well-controlled trial that supports the ICS-sparing effects of montelukast over and above those of placebo. The dilemma of how to represent the trial and the results in product labeling will require further discussion.

5.4.2.1. Study 029 [79:12783]: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, Two-Period, Parallel-Group Study to Assess the Clinical Effect of Montelukast with Concomitant Administration of and Removal of Inhaled Beclomethasone in Asthmatic Patients.

5.4.2.2. Protocol Review

This study had several objectives including comparing the clinical benefit of adding montelukast to existing inhaled beclomethasone as well as comparing the clinical efficacy of montelukast monotherapy to inhaled beclomethasone monotherapy.

In order to achieve these objectives nonsmoking male and non-pregnant female patients between the ages of 15 and 85 were eligible to enter Period I (see schematic below) provided they met the following criteria: FEV1 between 50 and 85% of predicted on a minimum of two of the four prerandomization visits, evidence of reversible airway obstruction (15% FEV1 response to albuterol). Additionally, the patient must have used one of the following inhaled corticosteroids (ICS) (beclomethasone, budesonide, flunisolide, or triamcinolone) for a minimum of six weeks at doses that do not exceed 250 ug twice daily for the seven days before the prestudy visit. After entering the study, all eligible patients were switched to beclomethasone (42 ug/puff ex-actuator) at a dose of four puffs twice daily as well as placebo montelukast tablet once daily in the evening. This commenced the four week, single-blind Period I during which time Daytime Symptom Scores (DSS) and FEV1 were measured to determine eligibility for randomization and to determine baseline values. In order to qualify for randomization, the patients must have had a total DSS of 64 and an average inhaled albuterol use of, at least, 1 puff per day over the last two weeks of Period I.

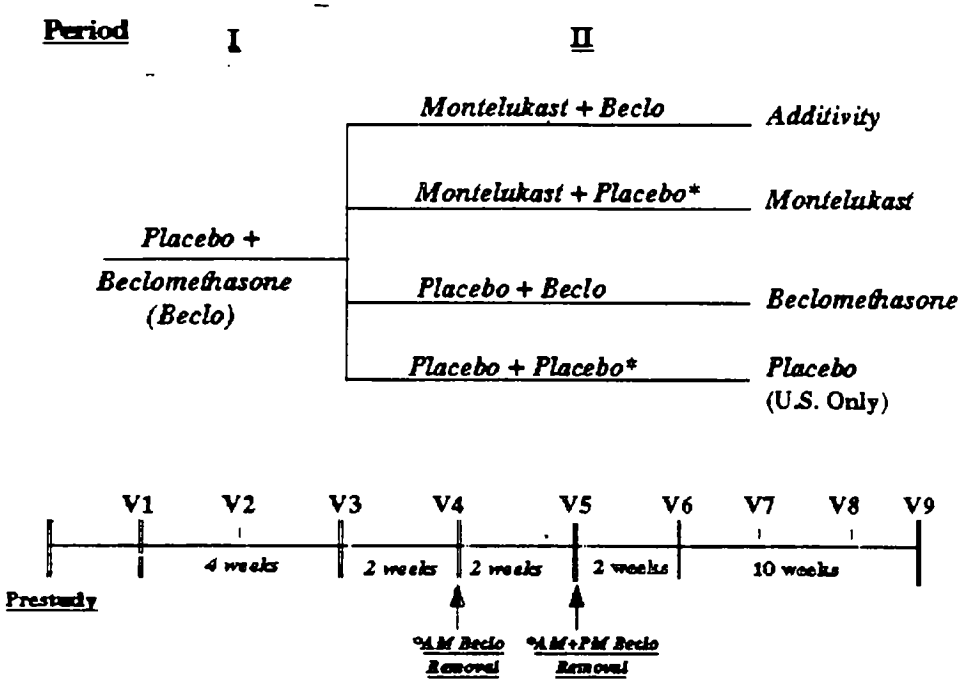
The patients had to be free of other significant pulmonary or other medical conditions. Patients taking oral, IV or IM corticosteroids, inhaled cromolyn/nedocromil, ketotifen oral or long acting inhaled beta-agonists or inhaled anticholinergics within acceptably defined washout periods were ineligible. Other specifically prohibited concomitant medications included warfarin, digoxin, antibiotics, terfenadine/astemizole/loratadine and OTC products containing caffeine, or beta-agonists. Inhaled albuterol and nasal cromolyn were permitted throughout the study. Nasal corticosteroid treatment for greater than one week in any one month period of time during the study was not permitted.

Eligible patients were then be randomized into one of the following four treatment groups

-Montelukast + inhaled beclomethasone for 16 weeks
-Montelukast + inhaled beclomethasone for 2 weeks then inhaled placebo for 14 weeks
-Placebo + inhaled beclomethasone for 16 weeks
-Placebo + inhaled beclomethasone for 2 weeks then inhaled placebo for 14 weeks.

The schematic for the protocol is shown in the figure below.

Study Design



Clinic visits were scheduled at 14 day intervals until visit 6. Subsequently, patients were seen in clinic at approximately three week intervals. Montelukast or montelukast placebo were administered once daily at bedtime without regard to food. Beclomethasone was administered with Aerochamber. Patient compliance was evaluated by tablet counts and by weight of beclomethasone canisters at each visit.

Patients were asked to keep a daily diary in which they recorded and scored daytime asthma symptoms during both Periods of the trial. The following questions were answered on a 0 to 6 scale.

-How often did you experience asthma symptoms today? (0= none, 6= all)
-How much did your asthma symptoms bother you today? (0=not at all, 6= severely)
-How much activity could you do today? (0=more than usual, 6= less than usual)
-How often did your asthma affect your activities today? (0=none, 6=all the time).

Patients were also asked to record the total number of puffs of albuterol used during the day, the AM PEFR, the pre-bedtime PEFR and the overnight asthma symptom score. In order to address this last parameter the patient answered the question "Did you wake up with asthma?" and quantify the number of puffs of albuterol used since going to bed. PEFRs was recorded as the best of three efforts

The schedule of procedures for the entire study is summarized in the table below.

Order of Procedures	Weeks / Visit	Prestudy	Period I: 0 / 1	2 / 2	4 / 3	Period II: 5 / 4	8 / 5	10 / 6	12 / 7	16 / 8	20 / 9	D
Informed consent		X										
Patient's global evaluation											X	X
Asthma-specific Quality-of-Life Questionnaire					X		X				X	X
Inclusion/exclusion criteria		X			X							
Clinical history		X										
Patient demonstrated competence in study procedures			X	X	X							
Reviewed concomitant therapy		X	X	X	X	X	X	X	X	X	X	X
Reviewed prestudy laboratory results			X									
Reviewed adverse experiences				X	X	X	X	X	X	X	X	X
Diary card collected and reviewed with patient[1]			X	X	X	X	X	X	X	X	X	X
Beclomethasone/placebo and albuterol inhalers returned			X	X	X	X	X	X	X	X	X	X
Tablets (montelukast/placebo) returned/counted				X	X	X	X	X	X	X	X	X
ECG (12-lead)		X			X						X	X
Chest x-ray or report reviewed -- required if entering Period II and not performed within past 12 months				X								
Vital signs (sitting BP, HR, RR, and oral temperature)		X	X	X	X	X	X	X	X	X	X	X
Screening number provided		X										
Allocation number provided					X							
Spirometry (FEV_1, FVC)[3]						X		X	X	X		
Spirometry (FEV_1, FVC) β-agonist reversibility[3]		X	X	X	X		X				X	X
Reviewed action plan for worsening asthma		X	X	X	X	X	X	X	X	X		
Laboratory safety tests[2]		X			X		X	X			X	X
Serum β-hCG pregnancy test (females only)[4]		X					X				X	X
Urine β-hCG pregnancy test (females only)					X	X		X	X	X		
Plasma samples for archiving					X		X				X	X
Physical examination		X									X	X
Physician's global evaluation											X	X
Beclomethasone/placebo and albuterol inhalers dispensed		X	X	X	X	X	X	X	X	X		
Tablets (montelukast/placebo) dispensed			X	X	X	X	X	X	X	X		
Diary card dispensed		X	X	X	X	X	X	X	X	X		

D = Discontinuation

1 The study coordinator reviewed the diary card to determine if the patient achieved the inclusion criteria and could be randomized.

2 Patient was asked not to perform strenuous exercise 3 days before a visit with laboratory safety tests.

3 Spirometry was done as the first procedure, after the Quality-of-Life Questionnaire, in order to have pre-meal spirometry testing performed between 0800 and 0900 AM.

4 The last pregnancy test was done 14 days after Visit 9 or Visit D.

If during Period I, a patient's asthma worsens and rescue with antiasthma medication other than albuterol was required, the patient was to be dropped from the protocol. If this occurs during Period II, the patient was to be treated in accordance with the algorithm outlined in Appendix 3.2 [79:12874]. If a patient required more than two rescues during Period II, the patient was discontinued from the study.

Two primary endpoints (FEV1 and Daytime Symptom Scores) were designated for comparisons between the montelukast plus beclomethasone versus beclomethasone only arms using ANOVA. This comparison was performed over the entire 16 week treatment period. A confidence interval comparison of the effects observed in the montelukast only versus beclomethasone only groups was proposed in order to assess comparability. The comparisons between the montelukast-only, beclomethasone-only and placebo groups was made over the last 10 weeks of the treatment in order to minimize the confounding effect due to administration of beclomethasone (in the montelukast and placebo groups) during the first 4 weeks of the treatment period. This allowed for washout of the beclomethasone treatment effect. Secondary endpoints included beta-agonist use, PEFRs, nocturnal awakenings, patient/physician globals, discontinuations due to asthma, number of rescues and asthma-specific quality of life evaluations. With regard to the latter endpoint, the self-administered questionnaire was completed at Visits 3, 5, and 9. No predefined total or domain-specific minimal important difference MID was declared in the protocol.

Two approaches to the data were to be used. The primary approach employed an ITT principle in which all individuals with efficacy measurements both at baseline an post-randomization were evaluated.

It is planned that approximately 1000 patients would enter Period I and that 750 patients (12 per center) would be randomized into Period II to allow completion of approximately 650 patients (200 in Groups A, B, and C and 50 in D). This was calculated to provide 95% power to dectect a 9.4 L difference in FEV1 and assumed 16.5% variability of the endpoint. Randomization was performed centrally [Appendix 3.8; 80:13379].

5.4.2.3. Results of Study 029

This study was conducted at seventy sites (22 US/ 48 International) in 17 countries in North America, Europe, Africa, Australia, Southeast Asia). A complete list of investigators may be found in Appendix 3.5 [79:12975] of the study report.
Patient Characteristics: 642 patients were randomized at Visit 4 (193 to montelukast + beclomethasone/ 199 to beclomethasone only, 201 to montelukast only and 48 to placebo) of which 48.6% were females and 91.9% were Caucasians. The vast majority of patients (88.5%) were between the ages of 18 and 65. Forty-four patients (6.9%) were older than 65 years of age [78:12433]. The mean baseline values for clinical endpoints for each treatment group are shown in the table below [78:12447].

Variable	*Beclo + Montelukast n=199*	*Beclomethasone n=199*	*Montelukast n=201*	*Placebo n=48*
FEV1 (L)	2.61	2.59	2.61	2.45
FEV1 (% Predicted)	71.64	71.02	72.44	71.20
Daytime Sxs (0-6)	2.17	2.17	2.14	2.36
B agonist use (puffs/day)	3.41	3.51	3.52	4.16
AM PEFR (L)	412.46	402.91	419.34	406.80
Awakenings per week	2.48	2.10	2.43	3.35

Of the 642 randomized patients, 614 (95.6%) had at least one secondary diagnosis. The majority of these involved respiratory system disorders predominantly allergic rhinitis (73.5-89.6% across treatment groups) [80:13985]. There were no significant differences in frequency or type of secondary diagnoses. Similar findings were noted for medications taken prior to study entry. Comparable numbers of patients in the four treatment groups (range 82-89.6%) took such medications the most common of which were OTC analgesics, antihistamines, oral contraceptives, and terbutaline (non-US patients)[80:13999]. Of the randomized patients, 87.2% took at least one concomitant medication during Period II. Again, the most commonly used medications included OTC analgesics, antihistamines, oral contraceptives. Prednisone was used more frequently in the placebo group (37.5%) than the other groups (3.6% for montelukast + beclomethasone, 10% for beclomethasone only, and 22.9% for montelukast only) [78:12475].

Dropouts

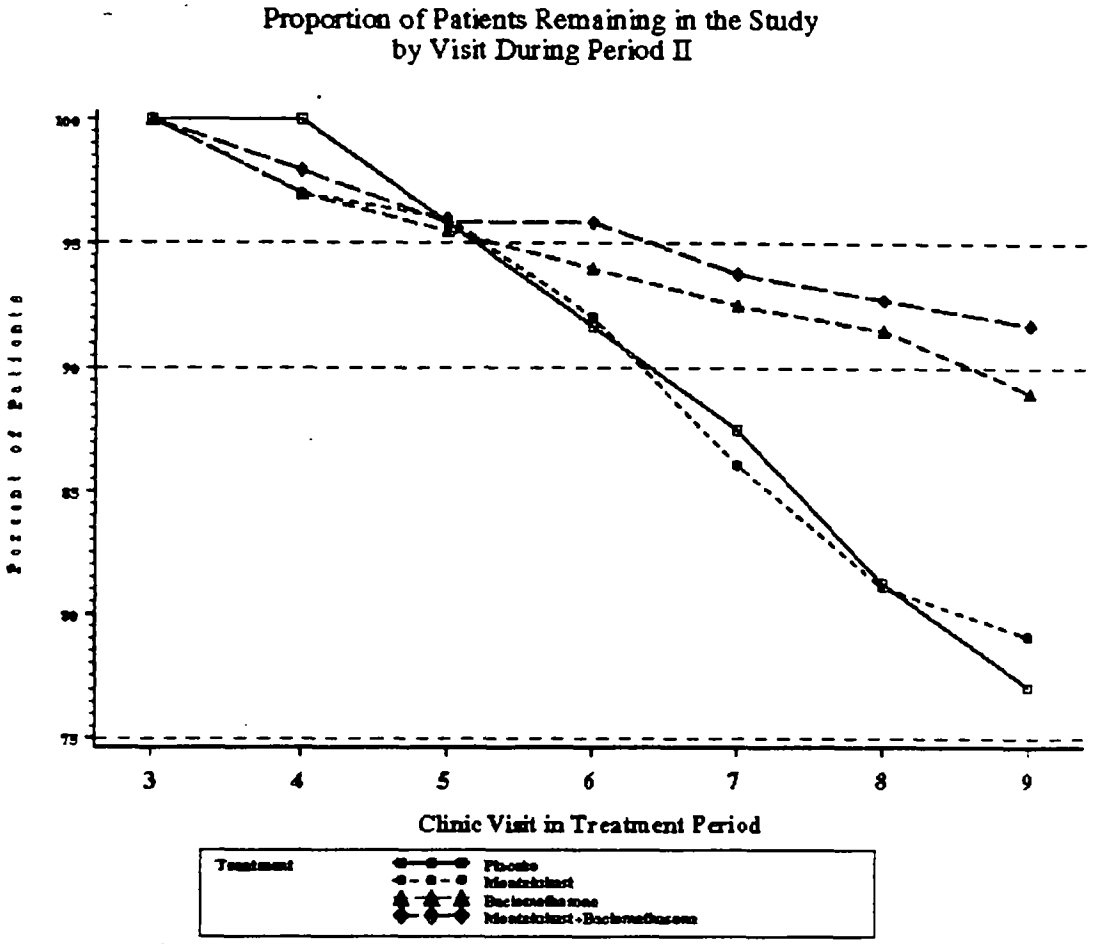
Of the 642 randomized patients, 551 (85.8%) completed the study. The reasons for dropout are summarized in the table below [78:12466]. The majority of adverse events (n=40, 81.6%) leading to discontinuation were related to asthma exacerbation/asthma attack.

	Total	Placebo[1,2]	Montelukast[2]	Beclomethasone	Montelukast + Beclomethasone
RANDOMIZED: Total	642	48	201	200	193
DISCONTINUED: Total	91 (14.2%)	11 (22.9%)	42 (20.9%)	22 (11.0%)	16 (8.3%)
Clinical adverse experience	49 (7.6%)	7 (14.6%)	27 (13.4%)	9 (4.5%)	6 (3.1%)
Laboratory adverse experience	3 (0.5%)	1 (2.1%)	0	2 (1.0%)	0
Patient withdrew consent	25 (3.9%)	3 (6.3%)	10 (5.0%)	4 (2.0%)	8 (4.1%)
Protocol deviation	11 (1.7%)	0	5 (2.5%)	5 (2.5%)	1 (0.5%)
Lost to follow-up	3 (0.5%)	0	0	2 (1.0%)	1 (0.5%)
COMPLETED: Total	551 (85.8%)	37 (77.1%)	159 (79.1%)	178 (89.0%)	177 (91.7%)

[1] U.S. sites only
[2] After blinded removal of beclomethasone

Discontinuations due to asthma exacerbation as a percentage of patients randomized is 1% for montelukast + beclomethasone (2/193), 10.9% for montelukast (22/201), 4.5% for

beclomethasone (9/200), and 14.6% for placebo (7/48). These numbers were determined from cross-checking the CRF listings with the randomization code [80:13379]. The proportion of patients remaining in the double-blind portion of the study are graphically in the figure below and support the efficacy conclusions discussed later.



Auditing and Checking

The following case report forms accompanied the study report in electronic format and available through the CANDA as PDF graphic images.

029-003	6996	Plit, Michael	Asthma Attack	15075
029-005	6964	Ringdal, Nils Ragnar	Common Cold	15213
029-009	6138	Becker, Allan B	Asthma,exacerbation	15405
029-009	6145	Becker, Allan B	Asthma,worsening	15643
029-013	6222	Hebert, Jacques	Asthma,exacerbation	15843
029-013	6274	Hebert, Jacques	Asthma,worsening	16019
029-013	6287	Hebert, Jacques	Asthma,worsening	16255
029-014	6174	Chapman, K	Asthma,worsening	16435
029-015	6821	Trakopoulos, George	Asthma,worsening	16667
029-015	6827	Trakopoulos, George	Asthma,worsening	16867
029-018	6808	Polyehronopoulos, Vl	Asthma,worsening	17091

029-019	6761	Brandli, O	Gastrointestinal Symptoms	17203
029-024	6234	Ernst, Pierre	Asthma,exacerbation	17337
029-026	6738	Saint-Remy, Jean-Mar	Eczema	17565
029-027	1390	Chervinsky, Paul	Serum Pregnancy Test Positive	17787
029-027	1702	Chervinsky, Paul	Asthma Attack	17981
029-028	1394	Condemi, John J.	Asthma,exacerbation	18191
029-028	1395	Condemi, John J.	Asthma,worsening	18293
029-028	1397	Condemi, John J.	Asthma,exacerbation	18447
029-029	1409	Galant, Stanley J.	Asthma,exacerbation	18579
029-030	1424	Gross, Gary	Asthma,exacerbation	18721
029-030	1426	Gross, Gary	Asthma,worsening	18899
029-030	1428	Gross, Gary	Asthma,worsening	19079
029-031	1445	Laforce, Craig	Asthma,exacerbation	19265
029-032	1466	Noonan, Michael J.	Serum Pregnancy Test Positive	19447
029-033	1506	Southern, D. Loren	Asthma,exacerbation	19595
029-034	1492	Segal, Allen	Asthma Attack	19751
029-035	6788	Dahl, Ronald	Gastritis	19893
029-035	6791	Dahl, Ronald	Asthma,worsening	20023
029-036	6772	Petersen, Bruno Nuch	Asthma,worsening	20225
029-036	6778	Petersen, Bruno Nuch	Asthma,worsening	20459
029-036	6784	Petersen, Bruno Nuch	Asthma,worsening	20695
029-037	6945	Woodcock, A	Influenza	20869
029-038	6893	Britton, Mark G	Asthma,worsening	21081
029-042	6909	Holgate, Stephen T	ALT Increased	21271
029-046	1360	Berger, W. E.	Asthma,worsening	21515
029-046	1362	Berger, W. E.	Asthma,worsening	21671
029-047	1537	Storms, William	Asthma,worsening	21843
029-052	6083	Kunkel, G	Cold	21951
029-054	6067	Vetter, Norbert	Parkinson's Disease	22179
029-054	6075	Vetter, Norbert	Asthma,exacerbation	22363
029-058	6166	Laviolette, Michel	Asthma,exacerbation	22503
029-058	6169	Laviolette, Michel	Hypertension	22715
029-059	6259	Fitzgerald, Mark J	Asthma,worsening	22919
029-060	6341	Stark, Donald F	Asthma,exacerbation	23089
029-060	6343	Stark, Donald F	Asthma,worsening	23307
029-061	6297	Blackie, Stephen	Asthma,worsening	23429
029-061	6307	Blackie, Stephen	Asthma,worsening	23639
029-062	6387	Day, James H	Asthma,exacerbation	23833
029-063	6364	Patel, Piyush	Asthma,exacerbation	24027
029-064	6184	Moote, William	Infection,respiratory	24245
029-068	1616	Reibman, J.	Asthma Attack	24427

Data from the first five (5) US-derived CRFs (Patient #'s: 1390, 1702, 1394. 1395, and 1397) were cross-referenced to the electronically submitted case report tabulations (line listings). No discrepancies were noted for selected laboratory, efficacy values, or designated treatment allocation.

There were no deaths in this trial. A qualitative review of the CRFs associated with these patients is contained in the ISS section of this review.

Efficacy Results

FEV1

Over the entire 16-week treatment period, the combination of montelukast and beclomethasone was statistically superior to beclomethasone as well as placebo. Beclomethasone was statistically significantly better than placebo and numerically superior to montelukast alone (p=0.099). The ITT results over the last 10 weeks of Period II are shown in the table below [78:12469]. The results of the per-protocol analysis were similar.

Analysis of FEV_1 (Average Over Last 10 Weeks of Treatment Period)
(Intention-to-Treat Approach)

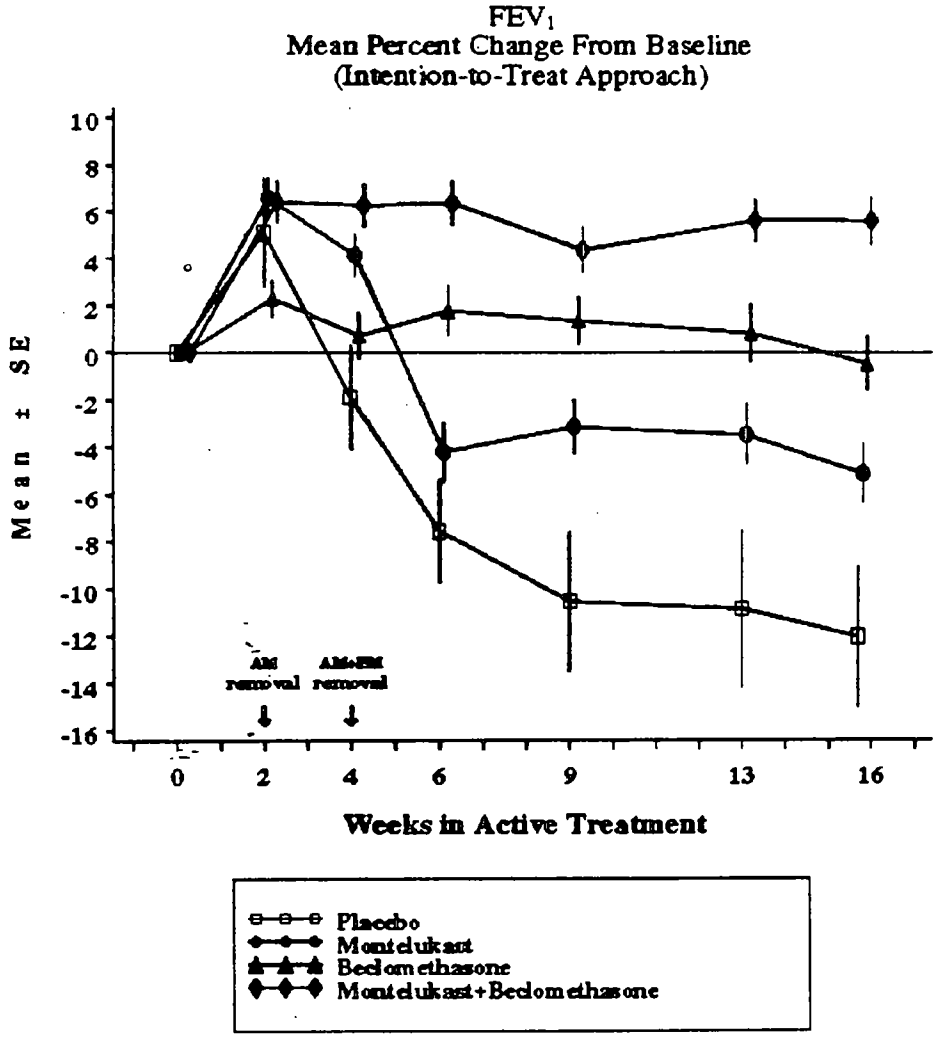
Treatment	N	Mean (L) Baseline	Mean (L) Treatment Period	Percent Change From Baseline Mean	SD	LS Mean	95% CI for Mean
Placebo	44	2.50	2.23	-11.45	16.91	-11.96	(-16.28, -7.64)
Montelukast	183	2.62	2.51	-5.02	13.79	-5.31	(-7.32, -3.30)
Beclomethasone	188	2.55	2.56	0.55	12.78	0.52	(-1.48, 2.53)
Montelukast+Beclomethasone	185	2.60	2.73	4.89	10.48	4.70	(2.67, 6.73)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast + Beclomethasone vs Beclomethasone	0.002	4.18	(1.55, 6.81)
Montelukast vs Beclomethasone	<0.001	-5.83	(-8.50, -3.17)
Placebo vs Beclomethasone	<0.001	-12.48	(-17.18, -7.79)

p-Value For Effect	
Treatment	<0.001
Study center	0.395

Root MSE of Percent Change = 12.77

These findings are represented graphically in the figure below [78:12471].

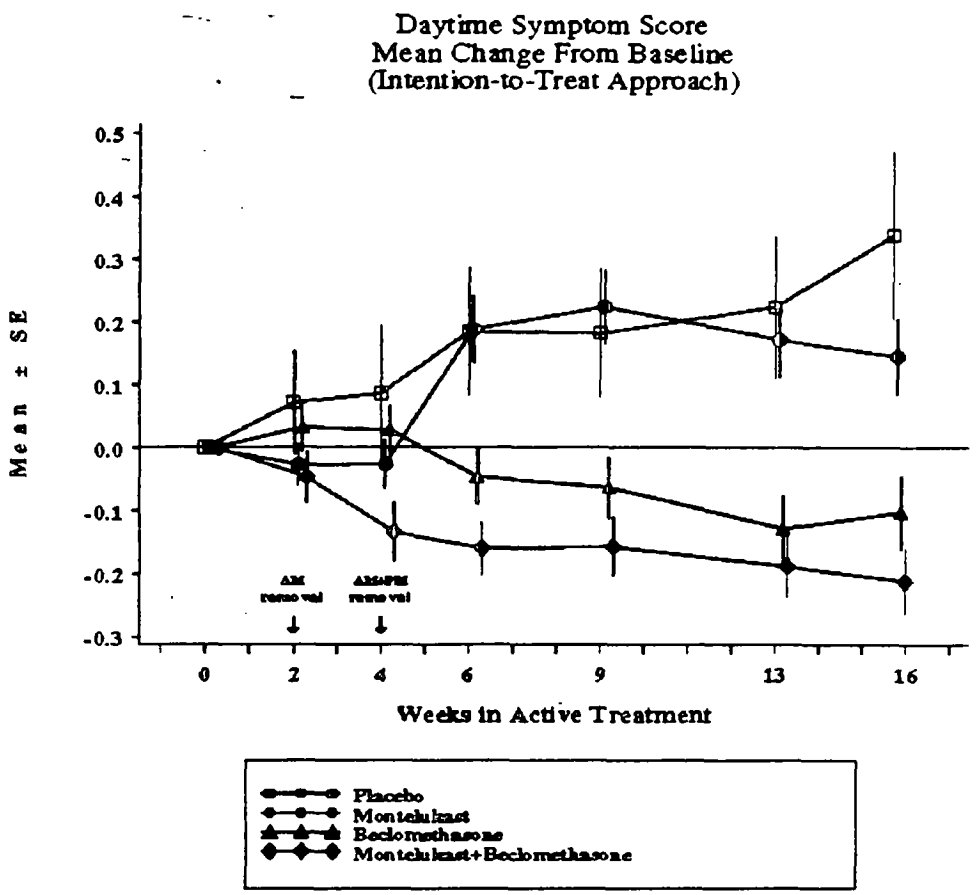


Time Course for FEV1: Summary and inferential statistics of the visit-by-visit data were also provided and are summarized in the table below [80:13689].

Visit	*M + B*	*M Alone*	*Beclo Alone*	*Placebo*	*p Value*
Baseline (L)	2.60	2.60	2.50	2.45	NS
Visit 4 (% Change)	6.41	6.58	2.29	5.09	M+B>B B>M,P
Visit 5	6.26	4.13	0.71	-1.88	M+B>B B>M
Visit 6	6.36	-4.21	1.76	-7.56	M+B>B B>M,P
Visit 7	4.35	-3.13	1.35	-10.55	M+B>B B>M,P
Visit 8	5.61	-3.48	0.81	-10.86	M+B>B B>M,P
Visit 9	5.60	-5.12	-0.47	-12.05	M+B>B B>M,P
Last Available Visit	5.50	-5.96	-0.45	-10.77	M+B>B B>M,P

Daytime Symptom Scores

This was the co-primary endpoint and the results (ITT analysis) are shown in the figure below [78:12475].



As can be seen, patients who were withdrawn from beclomethasone and randomized to either montelukast or placebo deteriorated over the course of Period II. On average, patients who remained on beclomethasone and received concomitant montelukast or placebo improved or remained stable. The difference between these groups over the 16 week period was statistically significant at p=0.041. Both groups containing beclomethasone as a component were statistically superior to montelukast or placebo monotherapy. Over the last 10 weeks of the study, the difference between montelukast plus beclomethasone and montelukast did not retain statistical significance; however, the magnitude of the effect of the combination was greater than beclomethasone alone (18% improvement for M+B versus 8% improvement for beclomethasone alone). Beclomethasone remained statistically significantly better than montelukast or placebo monotherapy over the last 10 weeks. These results are shown in the table below [78:12473].

Analysis of Daytime Symptom Score (Average Over Last 10 Weeks of Treatment Period)
(Intention-to-Treat Approach)

Treatment	N	Mean (Score)		Change From Baseline			
		Baseline	Treatment Period	Mean	SD	LS Mean	95% CI for Mean
Placebo	44	2.37	2.69	0.32	0.72	0.31	(0.08, 0.54)
Montelukast	183	2.13	2.39	0.27	0.76	0.27	(0.17, 0.38)
Beclomethasone	188	2.17	2.09	-0.08	0.68	-0.09	(-0.20, 0.02)
Montelukast+Beclomethasone	185	2.17	1.99	-0.18	0.61	-0.18	(-0.29, -0.07)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast + Beclomethasone vs Beclomethasone	0.207	-0.09	(-0.23, 0.05)
Montelukast vs Beclomethasone	<0.001	0.36	(0.22, 0.50)
Placebo vs Beclomethasone	0.002	0.40	(0.15, 0.65)

p-Value For Effect	
Treatment	<0.001
Study center	0.050

Root MSE of Change = 0.68

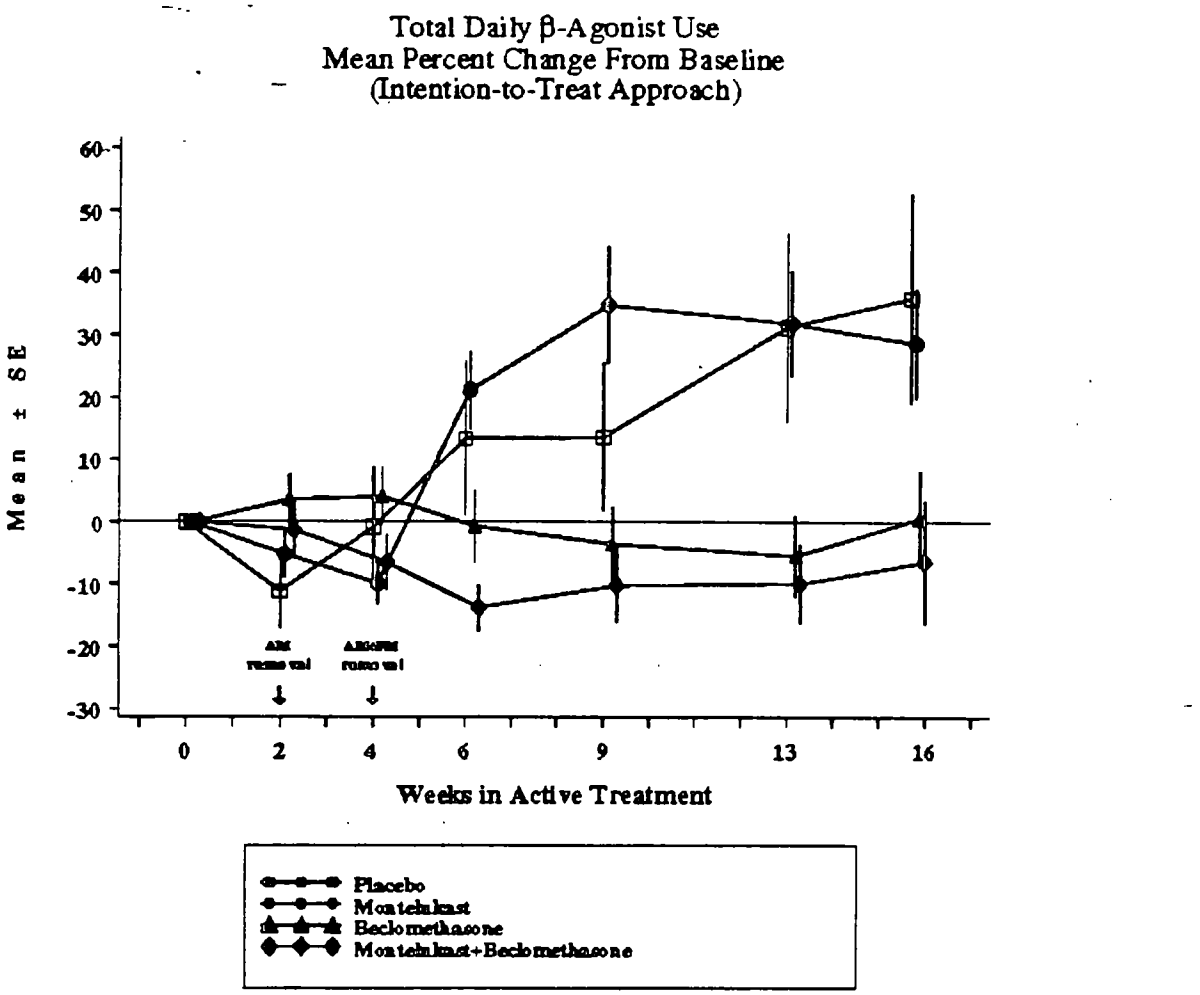
Time Course for Daytime Symptoms: Summary and inferential statistics of the visit-by-visit data were also provided and are summarized in the table below [80:13689].

Visit	*M + B*	*M Alone*	*Beclo Alone*	*Placebo*	*p Value*
Baseline (L)	2.18	2.16	2.18	2.36	NS
Visit 4 (% Change)	-0.05	-0.03	0.03	0.07	NS
Visit 5	-0.13	-0.03	0.03	0.09	M+B>B
Visit 6	-0.16	0.19	-0.05	0.18	B>M
Visit 7	-0.16	0.22	-0.06	0.18	B>M
Visit 8	-0.19	0.17	-0.13	0.22	B>M,P
Visit 9	-0.21	0.15	-0.10	0.34	B>M,P
Last Available Visit	-0.19	0.21	-0.08	0.33	B>M,P

Secondary Endpoints

Beta-agonist Use

The total daily beta-agonist use as a mean percent change from baseline is shown in the following figure. The mean daily baseline beta-agonist requirements for all groups ranged from 3.38 to 4.16 puffs.



As can be seen, the placebo and montelukast monotherapy groups deteriorated after withdrawal of beclomethasone. Statistically significant differences between the montelukast + beclomethasone and the beclomethasone-only groups was not demonstrated in either the 16 week or last 10 week ITT analyses. Beclomethasone was statistically better than montelukast monotherapy and placebo in both analyses [78:12478].

Peak Expiratory Flow Rates (PEFRs)

For AM PEFRs, the mean baseline values were comparable and ranged from 406.80 to 419.43 L/min. Statistically significant differences between the montelukast + beclomethasone versus the beclomethasone-only group was demonstrated in the 16 and 10 week analyses. Beclomethasone was statistically better than montelukast monotherapy and placebo for both analyses [78:12482]. For PM PEFRs, the mean baseline values were comparable and ranged from 416.33 to 430.38 L/min. Although the montelukast + beclomethasone treatment arm was numerically superior to beclomethasone, the difference was not statistically significant. Beclomethasone was statistically significantly better than montelukast monotherapy and placebo [78:12500]. The tables below summarize the findings.

Analysis of AM PEFR (Average Over Last 10 Weeks of Treatment Period)
(Intention-to-Treat Approach)

Treatment	N	Mean (L/min) Baseline	Mean (L/min) Treatment Period	Change From Baseline Mean	SD	LS Mean	95% CI for Mean
Placebo	44	412.28	386.82	-25.46	44.62	-27.10	(-38.96, -15.25)
Montelukast	184	419.88	404.61	-15.27	39.46	-15.37	(-20.87, -9.87)
Beclomethasone	187	406.07	409.96	3.89	31.07	4.01	(-1.50, 9.53)
Montelukast+Beclomethasone	185	411.17	422.89	11.72	31.44	11.43	(5.85, 17.00)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast + Beclomethasone vs Beclomethasone	0.044	7.41	(0.19, 14.64)
Montelukast vs Beclomethasone	<0.001	-19.38	(-26.70, -12.06)
Placebo vs Beclomethasone	<0.001	-31.12	(-44.05, -18.19)

p-Value For Effect	
Treatment	<0.001
Study center	0.502

Root MSE of Change = 35.06

Analysis of PM PEFR (Average Over Last 10 Weeks of Treatment Period)
(Intention-to-Treat Approach)

Treatment	N	Mean (L/min) Baseline	Mean (L/min) Treatment Period	Change From Baseline Mean	SD	LS Mean	95% CI for Mean
Placebo	44	424.29	406.53	-17.76	45.37	-19.11	(-29.90, -8.32)
Montelukast	184	432.07	419.82	-12.26	35.75	-12.32	(-17.33, -7.31)
Beclomethasone	188	419.05	422.48	3.43	28.18	3.34	(-1.67, 8.35)
Montelukast+Beclomethasone	185	428.51	434.31	5.80	28.75	5.68	(0.60, 10.75)

Comparison Between Treatments	p-Value	LS Mean	95% CI for Difference
Montelukast + Beclomethasone vs Beclomethasone	0.486	2.33	(-4.24, 8.91)
Montelukast vs Beclomethasone	<0.001	-15.67	(-22.32, -9.01)
Placebo vs Beclomethasone	<0.001	-22.45	(-34.20, -10.71)

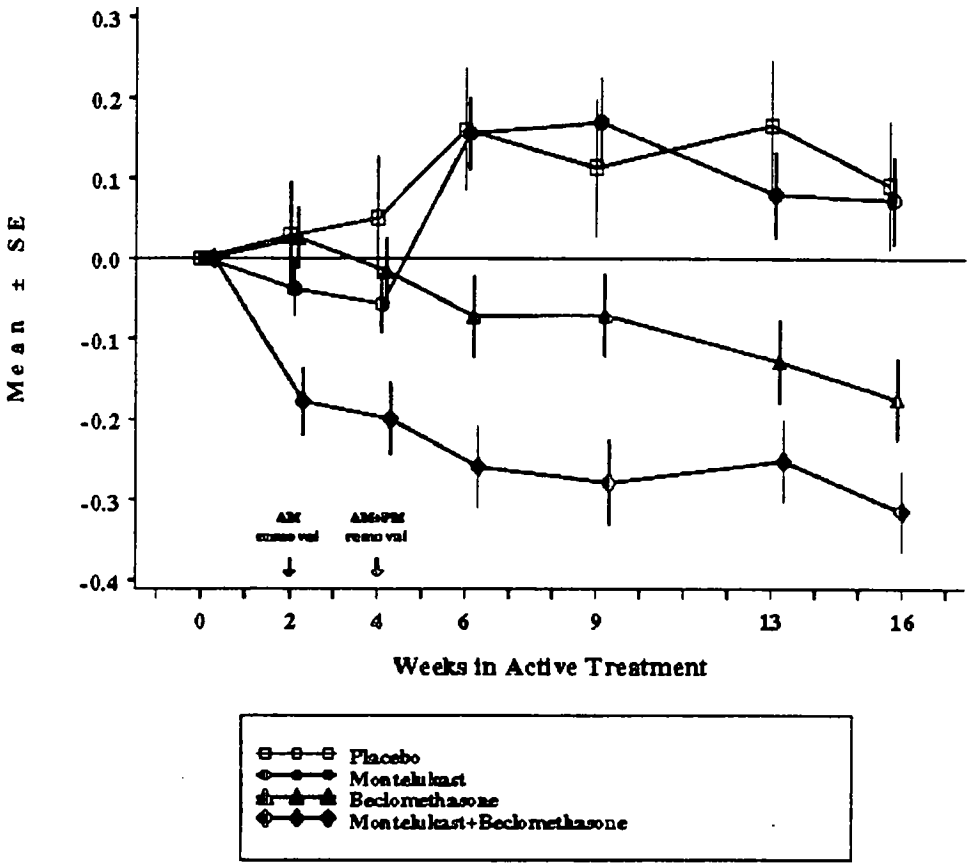
p-Value For Effect	
Treatment	<0.001
Study center	0.131

Root MSE of Change = 31.93

Nocturnal Asthma Score

The figure below shows the mean change from baseline in nocturnal asthma score over the 16 week treatment period in the prespecified subset of nocturnal asthmatic patients. The montelukast plus beclomethasone group demonstrated a significant improvement versus beclomethasone monotherapy (p=0.010). The M + B group was not superior to beclomethasone when analyzed over the 10 week treatment period. Beclomethasone monotherapy was statistically superior to montelukast monotherapy and placebo over the 16 and 10 week analysis periods.

Nocturnal Asthma Score--Nocturnal Asthmatic Patients Only
Mean Change From Baseline
(Intention-to-Treat Approach)



Other Endpoints

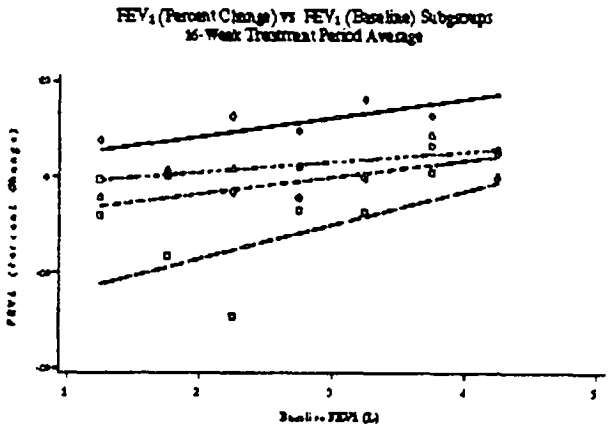
Montelukast plus beclomethasone was superior to beclomethasone alone for physician's but not patient's global evaluations [78:12506].

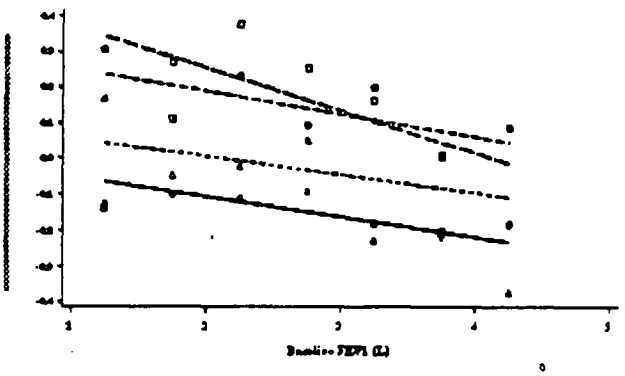
For asthma-specific quality of life, four domains were analyzed (activity, symptoms, emotions, and environment). In the last available visit day assessments, montelukast plus beclomethasone was not superior to beclomethasone alone for any domain. Beclomethasone was superior to montelukast and placebo for the domains of symptoms and emotions while beclomethasone was only superior to montelukast for the domains of activity and environment [78:12510]. MID criteria (0.5 unit MID) were not met for any of the between group comparisons for the overall or any individual QOL domain (except Symptoms in which M+B was 0.51 greater than placebo) over the 16 week treatment period.

For the endpoint of asthma exacerbation, montelukast plus beclomethasone was statistically superior to beclomethasone monotherapy. Beclomethasone was statistically superior to montelukast monotherapy and placebo over the sixteen week treatment period [78:12529]. The same trends were noted for the endpoint of asthma attacks and need for corticosteroid rescue [78:12533].

Subgroup Interactions and Treatment Consistency:

Treatment effects were consistent across all subgroups (race, age, sex). Analyses of response by baseline values were conducted. The following figures demonstrate the consistency of response for the primary efficacy variables FEV1 and Daytime Symptom Scores.





Reviewer Information Requests: The following comment was communicated to the sponsor.

Please clarify whether and which inhaled corticosteroids used in this trials are US formulations.

The inhaled beclomethasone was the US formulation

Reviewer Conclusions on Study 029: This study had several important findings. First, in patients who are 'controlled' on inhaled beclomethasone, it is better to leave them on beclomethasone rather than switching them to montelukast. Secondly, it does not appear that adding montelukast to an existing beclomethasone regimen significantly improves asthma control as represented by Daytime Asthma Symptoms, backup beta-agonist use, or nocturnal asthma scores. Although montelukast added to beclomethasone was superior to beclomethasone alone for the endpoint of FEV1, the initial dose of beclomethasone was low (four puffs of 42 mcg/puff twice daily) and the study did not ask the more relevant question of whether it is safer and more effective to titrate beclomethasone to desired effect or to add montelukast to the existing 'subtherapeutic' regimen of beclomethasone. In this light, this study does not support a claim for montelukast to be used as an adjuvant to beclomethasone or other ICS therapy. In fact, it

confirms the finding of Study 020 that low dose beclomethasone is more effective than montelukast in the treatment of mild to moderate asthma.

5.5 Long-Term Efficacy of Montelukast in Asthma

A Long-Term Efficacy Update Report (LTEUR) was submitted to the NDA on September 4, 1997. The report provided an updated cumulative data on efficacy from the open-label extension periods of adult studies 009, 015, 020 and 031 and the pediatric efficacy trial (049). As of December 6, 1996 (cut-off period for LTEUR) a cumulative total of 944 adult and 245 pediatric patients with asthma have been treated with montelukast or active comparator in the extension trials. The data provided in the LTEUR focus on studies 020 and 031. These data are not blinded or placebo-controlled and were not obtained from a randomized cohort (participation in extension periods was optional); however, they do support the claim that montelukast provides long-term control of asthma without tolerance/tachyphylaxis.

5.6 Studies of Airway Inflammation

5.6.1 Antigen Challenge Studies

Study 050 [70:7092]: A Double-Blind, Placebo-Controlled, Randomized, 2-Period Crossover, Multiple-Dose Montelukast Antigen Challenge Study in Mild Asthmatics.

and

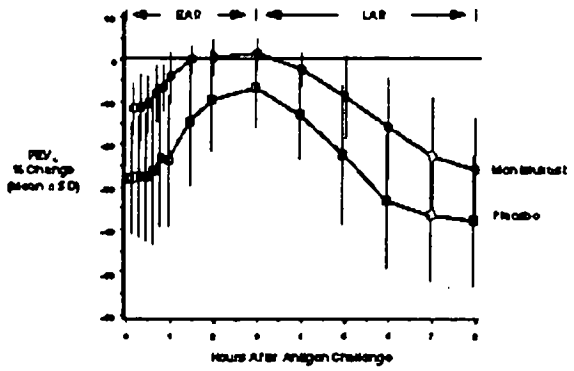
Study 056 [85:17239]: A Double-Blind, Placebo-Controlled, Parallel-Group Study Investigating the Ability of Montelukast to Affect Inflammatory Parameters in the Airways of Asthmatics.

The patient's age and FEV1 at baseline for the Antigen Challenge and Sputum Studies (Protocols 050 and 056,respectively) are summarized in Table D-27. Antigen challenge is used as a preclinical and clinical model to study asthma. It causes early (0 to 3 hours) and late (3 to 8 hours) bronchoconstriction after the challenge as well as the cellular influx of cells. The table below indicates the baseline characteristics of the patients enrolled in the two trials.

Study	N[1]	Montelukast Daily Dose (mg)	Description	Treatment Duration	Median Age Years (Range)	FEV$_1$ % Predicted (Mean ± SD)
Protocol 050[2]	12	10	Antigen Challenge	3 days	25.0 (20 to 36)	90.0 ± 9.3[3]
Protocol 056[4]	40	10	Sputum	4 weeks	26.0 (19 to 66)	69.1 ± 12.9

[1] Number of patients randomized
[2] Crossover study
[3] Parallel-group study
[4] Measured at pre-study

Antigen challenge (house dust mite) was performed after 2 days of montelukast, or placebo therapy. The figure and table below show montelukast, compared with placebo, significantly inhibited the EAR (75.4%) and LAR (56.9%) as measured by the AUC.



Endpoint	Percent Inhibition Versus Placebo	
	EAR	LAR
AUC (% fall FEV_1 •hr)	75.4*	36.9*
Maximum fall in FEV_1	53.6*	36.4*
* p ≤ 0.050, compared with placebo EAR = early asthmatic response LAR = late asthmatic response		

5.6.2. Peripheral Blood Eosinophils

As part of the safety evaluations in the Phase 2 and 3 studies, eosinophils counts were performed at baseline and at various post-randomization timepoints. A consistent finding in these studies was the decrease in peripheral blood eosinophils in patients treated with montelukast, shown in the table below. Eosinophils were decreased by up to 29.5%, compared with placebo. No other cell types showed a similar change. In Study 020, compared with placebo, montelukast decreased the peripheral blood eosinophils to the same extent as beclomethasone (200 mg twice daily with a spacer device) -0.06 and -0.05 10 3 /mL, respectively; 21.1% for montelukast and 20.0% for beclomethasone.

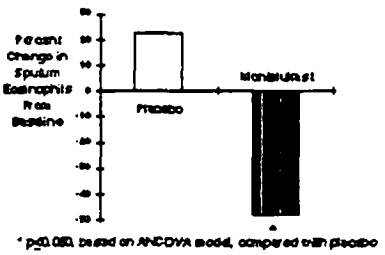
Study	N*	Treatment Duration (Weeks)	Mean Baseline Eosinophils ($10^3/\mu L$)	Difference in LS Mean† (95% CI) MONT-PBO	Percent Change in Eosinophils‡
Protocol 009	339	6	0.28	-0.03 (-0.07, 0.02)	-10.7
Protocol 025	277	3	0.29	-0.06 (-0.12, 0.00)	-20.7
Protocol 020	522	12	0.37	-0.05 (-0.10, -0.00)	-16.2§
Protocol 051	677	12	0.32	-0.04 (-0.07, -0.02)	-12.5§
Protocol 042	109	12	0.26	-0.04 (-0.10, 0.02)	-15.4
Protocol 056	38	4	0.44	-0.13 (-0.23, -0.04)	-29.5§
* Number of patients randomized into the montelukast and placebo groups included in the primary analysis † Least square mean ‡ Compared with placebo § p ≤ 0.050 compared with placebo					

In Study 029 (Additivity/Removal Study), all patients were using inhaled beclomethasone prior to randomization. Complete removal of beclomethasone in patients randomized to the placebo group caused the peripheral blood eosinophil levels to rise approximately 39%, from 0.23 x 10 3 /mL to 0.32 x 10 3 /mL. In patients using montelukast, the complete removal of beclomethasone did not increase the eosinophil counts significantly and were similar to that of the beclomethasone group; 0.28 x 10 3 /mL compared with 0.26 x 10 3 /mL. The patients receiving montelukast plusbeclomethasone had less eosinophils compared with the beclomethasone group, after 16 weeks of treatment.

5.6.3 Airway Eosinophils

The effect of montelukast on airway eosinophils was evaluated in two trials. In the Sputum Study 056 [85:16758], sputum eosinophils at baseline (percent of non-squamous cells) in the montelukast and placebo groups were 7.5 and 14.5%, respectively. Montelukast treatment for 4 weeks caused a 48% reduction from baseline in sputum eosinophils compared with a 23%

increase in placebo ($p < 0.050$, based on ANCOVA), as shown in the figure below. No other cell types were affected.



The final results of the Bronchial Biopsy Study 059 [85:17239 were not submitted in the NDA. They were, nowever, submitted to the IND on November 5, 1997. In the study, the first laboratory deviated from protocol-defined procedures in the reading of the bronchial biopsy specimens. The specimens were analyzed by a second laboratory and there was no significant difference noted between montelukast and placebo for the endpoints of the number of total and activated eosinophils and tryptase-positive cells in the bronchial submucosa after six weeks of treatment.

Reviewer Comments on Airway Inflammation Trials: While the data generated from these trials support the effect of montelukast on blood and airway eosinophil populations and the ability to mediate the late phase response to antigen challenge, they do not support the categorization of montelukast as an anti-inflammatory agent. These data may be represented in the product label; however, they may not be used to support the labeling of montelukast as "anti-inflammatory."

Overall Reviewer Comments on the Efficacy of Montelukast:

All Phase 3 studies employed a once-daily evening dosing schedule without regard to food/meals. There were no studies comparing the efficacy of morning versus evening once-daily dosing. In this light, the product label will be explicit in recommending evening dosing exclusively. Given that there is a food effect on montelukast bioavailability, it is wise that the patients were dosed at bedtime without regard to meals. This obviates the need for food/dosing labeling restrictions.

Montelukast is effective in the treatment of mild to moderate asthma. Onset of action has been shown to occur within one day of treatment for the endpoints of Daytime Symptoms, beta-agonist use, AM PEFR and nocturnal asthma scores. First-dose bronchodilatory effects (i.e. FEV1) were not evaluated in Phase 3 trials; however, previous data indicate that the first dose effect on FEV1 is not significant (Study 009). Post-treatment observations indicate that no rebound phenomenon exists after withdrawal of montelukast in this patient population. These studies were also important in confirming the once-daily dosing regimen. End-of-dosing interval evaluations of peak expiratory flow rates demonstrated montelukast to be statistically significantly better than placebo.

Montelukast is effective in asthmatic patients with demonstrated aspirin sensitivity; however, it has not been shown to be of more value in these patients than in the population of general asthmatics. Importantly, montelukast has not been demonstrated to truncate the response to aspirin in these patients and, consequently, allow such patients to be treated with aspirin or NSAIDs.

The data do not demonstrate that montelukast impacts significantly on asthma-specific quality of life evaluations. The data further indicate that inhaled beclomethasone dosed

at 400 mcg/day is statistically superior to montelukast and placebo for the co-primary endpoints of Daytime Symptoms and FEV1 and superior to placebo for overall QOL and the individual QOL domains of activity, symptoms, and emotions.

Montelukast is not effective as monotherapy in the truncating exercise induced exacerbations of asthma. Although montelukast demonstrated statistically significant superiority over placebo for the mean effects on the AUC and Maximum Percent Fall endpoints, the categorical analyses clearly indicate that the majority of patients randomized to either montelukast or placebo had significant (i.e, >20%) maximum decrements in FEV1 with exercise. Montelukast shifted the population response to exercise; however, it did not truncate a significant effect in the majority of patients. This observation is confirmed by the secondary endpoint of rescue beta-agonist use. This endpoint indicated that although montelukast significantly decreased the need for rescue, there were patients that, nevertheless, required rescue with an inhaled beta-agonist during the exercise challenge. The exercise studies do, however, serve as indicators of montelukast activity in asthma.

The inhaled corticosteroid-sparing trial (046) has serious methodological flaws which make the treatment differences in the primary endpoint difficult to interpret from a clinical perspective. The study, as such serves as a bioassay evaluating the effect of montelukast in allowing the taper of inhaled corticosteroids. The benefit of this strategy is unclear, especially in the context of the results of Study 029 (Montelukast-ICS additive study) in which it is clear that asthma control deteriorates when switched from low dose inhaled corticosteroids to montelukast. In any case, Study 029 demonstrates that treatment with montelukast allows patients to taper their ICS requirements or, in a minority of cases, even have there inhaled corticosteroids discontinued without serious deterioration in asthma control over a twelve week treatment period. Given the favorable risk-benefit profile of ICS it remains to be seen whether such a strategy would be in the best interests of all patients who might benefit from therapy in addition to as-needed inhaled beta-agonists (i.e. chronic persistent asthmatics). The real issue is whether the results of this study may be extrapolated to a population of asthmatics on high dose inhaled or systemic corticosteroids who may be the real beneficiaries of an agent that allows steroid tapering.

In patients who are 'controlled' on inhaled beclomethasone, Study 029 demonstrates it is better to leave them on beclomethasone rather than switching them to montelukast. In this study, adding montelukast to an existing beclomethasone regimen significantly improved FEV1 and AM PEFR. The combination, however, was not statistically superior to beclomethasone as represented by Daytime Asthma Symptoms, backup beta-agonist use, or nocturnal asthma scores. Although montelukast added to beclomethasone was superior to beclomethasone alone for the endpoint of FEV1, the initial dose of beclomethasone was low (four puffs of 42 mcg/puff twice daily) and the study did not ask the more relevant question of whether it is safer and more effective to titrate beclomethasone to desired effect or to add montelukast to the existing 'subtherapeutic' regimen of beclomethasone. In this light, this study only weakly supports a claim for montelukast to be used as an adjuvant to beclomethasone or other ICS therapy. In fact, it confirms the finding of Study 020 that low dose beclomethasone is more effective than montelukast in the treatment of mild to moderate asthma.

6.0 Integrated Summary of Safety

6.1 Overview

The safety profile of montelukast is based on data from 10 Phase 2b/3 double-blind efficacy trials in adults and from the long-term, open-label, safety extensions of some of these trials. All double-blind safety data from these and the Phase 1/2a studies were submitted and summarized in the initial submission. The long-term safety data from the extension periods of Studies 009, 015, 020 and 031 were submitted in an integrated format in the four-month safety update (June 19, 1997). The safety database is presented in four pooled data groups: primary studies (020 and 031), all Phase 2b/3 Studies; phase 1/2a Studies; and the long term extensions to studies 009, 020 and 031. The primary studies provide the safety comparison to placebo for the purposes of quantification of adverse clinical and laboratory events relative to placebo. Since many of the other 2b/3 studies investigated multiple doses of montelukast, adverse events involving montelukast-treated patients were reported as a single group and compared to placebo. Most of these studies involved higher doses of montelukast than is proposed for marketing.

6.2 Potential Risks Based on Pharmacologic Properties and Preclinical Studies

In animal testing, the gastrointestinal system was the main target of dose-limiting toxicity. There were dose-related emesis and bowel effects in monkeys and rodents. At approximately 100 times the clinical dose, there were elevations in serum transaminases (2-3x control) in rats that were not accompanied by hepatic histologic changes. An suggested montelukast might be associated with hemolysis; however, there was not evidence of hemolysis *in vivo* in multiple-dose intravenous studies. Post-marketing experience with a marketed leukotriene antagonist, zafirlukast, indicated an association with eosinophilic tissue infiltration including Churg-Strauss vasculitis predominantly in patients with severe asthma undergoing systemic steroid taper after instituting zafirlukast. A causal relationship has not been established and the question of whether this phenomenon represents an unmasking of a pre-existing condition or is caused by leukotriene-receptor blockade remains unanswered. Since Merck's montelukast program includes inhaled steroid-tapering studies, this issue will be scrutinized; however, it is likely that the rarity of the phenomenon will preclude any definitive conclusion.

6.3 Overall Extent of Exposure in Adults

Two thousand six hundred and six subjects/patients received montelukast: 1955 in Phase 2b/3 studies, 76 in extension periods (originally randomized to placebo during double-blind portion of study), and 575 in the thirty-one Phase 1/2a trials. A small number of persons participated in multiple trials; 48 were treated with montelukast in two studies and 5 in three studies, resulting in 2548 distinct subjects/patients treated with at least one dose of montelukast. Subjects were treated with up to 900 mg per day for one week and asthmatic patients received total daily doses up to 600 mg for ten days. The breakdown of montelukast dose and duration is shown in the table below [96:192].

	Treatment Day Intervals						
Dose Range	1 to 5	6 to 15	16 to 25	26 to 35	36 to 45	46 and over	# Subjects
Phase I/2a Studies							
All Doses	223	283	1	4	58	6	575
Phase 2b/3 Studies							
2 to 9 mg	0	2	68	2	0	0	72
10 mg	33	16	90	72	102	1290	1603
11 to 50 mg	94	4	71	6	41	7	223
51-100 mg	4	4	0	3	92	13	116
101-200 mg	53	2	1	1	50	6	113
>200 mg	57	0	0	0	0	0	57
All Doses	15	25	230	82	282	1321	1955

One thousand five hundred fifteen subjects/patients received at least one dose of placebo.

The table below shows the extent of the long-term, open-label safety database obtained from the extension periods of Studies 009, 020 and 031 [Safety Update:13].

	Treatment Intervals (in Months)					
Dose Range	<3	3 to <6	6 to <12	12 to <24	24 or greater	# Patients
10 mg	56	62	329	179	18	644
11 to 50 mg	41	4	27	0	0	72
51-100 mg	22	29	0	0	0	51
101-200 mg	24	39	10	0	0	73
>200 mg	4	0	0	0	0	4
All Doses	81	68	337	187	21	694

The breakdown of the number of patients by total continuous montelukast exposure is presented in the table below. Unlike the previous table, this table includes the double-blind efficacy period and is defined as the longest continuous treatment interval without protocol-defined placebo washout periods or time off-drug. All patients received at least 10 mg/day of montelukast for the entire treatment period.

<6 Months	*6 Months to <1 year*	*1 Year to <2 years*	*2 Years to <3 years*	*3 Years or More*	*Total*
125	89	431	30	19	694

6.4 Characteristics of the Adult Safety Population

The baseline patient characteristics in the Primary (Studies 020/031) and Phase 2b/3 Studies are shown in the table below.

	Primary Studies		*Phase 2b/3 Studies (Including Primary Studies)*		
	Montelukast n=795	Placebo n=530	Montelukast n=1955	Beclometh n=251	Placebo n=1180
Gender					
Female	462 (58%)	291 (55%)	959 (49%)	251 (65%)	610 (52%)
Male	333 (42%)	239 (45%)	996 (51%)	87 (35%)	570 (48%)
Age (years)					
<18	49 (6%)	26 (5%)	76 (4%)	13 (5%)	48 (4%)
18 to 64	720 (91%)	485 (92%)	1813 (93%)	226 (90%)	1090 (92%
65 or greater	26 (3%)	19 (3%)	66 (3%)	12 (5%)	42 (4%)
Mean ± SD	35.3 ± 14	35.6 ± 14	36.5 ± 14	37.4 ± 15	36.8 ± 14
Race					
Caucasian	571 (72%)	378 (71%)	1600 (82%)	119 (47%)	947 (80%)
Hispanic	142 (18%)	92 (17%)	189 (10%)	86 (34%)	116 (10%)
Black	26 (3%)	20 (4%)	86 (4%)	7 (3%)	43 (4%)
Other	56 (7%)	40 (8%)	80 (4%)	39 (16%)	74 (6%)

The vast majority of patients had asthma of mild to moderate severity. Secondary diagnoses and concomitant therapies were comparably distributed across treatment groups. As described in the efficacy review of the individual studies, approximately 95% of the patients in the Phase 2b/3 studies had secondary diagnoses [96:196]. The vast majority of these involved respiratory system disorders, predominantly allergic rhinitis . There were no significant differences in the frequency or type of secondary diagnoses. Similar findings were noted for concomitant medications. Comparable numbers of montelukast and placebo patients (~85%) took such medications [96:200]. The most common therapies included antihistamines, decongestants, analgesics, and oral contraceptives.

6.5 Clinical Adverse Experiences

6.5.1 Adverse Events in Double-Blind Periods of Phase 2b/3 Trials

The clinical adverse event profile for the double-blind portions of the Primary (Studies 020/031) and Phase 2b/3 studies are shown in the tables below. In the primary studies, withdrawals due to adverse events were higher in the placebo group than the montelukast group (4.3% and 2.1%, respectively). This difference was statistically significant at p=0.032).

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Number (%) of patients with one or more adverse experiences postrandomization	394 (74.3)	561 (70.6)	841 (71.3)	1299 (66.4)	160 (63.7)
with drug-related adverse experiences	41 (7.7)	82 (10.3)	113 (9.6)	211 (10.8)	31 (12.4)
with serious adverse experiences	5 (0.9)	8 (1.0)	17 (1.4)	19 (1.0)	1 (0.4)
with serious drug-related adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	23 (4.3)	17 (2.1)	61 (5.2)	73 (3.7)	5 (2.0)
withdrawn from therapy due to a serious adverse experience	1 (0.2)	5 (0.6)	3 (0.3)	11 (0.6)	1 (0.4)
withdrawn from therapy due to a drug-related adverse experience	4 (0.8)	5 (0.6)	13 (1.1)	14 (0.7)	2 (0.8)
Deaths	0	1 (0.1)	0	1 (0.1)	0

This table does not include those adverse experiences that occurred before randomization.

The one death involved a 50 year old male who was a passenger in a fatal motor vehicle accident. There was an additional death in a beclomethasone patient who died from pancreatic cancer and disseminated intravascular coagulation 20 days after having been on beclomethasone (Study 020) for 44 days. A more detailed listing of patients in the primary studies who discontinued treatment due to adverse events is shown in the table below [96:224]. The frequencies seen in all Phase 2b/3 studies are similar to those noted below [96:226]

Adverse Experience	Placebo N = 530	Montelukast N = 795
Asthma-Related		
Dyspnea	0	1 (AN 4678)[1]
Asthma	14	7 (AN 5293)[2]
Bronchitis	2	0
Respiratory failure	0	1
Anxiety	0	1
Depression	1 (AN 3959)[1]	1 (AN 4285)[1]
Discomfort, pharyngeal	1	0
Edema, eyelid	1 (AN 5964)[1]	0
Edema, facial	1 (AN 4236)[1]	0
Endometriosis	1	0
Epididymitis	0	1
Gastritis	0	1
Headache	1 (AN 4648)[1]	0
Menstruation disorder	1	0
Pain, back	0	1 (AN 4597)[1]
Reaction, vasovagal	0	1
Trauma	0	1
Urticaria	0	1 (AN 5650)[1]
Total	**23 (4.3%)**	**17 (2.1%)**
Total (without asthma-related experiences)	**7 (1.3%)**	**8 (1.0%)**
Total drug related	**4 (0.8%)**	**5 (0.6%)**

[1] Patients discontinued due to adverse experiences considered drug related by the investigator

[2] The only patient of the 7 who was discontinued due to an adverse experience considered drug related by the investigator

The tables below show the body system specific adverse event profiles obtained during the double-blind periods and will serve as the basis of the ADVERSE REACTIONS section of the product label.

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Number (%) of patients with one or more clinical adverse experiences post-randomization	394 (74.3)	561 (70.5)	841 (71.3)	1299 (66.4)	160 (63.7)
Body as a Whole/Site Unspecified	**51 (9.6)**	**101 (12.7)**	**133 (11.3)**	**244 (12.5)**	**34 (13.5)**
Asthenia/fatigue	6 (1.1)	16 (2.0)	14 (1.2)	35 (1.8)	5 (2.0)
Fever	3 (0.6)	11 (1.4)	11 (0.9)	30 (1.5)	2 (0.8)
Flu-like illness	8 (1.5)	9 (1.1)	20 (1.7)	22 (1.1)	2 (0.8)
Pain, abdominal	12 (2.3)	27 (3.4)	29 (2.5)	56 (2.9)	8 (3.2)
Pain, chest	6 (1.1)	7 (0.9)	17 (1.4)	25 (1.3)	4 (1.6)
Trauma	2 (0.4)	7 (0.9)	10 (0.8)	20 (1.0)	4 (1.6)
Cardiovascular System Disorders[4]	**6 (1.1)**	**15 (1.9)**	**16 (1.4)**	**34 (1.7)**	**3 (1.2)**
Digestive System Disorders	**55 (10.4)**	**118 (14.8)**	**151 (12.8)**	**281 (14.4)**	**36 (14.3)**
Diarrhea	11 (2.1)	30 (3.8)	36 (3.1)	61 (3.1)	5 (2.0)
Dry mouth	3 (0.6)	8 (1.0)	7 (0.6)	15 (0.8)	3 (1.2)
Dyspepsia	5 (0.9)	19 (2.4)	13 (1.1)	42 (2.1)	2 (0.8)
Flatulence	7 (1.3)	5 (0.6)	9 (0.8)	11 (0.6)	2 (0.8)
Gastritis	1 (0.2)	5 (0.6)	2 (0.2)	9 (0.5)	6 (2.4)
Gastroenteritis, infectious	1 (0.2)	14 (1.8)	6 (0.5)	29 (1.5)	0
Nausea	11 (2.1)	20 (2.5)	35 (3.0)	50 (2.6)	5 (2.0)
Pain, dental	1 (0.2)	13 (1.6)	12 (1.0)	34 (1.7)	5 (2.0)
Vomiting	2 (0.4)	12 (1.5)	16 (1.4)	23 (1.2)	2 (0.8)
Endocrine Disorders[4]	**0**	**1 (0.1)**	**0**	**1 (0.1)**	**1 (0.4)**
Hemic and Lymphatic Disorders[4]	**0**	**3 (0.4)**	**2 (0.2)**	**8 (0.4)**	**1 (0.4)**
Metabolic/Nutritional/Immune Disorders[4]	**4 (0.8)**	**7 (0.9)**	**15 (1.3)**	**16 (0.8)**	**1 (0.4)**
Musculoskeletal Disorders	**59 (11.1)**	**95 (11.9)**	**144 (12.2)**	**233 (11.9)**	**20 (8.0)**
Myalgia	13 (2.5)	19 (2.4)	30 (2.5)	44 (2.3)	4 (1.6)
Pain, back	19 (3.6)	23 (2.9)	38 (3.2)	51 (2.6)	5 (2.0)

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Nervous System/Psychiatric Disorders	**120 (22.6)**	**182 (22.9)**	**262 (22.2)**	**444 (22.7)**	**58 (23.1)**
Depression	4 (0.8)	10 (1.3)	5 (0.4)	12 (0.6)	1 (0.4)
Dizziness	9 (1.7)	21 (2.6)	16 (1.4)	38 (1.9)	5 (2.0)
Headache	97 (18.3)	141 (17.7)	214 (18.1)	359 (18.4)	47 (18.7)
Insomnia	3 (0.6)	12 (1.5)	15 (1.3)	25 (1.3)	3 (1.2)
Respiratory System Disorders	**309 (58.3)**	**398 (50.1)**	**621 (52.6)**	**858 (43.9)**	**113 (45.0)**
Asthma	131 (24.7)	144 (18.1)	233 (19.7)	275 (14.1)	48 (19.1)
Bronchitis	26 (4.9)	29 (3.6)	42 (3.6)	47 (2.4)	7 (2.8)
Congestion, nasal	5 (0.9)	13 (1.6)	15 (1.3)	32 (1.6)	0
Cough	11 (2.1)	16 (2.0)	28 (2.4)	52 (2.7)	4 (1.6)
Infection, respiratory	4 (0.8)	7 (0.9)	9 (0.8)	18 (0.9)	6 (2.4)
Infection, respiratory, upper	124 (23.4)	177 (22.3)	290 (24.6)	420 (21.5)	33 (13.1)
Influenza	22 (4.2)	42 (5.3)	46 (3.9)	82 (4.2)	17 (6.8)
Pharyngitis	40 (7.5)	47 (5.9)	83 (7.0)	105 (5.4)	16 (6.4)
Rhinitis	11 (2.1)	9 (1.1)	16 (1.4)	15 (0.8)	10 (4.0)
Rhinitis, allergic	6 (1.1)	13 (1.6)	16 (1.4)	21 (1.1)	4 (1.6)
Rhinorrhea	1 (0.2)	3 (0.4)	2 (0.2)	11 (0.6)	4 (1.6)
Sinusitis	29 (5.5)	33 (4.2)	51 (4.3)	79 (4.0)	6 (2.4)
Tonsillitis	3 (0.6)	3 (0.4)	5 (0.4)	4 (0.2)	7 (2.8)
Skin/Skin Appendage Disorders	**27 (5.1)**	**60 (7.5)**	**87 (7.4)**	**152 (7.8)**	**18 (7.2)**
Acne	2 (0.4)	6 (0.8)	3 (0.3)	7 (0.4)	3 (1.2)
Pruritus	2 (0.4)	4 (0.5)	11 (0.9)	13 (0.7)	3 (1.2)
Rash	5 (0.9)	17 (2.1)	14 (1.2)	32 (1.6)	5 (2.0)
Special Sense Disorders	**12 (2.3)**	**28 (3.5)**	**36 (3.1)**	**74 (3.8)**	**6 (2.4)**
Conjunctivitis	1 (0.2)	2 (0.3)	4 (0.3)	10 (0.5)	3 (1.2)
Urogenital System Disorders	**27 (5.1)**	**36 (4.5)**	**44 (3.7)**	**73 (3.7)**	**13 (5.2)**
Infection, urinary tract	12 (2.3)	7 (0.9)	15 (1.3)	19 (1.0)	4 (1.6)
Menstruation disorder	4 (0.8)	11 (1.4)	8 (0.7)	18 (0.9)	4 (1.6)

[1] All individual adverse experiences categorized in this body system are <1%.
This table contains counts of patients. Although a patient may have two or more clinical adverse experiences, the patient is counted only once in "Number (%) of patients with one or more clinical adverse experiences."
This table does not include those adverse experiences that occurred before randomization.

As can be seen, the frequency of clinical adverse experiences is, generally, comparable between montelukast and placebo-treated patients. Patients who received montelukast had increased frequency of gastrointestinal adverse events in the primary studies (i.e. abdominal pain, diarrhea, dyspepsia, nausea, vomiting) and there was a statistically significant difference in the frequency of infectious gastroenteritis (1.8% for montelukast versus 0.2% for placebo, p=0.007). All 14 cases of infectious gastroenteritis were noted in Study 031 and there was no increased frequency of infectious gastroenteritis in the other Phase 2b/3 studies. These events were generally transient, self-limited, and did not require discontinuation of montelukast. Four of the 14 patients also experienced flu-like symptoms within approximately 7 days of the occurrence of infectious gastroenteritis. No patients dropped out of Study 031 because of infectious gastroenteritis [81:14182]. In the long-term extension studies, the frequency of infectious gastroenteritis was low (1.6% for montelukast and 1.2% for beclomethasone) [Safety Update:36].

In the primary studies, respiratory system disorders were statistically significantly more frequent in the placebo treated patients (p=0.003). This was predominantly driven by the increased frequency of 'asthma' as an adverse event in the placebo patients. Respiratory infections were comparable in frequency between treatment groups.

Reviewer comment: The profile of common adverse events for montelukast in double-blind periods is, generally, unremarkable. The increased frequency of infectious gastroenteritis is puzzling since it occurred only in one study and there is no increased frequency of infection in other organ systems. There is insufficient information provided in the NDA to allow for a determination of causality. The sponsor has been asked to

provide the case report forms as well as a detailed analysis the phenomenon (e.g. how was diagnosis made?, viral or bacterial?, common study sites?, age/gender predilection, etc.). Without satisfactory explanation as to why this AE is unlikely to be due to montelukast, it deserves specific mention in the product label.

6.5.2 Nonfatal Serious Clinical Adverse Experiences

The table below shows the nonfatal serious clinical adverse experiences in the Phase 2b/3 studies. Forty-four such events occurred after randomization in 36 patients [96:215]. There were no differences in the type or frequency between treatment groups. Of note, none of these were considered drug-related by the investigators.

	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Total number (%) of patients with one or more nonfatal serious adverse experiences postrandomization	17 (1.4)	18 (0.9)	1 (0.4)
Body as a whole/site unspecified	0	1 (0.1)	1 (0.4)
Cardiovascular system disorders	0	1 (0.1)	0
Digestive system disorders	0	4 (0.2)	0
Metabolic, nutritional, immune disorders	1 (0.1)	0	0
Musculoskeletal disorders	1 (0.1)	3 (0.2)	0
Nervous system and psychiatric disorders	1 (0.1)	1 (0.1)	0
Respiratory system disorders	11 (0.9)	6 (0.3)	0
Skin and skin appendage disorders	3 (0.3)	0	0
Urogenital system disorders	1 (0.1)	2 (0.1)	0

[1] No serious adverse experience was considered drug related by the investigators.
This table does not include those adverse experiences that occurred before randomization.
Although a patient may have an adverse experience in more than one body system, the patient is counted only once in "Total number (%) of patients with one or more nonfatal serious adverse experience."

The respiratory system events predominantly consisted of asthma-exacerbations. The four montelukast patients who had 'digestive system disorders' consisted of a 17 year old female with congenital Schatzki's ring requiring esophageal dilatation who had severe reflux esophagitis for five days and continued montelukast therapy; a 39 year old male with a history of GI reflux/gastritis who had severe gastritis lasting 19 days and discontinued montelukast; a 24 year old male who had a gastrointestinal hemorrhage who discontinued montelukast; and a 47 year old female who had appendicitis not requiring discontinuation of study medication.

6.5.3 Clinical Adverse Events in Phase 1/2a Studies

The relative frequencies of clinical adverse events in these studies were comparable to the longer term Phase 2b/3 studies and similar across treatment groups [96:253]. There were no deaths and only two dropouts due to adverse events (one placebo patient had an asthma exacerbation and one montelukast patient had SVT five days after discontinuing montelukast).

6.5.4 Clinical Adverse Events in Long-Term Extension Trials

The safety update (June 19, 1997) contained updated safety data received by December 6, 1996. As of that date, only one of the extension trials (020) was completed. Studies 009, 015 and 031 were ongoing and, therefore, complete data on all patients are not available. Overall, the long-term clinical adverse event profile of montelukast was similar to that of beclomethasone. These data are summarized in the tables below.

	Montelukast n=694	*Beclomethasone n=250*
Number (%) patients with one or more adverse experiences	539 (78%)	185 (74%)
with drug related AEs	68 (10%)	22 (9%)
with serious AEs	17 (2%)	8 (3%)
with serious drug-related AEs	0	1 (<1%)
withdrawn due to AE	33 (5%)	10 (4%)
withdrawn due to serious AE	5 (<1%)	2 (<1%)
withdrawn due to drug-related AE	8 (1%)	0
withdrawn due to serious drug-related AE	0	0
Deaths	0	0

In the montelukast treated patients, the highest frequency of adverse events by body system occurred in the respiratory (64%), nervous (24%) and musculoskeletal systems (22%). Individual adverse events with the highest frequency were URI (31%), asthma (29%), and headache (19%). The incidence of adverse events by body system and by individual adverse experiences was generally similar between montelukast and beclomethasone. The frequency of specific digestive system adverse events is shown in the table below.

	Montelukast n=694	*Beclomethasone n=250*
Abdominal pain	30 (4.3%)	9 (3.6%)
Diarrhea	25 (3.6%)	7 (2.8%)
Dyspepsia	15 (2.2%)	3 (1.2%)
Gastritis	6 (0.9%)	2 (0.8%)
Infectious Gastroenteritis	11 (1.6%)	3 (1.2%)
Nausea	16 (2.3%)	7 (2.8%)
Vomiting	8 (1.2%)	2 (0.8%)

Of note, the frequency of infectious gastroenteritis remained higher in the montelukast patients than in the beclomethasone treated patients.

There was an increased frequency of musculoskeletal disorders in the montelukast-treated patients (21.5% for montelukast versus 12% for beclomethasone). These can be most easily categorized into one of four groups: myalgia/muscle cramps, pain, musculoskeletal trauma, and other (e.g arthralgia). In all groups, the frequency of adverse events in the montelukast treated patients was greater than that seen in the beclomethasone treated patients. In all cases, the episodes either resolved while continuing study therapy or were ongoing but did not necessitate discontinuation of study therapy. There is no mechanism based explanation for the higher frequency of musculoskeletal adverse events seen in the montelukast group. Preclinical studies did not reveal the musculoskeletal system to be a target toxicity organ for montelukast.

Clinical Adverse Experiences Over Time (in Extension Studies)

The sponsor conducted an analysis of the frequency of clinical adverse events over time (SU:298]. The tables below summarize the data for montelukast and beclomethasone.

Montelukast

	<6 months n=694	*6 months to <1 year n=569*	*1 to 2 years n=480*	*2 years or greater n=49*
Number (%) patients with one or more adverse experiences	529 (77%)	381 (69%)	190 (40%)	20 (48%)
with drug related AEs	96 (14%)	17 (3%)	10 (2%)	0
with serious AEs	9 (1%)	8 (1%)	2 (<1%)	0
with serious drug-related AEs	0	0	0	0
withdrawn due to AE	19 (3%)	12 (2%)	1 (<1%)	0
withdrawn due to serious AE	3 (<1%)	2 (<1%)	0	0
withdrawn due to drug-related AE	6 (<1%)	2 (<1%)	0	0
withdrawn due to serious drug-related AE	0	0	0	0
Deaths	0	0	0	0

Beclomethasone

	<6 months n=250	6 months to <1 year n=225	> 1 year n=185
Number (%) patients with one or more adverse experiences	185 (77%)	381 (69%)	190 (40%)
with drug related AEs	32 (13%)	10 (4%)	1 (<1%)
with serious AEs	1 (<1%)	4 (2%)	3 (2%)
with serious drug-related AEs	0	1 (<1%)	0
withdrawn due to AE	4 (2%)	2 (<1%)	4 (2%)
withdrawn due to serious AE	0	1 (<1%)	1 (<1%)
withdrawn due to drug-related AE	0	0	0
withdrawn due to serious drug-related AE	0	0	0
Deaths	0	0	0

These data were also analyzed by specific adverse event with similar findings. These data support the contention that there is no evidence of cumulative dose toxicities for montelukast.

6.5.5 Serious Clinical Adverse Experiences

There was one death in an extension study. A 62 year old male experienced abdominal pain and vomiting approximately one year after entering the extension period for Study 015. He was diagnosed with peritonitis but did not respond to antibiotics. He was taken to surgery and found to have a torsion radix mesenteric. He eventually succumbed to a cardiac arrest secondary to pulmonary embolism two days post-surgery.

The incidence of nonfatal serious clinical adverse experiences was similar between the montelukast (2.4%) and beclomethasone (3.2%) groups. Three patients (2 montelukast, 1 beclomethasone) patients were discontinued due to serious clinical adverse experiences. One of the montelukast patients was a 56 year old female who had a severe asthma exacerbation. The other was a 58 year old female who was diagnosed with breast cancer after 322 days of continuous montelukast therapy. The frequency of discontinuations due to any clinical adverse experiences was similar between montelukast and beclomethasone groups (4.7% and 4%, respectively). The cumulative frequency of nonasthma-related discontinuations was 2.2% and 1.6% of patients in the montelukast and beclomethasone groups, respectively.

6.5.6 Eosinophilic Conditions/Churg-Strauss Vasculitis

There was no evidence of a Churg-Strauss vasculitis or eosinophilic variant in the safety database. Given the relative rarity of the event in the population and the experience with zafirlukast, it is not surprising. The phenomenon appears to manifest in the context of systemic steroid tapering in severe asthmatics. This was not the population studied in the NDA.

6.6 Laboratory Adverse Events

Standardized laboratory safety measurements (i.e. hematology, blood chemistry, urinalysis) were performed in all patients in all studies to evaluate the safety profile of montelukast. In the Phase 2b/3 studies, a central laboratory was used. A few non-US study sites used a local laboratory. Extension study sites used the same laboratory used in the double-blind period. By and large, the Phase 1/2a studies used local laboratories. In addition to protocol-specified laboratory tests, some additional tests were performed on some patients to follow-up on observed clinical/laboratory findings. For the Phase 2b/3 double blind and extension periods, the percent of patients falling outside the predefined limits of change from baseline for hematocrit, WBC, lymphocytes, platelets, bilirubin, AST and ALT was identified and compared between treatment groups. To be included in these analyses, patients had to have both a baseline and at least one postrandomization measurement. Laboratory adverse experiences are attributed to the therapy received the day prior to the laboratory sample collection.

Reviewer comment: The sponsor was asked to provide the reference normal ranges for the laboratories. This information was submitted to the NDA on December 8, 1997 and may be found in Appendix A of this review.

6.6.1 Incidence of Laboratory Adverse Experiences

The laboratory adverse experience profile for the Primary and Phase 2b/3 studies is shown in the table below. There were no statistically significant differences between treatment groups in any category for the primary studies (Studies 020/031) or all Phase 2b/3 studies. All withdrawals from montelukast therapy were due to positive pregnancy tests [96:266].

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Number of patients with one or more laboratory tests postrandomization	525	788	1171	1935	249
Number (%) of patients with one or more adverse experiences	33 (6.3)	55 (7.0)	77 (6.6)	120 (6.2)	15 (6.0)
with drug-related adverse experiences	7 (1.3)	8 (1.0)	22 (1.9)	37 (1.9)	1 (0.4)
with serious adverse experiences	0	0	0	0	0
withdrawn from therapy due to adverse experiences	2 (0.4)	3 (0.4)	6 (0.5)	4 (0.2)	1 (0.4)
withdrawn from therapy due to a drug-related adverse experience	0	0	1 (0.1)	0	0

This table does not include those adverse experiences that occurred before randomization.

The frequency of laboratory adverse events by treatment group is shown in the tables below. There were no significant differences between treatment groups [96:268].

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Number of patients with one or more laboratory tests postrandomization	525	788	1171	1936	249
Number (%) of patients with one or more laboratory adverse experiences	33 (6.3)	55 (7.0)	77 (6.6)	120 (6.2)	15 (6.0)
Hematology					
Eosinophils increased	0/525	0/788	3/1168 (0.3)	4/1934 (0.2)	0/249
Hematocrit decreased	0/525	0/788	1/1170 (0.1)	0/1933	0/249
Hematocrit increased	0/525	0/788	0/1170	1/1933 (0.1)	0/249
Hemoglobin decreased	0/525	2/788 (0.3)	1/1170 (0.1)	2/1934 (0.1)	2/249 (0.8)
Hemoglobin increased	0/525	0/788	0/1170	1/1934 (0.1)	0/249
Leukocyte count increased	5/525 (1.0)	3/788 (0.4)	7/1168 (0.6)	5/1934 (0.3)	1/249 (0.4)
Leukocytes decreased	2/525 (0.4)	6/788 (0.8)	5/1168 (0.4)	9/1934 (0.5)	0/249
Lymphocytes decreased	0/525	0/788	1/1168 (0.1)	0/1934	0/249
Neutrophils decreased	3/525 (0.6)	3/788 (0.4)	5/1149 (0.4)	6/1900 (0.3)	2/249 (0.8)
Neutrophils increased	5/525 (1.0)	3/788 (0.4)	7/1149 (0.6)	5/1900 (0.3)	1/249 (0.4)
Platelet count decreased	0/525	1/787 (0.1)	1/1168 (0.1)	2/1932 (0.1)	1/249 (0.4)
Platelet count increased	1/525 (0.2)	0/787	1/1168 (0.1)	0/1932	0/249
Blood Chemistry					
Alkaline phosphatase increased	0/525	3/788 (0.4)	0/1170	4/1934 (0.2)	0/249
ALT increased	10/525 (1.9)	15/788 (1.9)	23/1170 (2.0)	41/1935 (2.1)	3/249 (1.2)
AST increased	6/525 (1.1)	11/788 (1.4)	14/1170 (1.2)	30/1935 (1.6)	4/249 (1.6)
Bicarbonate decreased	1/525 (0.2)	0/787	1/1170 (0.1)	0/1933	0/249
BUN increased	0/525	0/788	0/1170	1/1934 (0.1)	0/249
Creatine phosphokinase[1] increased	1/3 (33.3)	1/6 (16.7)	1/6 (16.7)	1/16 (6.3)	0/2
Hypercalcemia	0/525	1/788 (0.1)	0/1170	1/1934 (0.1)	0/249
Hyperglycemia	2/525 (0.4)	4/788 (0.5)	5/1170 (0.4)	6/1934 (0.3)	0/249
Hyperkalemia	0/525	1/788 (0.1)	1/1170 (0.1)	3/1934 (0.2)	1/249 (0.4)
Hyperphosphatemia	0/525	1/788 (0.1)	0/1170	1/1934 (0.1)	0/249

	Primary Studies		Phase IIb/III Studies (Including Primary)		
	Placebo (N = 530)	Montelukast (N = 795)	Placebo (N = 1180)	Montelukast (N = 1955)	Beclomethasone (N = 251)
Blood Chemistry (Cont.)					
Hypocalcemia	0/525	0/788	1/1170 (0.1)	2/1934 (0.1)	0/249
Hypochloremia	0/525	0/788	1/1170 (0.1)	0/1934	0/249
Hypoglycemia	0/525	0/788	1/1170 (0.1)	0/1934	0/249
Hypokalemia	1/525 (0.2)	1/788 (0.1)	1/1170 (0.1)	2/1934 (0.1)	0/249
Hyponatremia	0/525	0/788	1/1170 (0.1)	0/1934	0/249
Hypophosphatemia	0/525	0/788	0/1170	2/1934 (0.1)	0/249
Pregnancy test[2] positive	3/289 (1.0)	4/477 (0.8)	8/582 (1.4)	6/888 (0.7)	1/177 (0.6)
Total serum bilirubin increased	2/525 (0.4)	1/788 (0.1)	3/1170 (0.3)	7/1934 (0.4)	0/249
Urinalysis					
Bacteriuria[1]	2/2 (100.0)	3/3 (100.0)	2/11 (18.2)	6/11 (54.5)	0/0
Glycosuria	0/525	0/788	0/1169	1/1934 (0.1)	0/249
Hematuria	5/520 (1.0)	6/783 (0.8)	8/1168 (0.7)	8/1934 (0.4)	2/249 (0.8)
Proteinuria	0/525	1/788 (0.1)	4/1169 (0.3)	4/1934 (0.2)	1/249 (0.4)
Pyuria	6/520 (1.2)	11/783 (1.4)	11/1159 (0.9)	19/1924 (1.0)	1/245 (0.4)
Urine yeast, nondiagnostic	0/520	0/783	1/1159 (0.1)	0/1924	0/245

[1] Nonprotocol tests performed by the investigator.
[2] Only female patients.
This table contains counts of patients. Although a patient may have two or more laboratory adverse experiences, the patient is counted only once in "Number (%) of patients with one or more laboratory adverse experiences."
This table represents counts of patients having specific laboratory adverse experiences in the following format: Number of patients with experience/number of patients tested (%).
This table does not include those adverse experiences that occurred before randomization.

6.6.2 Predefined Limits of Change Analysis

The tables below show the analysis of predefined limits of change from baseline [96:278]. In the primary studies (Studies 020/031), there was a statistically significant between group difference for increased WBC count (p=0.038).

Laboratory Parameter (Unit)	Predefined Limit of Change[1]	Treatment	Primary Studies Frequency (%)	Primary Studies p-Value[2]	Phase IIb/III Studies (Including Primary) Frequency (%)
Hematocrit (%)	Decrease ≥20% from baseline and < LLN	Placebo Montelukast Beclomethasone	3/525 (0.6) 4/787 (0.5) –	>0.999	4/1169 (0.3) 8/1932 (0.4) 1/248 (0.4)
	Increase ≥20% from baseline and > ULN	Placebo Montelukast Beclomethasone	0/525 (0.0) 3/787 (0.4) –	0.279	0/1169 (0.0) 3/1932 (0.2) 2/248 (0.8)
WBC count ($10^3/\mu L$)	Decrease ≥20% from baseline and < LLN	Placebo Montelukast Beclomethasone	41/525 (7.8) 82/788 (10.4) –	0.122	75/1167 (6.4) 150/1934 (7.8) 18/249 (7.2)
	Increase ≥20% from baseline and > ULN	Placebo Montelukast Beclomethasone	48/525 (9.1) 47/788 (6.0) –	0.038	78/1167 (6.7) 92/1934 (4.8) 24/249 (9.6)
Lymphocytes ($10^3/\mu L$)	Decrease ≥20% from baseline and < LLN	Placebo Montelukast Beclomethasone	17/525 (3.2) 27/788 (3.4) –	>0.999	33/1167 (2.8) 59/1934 (3.1) 15/249 (6.0)
	Increase ≥20% from baseline and > ULN	Placebo Montelukast Beclomethasone	14/525 (2.7) 19/788 (2.4) –	0.858	24/1167 (2.1) 36/1934 (1.9) 10/249 (4.0)

Laboratory Parameter (Unit)	Predefined Limit of Change[1]	Treatment	Primary Studies Frequency (%)	Primary Studies p-Value[2]	Phase IIb/III Studies (Including Primary) Frequency (%)
Platelet count (10^3/µL)	Decrease ≥25% from baseline and < LLN	Placebo	0/525 (0.0)	>0.999	1/1166 (0.1)
		Montelukast	1/786 (0.1)		2/1929 (0.1)
		Beclomethasone	–		2/249 (0.8)
	Increase ≥50% from baseline and > ULN	Placebo	3/525 (0.6)	0.381	5/1166 (0.4)
		Montelukast	9/786 (1.1)		14/1929 (0.7)
		Beclomethasone	–		2/249 (0.8)
Bilirubin (mg/dL)	Increase ≥50% from baseline and > ULN	Placebo	12/525 (2.3)	0.722	25/1169 (2.2)
		Montelukast	21/788 (2.7)		47/1934 (2.4)
		Beclomethasone	–		7/249 (2.8)
AST (U/L)	Increase ≥100% from baseline and > ULN	Placebo	17/525 (3.2)	0.877	34/1169 (2.9)
		Montelukast	28/788 (3.6)		53/1935 (2.7)
		Beclomethasone	–		11/249 (4.4)
ALT (U/L)	Increase ≥100% from baseline and > ULN	Placebo	30/525 (5.7)	0.905	54/1169 (4.6)
		Montelukast	47/788 (6.0)		80/1935 (4.1)
		Beclomethasone	–		9/249 (3.6)

[1] LLN = lower limit of normal; ULN = upper limit of normal.
[2] Based on two-sided Fisher's Exact Test.
[Refs. D-32 to D-41]

The effect of montelukast on liver function tests was of particular concern and the sponsor performed an analysis of the Phase 2b/3 studies in which all patients with an AST or ALT above the upper limits of normal were identified and classified by their multiples above the upper limit. In the double-blind portion of these studies, only one patient (placebo) discontinued therapy due to an increase ALT. Generally, transaminase elevations were transient, self-limited, and did not necessitate discontinuation. The results are shown in the tables below [96:280].

Treatment	Primary Studies N	Primary Studies Number of Patients (%) >ULN[1] ALT	Primary Studies Number of Patients (%) >ULN[1] AST	Phase IIb/III Studies (Including Primary) N	Phase IIb/III Studies (Including Primary) Number of Patients (%) >ULN[1] ALT	Phase IIb/III Studies (Including Primary) Number of Patients (%) >ULN[1] AST
Placebo	525	66 (12.6)	29 (5.5)	1169[2]	135 (11.5)	66 (5.6)
Montelukast	788	126 (16.0)	59 (7.5)	1934[2]	248 (12.8)	127 (6.6)
Beclomethasone	–	–	–	249	29 (11.6)	15 (6.0)

[1] Based on the highest postrandomization value.
[2] The 2 patients (1, placebo and 1, montelukast) in Protocol No. 009 who discontinued because of laboratory abnormalities present in the prerandomization blood sampling (immediately prior to administration of double-blind study medication) were not included [Ref. D-32].

ALT

Treatment	N	Class Interval (Times Above ULN) >2 and ≤3	>3 and ≤4	>4 and ≤5	>5 and ≤6	>6 and ≤7	>7 and ≤8	>8	Total >2 X ULN
Primary Studies									
Placebo	525	3 (0.6)	2 (0.4)	0	0	0	0	1 (0.2)	6 (1.1)
Montelukast	788	8 (1.0)	2 (0.3)	0	0	0	2 (0.3)	0	12 (1.5)
Phase IIb/III Studies (Including Primary)									
Placebo	1169	9 (0.8)	3 (0.3)	0	0	0	0	1 (0.1)	13 (1.1)
Montelukast	1934	24 (1.2)	5 (0.3)	1 (0.1)[1]	1 (0.1)[1]	0	2 (0.1)	1 (0.1)[1]	34 (1.8)
Beclomethasone	249	2 (0.8)	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)	5 (2.0)

[1] Incidence was 0.05%

AST

Treatment	N	Class Interval (Times Above ULN)							Total
		>2 and ≤3	>3 and ≤4	>4 and ≤5	>5 and ≤6	>6 and ≤7	>7 and ≤8	>8	>2 X ULN
Primary Studies									
Placebo	525	3 (0.6)	1 (0.2)	1 (0.2)	0	0	0	1 (0.2)	6 (1.1)
Montelukast	788	5 (0.6)	1 (0.1)	1 (0.1)	0	0	0	1 (0.1)	8 (1.0)
Phase IIb/III Studies (Including Primary)									
Placebo	1169	4 (0.3)	1 (0.1)	2 (0.2)	1 (0.1)	0	0	1 (0.1)	9 (0.8)
Montelukast	1934	11 (0.5)	5 (0.3)	1 (0.1)[1]	3 (0.2)	0	0	1 (0.1)[1]	21 (1.1)
Beclomethasone	249	0	2 (0.8)	0	1 (0.4)	0	0	1 (0.4)	4 (1.6)

[1] Incidence was 0.05%

Reviewer comment: The sponsor did not provide summary statistics (mean with standard deviations and ranges) for laboratories. The sponsor was asked to provide these for the following laboratories: AST, ALT, total bilirubin, WBC, platelets and hemoglobin for the baseline and last available postrandomization visit during the double-blind period for montelukast and placebo for the primary and Phase 2b/3 trials. It was also requested that AST, ALT, and bilirubin also be broken down by sex. These were requested to assess the central tendencies of the population across treatment groups. The breakdown by sex for liver function tests was done because sex differences in hepatotoxic potential has been noted for other drugs. Unity scatterplots for the laboratory parameters of AST, ALT, total bilirubin, WBC, platelets, and hemoglobin were also requested. In order to be able to visualize the greatest potential drug effect across a population, the plots were constructed with the highest prerandomization value on the x-axis and the most extreme post-randomization value on the y-axis. For AST, ALT, and total bilirubin, the most extreme was designated as the highest post-randomization value. For hemoglobin, it was the lowest post-randomization value. For platelets, the scatterplots were constructed using both the highest and lowest post-randomization values. All plots were constructed separately for the double-blind and extension periods for the primary and Phase 2b/3 studies. The sponsor provided these analyses on December 8, 1997 and they are summarized in the tables below.

Primary Studies (Studies 20 and 031 Pooled)

Parameter	*Treatment*	*n*	*Baseline*	*Last Visit*	*Change from Baseline*
ALT (U/L)	Placebo	524	21.17	21.54	0.37
	Montelukast	787	21.12	21.73	0.61
	Beclomethasone	249	20.44	20.54	0.10
AST (U/L)	Placebo	524	20.35	19.42	-0.93
	Montelukast	787	20.42	20.41	-0.01
	Beclomethasone	249	19.67	19.88	0.21
Total Bilirubin	Placebo	524	0.58	0.59	0.00
	Montelukast	787	0.62	0.60	-0.02
	Beclomethasone	249	0.61	0.62	0.01
Hemoglobin	Placebo	523	14.72	14.67	-0.05
	Montelukast	787	14.64	14.49	-0.16
	Beclomethasone	249	14.72	14.62	-0.09
Platelet Count	Placebo	523	273.42	278.76	5.22
	Montelukast	787	278.91	275.64	-3.19
	Beclomethasone	249	286.85	282.18	-4.66
Total WBC	Placebo	523	6.48	6.58	0.10
	Montelukast	787	6.53	6.37	-0.16
	Beclomethasone	249	6.93	6.80	-0.12

Analysis by Sex of Selected Laboratory Data from Primary Studies (020 and 031)

	Change from Baseline					
Sex		Males			Females	
Treatment	Placebo	Monteluk	Beclometh	Placebo	Monteluk	Beclometh
ALT	0.59	0.70	-0.02	0.19	0.55	0.17
AST	-0.74	0.64	0.39	-1.08	-0.47	0.12
Total Bilirubin	0.01	-0.02	0.01	0.00	-0.01	0.01

Phase 2b/3 Studies (009, 025, 015, 020, 029, 031, 042, 046, 056, 059, Pooled)

Parameter	*Treatment*	*n*	*Baseline*	*Last Visit*	*Change from Baseline*
ALT (U/L)	Placebo	1163	20.89	21.38	0.50
	Montelukast	1926	21.24	21.73	0.49
	Beclomethasone	245	20.34	20.28	-0.05
AST (U/L)	Placebo	1163	19.98	19.77	0.21
	Montelukast	1926	20.25	20.39	-0.14
	Beclomethasone	245	19.69	19.79	0.10
Total Bilirubin	Placebo	1163	0.59	0.59	0.00
	Montelukast	1925	0.61	0.60	-0.01
	Beclomethasone	245	0.61	0.62	0.01
Hemoglobin	Placebo	1159	14.72	14.57	0.00
	Montelukast	1924	14.68	14.58	-0.11
	Beclomethasone	245	14.71	14.62	-0.09
Platelet Count	Placebo	1156	269.57	270.99	1.41
	Montelukast	1918	270.50	267.37	-2.98
	Beclomethasone	245	285.69	280.52	-5.17
Total WBC	Placebo	1157	6.46	6.49	0.04
	Montelukast	1925	6.45	6.37	-0.09
	Beclomethasone	245	6.91	6.79	-0.12

Analysis by Sex of Selected Laboratory Data from Primary Studies (Pooled Phase 2b/3 Studies)

	Change from Baseline					
Sex		Males			Females	
Treatment	Placebo	Monteluk	Beclometh	Placebo	Monteluk	Beclometh
ALT	0.50	0.61	0.12	0.49	0.37	-0.15
AST	-0.29	0.30	0.34	-0.13	-0.04	-0.03
Total Bilirubin	0.01	-0.01	0.01	-0.01	-0.01	0.01

Numerous scatterplots were submitted in response to the reviewer's request. A representative sampling of these for transaminases in the double-blind treatment period is contained in Appendix B.

6.6.4 Laboratories in Phase 1/2a Studies

The laboratory adverse event profile for the Phase 1/2a studies is shown in the table below [96:302].

	Placebo (N = 320)	Montelukast (N = 562)	Montelukast and Drugs (N = 114)	Placebo and Drugs (N = 91)	Other Drugs (N = 74)
Number of subjects/patients with one or more laboratory tests postrandomization	306	539	91	67	74
Number (%) of subjects/patients with one or more drug-related laboratory adverse experiences	2 (0.7)	7 (1.3)	9 (9.9)	6 (9.0)	7 (9.5)
Blood Chemistry					
ALT increased	0/305	4/535 (0.7)	6/91 (6.6)	6/67 (9.0)	6/74 (8.1)
AST increased	2/305 (0.7)	2/535 (0.4)	0/91	0/67	3/74 (4.1)
GGT[2] increased	0/0	1/2 (50.0)	0/0	0/0	0/0
Serum creatinine increased	0/305	1/537 (0.2)	0/91	0/67	0/74
Total serum bilirubin increased	1/305 (0.3)	2/536 (0.4)	3/91 (3.3)	0/67	0/74

[1] Considered by the investigator to be possibly, probably, or definitely drug related.

[2] Nonprotocol tests performed by the investigator.

This table contains counts of subjects/patients. Although a subject/patient may have two or more laboratory adverse experiences, the subject/patient is counted only once in "Number (%) of subjects/patients with one or more drug-related laboratory adverse experiences."

Adverse experiences that occurred while subjects/patients were off drug are attributed to the previous drug/dosage taken.

This table represents counts of subjects/patients having specific laboratory adverse experiences in the following format: Number of subjects/patients with experience/number of subjects/patients tested (%).

This table does not include those adverse experiences that occurred before randomization.

As can be seen, increased serum transaminases and total bilirubin accounted for the majority of drug related adverse experiences in all groups in Phase 1/2a studies. Five subjects (4 montelukast, 1 placebo) discontinued from therapy due to postrandomization laboratory adverse experiences. Three of the montelukast patients discontinued due to elevations in transaminases in a single oral dose PK study (014). All three patients were males between 19 and 25 years of age and had their increased LFTs two or more days after receiving a 200 mg dose of montelukast. Two of the patients had AST increase to over 200 U/L. These patients also had elevated CPK due to strenuous exercise prior to blood drawing. The fourth montelukast patient was a 23 year old female who was discontinued from a digoxin interaction study because of low potassium (2.82 mmol/L). This patient had pretreatment subnormal K+ levels.

6.6.5 Laboratories in Adult Open-Label Extension Trials

Laboratories obtained during the open-label extension periods were handled in similar fashion to those obtained during the double-blind periods. That is, sensitivity analyses based on predefined limits of change were conducted. Generally, the frequency of abnormal laboratories was comparable across treatment groups. Since hepatotoxicity is a concern for this drug, a sensitivity analysis for AST and ALT is presented in the tables below.

ALT

		Class Interval (Times Above ULN)				
	n	>2 and ≤ 6	>3 and ≤ 4	>4 and ≤ 5	Total >2 ULN	Total > ULN
Montelukast	682	8 (1.2%)	3 (0.4%)	0	11 (1.6%)	105 (15.4%)
Beclometh	241	3 (1.2%)	2 (0.8)%	1 (0.4%)	6 (2.5%)	34 (14.1%)

AST

		Class Interval (Times Above ULN)				
	n	>2 and ≤ 6	>3 and ≤ 4	>4 and ≤ 5	Total >2 ULN	Total > ULN
Montelukast	682	4 (0.6%)	1 (0.1%)	1 (0.1%)	6 (0.9%)	48 (7.0%)
Beclometh	241	4 (1.7%)	1 (0.4%)	0	5 (2.1%)	17 (7.1%)

A total of seven and four patients in the montelukast and beclomethasone groups, respectively, discontinued treatment due to a laboratory adverse experience. All but one patient in each treatment group discontinued due to a positive pregnancy test. One montelukast patient and one beclomethasone patient discontinued due to increased LFTs. The montelukast patient was a 41 year old male in Study 009 who had an AST of 40 U/L (ULN= 36 U/L) after having received 200 mg montelukast a day for 79 days.

6.7 Other Safety Evaluations

6.7.1 Electrocardiograms

Twelve lead ECGs were obtained at baseline and at the end of the double-blind period for patients in the placebo controlled efficacy trials. These ECGs were only read qualitatively and no measurement of intervals was provided. The richest source of quantitative ECG data is contained in Study 009 in which daily montelukast doses up to 200 mg were studied. ECGs were obtained at baseline and three times during the six week double-blind period. Intervals (PR, QRS, QT and QTc) were measured for each ECG for each patient and were provided in the case report tabulations. Perusal of these data listings did not reveal any significant effect of montelukast on cardiac depolarization/repolarization and no clinically significant change from baseline readings in any particular patient. No clinically significant arrhythmias were captured on ECG. Additionally, quantitative ECG interval analyses were performed in several of the clinical pharmacology trials including Studies 002 [60:1197], 004 [61:1589] and 048 [68:6101]. Studies 002 and 004 investigated single doses of montelukast (not TBM formulations up to 800 mg) in mild to moderate asthmatics. ECGs were obtained at intervals up to 24 hours after dosing and evaluated quantitatively and qualitatively. Although mean ECG interval data were not presented, both studies reported all qualitative and quantitative ECG abnormalities. There is no evidence of dose-related changes from baseline in either of these studies. The cardiac repolarization effect of montelukast in combination with terfenadine was assessed in Study 048 in which multiple-dose montelukast (steady-state) was added to steady-state dosing of terfenadine. There were no differences in the QTc pharmacodynamics between the terfenadine only and terfenadine plus montelukast treatment periods. Of note, montelukast did not affect the pharmacokinetics of parent terfenadine or its metabolite. Although it would have been desirable to have the Phase 2b/3 ECG interval data analyzed by dose (means and sensitivity analyses), the preclinical and existing clinical data as well as the previous experience with other leukotriene antagonists do not raise concern regarding a potential effect of montelukast on cardiac electrophysiology.

6.7.2 Evaluation of Hemolysis

Serum haptoglobin was measured in one clinical study utilizing both the oral and intravenous formulations of montelukast to address the preclinical observation that hemolysis of washed human RBCs occurs with exposure to montelukast. There was no evidence of hemolysis with either the oral or intravenous formulation determined by analysis of haptoglobin, bilirubin, and hematocrit. Hematocrit and bilirubin were also measured in the Phase 2b/3 double-blind and extension studies and no evidence of a hemolytic phenomenon was noted.

6.7.2 Pregnancy

Patients were discontinued from study therapy after a positive pregnancy test was obtained. In total, 27 randomized patients (8 placebo, 15 montelukast, 4 beclomethasone) became pregnant on study. Eleven of these occurred during the extension periods. As of March 24, 1997, ten healthy infants were born (2 placebo, 6 montelukast, 1 beclomethasone) and 1 pregnancy was progressing normally. The remaining 16 pregnancies were not carried to term. Eleven were electively aborted and five (1 placebo, 2 montelukast, 2 beclomethasone) were spontaneously aborted.

6.7.3 Drug-Demographic Interactions

There were no obvious differences in the adverse event or laboratory safety profile when analyzed by age, sex, or race. Any slight differences among montelukast groups were also observed in placebo and beclomethasone groups.

6.7.4 Vital Signs

There were no mean differences between placebo and montelukast on vital signs including heart rate, systolic blood pressure, diastolic blood pressure and oral temperature during the double-blind treatment periods in the primary studies (Studies 020 and 031).

6.8 Case Report Forms

The following is a list of the Case Report Forms of deaths and dropouts due to adverse events. These were submitted in electronic format only and were individually reviewed. In addition, the sponsor provided detailed narratives of the patients listed below who took part in the Phase 2b/3 double-blind [94:22849] and extension studies [SU:356]. These were also reviewed in detail. No significant additional safety concerns were generated as a result of these reviews.

Deaths

Protocol -Study	Patient Allen. Number	Investigator	Cause of Death
020-036	5591	Kramer, Mordechai R	Trauma,head

Discontinued Due to AE's

Protocol -Study	Patient Allen. Number	Investigator	Reason
003-001	96	James, Ian Meurig	WBC Increased
007-002	43	Chervinsky, Paul	Asthma,exacerbation
007-002	68	Chervinsky, Paul	Rash,arms
007-003	54	Bewtra, Againdra	URI
008-001	153	Hulm, Richard	Dermatitis,atopic
009-003	434	Appel, David W.	Schizoeffective Disorder
009-005	536	Brandon, Milan	Sinusitis,acute
009-006	607	Bronsky, Edwin	Paranoia
009-007	461	Busse, William	Sinusitis
009-008	319	Chervinsky, Paul	Otitis
009-008	321	Chervinsky, Paul	Asthma,exacerbation
009-008	324	Chervinsky, Paul	Adenopathy,cervical
			Erythema,throat
009-011	543	Edwards, Thomas B.	Asthma,exacerbation
			Bronchitis
009-015	507	Munk, Z.	Pain,chest Wall Anterior
009-016	548	Murray, John	Asthma,exacerbation
009-016	854	Murray, John	ALT Increased
009-017	551	Noonan, Michael J.	Infection,eye
009-017	885	Noonan, Michael J.	ALT Increased
			AST Increased
			Serum Alkaline Phosphatase Inc
009-018	582	Grossman, Jay	Edema,ankle
			Edema,leg
009-019	519	Prenner, Bruce	Neoplasm,breast,malignant
009-019	520	Prenner, Bruce	Bronchitis,acute
009-019	521	Prenner, Bruce	Bronchitis
009-022	900	Seltzer James	Asthma,exacerbation
009-023	398	Storms, William	Ache,joints
			Ache,muscle
			Adenopathy,inguinal
			Temperature Increased
009-024	879	Strek, Mary	AST Increased
009-027	423	Wanderer, Alan A.	Asthma,exacerbation
			Cold
			Sinus Infection

Discontinued Due to AE's (Continued)

Protocol -Study	Patient Allen Number	Investigator	Reason
009-030	466	Kramer, M.	Asthma, worsening
012-001	726	Hunt, Thomas L.	Rash
012-001	731	Hunt, Thomas L.	Urticaria
012-001	746	Hunt, Thomas L.	ALT Increased
012-001	790	Hunt, Thomas L.	ALT Increased
013-002	962	Bronsky, Edwin	Urinary Tract Infection
014-001	935	Scardella, Anthony T	Ventricular Premature Systole
014-001	938	Scardella, Anthony T	Supraventricular Tachycardia
014-001	944	Scardella, Anthony T	ALT Increased
			AST Increased
			GGT Increased
014-001	946	Scardella, Anthony T	ALT Increased
			AST Increased
			CPK Increased
			Serum LDH increased
014-001	949	Scardella, Anthony T	CPK Increased
			Serum LDH increased
			ALT Increased
			AST Increased
015-003	1867	Kowalski, Marek	Headache
017-001	1123	Casale, Thomas	Chills
			Vomiting
020-001	5422	Ortega, Hector J	Serum Pregnancy Test Positive
020-003	5917	Pineiro, Andres	Asthma Attack
020-003	5919	Pineiro, Andres	Suicide Attempt
020-003	5930	Pineiro, Andres	Asthma Attack
020-003	5955	Pineiro, Andres	Hypotension, arterial
020-005	5106	Jardim, Jose R	Thromboembolism, pulmonary
020-006	5176	Quagliato, Reynaldo	Papules, abdomen
020-008	6029	Bateman, Eric D	Asthma Attack
020-008	6031	Bateman, Eric D	Asthma, worsening
020-008	6042	Bateman, Eric D	Asthma, worsening
020-010	5997	Bernstein, Maxwell	Asthma Attack
020-012	5886	Villaran Ferreyros,	Serum Pregnancy Test Positive
020-013	5369	Torres, Carlos Artur	Asthma, worsening
020-015	5233	Galleguillos, Fabian	Asthma Attack
020-018	5800	Prieto, Fernando H	Asthma Attack
020-019	5727	Perez-Padilla, Jose	Asthma, exacerbation
020-019	5740	Perez-Padilla, Jose	Asthma, worsening
020-021	5499	Rodriguez-Gomez, G	Serum Pregnancy Test Positive
020-022	5982	Olaguibel-Rivera, Jo	Dyspepsia

Discontinued Due to AE's (Continued)

Protocol -Study	Patient Allen. Number	Investigator	Reason
020-024	5308	Iordanoglou, John	Asthma,worsening
020-024	5312	Iordanoglou, John	Gastritis
020-025	5293	Siafakas, Nikolaos	Asthma Attack
020-025	5296	Siafakas, Nikolaos	Epididymo-Orchitis
020-026	5646	Bonifazi, Floriano	Menstrual Flow,dec
020-026	5649	Bonifazi, Floriano	Diarrhea
020-026	5650	Bonifazi, Floriano	Urticaria
020-028	5703	Guerra, Jeremias	Serum Pregnancy Test Positive
020-028	7027	Guerra, Jeremias	Serum Pregnancy Test Positive
020-029	5654	Todisco, Tommaso	Asthma Attack
020-029	5678	Todisco, Tommaso	Asthma Attack
020-029	5684	Todisco, Tommaso	Syncope,vasovagal
020-029	5686	Todisco, Tommaso	Neoplasm
020-032	5039	Boehning, W.	Asthma,worsening
020-033	5964	Picado-Valles, Cesar	Edema,eyelid
020-034	5670	De Benedetto, Fernan	Asthma Attack
020-036	5594	Kramer, Mordechai R	Asthma,worsening
020-036	5598	Kramer, Mordechai R	ALT Increased
020-037	5621	Weiler Ravell, Danie	Fatigue
020-037	5625	Weiler Ravell, Danie	Asthma,worsening
020-037	5627	Weiler Ravell, Danie	Asthma,worsening
020-037	5631	Weiler Ravell, Danie	Asthma,worsening
020-037	5633	Weiler Ravell, Danie	Asthma,worsening
020-038	5017	Ben-Dov, Issachar	Serum Pregnancy Test Positive
020-038	5612	Ben-Dov, Issachar	Irritation,throat
020-039	5695	Vagliasindi, Mario	Serum Pregnancy Test Positive
025-004	2717	Chervinsky, Paul	Serum Pregnancy Test Positive
025-009	2586	Harris, William G.	Bleeding,gastrointestinal
025-011	2599	Laforce, Craig	Asthma,exacerbation
025-018	2839	Prenner, Bruce	Erythema Multiforme
029-003	6996	Plit, Michael	Asthma Attack
029-005	6964	Ringdal, Nils Ragnar	Common Cold
029-009	6138	Becker, Allan B	Asthma,exacerbation
029-009	6145	Becker, Allan B	Asthma,worsening
029-013	6222	Hebert, Jacques	Asthma,exacerbation
029-013	6274	Hebert, Jacques	Asthma,worsening
029-013	6287	Hebert, Jacques	Asthma,worsening
029-014	6174	Chapman, K	Asthma,worsening
029-015	6821	Trakopoulos, George	Asthma,worsening
029-015	6827	Trakopoulos, George	Asthma,worsening
029-018	6808	Polychronopoulos, Vl	Asthma,worsening

Discontinued Due to AE's (Continued)

Protocol -Study	Patient Allen. Number	Investigator	Reason
029-019	6761	Brandli, O	Gastrointestinal Symptoms
029-024	6234	Ernst, Pierre	Asthma,exacerbation
029-026	6738	Saint-Remy, Jean-Mar	Eczema
029-027	1390	Chervinsky, Paul	Serum Pregnancy Test Positive
029-027	1702	Chervinsky, Paul	Asthma Attack
029-028	1394	Condemi, John J.	Asthma,exacerbation
029-028	1395	Condemi, John J.	Asthma,worsening
029-028	1397	Condemi, John J.	Asthma,exacerbation
029-029	1409	Galant, Stanley J.	Asthma,exacerbation
029-030	1424	Gross, Gary	Asthma,exacerbation
029-030	1426	Gross, Gary	Asthma,worsening
029-030	1428	Gross, Gary	Asthma,worsening
029-031	1445	Laforce, Craig	Asthma,exacerbation
029-032	1466	Noonan, Michael J.	Serum Pregnancy Test Positive
029-033	1506	Southern, D. Loren	Asthma,exacerbation
029-034	1492	Segal, Allen	Asthma Attack
029-035	6788	Dahl, Ronald	Gastritis
029-035	6791	Dahl, Ronald	Asthma,worsening
029-036	6772	Petersen, Bruno Nuch	Asthma,worsening
029-036	6778	Petersen, Bruno Nuch	Asthma,worsening
029-036	6784	Petersen, Bruno Nuch	Asthma,worsening
029-037	6945	Woodcock, A.	Influenza
029-038	6893	Britton, Mark G	Asthma,worsening
029-042	6909	Holgate, Stephen T	ALT Increased
029-046	1360	Berger, W. E.	Asthma,worsening
029-046	1362	Berger, W. E.	Asthma,worsening
029-047	1537	Storms, William	Asthma,worsening
029-052	6083	Kunkel, G	Cold
029-054	6067	Vetter, Norbert	Parkinson's Disease
029-054	6075	Vetter, Norbert	Asthma,exacerbation
029-058	6166	Laviolette, Michel	Asthma,exacerbation
029-058	6169	Laviolette, Michel	Hypertension
029-059	6259	Fitzgerald, Mark J	Asthma,worsening
029-060	6341	Stark, Donald F	Asthma,exacerbation
029-060	6343	Stark, Donald F	Asthma,worsening
029-061	6297	Blackie, Stephen	Asthma,worsening
029-061	6307	Blackie, Stephen	Asthma,worsening
029-062	6387	Day, James H	Asthma,exacerbation
029-063	6364	Patel, Piyush	Asthma,exacerbation
029-064	6184	Moote, William	Infection,respiratory
029-068	1616	Reibman, J.	Asthma Attack

Discontinued Due to AE's (Continued)

Protocol Study	Pediatric Allerg. Number	Investigator	Reason
031-002	3917	Bensch, G.	Anxiety
031-003	3931	Berger, W. E.	Bronchitis
031-003	3940	Berger, W. E.	Asthma, worsening
031-003	3942	Berger, W. E.	Bronchitis, acute
031-005	3949	Brandon, Milan	Serum Pregnancy Test Positive
031-005	3959	Brandon, Milan	Depression
031-007	4551	Brown, C.	Serum Pregnancy Test Positive
031-010	4003	Condemi, John J.	Serum Pregnancy Test Positive
031-012	4018	Daniel, D. L.	Serum Pregnancy Test Positive
031-017	4062	Goldstein, Marc F.	Asthma, exacerbation
031-019	4082	Harris, William G.	Anxiety
031-020	4100	Hendelas, L.	Fatigue
031-022	4114	Kemp, James P	Asthma, exacerbation
031-023	4466	Korenblat, Phillip E	Right Bundle Branch Block
031-031	4524	Nelson, Harold	Respiratory Arrest
031-032	4216	Noonan, Michael J.	Serum Pregnancy Test Positive
031-032	4229	Noonan, Michael J.	Depression
031-034	4597	Owens, Gregory R.	Pain, back
031-036	4231	Pearlman, David S.	Asthma, worsening
031-036	4235	Pearlman, David S.	Asthma, exacerbation
031-036	4236	Pearlman, David S.	Edema, facial
031-037	4246	Pedinoff, Andrew	Asthma, worsening
031-037	4249	Pedinoff, Andrew	Endometriosis, probable
031-037	4255	Pedinoff, Andrew	Asthma, exacerbation
031-038	4272	Prenner, Bruce	Asthma, exacerbation
031-040	4285	Segal, Allen	Depression
031-041	4411	Seltzer, James	Asthma, exacerbation
031-041	4414	Seltzer, James	Asthma, exacerbation
031-041	4423	Seltzer, James	Asthma, exacerbation
031-042	4295	Storms, William	Serum Pregnancy Test Positive
031-044	4316	Stricker, W.	Asthma, exacerbation
031-045	4323	Sveum, R. J.	Asthma, exacerbation
031-045	4327	Sveum, R. J.	Asthma, exacerbation
031-047	4342	Taylor, J. R.	Asthma, exacerbation
031-049	4369	Weisberg, Stephen	Asthma, exacerbation
031-050	4576	White, Richard	Asthma, worsening
031-051	4387	Wolfe, J. D.	Nausea
031-052	4648	Finn, Albert F.	Headache
031-052	4649	Finn, Albert F.	Gastritis
031-054	4678	Tinkelman, David G	Difficulty Breathing
034-001	11	Van Nispen, C	Syncope, vasovagal

Discontinued Due to AE's (Continued)

Protocol -Study	Patient Allen. Number	Investigator	Reason
039-002	9034	Chervinsky, Paul	Infection, Urinary Tract
039-002	9035	Chervinsky, Paul	Varicella
040-002	9878	Kemp, James P	Asthma, worsening
042-002	4850	Busse, William	Asthma, exacerbation
042-003	4831	Hendeles, L.	Sinusitis
042-003	4835	Hendeles, L.	Asthma Attack
042-003	4844	Hendeles, L.	Serum Pregnancy Test Positive
042-003	4846	Hendeles, L.	Asthma, worsening
042-005	4912	Pearlman, David S.	Respiratory Distress
042-005	4923	Pearlman, David S.	Asthma, exacerbation
046-001	7223	Edwards, Thomas B.	Asthma, exacerbation
046-007	7297	Pearlman, David S.	Asthma, exacerbation
046-007	7298	Pearlman, David S.	Bronchitis
046-007	7300	Pearlman, David S.	Asthmatic Bronchitis
046-009	7324	White, Richard	Asthma, exacerbation
046-011	7455	Godard, Philippe	Asthma Attack
046-013	7340	Israel, Elliott	Asthma, exacerbation
046-013	7348	Israel, Elliott	Asthma, exacerbation
046-013	7395	Israel, Elliott	Asthma, exacerbation
046-019	7490	Fitzgerald, Mark J	Asthma, worsening
046-019	7494	Fitzgerald, Mark J	Asthma, worsening
046-019	7495	Fitzgerald, Mark J	Asthma, worsening
046-024	7361	Scardella, Anthony T	Reaction, anaphylactic
049-002	9142	Bernstein, Jonathon	Asthma, worsening
049-003	9160	Blake, Kathryn	Asthma, exacerbation
049-005	9186	Dockhorn, Robert J	Head Nodding Movement
049-008	9241	Galant, Stanley J.	Asthma, exacerbation
049-013	9295	Metz, Jonathan	Pneumonia
049-016	9346	Pedinoff, Andrew	Dehydration
049-020	9399	Schwartz, Robert H.	Total Serum Bilirubin Inc
049-023	9451	Shapiro, Gail	Asthma, exacerbation
049-028	9516	Weinstein, Steven F.	Asthma, exacerbation
049-032	9576	Zieming, William	ALT Increased
049-044	9829	Becker, Allan B	Asthma, worsening
049-044	9832	Becker, Allan B	Headache, worsening
049-047	9728	Finn, Albert F.	URI
049-052	9754	Weiss, Steven G.	Rash, urticarial
049-052	9755	Weiss, Steven G.	Asthma, exacerbation
049-053	9723	Cromar, Brad	Segmented Neutrophils Dec
053-001	6433	De Schepper, P	Serum Potassium Decreased
056-002	1917	Hendeles, L.	Sarcoidosis

Discontinued Due to AE's (Continued)

Protocol -Study	Patient Allen. Number	Investigator	Reason
056-004	6475	Hargreave, F	Asthma, exacerbation
056-005	6485	Boulet, L-P.	Soreness, stomach
059-003	6577	Davies, Robert J	Collapse
059-003	6584	Davies, Robert J	Asthma, exacerbation
059-005	2880	Villaran Fernayros,	Pneumonia, right

7.0 Final Safety Update (SU-2)

A final safety update (SU-2) was submitted to the NDA on September 29, 1997 at the request of the reviewing medical officer. In the report, additional updated cumulative extension study safety information is provided. The Merck in-house cut-off date for reporting these data was April 24, 1997. The data, at the request of the medical officer, is limited to serious adverse events that occurred in these extension studies subsequent to the previous safety update. There were no additional deaths for the SU-2 reporting period. Two montelukast patients were discontinued from study due to serious clinical adverse events. One was a 72 year old female who developed cellulitis after 36 days of montelukast. The other involved the diagnosis of a

'kidney cyst' in a 39 year old male after 1228 days of montelukast therapy. Neither adverse event was considered drug related by the investigators.

Reviewer comments and conclusion on the safety profile of montelukast

The safety of montelukast has been evaluated in an extensive short and long-term clinical program. As predicted by preclinical studies, the clinical toxicity profile of montelukast focuses on the gastrointestinal system. Clinical adverse events involving diarrhea, vomiting, nausea, abdominal pain, and dyspepsia are reported at a higher frequency in montelukast treatment groups. The frequency of infectious gastroenteritis is statistically significantly higher in the montelukast treatment group than in the placebo or beclomethasone treated patients. Most of the reports of this finding are from one clinical trial (031) and a satisfactory explanation of this phenomenon is not apparent from the data provided. It might be considered that modulation of leukotrienes may alter patient's resistance to infection; however, the frequency of infection in other organ system is not higher in the montelukast treated population. Extensive laboratory evaluation in double-blind and open-label extension periods again reveals the montelukast treated patients to have a higher frequency of elevated transaminases. Sensitivity analyses indicate that these elevations are, for the most part mild (less than three times the upper limit of normal) and normalize with continued therapy. There did not appear to be a sex-related propensity for developing increased serum transaminases while receiving montelukast. There was no evidence of drug-induced hepatitis in any patient receiving montelukast. Importantly, available data from the long-term extension studies demonstrate that the frequencies of montelukast associated toxicities decrease with time providing some reassurance that the toxicity profile of montelukast is not related to the cumulative dose received. Montelukast does not appear to have an effect on cardiac electrophysiology. No evidence of Churg-Strauss syndrome or eosinophilic variants were noted. Given the rarity of the event in the population and the experience with another marketed LTD4 antagonist, this is not surprising. The phenomenon appears to manifest in the context of systemic steroid tapering in more severe asthmatics. This was not the population studied in the NDA.

Montelukast appears to be safe at the proposed dose for marketing. Information regarding gastrointestinal toxicities should be represented in the label. Further information regarding the specific nature of infectious gastroenteritis reported in Study 031 is pending and will be dealt with in a separate review.

8.0 Review of DSI Audits

Three sites were chosen for auditing by DSI for NDA 20-829. In each case, in addition to the usual auditing procedures, the FDA inspector was provided with efficacy data listings from the NDA database submitted to FDA. The FDA inspector compared the data listings to the source documents at each audit site. The following sites were audited.

Study 031: Site 013: Dr. Robert Dockhorn, Lenexa Kansas
Study 042: Site 002: Dr. William Busse, Madison Wisconsin
Study 046: Site 010: Dr. James Wolfe, San Jose, California

Drs Dockhorn and Wolfe were classified as NAI and no FDA 483s were issued. Each site had minor findings that do not affect data integrity. In each case, there were no data discrepancies between the NDA data (provided by MO) and the source documentation.

Dr. Busse was issued an FDA 483 and classified as VAI. There were no discrepancies between the NDA data (provided by MO) and the source documentation; however, there were problems

noted that may have affected study conduct and analysis. The inspector noted that the original consent form used for all patients at this site did not accurately reflect the study protocol. It was documented, however, that the study protocol (and not the informed consent version of the protocol) was followed. It was further noted that a patient (AN4854) was incorrectly enrolled in the study which required a protocol-specified asthma history of one year. This patient had only been diagnosed with asthma three months prior to enrollment. The inspector further noted that there were minor drug inventory and labeling inaccuracies for four subjects (ANs 4855, 4851, 4853, and 4854). Finally, the inspector noted that Merck had incorrectly excluded five subjects from the per-protocol efficacy analysis. Merck responded to this by conducting a detailed review of the efficacy data and handling procedures for Study 042 [Submission of July 15, 1997 to NDA 20-829]. Merck noted that for most of the Phase 3 studies for montelukast, the PFT data were electronically transferred (via modem) directly from the spirometer at the study site to an Oracle-based database at Merck. However, in Study 042,, due to the complex nature of the exercise and methacholine challenges, data entry into the database was handled differently. PFT data were manually coded, entered by double data entry procedures, and uploaded directly into the clinical data management system. The lack of automated data entry integrity checks and the increased complexity of data management provided the potential for more data entry and handling errors in this protocol. Approximately 43,553 individual data fields for pulmonary function values for exercise and methacholine challenges were hand keyed for this study. Errors in 232 data fields were identified, representing a 0.53% error rate. Missing data, incorrectly keyed data, and/or data in the wrong location in the database accounted for these discrepancies between the case report data and the clinical data management system. New intention-to-treat and per-protocol analyses were performed on the revised corrected database and demonstrated nearly identical results to those reported in the NDA for Study 042.

Reviewer comment on DSI audits: No problems were found with two investigators. At all three sites, there were no discrepancies between the NDA data provided and the source documents. Inspector findings at the Busse site called into question the data integrity of Study 042; however, Merck conducted a complete audit of all sites from that study and a reanalysis of efficacy based on the revised, corrected data. No differences were found between the analyses in the NDA and the revised analyses. No further action is indicated.

9.0 Labeling

Product labeling will be reviewed separately. The tradename Singulair® has been found acceptable by the Division.

10.0 Overall Conclusions

Please refer to Executive Summary on Safety and Efficacy at the beginning of this review document.

11.0 Reviewer Recommendation

Montelukast should be approved for the prophylaxis and chronic treatment of asthma in adults.