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APPLICATION NUMBER: 20-830

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #: 20-830	APPLICATION TYPE: NDA
SPONSOR: Merck	PRODUCT/PROPRIETARY NAME: Singulair
	USAN / Established Name: montelukast
CATEGORY OF DRUG: LTD4 antagonist	ROUTE OF ADMINISTRATION: oral
MEDICAL REVIEWER: A. Trontell	REVIEW DATE: January 20, 1998

SUBMISSIONS REVIEWED IN THIS DOCUMENT

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RELATED APPLICATIONS

Document Date:	APPLICATION Type:	Comments:
21 Feb 97	NDA 20-829	Singulair Adult Indication

Overview of Application/Review: Pediatric indication for ages 6 to 14 years; please see accompanying review

Outstanding Issues: Labeling and potential Phase IV pediatric commitment

Recommended Regulatory Action: Approval

N drive location:

NDA's:

Efficacy / Label Supp.: <input checked="" type="checkbox"/> <u>Approvable</u>	Not Approvable
Signed: Medical Reviewer:	Date: <u>1/22/98</u>
Medical Team Leader: _____	Date: <u>1/20/98</u>

T.L. note: see T.L. memo for overview of pediatric indication.
 1/20/98

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Executive Summary of Efficacy, Safety, and Approvability

The pediatric NDA for Singulair consists of data on a total of 488 patients aged 6 to 14 years, with 321 patients exposed to one or more doses of montelukast. A total of four protocols were conducted to assess pharmacokinetics/dose, efficacy in chronic asthma, and efficacy in exercise-induced bronchoconstriction. Studies of steroid reduction and aspirin-sensitive asthmatics were not done in the pediatric population. The pediatric Chronic Asthma study and its safety extension (Protocol 049) and the Pediatric Exercise Study (Protocol 040) were pivotal to the determination of efficacy. These studies and the pharmacokinetic studies (single dose in Protocol 036, multiple dosing in Protocol 039) constituted the safety data base for montelukast.

EFFICACY

In the Chronic Asthma study and its safety extension (Protocol 049) montelukast administered as a 5 mg chewable tablet once-daily improved pulmonary function in children aged 6 -14 years with chronic asthma. Over 8 weeks of therapy, improvement was manifest in a statistically significant mean FEV1 increase that was approximately 4.5% greater than placebo controls. Improvement in FEV1 was maintained over 6 months of open-label use. The magnitude of the montelukast treatment effect was less than was seen in adult studies.

Secondary efficacy parameters in Protocol 049 were generally supportive of montelukast efficacy, although statistical significance was achieved only for reduction in as-needed β -agonist use. This reduction amounted to approximately 1/3 fewer puffs a day than placebo controls, a decline of small clinical impact. Onset of action analyses did not demonstrate a first-dose effect in pediatric patients, in contrast to clinical studies in adults. The only end-of-dosing interval endpoint in the pediatric chronic asthma studies, evening PEFr, was unchanged in montelukast patients relative to placebo.

End-of-dosing interval efficacy was demonstrated in asthmatic children aged 6 -14 years in the pediatric exercise study. A statistically significant improvement in the mean AUC_{0-60 min} and maximum percentage fall in FEV1 post-exercise was seen after 2 evening doses of the 5 mg montelukast as the chewable tablet. Notwithstanding these significant mean changes, there was substantial individual variability in response, with some patients actually worsening on montelukast therapy. Similar limitations were found in the adult EIB studies, where the magnitude of the treatment effect was comparable to that seen in the pediatric study.

SAFETY

Montelukast was generally well tolerated in 6- to 14-year-old patients, based upon a safety data base where approximately 80% of exposed patients had prolonged exposures (8 weeks to 17 months). There were no clinically meaningful differences in the adverse experience incidence in relation to duration of montelukast exposure, age, gender, race/ethnic group, or use of concomitant therapies.

The overall profile of clinical adverse experiences seen with montelukast was not serious and was comparable to that seen in the adult montelukast program. Adverse experiences that occurred in <1% of adult montelukast patients, but which occurred in \geq 2% of pediatric patients and at elevated rates in montelukast compared to placebo included viral infection, laryngitis, pharyngitis, sinusitis, otitis, diarrhea, and nausea. Across the entire montelukast pediatric program, urogenital

system disorders were seen exclusively among patients treated with montelukast, but the rate of these disorders was <2%.

In Protocol 049 and its extension, clinical adverse experiences that were serious or led to study discontinuation were somewhat more common among montelukast patients than placebo controls, and consisted chiefly of asthma exacerbations. These findings may speak more to the efficacy than the safety of montelukast in pediatric patients.

As in adults, safety data suggest that montelukast may have some effect upon liver function in the pediatric population. Low-level transaminase elevations (<2 times ULN) occurred more commonly among montelukast patients than placebo controls, and laboratory adverse experiences of elevated transaminases (2 to 3 times ULN) or bilirubin (~2 times ULN) were seen more commonly among montelukast pediatric patients. No clinical liver disease was observed in any affected patient.

No studies were conducted on the potential for growth suppression in children and adolescents exposed to montelukast.

APPROPRIATENESS OF PEDIATRIC DOSAGE

The dosage of 5 mg montelukast once daily for ages 6 - 14 years was based upon pharmacokinetic studies designed to find the pediatric dose that gave comparable AUCs to adults where efficacy had been shown with the 10 mg FCT. No pediatric dose-ranging efficacy trials were conducted. Although statistically significant efficacy was found in the pediatric chronic asthma and exercise endpoints, optimal dosing was not convincingly demonstrated. The treatment effect in chronic asthma was less than adults, end-of-dosing interval efficacy was limited and seen only in the exercise study, and onset of action was not well-established.

APPROVABILITY

Based upon the acceptable efficacy and safety profiles as reviewed in this document, the Singulair 5 mg chewable tablet is approvable from the clinical standpoint. Revisions are needed in the labeling and are described in general terms in the labeling section of this review.

**APPEARS THIS WAY
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Introduction and Approach

BACKGROUND

Montelukast (MK-0476) is a selective leukotriene (LTD₄) receptor antagonist that blocks the action of the cysteinyl leukotrienes LTC₄, LTD₄, and LTE₄. These leukotrienes appear to mediate aspects of pathologic lung function including mucus production, decreased mucociliary clearance, changes in vascular permeability, and smooth muscle contraction leading to bronchoconstriction or vasoconstriction. Blockade of the CysLT₁ receptor by a variety of receptor antagonists has been associated with improvement in the signs and symptoms of bronchial asthma.

PROPOSED PEDIATRIC INDICATION

Singulair is indicated in pediatric patients 6 years of age and older for the prophylaxis and chronic treatment of asthma. The sponsor's proposed labeling seeks this indication for both adults and children, and also specifies the prevention of day and nighttime symptoms, the treatment of aspirin-sensitive patients, and the prevention of exercise-induced bronchoconstriction.

HOW SUPPLIED

For children aged 6 - 14 years, 5 mg (pink, cherry-flavored) chewable tablets.

PROPOSED DOSE

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

REVIEWER APPROACH AND NOTATIONS

NDA 20-829 for montelukast use in adult asthmatics aged 15 years and older was submitted simultaneously with 20-830 and was reviewed by another medical officer. Chemical structure and clinical pharmacokinetics sections from that review are not reproduced here.

Two efficacy trials were conducted to support the pediatric indication of montelukast for children aged 6 - 14 years. A chronic asthma study (Protocol 049) was conducted in a double-blinded fashion for 8 weeks, followed by an open label safety extension. Both phases of this study are discussed under Protocol 049, and that summary incorporates and synthesizes all safety updates. The second efficacy trial (Protocol 040) was a crossover study examining the efficacy of montelukast in exercise-induced bronchoconstriction. Auditing and checking of case report forms by the medical reviewer for Protocols 040 and 049 are described separately from the protocols, under the Data Auditing and Checking section of this review.

Pediatric pharmacokinetic studies (036 and 039) are discussed in two places in this review. The first is in the section on pediatric dose selection, which briefly describes their application to dose selection for the pediatric clinical program. More detailed discussion of safety findings of these protocols is found in the two sections of this review which describe each protocol. Detailed analyses of the pharmacokinetic findings of these studies can be found in the review by the Biopharmaceutics reviewer. No case report forms were filed for these studies, so no medical review spot-checking was done.

References in brackets [] refer to volume and page number from the application hard copy, [Volume: page number]. The safety updates are also bracketed in reference their number (either 1 or 2), volume, and page number, [Number: Volume: page number].

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Abbreviations: Well-understood clinical and pharmacokinetic abbreviations are used in this document without reference. Other abbreviations are defined the first time they are used in a section. Some of the more commonly used abbreviations are defined below.

AE	Adverse experience
CRF	Case report form
CT	Chewable tablet (refers to 5 mg formulation)
EIB	Exercise-induced bronchoconstriction
FCT	Film-coated tablet (refers to 10 mg formulation)
LLN	Lower limit of normal
QOL	Quality of Life
ULN	Upper limit of normal

Dose Selection For The Pediatric Population (Age 6-14 Years)

Based on the similarity of asthma in pediatric and adult patients, the pediatric dose was selected to provide a pharmacokinetic (AUC) profile comparable to that of the 10 mg film-coated tablet (FCT) in adults. No pediatric dose-ranging efficacy trials were conducted. The 10 mg FCT was the lowest dose identified in adult dose-ranging studies to have significant effects on measures of airway obstruction and patient-reported endpoints in chronic asthma and exercise-induced bronchoconstriction (EIB) as described below.[2:C-31 to C-35]

Adult dose selection: Dose-ranging studies were conducted in asthmatic adults with daily doses ranging from 2 mg to 200 mg of montelukast, and with twice-daily dosing of 10 or 50 mg. Once-daily dosing was found to be equally effective as twice daily dosing, and no dose-response relationship was seen with measures of airway obstruction such as FEV₁ and PEF_R. The effect on patient-reported endpoints (symptoms, β -agonist use, exacerbation rates, and quality of life) was significantly improved over placebo with doses of 10 mg or greater.

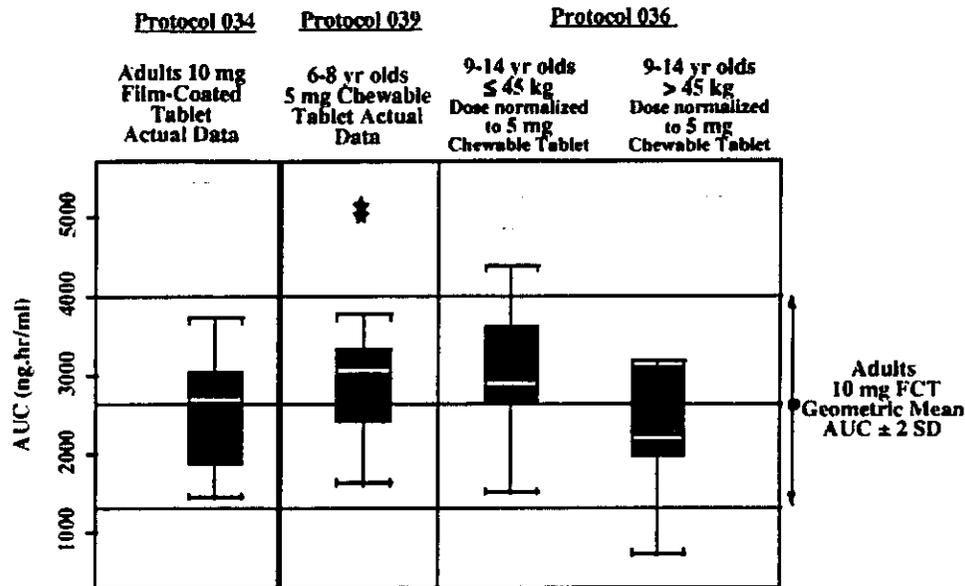
A low-dose-ranging EIB study of 0.4, 2, 10 and 50 mg of montelukast dosed at bedtime distinguished the 10 and 50 mg doses as statistically significant from placebo and providing greater EIB inhibition than either 0.4 or 2 mg. The findings from the asthma and EIB studies, as well as the finding that the 10 mg dose had a significant effect at the end of the dosing interval in both chronic asthma (pm PEF_R) and EIB (inhibition of EIB), led to the selection of the 10 mg once-daily bedtime dose for the adult Phase III studies.

Tanner pubertal stages 4 and 5 adolescents had similar plasma profiles compared with adults, so patients 15 years of age or older were included in the adult Phase III efficacy trials using the adult 10 mg FCT.

Pediatric dose selection: The pediatric dose for the chewable tablet (CT) was selected to provide a pharmacokinetic (AUC) profile comparable to that of the 10 mg film-coated tablet (FCT) in adults. Two pharmacokinetic studies (Protocols 036 and 039) were conducted to determine the plasma profile in pediatric patients. Protocol 036 was a single-dose study in 9- to 14-year-old patients given a single dose of montelukast according to body weight (6-mg film-coated tablet [3 x 2-mg tablets] for ≥ 45 kg and 10-mg film-coated tablet for >45 kg) to approximate the adult dose of montelukast. Protocol 039 was a multiple-dose study in 6- to 8-year-old patients in which a 5-mg chewable tablet of montelukast was administered. [2:C-35 to C-37]

The optimum pediatric dose for 6- to 14-year-old patients was determined by normalizing the data from these pharmacokinetic studies to a 5-mg chewable tablet AUC value. This was based upon the observed dose proportionality of the chewable tablet and the 20% difference in the AUC between the chewable and film-coated tablets. The figure below depicts actual (for the 6-to 8-year-olds) and normalized (for the 9- to 14-year-olds) AUC values. The actual AUC data from the adult 10-mg film-coated tablet dose are also presented for comparison.

Actual AUC (6 to 8 Year Olds) or Dose-Normalized AUC to a 5-mg Chewable Tablet Dose (9 to 14 Year Olds) Compared With Actual Adult AUC (10-mg Film-Coated Tablet)



Note: The gray horizontal lines represent the geometric mean AUC \pm 2 SD for the 10-mg film-coated tablets in adults. The bottom and the top of each box represent the 25th and 75th percentile of the AUC data, respectively. The white line within each box represents the median. The bars represent the furthest data points within the predefined non-outlier range. The asterisks represent potential outliers.

The actual and normalized AUCs for the 5-mg chewable tablet were felt by the sponsor to demonstrate the comparability of pharmacokinetic profile of montelukast across the 6- to 14-year-old age range to that observed with the 10-mg film-coated tablet in adults. The 5-mg chewable tablet dose of montelukast once daily at bedtime was therefore selected as the dose for clinical efficacy trials in this age range.

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Protocol 049

A Multicenter, Double-Blind, Randomized, Parallel-Group Study Comparing MK-0476 to Placebo in 6- to 14-Year-Old Patients With Chronic Asthma, With Montelukast Treatment Extension

SUMMARY

In an eight-week, double-blind, placebo-controlled trial of 336 children aged 6 - 14 years with mild to moderate asthma, montelukast chewable tablets dosed each evening at 5 mg/day resulted in a statistically significant improvement in the primary efficacy endpoint, average percentage change in baseline FEV1. Montelukast therapy was associated with ~4.5% increase in average FEV1 over placebo controls, an increase of uncertain clinical significance on a population basis. Three of the four secondary efficacy endpoints (change in baseline AM PEFr, change in daytime symptoms, nocturnal asthma score) showed greater mean clinical efficacy with montelukast than with placebo but did not achieve statistical significance. The fourth secondary endpoint, use of as-needed beta-agonists, was statistically improved over placebo when analyzed according to percentage change, but mean absolute reduction in use (approximately 1/3 puff daily for montelukast compared to placebo) was not statistically significant nor clinically compelling in light of mean baseline use of approximately 3 puffs daily. Four tertiary endpoints included in the sponsor's proposed labeling were supportive of montelukast efficacy; pediatric asthma-specific quality of life, overall and parental global evaluations, asthma exacerbations, and peripheral blood eosinophil counts had statistically significant improvements of montelukast over placebo. Additional efficacy endpoints showed slight improvement for montelukast over placebo but did not achieve statistical significance: percentages of asthma-free days, patients with asthma attacks, patients requiring corticosteroid rescue, days missed from school because of asthma, and nocturnal awakenings due to asthma (assessed in a subpopulation of 89 patients with baseline symptoms).

With respect to the appropriateness of the 5 mg dose and the once-daily (evening) dosing interval, the only end-of-dosing interval endpoint (mean evening PEFr) was no better among montelukast patients than controls. Post-hoc regression analyses of onset of action demonstrated consistency in montelukast efficacy over time, but did not establish that treatment effect was achieved after the first dose. Comparison of daily diary means for daytime symptom score, am PEFr, and total daily β -agonist use (percentage change) did not evidence any statistically or clinically meaningful benefit to montelukast therapy on day 1 of therapy with the exception of the percentage change in total β -agonist use.

Serious adverse experiences in the 8 week double-blinded trial and its open-label extension occurred exclusively in montelukast-treated patients, with rates of 2.2% and 4.8% respectively. The majority of these serious events consisted of hospitalizations for worsening asthma; discontinuations for worsening asthma were also greater in montelukast than either placebo or active control patients. Clinical adverse experiences of headache, fever, and sinusitis, and otitis were elevated in montelukast patients. Selected infectious/inflammatory conditions also appeared elevated in different body systems with montelukast therapy in the open label extension. Elevations in serum transaminases <2 times the ULN occurred more commonly in montelukast patients, and elevations to 2-3 times the ULN were infrequent but more common in montelukast patients than placebo. Three children in the study extension had poorly explained changes in liver function while on montelukast therapy: increased bilirubin (1 patient) and transaminases (2 patients).

PROTOCOL

Objective

The primary objective of this protocol was to establish the safety, tolerability, and efficacy of montelukast for up to 6 months in 6 to 14 year old patients with chronic asthma.

Overview

This was a multicenter, double-blind, randomized, parallel-group study comparing a single dose of montelukast to placebo in 6- to 14-year-old patients with chronic asthma. There were 3 study periods:

- Period I, a 2 week single-blind placebo run-in period followed by randomization of eligible patients;
- Period II, an 8 week double-blinded efficacy period comparing montelukast to placebo; and
- Period III, an elective 16 week open, controlled safety extension during which patients received either montelukast or inhaled beclomethasone as described below under Study Design

Visits occurred weekly during Period I, biweekly during Period II, and every 4 weeks during Period III. Principal study procedures are summarized in the table on the following page [derived from 90:D-20190].

Treatment

Patients randomized to receive montelukast were supplied 5 mg chewable tablets to be taken at bedtime; the formulation number was MR-3247 and control numbers were WP-B495 and CA-A141. Placebo tablets were formulation MR-3250, with identical control numbers to the montelukast tablet. Patients routinely taking inhaled corticosteroids and who were on a stable dose for at least one month prior to study entry were allowed to continue their usual dose; up to 40% of enrolled patients were allowed such treatment. All patients were allowed to use as-needed inhaled β -agonist therapy (Salbutamol, supplied as Ventolin™, formulation numbers 5ZPA021, 5ZPA031, 5ZPA045, and MR-3179 and releasing 90 mcg from the mouthpiece per actuation) throughout the study [Table 7, 90:D-19707]. Aerochamber spacer devices were dispensed as needed.

Protocol 049-05 Evaluation Procedures

Procedure	Run-In			Blinded Efficacy Trial				Open, Controlled Safety Extension				D
	Period I			Period II				Period III				
	0	1	3	5	7	9	11	15	19	23	27	
Wk Visit	Pre	1	2	3	4	5	6	7	8	9	10	
History	X											
Inclusion/Exclusion review	X		X									
Physical exam, height, weight, Tanner staging	X						X				X	X
Lab safety tests (urine, blood)	X		X	X	X		X	X		X	X	X
12 lead ECG	X						X				X	X
Spirometry, Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
β -agonist reversibility	X	X	X				X					X
Quality of Life Questionnaire			X				X				X	X
Global Evaluations (by patient, parent, investigator)							X				X	X
Plasma sample for archive							X					X
Urine HCG in females that have begun menses		X	X	X	X	X		X	X	X		

Explicit criteria and an action plan for the treatment of worsening asthma during Period II were specified in the protocol [90:D-20264]. Initial, physician-guided therapy was to use nebulized albuterol, followed as deemed necessary by oral prednisone at specified mg/kg doses. Need for oral prednisone beyond 5 days, use of iv or im corticosteroids, addition of inhaled corticosteroids or change in usual inhaled corticosteroid dose, or use of any theophylline were causes for study discontinuation.

During Period III, children receiving beclomethasone who were not already using it during Period II were given inhalers (50 mcg/puff) provided by formulation numbers were 5ZPA048, MR-3218 [91:D-20999]. Patients took 2 puffs tid, timed after the am and pm PEFr measurements. Patients already on beclomethasone during Period 2 continued their usual dose, and patients on other inhaled corticosteroids during Period II were to continue their same medication/dose/dose interval throughout Period III. did not supply inhaled corticosteroids other than beclomethasone.

Nasal cromolyn, Emla cream, and vaccines could be used as needed throughout the study. Use of the following asthma and allergy medications [90:D-20209ff] was not allowed throughout the study (and for varying times prestudy as described under item 6 in exclusion criteria below) :

- iv, im, oral corticosteroids (except restricted oral use specified for rescue therapy)
- theophylline
- orally inhaled cromolyn
- nedocromil
- oral or long-acting β -agonists
- OTC or Rx products containing caffeine, theophylline/aminophylline, or β -agonist preparation
- terfenadine
- loratadine
- astemizole
- aspirin and NSAIDs in sensitive patients or individuals without previous exposure to these compounds

In addition, the following allergy medications and antibiotics were restricted in type, timing, or duration of use :

- Amoxicillin, Augmentin, and Ceftin were permitted for treatment of infection during the course of the study. A maximum of one 14-day course was allowed except for the treatment of sinusitis where up to 21 days of therapy per month was allowed. Antibiotic therapy could not exceed 21 days in a 2 month period of time
- Nasal corticosteroids could not be used for greater than 1 week in any 1-month period of time during Periods I and II, but were allowed as needed in Period III
- Antihistamines were to be withheld for 48 hours prior to clinic visits

In addition, the following medications were restricted from 2 weeks prior to the prestudy visit and throughout the study: warfarin, digoxin, cimetidine, metaclopramide, phenobarbital, dilantin, and β -adrenergic blocking agents including ocular preparations.

Concomitant Drug Treatment Before Clinic Visits: Prior to study visits, short- and intermediate-acting antihistamines were to be withheld for 48 hours, caffeinated beverages for 8 hours, inhaled β -agonists for 6 hours, and beclomethasone (or other inhaled CS) for 1 hour. If use occurred within these restricted time periods, it was to be noted on the case report forms and the visit rescheduled.

Patients

The following inclusion and exclusion criteria were used in patient selection.

Inclusion criteria [90:D-20201ff)

1. Male or female aged 6 to 14 years
2. Weight within 40% of 5th to 95th percentile weight range from NCHS.
3. No history of ever smoking
4. Met all of the following four asthma criteria
 - Typical symptoms including but not limited to cough, wheezing and SOB with periodic episodes requiring treatment with bronchodilators
 - FEV1 \geq 50% and \leq 85% predicted while off β -agonist for 6 hours, documented on least 2 occasions during the Prestudy Visit, Visit 1, and/or Visit 2
 - An increase in FEV1 of at least 15% between 20 to 30 minutes after inhaled β -agonist administration on least 2 occasions during the Prestudy Visit, Visit 1, and/or Visit 2
 - A minimum biweekly diary symptom score of 21 during Period I (potential range of total daily scores, 0 - 15)
5. Patient's present asthma therapy included a minimum average of one puff daily of short-acting inhaled beta-agonists during Period I
6. Patient able to perform PFT and PEFr measurements reliably
7. Patient in otherwise good, stable health on the basis of H&P, routine lab data
8. All parents/guardians and 9 to 14 year olds able to comprehend the questions on the asthma diary card.
9. Females that have begun menses must have had negative β -HCG at the Prestudy visit, and use appropriate contraception from 2 weeks prior to treatment and until 14 days poststudy

Reviewer comment: *In the extreme, the weight criteria under inclusion criterion #2 would allow children with weights as low as 10 kg or as great as 100 kg to be included.*

Exclusion Criteria [90:D-20202]

1. Patient had evidence of active, clinically significant sinus disease within 3 weeks of study visit
2. Patient had any active, acute, or chronic pulmonary disorder other than asthma
3. History of intubation for asthma
4. ER visit or hospitalization for asthma within 1 month of prestudy visit
5. Patient had unresolved signs and symptoms of an upper respiratory tract infection (URI) or had had a URI within 3 weeks of the study visit

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6. Medications

- Initiation of immunotherapy within 6 months of prestudy visit and/or anticipated change in dose over the course of the study
 - Astemizole within 3 months of study visit
 - Use of oral, im, or iv steroids within 1 month of prestudy visit.
 - Inhaled steroids within 1 month of prestudy visit with the exception of those patients (up to 40% of participants) allowed to continue on inhaled daily dose if no change in dose for at least 1 month before prestudy visit
 - Use within 2 weeks of prestudy visit of cromolyn, nedocromil, oral or long-acting β -agonists, atrovent, terfenadine, or loratadine
 - Use of theophylline or theophylline-like drugs within 1 week of the prestudy visit
7. Clinically significant disease of GI, cardiovascular, hepatic, neurological, renal, GU, or hematological systems, or hypertension (>130/90)
 8. History of any clinically significant adverse experience of a serious nature (ie. Angioedema, anaphylaxis) to a marketed or investigational drug, or is otherwise sensitive to inhaled beclomethasone, inhaled β -agonist, or their components
 9. History of any illness requiring an excluded medicine, or that is life-threatening, or that would restrict participation or completion, or would pose additional risk to administering montelukast to the patient
 10. Patient or parent is mentally or legally incapacitated
 11. Patient is hospitalized
 12. Pregnant or nursing females, or ≤ 8 weeks postpartum
 13. Planned travel or move for > 16 days during course of the study
 14. Current or former use of illicit drugs or alcohol
 15. Donation of one unit of blood, or participation in any drug trial within 8 weeks of prestudy visit
 16. Major surgery within 4 weeks of prestudy visit
 17. In a situation or having a condition which may interfere with optimal participation
 18. Previous participation in a montelukast study
 19. Patient and parent unable or unwilling to comply with study procedures during Period I as reflected in entry of diary data or medication compliance

Study Design

During the Prestudy Visit of Period I, patients were screened for eligibility as well as compliance with data collection and medications. Compliance, medication use, and baseline symptomatology were assessed using 4 additional eligibility criteria [90:D-20217] to determine entry in Study Period II.

According to eligibility and randomization done during Visit 2, Period II patients received double-blinded treatment with either montelukast or placebo in addition to prn albuterol. Visits were to occur within a 14 (± 3) day window. Upon completing Visit 5 (following 6 weeks of therapy), patients were asked to participate for an additional 16 weeks in the open, controlled extension. For those who choose not to participate, Visit 6 (following 8 weeks of therapy) served as the Poststudy visit.

Reviewer comment: *No off-drug follow-up occurred for the majority of montelukast patients unless an adverse event was being followed; rebound worsening of asthma upon drug withdrawal was therefore not determined. The medical reviewer of the adult protocols found no evidence for rebound worsening after montelukast discontinuation, and there is no reason to suspect the pediatric experience would be different from that of adults.*

During Period III, patients received treatment with either montelukast or inhaled beclomethasone according to their allocation assignment at the end of Period I. Patients who received montelukast during the Period II were divided into 2 groups to receive either inhaled beclomethasone or continued montelukast. Patients who received placebo during Period II received either

montelukast or inhaled beclomethasone. Patients that were on inhaled corticosteroids during Period II continued therapy during Period III with the same medication and dose as was used Period II. Further details are provided in the Treatment section of this protocol review.

Discontinuation criteria: Patients were to be discontinued for any "rescue" of worsening asthma beyond salbutamol during Period I. During Period II, only one "rescue" was allowed, whereas during Period III, more than one rescue was permitted. Other criteria for discontinuation during Periods II and III included use of an excluded medication, interruption of study drug administration for more than 5 consecutive days, a clinical or lab adverse event that jeopardized the patient's health or rendered the patient or parent unable to complete the study, or patient pregnancy. Replacement for discontinued patients was allowed only in Period I. Discontinuations due to asthma were defined [D-19783].

Endpoints

The primary efficacy endpoint for this study was FEV1 assessed at each clinic visit. The Data Analysis Plan [90:D-20307] further defined the primary efficacy endpoint as the percent change from baseline for FEV1 averaged from Period II data.

Key secondary endpoints were based upon data from daily diary entries of the following: self-determined daily PEFr, total daily β -agonist use, nocturnal awakenings due to asthma, and daytime symptom scores. Tertiary endpoints included separate global assessments by the patient, parent, and the physician [90:D-20234]; an asthma-specific quality of life in 9 to 14 year old patients only [90:D-20281-20284]; school loss; number of defined asthma attacks [90:D-20230] and exacerbations [90:D-20229], and amount and need for the prespecified asthma rescue plan. All efficacy parameters were collected at the end of Study period II or upon discontinuation prior to study completion.

Diary records: The asthma diary card was validated according to the sponsor (their reference 2.1.7) but not previously used in randomized, placebo-controlled studies. Children aged 9 to 14 years were to complete diary cards with parental supervision, whereas the parents of 6 to 8 year olds entered data after asking their child the diary questions. Evening scoring of symptoms was done just before taking study medication and going to bed.

Reviewer comment: *The timing of symptom scoring in relation to PEFr was not specified in the protocol, so these two measures may be correlated.*

PEFR records: Evening PEFr was to be measured at bedtime before administration of medications. The morning PEFr was to be taken upon arising before taking any medications. If albuterol was used within 4 hours of either the AM or PM PEFr measurements, the patient was to take his/her PEFr before taking albuterol and note this value and its timing on the diary card.

Reviewer comment: *Compliance with albuterol timing before PEFr measurements was not analyzed by the sponsor. If compliance was poor and patients titrated themselves to comfort, this could act to minimize treatment differences in PEFr.*

Global evaluations by patient, parent/guardian, and investigator all used the same 7 point scale as follows:

- | | |
|----|-------------------|
| 3 | Very much better |
| 2 | Moderately better |
| 1 | A little better |
| 0 | Unchanged |
| -1 | A little worse |
| -2 | Moderately worse |
| -3 | Very much worse |

A pediatric quality of life questionnaire published by Juniper, Guyatt et al. [90:D-19950ff] and validated on the basis of 52 asthmatic children aged 7 - 17 years was administered to 9 to 14 year old children only. This instrument has three domains (activity, symptoms, and emotions) as well as an overall score. No minimal important difference (MID) was prespecified by the sponsor, although the manuscript includes such values for the overall instrument and each of its three domains. The MIDs ranged from 0.28 for emotions to 0.70 for activities, with the overall MID being 0.42. According to Juniper et al., the activity and symptoms domains are moderately correlated with clinical asthma control, and all 3 domains are moderately correlated with beta-agonist use and morning PEFr. None of the domains correlate with clinic FEV1 percent predicted values.

Asthma exacerbations were defined in the Data Analysis Plan as meeting one or more of 5 criteria [90:D-20328], and asthma free days were defined as meeting all of 3 criteria, including ≤ 2 puffs/day β -agonist use [90:D-20329].

Reviewer comment: *Of note, the only end-of-dosing interval endpoint evaluated in this study was patient-reported evening PEFr.*

Analysis Plan

The Data Analysis Plan [90:D-20307] defined the primary efficacy endpoint of as the percent change from baseline for FEV1 averaged from Period II data. The validity of this approach was assessed by an analysis of the rate of change of FEV1 over the 8-week treatment period. No adjustment for height growth was anticipated, although a corroborative ANCOVA using change in height as a covariate was done. By the medical officer's calculations, the expected percentage increase in FEV1 over 2 months for a growing child would be approximately 2%.

The four key secondary endpoints were defined to be the average of the following Period II endpoints: Daytime Symptom Score change from baseline, am PEFr change from baseline, the Total Daily Beta-Agonist Use percent change from baseline, and the Nocturnal Asthma Score change from baseline.

ANOVA with factors for treatment, study center, and stratum (inhaled corticosteroid use) was used to analyze the primary and secondary efficacy parameters. Baseline values for all analyses were predefined; baseline FEV1 was the average of the Period 1 measurements. [90:D-20334]

Power analyses showed adequate group sizes for the primary FEV1 endpoint, where sample sizes of 144 patients in the montelukast group and 96 patients in the placebo group were projected to have 90% power (two sided, with alpha equal to 0.050) to detect a 7.1 percentage point change from baseline between the two treatment groups. [90:D-20247] This detectable difference was estimated based on the assumption that the variability in percent change from baseline in FEV1 in the pediatric study would be similar to adult studies (SD=16.5%) [90:D-20323ff]. Other endpoints were not adjusted for multiple comparisons, since these evaluations were considered supportive and as "signposts to the relative ranking of treatment effects". [90:D-20247] Low power was expected for the subpopulation administered the Quality of Life Questionnaire, and small to moderate power was projected for the symptomatic subpopulation in which nocturnal awakenings were examined. No quantitative power analyses were described for these endpoints. All statistical tests were two sided with alpha equal to 0.050.

Two approaches were used for the analysis of efficacy data. The primary approach used all-patients-randomized, and included all patients with efficacy measurements at both baseline and during the treatment protocol. The secondary approach (per-protocol) was applied to the primary and key secondary efficacy endpoints and excluded patients and/or data points with defined protocol deviations based on a set of prespecified criteria; these criteria described treatment drug compliance, concomitant allowable medication use, completion of daily records, and PEFr

recordings [90:D-20332-20334]. Per-protocol allowances were less stringent than specified in the actual protocol.

The Statistical Data Analysis Plan [90:D-20315] for the intent to treat analyses of the averaged values for a treatment period did not impute any missing values. Unscheduled visits and discontinuations were included in treatment averages. Similarly, imputation was not used in the per-protocol analyses.

For the global evaluations by patient, parent/guardian, and investigator, each was analyzed according to its 7 category scale, as well as collapsed in to three categories of "better", "unchanged", and "worse". Because of large expected variations in these measures, a composite endpoint of the average score was planned for analysis as well.

Non-primary, non-secondary endpoints: The clinical study report describes an onset of action analysis plan using daytime symptom score, patient-reported AM PEFr, and total daily beta-agonist use [90:D-19790]. This analysis was not specified in either the protocol or the data analysis plan [90:D-20312-20313].

Randomization

Based upon the allocation schedule, randomization to Period 2 and Period 3 was done at a single point in time. Patients were allocated to one of four groups as follows using a computer-generated, randomization schedule with a blocking factor of 5 (3 montelukast, 2 placebo):

<u>Period 2</u>	<u>Period 3 (Open use continuation)</u>
Montelukast	Beclomethasone
Montelukast	Montelukast
Placebo	Beclomethasone
Placebo	Montelukast

Random comparison of 25 domestic and 5 international Patient Abstracts Listings [Case Report Tabulations] to the Computer-Generated Allocation Schedule [90:D-20624ff] showed no inconsistencies in treatment assignment.

CHARACTERISTICS OF ENROLLED PATIENTS

Of the 336 patients randomized, 80.1% were Caucasian, 12.8% Black, 4.5% Hispanic, and 2.7% other origins. Males accounted for 64.6% of the overall population. Gender and ethnicity were similar in treated and placebo children. Children aged 6 to 11 years accounted for 53.3% of the patients overall, and children aged 12 to 14 years, 46.1%. Of all study children, 57 or 17.0% were aged 6 to 8 years; 11 of these were 6 years old, and 16 were 7 years old. [Merck response of 11/24/97 to FDA request]. Two patients (0.6%) turned 15 between the prestudy visit and the randomization visit when age was recorded.

There were 201 patients randomized to montelukast treatment and 135 to placebo. The montelukast and placebo groups were similar in mean age, weight, height, duration of asthma, and smoking history. With respect to asthma characteristics, the two groups were largely similar. The montelukast group had a higher percentage of patients with concurrent inhaled corticosteroid use (38.8% versus 32.6% placebo), use of immunologic substances, and use of cold remedies [90:D-19813]. Allergic rhinitis was also slightly greater in montelukast patients (95.9% versus 91.9%) [90:D-19804]. Mean values for baseline FEV1, total daily β -agonist use, and am PEFr were similar between the montelukast and placebo, with the overall FEV1 averaging $71.7 \pm 9.55\%$ predicted and the average number of puffs/day of beta-agonist being 3.30 ± 1.95 [90:D-19806].

Secondary diagnoses were present in 98.5% of both the montelukast and placebo groups, with montelukast patients having a greater rate of nervous system and psychiatric disorders (43.3% versus 35.6% placebo), largely due to headache (33.3% versus 27.4% placebo). The use of any non-bronchodilator drug therapy within 30 days of the start of the study was similar for montelukast and placebo patients [90:D-19809], although montelukast patients had greater historical use of bronchodilators other than albuterol (10.9% versus 5.2%) and of hormones/synthetic substitutes (46.8% versus 37.8% placebo) including inhaled, intranasal, and topical corticosteroids.

Period II was completed by 314(93.5%) of the randomized patients. Overall, discontinuations were similar in the montelukast group (12 patients, or 6.0%) and placebo group (10 patients, or 7.4%).

EFFICACY FINDINGS

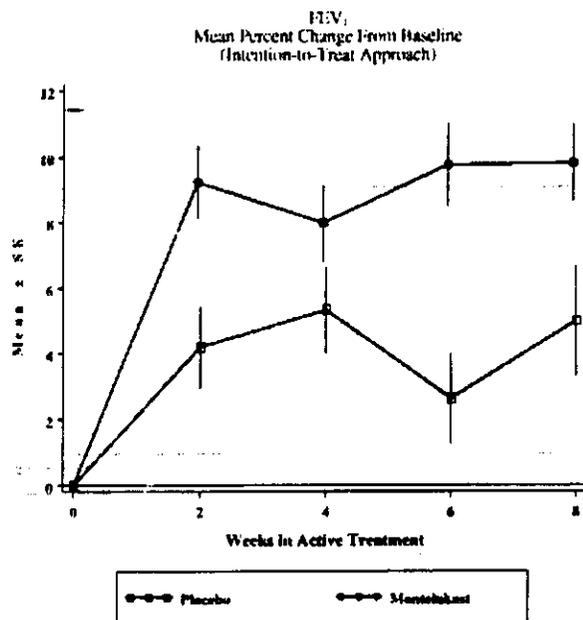
Efficacy population: Five patients (3 montelukast, 2 placebo) from one study center were excluded from all efficacy analyses because of significant deviations from good clinical practice standards, leaving a total of 331 randomized patients (198 montelukast, 133 placebo). Intent-to-treat efficacy analyses excluded an additional two to four patients from selected endpoint efficacy analyses because of missing baseline or treatment period data; these exclusions were evenly balanced in number between the montelukast and placebo groups [90:D-19819]. Because of the small number of these patients, their CRFs were not solicited from the sponsor.

FEV1 (Primary Efficacy Endpoint): Mean baseline FEV1 was the same for the montelukast and placebo groups. Compared with placebo, montelukast demonstrated a significant improvement in FEV1 percent change from baseline ($p < 0.001$). Averaged over the 8-week treatment period, mean percent change from baseline was 4.16% and 8.71% for the placebo and montelukast groups, respectively [Table 20, 90:D-19821]. The difference in LS (least square) means between the two treatment groups was 4.65%, with a 95% confidence interval of (1.92, 7.38).

Additional non-protocol statistical analyses of the effect of montelukast on FEV1 were confirmatory of the averaged FEV1 percent change. The analysis based on change from baseline in FEV1 percent predicted values, on FEV1 change from baseline, and the analysis of covariance of the percent change from baseline in FEV1 with height change as covariate demonstrated similar results [90:D-20748-20751]. Weekly results generally confirmed the averaged results as illustrated in the figure below. Weeks 2, 4, 6, and 8 correspond to visits 3, 4, 5, and 6, respectively. With the exception of visit 4 (week 4 of active treatment) the weekly percent change from baseline FEV1 was statistically greater in the montelukast group than in the placebo group ($p < 0.05$) [91:D-20774, -20779, -20784, -20789]. Analysis of the last available visit data also demonstrated a statistically significant increase in the percent change in FEV1 for montelukast compared to placebo, 9.04% versus 4.80% [90:D-20798].

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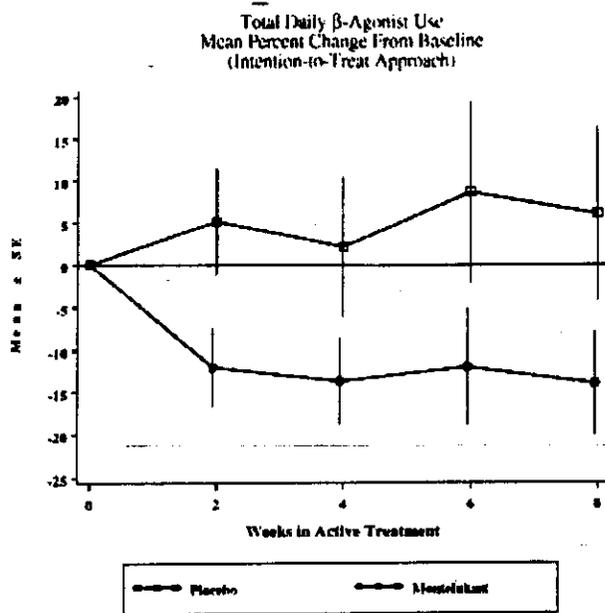
Total Daily Beta-Agonist Use (Key Secondary Endpoint): Mean baseline values for total daily beta-agonist use (3.24 and 3.34 puffs/day for the placebo and montelukast groups, respectively) were comparable between the treatment groups. The mean change from baseline was -0.23 and -0.56 puffs/day for the placebo and montelukast groups, respectively. The difference in LS means between the two treatment groups based on change from baseline was -0.36 puffs/day, with a 95% confidence interval of (-0.75, 0.04) and $p=0.08$ [91:D-20753].

When analyzed according to the percentage change averaged over the 8-week treatment period, the placebo and montelukast groups had mean percent changes from baseline of 8.20% and -11.66%, respectively. The difference in LS means between the two treatment groups was -22.49%, with a 95% confidence interval of (-39.49, -5.49). In the placebo group, the paradoxical increase in average mean percentage beta agonist use when compared to the mean decline in absolute use reflects the low baseline values, magnification of effect by transforming small changes into percentages, and the role of outliers in computing means. The figures on the following page illustrate the differences between the two analyses [91:D-19825, D-20754].

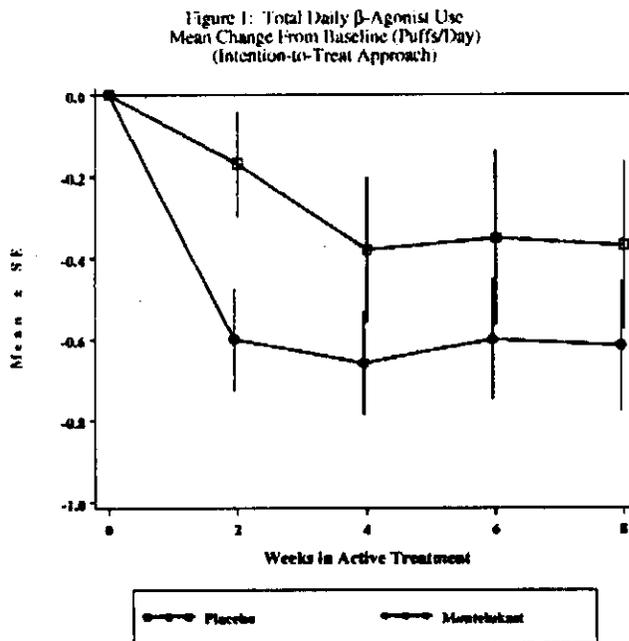
AM PEFr (Key Secondary Endpoint): Two sets of AM PEFr measurements were analyzed. One set included daily measurements obtained by the patient at home using a [redacted]. An additional set included PEFr measurements obtained during scheduled clinic visits using the [redacted] analyzed as an additional efficacy endpoint.

Mean patient-reported PEFr values were similar at baseline for placebo and montelukast patients (313.24 and 311.53 L/min respectively), and mean changes in AM values over the 8 week treatment were not significantly different (7.09 and 9.48 L/min respectively for placebo and montelukast). The placebo group showed steady improvement in self-reported AM PEFr over the course of Period II; this improvement was not seen in the clinic PEFr measurements. Clinic measurements of mean baseline PEFr values of placebo and montelukast patients were similar, but lower than patient-reported values by approximately 45 L/min. The averaged mean change in clinic-measured PEFr from baseline for montelukast was significantly greater than placebo, with a difference in LS means of 9.93 L/min (95% CI 0.89, 18.96). Review of the individual visit results showed that only Visit 5/week 6 achieved a statistically significant difference between montelukast

Total Daily β -Agonist Use, Represented as Mean Percent Change from Baseline (top figure) and as the Mean Change from Baseline (lower figure)



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and placebo [91:D-20795-20797]. Per protocol analyses were consistent with a lack of a meaningful montelukast effect upon patient-reported AM PEFR.

Reviewer comment: *Preclinic washout periods for antihistamines and bronchodilators may have contributed to the difference between clinic measurements and self-reported PEFR.*

Daytime Symptom Score (Key Secondary Endpoint): These scores were derived from the Patient Daily Diary, which was validated by Merck for its ability to discriminate stable, unstable, and improving asthmatic children [93:D-22161ff]. No absolute change in average symptom score was prespecified as clinically significant. The score constituted 3 questions about the degree of trouble breathing, bothersomeness, and activity limitation that occurred during the day due to asthma, with each question scaled from 0 (no symptoms) to 5 (maximal symptoms).

Mean baseline values (1.26 and 1.28 for the placebo and montelukast groups, respectively) were comparable between the treatment groups. Averaged over the 8-week treatment period, mean change from baseline was -0.12 and -0.19 for the placebo and montelukast groups, respectively. The difference in LS means between the two treatment groups was -0.07 score, and was not statistically significant, though it favored montelukast.

Nocturnal Asthma Score (Key Secondary Endpoint): A total of 89 patients (26.9%) met the subgroup analytic criteria of having nocturnal awakenings (≥ 2 nights/week during Period I). Of these, 32 were placebo patients and 57 were montelukast patients. Nocturnal asthma scores were recorded on the diary card and scaled between 0 (no wake-ups) and 3 (awake all night). Mean baseline values (0.70 and 0.73 for the placebo and montelukast groups, respectively) were similar between the treatment groups. Averaged over the 8-week treatment period, the placebo and montelukast groups had mean changes from baseline of -0.14 and -0.23, respectively [90:D-19833ff]. The difference in LS means between the two treatment groups, -0.10 score was not statistically significant. The analysis of nocturnal asthma score based on all patients demonstrated similar results [91:D-20756].

Additional Analyses of Primary and Secondary Endpoints: Prespecified subgroup interactions analyzed by ANOVA were not statistically significant. In particular, the treatment by age interaction analyzed categorically (6 - 11 years versus 12 - 14 years) was not significant. Additional tests of age interaction requested by the FDA for ages 6-8, 9-11, and 12-14 years showed no statistically significant interaction [Merck response of 11/24/97 to FDA request]. Stratified analyses revealed marked variability in efficacy according to individual Tanner Stage, but no consistent pattern with Tanner stage was seen across the 5 endpoint measures. Subgroup analyses by ethnicity revealed that the 24 Black participants on montelukast consistently had diminished or equivalent efficacy findings than the 18 placebo patients [91:D-20694ff]. According to the Medical Reviewer for NDA 20-829, no racial differences of this type were noted in any of the adult studies.

Onset of action analysis (claimed in proposed label): Although not a prespecified analysis for the pediatric study, the sponsor used the percent change in beta-agonist use, the change in patient-reported PEFR, and the change in daytime symptom scores to analyze onset of treatment effect. According to the Statistical Reviewer, the sponsor fit a regression line using repeated measures analysis to calculate an intercept and slope, the former to test for a difference in early treatment effects and the latter to show consistency of difference of montelukast from placebo over time. Using this approach, the intercept for montelukast was statistically improved for total daily β -agonist use and am PEFR. Daytime symptom scores were improved but not significantly [90:D-19838].

Because the application analyses were modeled and did not make straightforward use of data from the first days of therapy, FDA requested crude daily analyses of the treatment effects of placebo versus montelukast for the first 7 treatment days. Using an ANOVA model with factors for treatment, study center, and stratum, there was a significantly greater percentage change in montelukast patients versus placebo in total daily β -agonist use on treatment days 1 and 2. In contrast, the daytime symptom score and am PEFR of montelukast patients only achieved statistically significant improvement over placebo after 5 days of therapy [Merck response of

11/24/97 to FDA request]. Comparison of daily means for daytime symptom score, am PEFR, and total daily β -agonist use (percentage change) likewise did not evidence any clinically meaningful benefit to montelukast therapy on day 1 of therapy with the exception of the β -agonist use endpoint [91:D-20662ff].

Reviewer comment: *According to the medical reviewer of the adult program, two placebo-controlled adult trials showed montelukast had onset of action at day 1 of therapy as measured by change in symptom scores, β -agonist use, AM PEFR, and nocturnal asthma scores. The pediatric data and modeling done by the sponsor are not convincing for a rapid (within the first day) onset of action. The difference seen between pediatric and adult onset of action findings is not well-explained, and may reflect problems with the chosen pediatric dose.*

Asthma-Specific Quality of Life (Tertiary Endpoint claimed in proposed label): Using statistical analysis of the pediatric asthma quality of life instrument of [redacted] without comparison to the authors' minimally important difference (MID) approach, montelukast demonstrated a significantly greater improvement than placebo in the 3 domains of symptoms, activity, and emotions, as well as their overall average. By medical reviewer analysis, the mean change from baseline in the montelukast group alone exceeded the minimal important differences defined by [redacted] for each of the 3 domains and the averaged overall score for quality of life [90:D-19956 and 90:D-19842-19849]. The placebo group increased its scores slightly and did not achieve mean changes at or above the MID levels. Using the analysis convention for the adult [redacted] quality of life instrument, the difference in the LS mean changes of montelukast and placebo patients achieved the minimally important differences only for overall score and for the emotions domain. (The difference of unadjusted treatment means was not statistically greater than the MID except for the emotion domain.)

Reviewer comment: *No "win" was prespecified for this endpoint or its components, and the sponsor's analyses showing statistical significance in all domains and overall do not follow the minimally important difference interpretation specified by [redacted] and colleagues in their publication concerning the instrument.*

Global Evaluations (Tertiary Endpoints claimed in proposed label): Of the parents', patients', and physicians' global rating of change over the course of Period II, only the parent's' global rating was significantly greater for montelukast than placebo by parametric and collapsed categorical analyses. The difference in LS means favored montelukast by 0.28 score, and 81.3% of parents of children on montelukast evaluated them as "better", compared to 70.8% of placebo parents. Patient and physician global evaluations favored montelukast improvement by 0.27 and 0.22 score respectively; these improvements were not statistically significant. By categorical analysis, 7.3% more patients were classified as "better" by their own ranking and 11% by their physicians' ranking. An overall analysis averaging all global scores was significantly better for montelukast than placebo when tested by parametric and categorical analyses. The averaged improvement with montelukast was 0.25 score, with 91.8% classified as "better" versus 80.8% with placebo. No minimally important difference was prespecified.

Asthma exacerbations (Tertiary Endpoint claimed in proposed label): Over the 8-week treatment period, the mean percent of days with an asthma exacerbation was 25.67% for placebo patients and 20.58% for montelukast patients; this difference achieved statistical significance ($p=0.049$) and amounts to approximately 3 fewer days with exacerbations over 8 weeks. The proportion of patients who experienced at least one asthma exacerbation was 95.5% for the placebo group and 84.8% for the montelukast group, $p=0.002$.

Peripheral Blood Eosinophils (Tertiary Endpoint claimed in proposed label): Mean baseline values for montelukast and placebo were comparable and within normal limits (0.47 and 0.44 $10^3/\text{mCL}$). Averaged over the 8-week treatment period, the montelukast group's eosinophils declined by a mean of 0.06 $10^3/\text{mCL}$, while the placebo group mean decline was 0.00 $10^3/\text{mCL}$.

The montelukast group decrease from baseline was statistically significant. Correlation analysis of eosinophils with changes in FEV1 for all patients combined and montelukast alone found correlation coefficients of approximately -0.15 that were statistically significant.

Evening PEFR (Tertiary Endpoint): Although the protocol did not specify whether PEFR measurements in the am, pm, or both were to be secondary endpoints, the data analysis plan limited analysis to morning PEFR. Placebo and montelukast patients had similar evening PEFR values at baseline, and the mean change for each group over the 8 weeks was virtually identical (~5.5 L/min).

Reviewer comment: *The absence of any effect in this end-of-dosing interval endpoint raises concerns about whether the appropriate dosing interval for pediatric patients was selected.*

Discontinuations due to worsening asthma: The small percentage of patients discontinuing for worsening asthma was greater in montelukast patients (3.5%) than controls (2.3%), but not significantly so.

Other tertiary endpoints: Six endpoints showed slight improvement for montelukast over placebo but did not achieve statistical significance. These included percentages of: "asthma-free" days with minimal β -agonist use, patients with asthma attacks, patients requiring corticosteroid rescue, and days missed from school because of asthma. Nocturnal awakenings due to asthma (assessed in a subpopulation of 89 patients with baseline symptoms) were likewise slightly reduced with montelukast treatment, but not at a statistically significant level.

Per Protocol and Other Analyses

Per-protocol analyses performed on the primary and four secondary key endpoints corroborated those from the intention-to-treat approach [91:D-20647-20651]. Per-protocol exclusions eliminated 18 patients (5.4%) on the basis of invalid baseline, invalid treatment period data, or protocol violations; the number eliminated from the montelukast group was approximately 3-4 times greater than the placebo group, with percentages being about 2-2.5 times greater in the montelukast group [91:D-20637-20642].

SAFETY RESULTS

Parameters Evaluated

Laboratory safety tests included hematology, blood chemistry, and urinalysis [90:D-20263] performed according to the schedule of assessments in Table A. Baseline values for bilirubin, alkaline phosphatase, BUN, creatinine, glucose, total wbc count, and platelets were considered acceptable if they fell within 10% of the upper or lower limits of normal values [90: D-20262]. For hematocrit, wbc count, platelet count, bilirubin, AST, and ALT, limits of change were predefined in the data analysis plan in terms of baseline and the upper or lower limits of normal [90:D-20319]. In addition, ALT and AST values were analyzed in terms of class intervals comprised of multiples above the ULN.

Safety Population

The safety population included patients who did not complete the study, as well as the 5 patients eliminated from efficacy analyses because of poor clinical practice standards. A total of 8 (4.5%) montelukast patients were discontinued secondary to either a clinical or laboratory adverse experience, compared to 3 (2.2%) of placebo patients. The balance of discontinuations were due to withdrawn consent, protocol deviation, or loss to follow-up [90:D-19618].

Clinical Adverse Experiences

Clinical adverse experiences were reported by 75.9% (255 patients) of the total sample (336 randomized patients), 75.6% (102) and 76.1% (153) of the placebo and montelukast patients, respectively.

Clinical Adverse Experiences Summary

	Placebo (N = 135)	montelukast (N = 201)
Number (%) of patients with one or more adverse experiences (postrandomization)	102 (75.6)	153 (76.1)
with drug-related adverse experiences	5 (3.7)	13 (6.5)
with serious adverse experiences	0	4 (2.0)
withdrawn from therapy due to adverse experiences	3 (2.2)	8 (4.0)
withdrawn from therapy due to a serious adverse experience	0	4 (2.0)
withdrawn from therapy due to a drug-related adverse experience	1 (0.7)	0
Deaths	0	0

Modified from [Table 49, 90:D-19873]

There were no statistically significant between-group differences in the frequency of adverse experiences by body system. [90:D-19874, Table 50]. Four patients with five adverse experiences had urogenital system adverse experiences, versus none in the placebo group. Post-correction cutoff revealed that two of the events (cystitis and urethral irritation) occurring in 1 patient (AN 9726) were considered by the investigator to be signs and symptoms of urethral stenosis (a pre-existing condition) and should not have been recorded as adverse experiences. The remaining adverse experiences in this body system, each occurring in 1 patient, included urinary tract infection, menstrual disorder (dysmenorrhea), and vaginal pain (irritation).

Of the 113 screening tests (Fisher's Exact) performed, 1 for each distinct clinical adverse experience, only 1 had a p-value <0.050: the frequency of allergic rhinitis was significantly greater in the placebo group (3.7%) than in the montelukast group (0%). *Allergic rhinitis was more common at baseline in montelukast patients than placebo, so the significance of this placebo finding is unclear and may represent regression to the mean.*

Headache occurred more commonly in the placebo group (21.5% of patients) than with montelukast (18.9%). When only those events considered to be possibly, probably, or definitely drug-related were considered, the proportion of montelukast patients with headache (3.5%) was higher than for placebo patients (0.7%). The drug-related headaches reported by patients in the montelukast group were generally mild to moderate in intensity and lasted a median of 11 days, beginning 2 to 52 days postrandomization (median, Study Day 11). The headache in the placebo group was mild in intensity and lasted for 25 days, beginning 4 days postrandomization. There were no significant differences between the two treatment groups in the frequency of drug-related adverse experiences.

Serious Clinical Adverse Experiences

All of the serious adverse experiences after randomization occurred in the montelukast group. Four patients (1.9%) had a total of 6 serious adverse experiences (2 pneumonia/asthma; 1 asthma; 1 dehydration), none of which considered drug related. All four patients had brief hospitalizations (ranging from 1 to 5 days) and rapidly recovered without sequelae. All patients were discontinued from therapy. The three patients with asthma were all male, two 8 years old and one 13 years old.

Clinical Adverse Experiences Occurring in \geq 1% of Montelukast Patients and at Higher Proportions than Placebo

	Placebo (N=135)	Montelukast (N=201)
Body as a Whole/Site Unspecified	29 (21.5)	40 (19.9)
Asthenia/fatigue	0	2 (1.0)
Fever	5 (3.7)	15 (7.5)
Infection, viral	2 (1.5)	4 (2.0)
Digestive System Disorders	23 (17.0)	30 (14.9)
Diarrhea	1 (0.7)	6 (3.0)
Dyspepsia	3 (2.2)	5 (2.5)
Nausea	5 (3.7)	8 (4.0)
Pain, dental	1 (0.7)	3 (1.5)
Musculoskeletal Disorders	11 (8.1)	20 (10.0)
Fracture, ankle, rt	0	2 (1.0)
Myalgia	0	2 (1.0)
Pain, leg	0	2 (1.0)
Pain, wrist	0	2 (1.0)
Nervous System and Psychiatric Disorders	31 (23.0)	42 (20.9)
Depression	0	2 (1.0)
Insomnia	0	2 (1.0)
Respiratory System Disorders	81 (60.0)	114 (56.7)
Congestion, pulmonary	1 (0.7)	3 (1.5)
Congestion, respiratory	0	3 (1.5)
Influenza	6 (4.4)	17 (8.5)
Laryngitis	1 (0.7)	4 (2.0)
Pharyngitis	17 (12.6)	28 (13.9)
Pneumonia	0	2 (1.0)
Sinusitis	2 (1.5)	11 (5.5)
Skin and Skin Appendage Disorders	7 (5.2)	9 (4.5)
Excoriation	1 (0.7)	2 (1.0)
Laceration	1 (0.7)	2 (1.0)
Special Sense Disorders	11 (8.1)	9 (4.5)
Otitis	1 (0.7)	5 (2.5)

Discontinuations Due to Clinical Adverse Experiences

Eleven of the 336 randomized patients (3.3%) discontinued due to a clinical adverse experience, 3 (2.2%) and 8 (4.0%) in the placebo and montelukast groups, respectively. Four of the 8 montelukast patients were discontinued because of serious adverse experiences described in the previous section. In total, 6 patients (3.0%) were discontinued from montelukast secondary to asthma, 2 of these with an associated diagnosis of pneumonia; the comparable number and percent of asthma-related discontinuations for placebo patients was 2 and 0.5%. Of the 6 montelukast patients hospitalized or withdrawn secondary to asthma, 5 were male and three were aged \leq 8 years. Of the two placebo discontinuations secondary to asthma, one was male and both were \geq 10 years of age.

Of the remaining two discontinued montelukast patients, one was withdrawn due to an upper respiratory infection, and the other to due to dehydration (described under serious AE above). One patient (placebo) withdrew due to an urticarial rash that was considered drug related by the investigator.

Laboratory Adverse Experiences

Of the 336 patients randomized, 1 montelukast patient was lost to follow-up and did not have postrandomization laboratory safety tests performed. Of the 335 patients analyzed, 13 (3.9%) had at least one laboratory adverse experience, 11 in the montelukast group (5.5%), and 2 (1.5%) of the placebo group. None of the events were serious, and none were considered drug related by the investigator. Two patients, both in the montelukast group, discontinued therapy due to a laboratory adverse experience: one for increased ALT, and one for decreased neutrophils. According to the [redacted] case report tabulations and case-report forms, both patients had baseline abnormalities in these parameters prior to beginning drug therapy. Their laboratory abnormalities are discussed in more detail in the laboratory discontinuation subsection that follows.

Specific laboratory adverse experiences occurring in $\geq 1\%$ of the montelukast patients and at higher levels than placebo patients are described in the following table, excerpted from table 58 [90:D-19889]. Differences between the two treatment groups in the frequency of adverse experiences were not statistically significant.

	Placebo	Montelukast
	N=135 No. (%)	N=200 No. (%)
Leukocytes decreased	1 (0.7)	2 (1.0)
ALT increased	1 (0.7)	3 (1.5)
AST increased	1 (0.7)	2 (1.0)
Serum glucose decreased	0	2 (1.0)
Pyuria	0	2 (1.0)

In both patients with decreased serum glucose (to 46 and 40 mg/dL), no clinical AEs were noted and normal values were obtained at prior and subsequent visits. The patient with decreased leukocytes is discussed in the following section describing discontinuations. Abnormal transaminase values are discussed under the section on LFT abnormalities.

Patients Discontinued Due to Laboratory Adverse Experiences

A 13 year old female patient discontinued montelukast on Study Day 19 [91:D-20871] because of a decreased total white cell count (2.87, normal range 4.35 to 13.65 $\times 10^3/\text{mCL}$) and neutrophil count (1.2, normal range 1.7 to 8.2 $10^3/\text{mCL}$). With the exception of the Prestudy Visit, at which time the neutrophil count was within normal limits (1.7 $10^3/\text{mCL}$), all other values were low (1.2 to 1.3 $10^3/\text{mCL}$), including the measurement immediately prior to randomization. Approximately 6 weeks after drug discontinuation, her total white cell count remained low but her neutrophil count had reached the normal range. No clear explanation for her laboratory abnormalities was found.

A 10 year old girl was discontinued in the beginning of Period III because of an elevated ALT measured at the end of Period II; her case is discussed in the section on LFT abnormalities. This child was from the study site eliminated from the efficacy analyses) because of deviations from good clinical practices.

Liver Function Abnormalities

Transaminase elevations considered to be adverse lab events occurred in a small number of patients. Adverse ALT elevations occurred in 3 (1.5%) montelukast patients and 1(0.7%) placebo patients. Elevations greater than 3 times the ULN were seen in two montelukast patients and no placebo patients. Viral serologies were negative in both montelukast patients. One montelukast patient was a 10 year old female discontinued secondary an ALT of 124 and an AST of 62; transaminase elevations had been noted prestudy and during the study, and seemed unlikely

related to study drug treatment in the opinion of the medical reviewer. The second montelukast patient was a 7 year old male whose ALT was elevated more than 4 times the ULN along with an AST of 71; both these values were noted during an intercurrent illness and resolved to normal values while on montelukast therapy. Again, this elevation did not appear to be treatment-related in the opinion of the medical reviewer.

Using the prespecified limits of change for ALT and AST ($\geq 100\%$ increase and $>ULN$), the following frequencies were noted:

Numbers/Percentage Exceeding Prespecified Limits of Change ($\geq 100\%$ increase and $>ULN$)

	<u>ALT</u>	<u>AST</u>
Placebo	1/135 (0.7%)	1/135 (0.7%)
Montelukast from [90:D-19893]	5/200 (2.5%)	3/200 (1.5%)

The incidence of any increases above the ULN was small in both placebo and montelukast patients, although the percentages were greater in the montelukast patients as seen below:

Numbers/Percentage Exceeding ULN

	<u>ALT</u>	<u>AST</u>
Placebo	3/135 (2.2%)	4/135 (3.0%)
Montelukast from [90:D-19894]	6/200 (3.0%)	12/200 (6.0%)

Parallel analysis by the medical reviewer of any elevation of AST or ALT above the ULN gave the following combined results:

Numbers/ Percentage Exceeding ULN

	<u>ALT or AST</u>	<u>ALT and AST</u>
Placebo	4/135 (3.0%)	3/135 (3.0%)
montelukast	14/200 (7.0%)	4/200 (6.0%)

Analyses by the sponsor of abnormal values revealed that with the exception of the 2 montelukast patients previously described with elevations in ALT >3 times the ULN, all patients with abnormal values fell between 1 and 2 times the ULN. Subclass analyses were performed and analyzed according to whether abnormal values of AST or ALT were present at baseline. These ALT analyses showed no greater rate of elevations over baseline in montelukast patients than placebo patients. Analyses of AST in 193 montelukast and 131 placebo patients with normal baseline values revealed a greater frequency of elevations in montelukast patients between 1.75 and 2 times the ULN (1 montelukast patient, 0 placebo patients) and between 1 and 1.25 the ULN (9 or 4.7% of montelukast patients, versus 3 or 2.3% of placebo patients).

Abnormal bilirubin values on montelukast did not exceed 1.4, and were not found in any patients with transaminase abnormalities.

OPEN LABEL SAFETY EXTENSION

A report of extension results was submitted with the application and covered events through 6/24/96; the first safety update report (SUR1) covered events from 6/24/96 to 12/6/96 as well as cumulatively, and the second safety update report (SUR2) covered events from 12/6/96 and 4/24/97 as well as cumulatively. Serious clinical adverse experiences out to 7/14/97 were also included in SUR2.

Of the 314 patients who completed the Period II evaluation, 78.3% or 246 (98 placebo, 148 montelukast) entered the open extension [90:D-19818]. One patient was discontinued from the extension because of elevated transaminases measured at the conclusion of Period II; this patient's discontinuation and findings were ascribed to Period II treatment. This resulted in a cumulative total of 245 patients with extension data, 207 for montelukast and 38 for inhaled steroids [SUR2, Vol 1:16]. Of the patients who entered the cumulative extension period, a total of 56 elected not to continue the subsequent extension period. Of these, 49 were from the montelukast treatment arm (23.7%) and 7 were in the inhaled steroids arm (18.4%). [Medical reviewer calculation based upon application, SUR1, & SUR2, and company response of 11/25/97 to FDA request for clarification.]

Extent of Patient Exposure

Patients took one 5 mg chewable tablet once daily, with the exception of 17 patients who were switched to the adult 10 mg film-coated tablet when they turned 15 years of age. During the extension period, the longest duration of montelukast treatment for any pediatric patient was 17 months. Inclusion of montelukast exposure during the double-blind portion of the trial showed 121 patients had been continuously treated for at least one year, 48 patients with exposure for 6 months to a year, and 38 patients with treatment less than 6 months. The calculated total person years of montelukast exposure was equivalent to 163 patient years, an average of about 9½ months over the 207 exposed patients. The inhaled steroids group total exposure was 30 person-years. [SUR2, Vol 2:22]

Baseline Characteristics

Meaningful comparison of montelukast and inhaled steroids patients is difficult because of the small numbers in the inhaled steroids group. Grossly, patient characteristics were similar, although the montelukast group had more patients of Caucasian race (83.6% versus 68.4% inhaled steroids) and more patients with secondary diagnoses of digestive system disorders (10.6% versus 5.3% inhaled steroids). Concomitant use of hormones/synthetic substitutes by montelukast extension patients was 53.5% in the first extension report, and 64.3% in the cumulative extension [SUR2.1:18]. Inhaled steroids had been used during Period II by approximately 38% of the patients taking montelukast during Period III [Merck response of 11/24/97 to FDA data request].

Efficacy

FEV1 and Quality of Life parameters were assessed during the extension period, and both montelukast and inhaled steroids patients were improved statistically over their prerandomization baseline. The LS mean percentage improvement in FEV1 was 12.42% for montelukast and 14.32% for inhaled steroids. The component and overall average quality of life scores were greater than the minimal important difference (MID) for each treatment, but the difference between treatment mean scores was less than the MID. There were no statistically significant differences in the average treatment effects for FEV1 and quality of life between montelukast and inhaled steroids [91:D-21010].

Clinical Adverse Experiences

Overall: The following table presents the overall clinical adverse experience profile of montelukast for the cumulative extension period. Rates of occurrence among montelukast patients were greater for all categories displayed below than for children receiving inhaled steroids. Drug-related and serious adverse experiences occurred in approximately 5% of montelukast-treated children, and all withdrawals due to adverse experiences occurred in the montelukast group.

Cumulative Clinical Adverse Experiences Summary

	Inhaled Steroids (N = 38)	Montelukast (N = 207)
Number (%) of patients with one or more adverse experiences during the extension	33 (86.8)	195 (94.2)
with drug-related adverse experiences	2 (5.3)	11 (5.3)
with serious adverse experiences	0	10 (4.8)
withdrawn from therapy due to adverse experiences	0	6 (2.9)
withdrawn from therapy due to a serious adverse experience	0	1 (0.5)
withdrawn from therapy due to a drug-related adverse experience	0	2 (1.0)
Deaths	0	0

Modified from [Table 9, SUR2.2:25].

Serious Clinical Adverse Experiences/Discontinuations From Therapy:

In the cumulative extension period, 11 serious clinical adverse experiences occurred in 10 montelukast patients (4.8%) and no inhaled steroids patients. Two additional serious adverse experiences occurred in 1 patient after the SUR2 cutoff; this patient (9832) had experienced a serious clinical AE of asthma included in the cumulative extension tally. Seven of the 11 serious clinical adverse experiences involved hospitalization for worsening asthma. Over the extension period, six patients in the montelukast group (2.9%) discontinued due to a clinical adverse experience whereas no inhaled steroids patients discontinued. Two of these discontinuations were due to headache, and two to worsening asthma. All 8 patients on montelukast who were hospitalized or discontinued secondary to worsening asthma in the pediatric extension were males \leq 11 years of age.

Reviewer comment: A similar pattern was noted during Period II of Protocol 049; all serious adverse experiences (a total of 6) occurred in the montelukast group, and 3 of the 4 patients involved had either asthma and/or pneumonia. These four patients were discontinued from therapy, along with an additional 4 patients. Six (3.0%) of the 8 discontinued patients were discontinued from montelukast during Period II secondary to asthma, 2 with an associated diagnosis of pneumonia. The comparable number and percent of asthma-related discontinuations for placebo patients was 2 and 0.5%.

Individual Adverse Experiences by Body System: The table on the following two pages highlights clinical adverse experiences from the cumulative extension period in which \geq 1% of montelukast patients were affected and at a greater percentage than inhaled steroid patients. Among the montelukast patients, the highest frequency of adverse experiences by body system occurred in the respiratory (83.6%), nervous (35.3%), and the body as a whole (35.3%) systems. Comparable percentages for the small number of inhaled steroid patients were \geq 10 percentage points lower. Individual adverse experiences with the highest incidences were URI (54.1%), asthma (37.2%) and headache (29.5%).

In the body as a whole "system", fever was the most common individual clinical adverse experience in montelukast patients, with a cumulative incidence of 11.6% compared to 5.3% in inhaled steroids patients. According to the sponsor, the episodes of fever were generally transient, self-limited, and associated with another clinical condition.

Reviewer comment: A greater incidence of fever compared to placebo controls was also seen in montelukast treated patients during Period II, 7.5% versus 3.7%.

With respect to the finding of increased fever in montelukast patients, an overview of all individual adverse experiences suggests that there may be a greater rate of inflammatory/infectious illnesses among montelukast patients than those on inhaled steroids. Inflammatory/infectious illnesses seen at greater rates in montelukast than inhaled steroid patients included infectious

gastroenteritis, bronchitis, URI, laryngitis, pharyngitis, sinusitis, tonsillitis, conjunctivitis, otitis, cystitis, and urinary tract infection.

Reviewer comment: *During period II, montelukast patients experienced rates of viral infection, laryngitis, pneumonia, sinusitis, influenza, and otitis that were $\geq 1\%$ and also greater than placebo controls; infectious gastroenteritis, bronchitis, pharyngitis, and URIs were not elevated over controls during Period II.*

Digestive system disorders had higher frequencies in each reporting period and in the cumulative montelukast group experience compared with the inhaled steroids group. The cumulative incidence was 29.5% in the montelukast group and 15.8% in the placebo group, respectively. Diarrhea, dyspepsia, infectious gastroenteritis, vomiting, and dental pain were each elevated over the inhaled steroids group; all episodes resolved on drug therapy [SUR2, Vol 2: Reference 22]. Mouth pain, tongue lesions, and aphthous stomatitis also occurred more commonly in montelukast patients than those on inhaled steroids.

Reviewer comment: *In comparison, Period II digestive system disorders were more common in placebo patients (17.0% versus 14.9% for montelukast), though montelukast patients experienced higher rates of diarrhea, dyspepsia, nausea, and dental pain.*

In the open label extension, respiratory system disorders as a whole occurred more commonly in montelukast patients than inhaled steroid patients. Asthma was noted in 37.2% of montelukast patients and 28.9% of inhaled steroid patients; as noted previously, discontinuations and serious adverse experiences of asthma occurred exclusively in the montelukast patients. Bronchitis, cough, and wheezing were each elevated in montelukast patients relative to inhaled steroid patients. Cough occurred at a greater incidence in montelukast patients than inhaled steroids patients (18.8% versus 13.2%), particularly during the first extension reporting period (12.2% montelukast versus 0% in inhaled steroids patients). Over the entire extension, sinusitis occurred at a greater rate in montelukast patients than inhaled steroids patients (17.9% versus 13.2%); an elevation was also seen in montelukast patients in the Period II portion of the study (5.5% versus 1.5% placebo).

Nervous system disorders were chiefly reports of headache. During the extension, the montelukast cumulative incidence of headache (29.5%) was greater than in inhaled steroid patients (18.4%) and led to the discontinuation of 2 montelukast patients from study therapy.

Musculoskeletal disorders, largely described as pain in a variety of body parts, were more common in montelukast patients in the study extension (20.8%) compared to inhaled steroids patients (15.8%). A small elevation over placebo patients was also seen in montelukast patients during Period II (10.0% versus 8.1% in placebo). Potentially related to the higher rate of musculoskeletal adverse experiences is the observation that montelukast patients experienced a greater rate of trauma, contusions, lacerations, and eye trauma than did inhaled steroid patients during the cumulative extension period.

Reviewer comment: *One potential (albeit speculative) explanation for the greater rates of musculoskeletal pain and trauma is that the montelukast patients may have been more physically active than their placebo or inhaled steroid counterparts*

In SUR1, 3 patients with myalgia or muscle cramp were reviewed to see if there was any corresponding elevation in ALT or AST; none was found.

Allergic rhinitis was elevated in placebo patients relative to montelukast patients during Period II, but the reverse was true during the extension period.

**Clinical Adverse Experiences Occurring in \geq 1% of Montelukast Patients
and at Higher Proportions than Inhaled Steroids , Open label extension**

	Montelukast (N=207)	Inhaled Steroids (N=38)
Body as a Whole/Site Unspecified	73 (35.3)	8 (21.1)
Asthenia/fatigue	6 (2.9)	1 (2.6)
Fever	24 (11.6)	2 (5.3)
Trauma	10 (4.8)	0
Digestive System Disorders	61 (29.5)	6 (15.8)
Diarrhea	17 (8.2)	1 (2.6)
Dyspepsia	5 (2.4)	0
Gastroenteritis, infectious	18 (8.7)	2 (5.3)
Lesion, tongue	2 (1.0)	0
Pain, dental	7 (3.4)	1 (2.6)
Pain, mouth	2 (1.0)	0
Stomatitis, aphthous	2 (1.0)	0
Vomiting	16 (7.7)	1 (2.6)
Hemic and Lymphatic Disorders	2 (1.0)	0
Musculoskeletal Disorders	43 (20.8)	6 (15.8)
Dislocation, joint	2 (1.0)	0
Fracture, nose	2 (1.0)	0
Myalgia	2 (1.0)	0
Pain, back	12 (5.8)	0
Pain, finger	3 (1.4)	0
Pain, foot	5 (2.4)	0
Pain, knee	4 (1.9)	0
Stiffness	2 (1.0)	0
Strain	3 (1.4)	0
Nervous System and Psychiatric Disorders	73 (35.3)	8 (21.1)
Concussion	4 (1.9)	0
Headache	61 (29.5)	7 (18.4)
Insomnia	2 (1.0)	0
Respiratory System Disorders	173 (83.6)	28 (73.7)
Asthma	77 (37.2)	11 (28.9)
Bronchitis	11 (5.3)	1 (2.6)
Congestion, nasal	19 (9.2)	1 (2.6)
Cough	39 (18.8)	5 (13.2)
Discomfort, pharyngeal	2 (1.0)	0
Hoarseness	2 (1.0)	0
URI	112 (54.1)	18 (47.4)
Laryngitis	4 (1.9)	0
Pharyngitis	43 (20.8)	10 (26.3)
Rhinitis	4 (1.9)	0
Rhinitis, allergic	5 (2.4)	0
Sinus disorder	2 (1.0)	0
Sinusitis	37 (17.9)	5 (13.2)
Tonsillitis	3 (1.4)	0
Wheezing	4 (1.9)	0

Clinical Adverse Experiences Occurring in \geq 1% of Montelukast Patients and at Higher Proportions than Inhaled Steroids, open-label extension (continued)

	Montelukast (N=207)	Inhaled Steroids (N=38)
Skin and Skin Appendage Disorders	48 (23.2)	11 (28.9)
Acne	2 (1.0)	0
Contusion	3 (1.4)	0
Eczema	5 (2.4)	0
Herpes simplex	2 (1.0)	0
Laceration	4 (1.9)	0
Rash	17 (8.2)	2 (5.3)
Special Sense Disorders	42 (20.3)	5 (13.2)
Conjunctivitis	4 (1.9)	0
Conjunctivitis, acute	2 (1.0)	0
Infection, eye	2 (1.0)	0
Otitis	13 (6.3)	1 (2.6)
Otitis externa	2 (1.0)	0
Otitis media	13 (6.3)	2 (5.3)
Pain, ear	5 (2.4)	0
Trauma, eye	2 (1.0)	0
Urogenital System Disorders	9 (4.3)	0
Cystitis	2 (1.0)	0
Infection, urinary tract	2 (1.0)	0
Menstruation disorder	4 (1.9)	0

Laboratory Adverse Experiences

Because not all patients had laboratory data for each reporting period of the extension, the denominator varied by 1 to 4 patients for montelukast patients, and 0 to 2 patients for the inhaled steroids group. The cumulative incidence of any laboratory adverse experience was similar in montelukast patients (8.2%) and inhaled steroids patients (8.1%), as was the cumulative incidence of ALT and AST abnormalities (1.9% for montelukast and 2.7% for inhaled steroids for both parameters). All drug-related adverse laboratory experiences (4, or 1.9%) occurred in the montelukast group, as did all the withdrawals from treatment due to any or drug-related laboratory AEs. Three montelukast patients (1.4%) had pyuria, in comparison to no inhaled steroids patients. Since narratives were not supplied by the sponsor for these patients, the significance of these findings is unclear. Two patients discontinued from the entire extension due to laboratory adverse experiences and are described in the following section.

Liver Function Abnormalities

Narratives supplied for the first extension report [92:D-21663], SUR1 [1.2:225], and SUR2 [3.2:21] mentioned 3 patients with changes in liver function tests that were either classified as laboratory adverse events or led to discontinuation from the study. One 13 year old male patient had an increased bilirubin first noted one month after starting montelukast during the extension; this patient had previously been on placebo. This value increased to a maximum of 2.4, with an elevated indirect component. Approximately 3 months after study drug discontinuation, the total bilirubin had declined but was still above normal (1.7). Hepatitis A, B, and C testing were normal. Tetracycline had also been administered for approximately 2 months before the LFT abnormalities were noted.

Two patients had unexplained elevations in transaminases. An 8 year old girl had an ALT elevated > 2 times ULN (to 87) and an AST to 1.7 times ULN (to 58). ALT and AST elevations were first noted approximately 3 months after starting montelukast; during Period II, the patient had received placebo. Transaminase values declined to normal within 1 month of discontinuing study drug. Hepatitis A, B, and C screening were normal, and CMV IgG titer was positive. The patient had no symptoms at the time the first elevations were noted.

The second patient with increased transaminases was a 14 year old male who was switched from placebo to montelukast treatment in the extension. He had normal transaminase values throughout the double-blind period, but approximately 4 months after starting montelukast, he was noted to have intermittent elevations of ALT on 8 of 11 assessments done over the next 10 months. These were generally less than 1.25 ULN and reached a maximum of 1.65 ULN (71 U/L). On the occasion of his highest two ALT elevations, he had an AST greater than the ULN by 1-2 U/L; 28 days after drug withdrawal both ALT had increased slightly. The patient's parent withdrew consent. Subsequent workup showed negative viral screens (for Hepatitis A, B, C, and for CMV), diffuse fatty infiltration of the liver on ultrasound, and no signs of acute or chronic liver disease by a gastroenterologist's exam. He was given a diagnosis of steatohepatitis secondary to either obesity or drug treatment.

Cumulative analyses of transaminases and bilirubin according to the prespecified limits of change from baseline (>ULN and \geq 100% baseline) showed no greater incidence of abnormalities in montelukast than inhaled steroids patients [SUR2, Vol 1:61]. When analyzed according to any increase above the ULN, the cumulative incidence of AST and ALT elevations was similar or less in montelukast patients than inhaled steroids patients. In the montelukast group, there was a total of 10 patients with ALT elevations (4.8%) and 19 patients with AST elevations (9.2%), the respective numbers and percentages for inhaled steroids were 4(10.8%) and 3 (8.1%). Both patients with ALT values > 2 times ULN were treated with montelukast, and the one patient with an AST value >3 ULN was treated with inhaled steroids.

CONCLUSIONS

Montelukast at 5 mg once-daily improves pulmonary function in children aged 6 -14 years with chronic asthma. The magnitude of improvement in children is less than in adults and is of uncertain clinical significance. No end-of-dosing data support the once-daily dosing in chronic asthma, and the low rate but exclusive occurrence of asthma hospitalizations among montelukast-treated patients further undermines confidence in the optimal efficacy of the 5 mg dose. No off-drug follow-up occurred for the majority of montelukast patients. With few minor exceptions, the adverse event profile for children is comparable to adults. Safety concerns over potential liver toxicity should be mentioned in the label. Although no instances of clinical liver disease occurred during the trial or its extension, low-level transaminitis was associated with montelukast treatment, and three children had poorly explained increases in transaminases or bilirubin associated with montelukast therapy. The potential for increased rates of infection based upon person-level analyses by the sponsor is suggestive, and is discussed under the integrated summary of safety section of this review.

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Protocol 040

A Double-Blind, Placebo-Controlled, 2-Period, Crossover Study to Evaluate the Effects of Chewable MK-0476 on Exercise-Induced Bronchoconstriction in 6- to 14-Year-Old Children (Tanner Stage I to V) With Mild-to-Moderate Asthma

SUMMARY

This randomized, double-blind, placebo-controlled, 2-period, crossover study examined exercise-induced bronchoconstriction (EIB) in 27 asthmatic children aged 6 - 14 years after two daily doses of either 5 mg chewable montelukast tablets or placebo. Exercise challenges were done between 19 and 24 hours after the second tablet was administered. Analysis of the primary endpoint, the mean area under the curve for FEV1 percent change from pre-exercise FEV1 over the first hour (AUC_{0-60 min}), found a statistically significant inhibition with montelukast when compared to placebo. Individual patients ranged from worsened AUC_{0-60 min} with montelukast (seen in 8 patients, with the greatest worsening being 47.61%) to much improved (8 patients with inhibition of AUC_{0-60 min} of 75% or greater). The mean maximum percent fall in FEV1 was also significantly less with montelukast treatment than placebo, with the LS mean difference was approximately 8%. Individual patient data showed 4 of the 25 patients completing the trial had >5% improvement over placebo in their maximum percent fall in FEV1. Mean time to recovery to within 5% of pre-exercise FEV1 was approximately 10 minutes shorter with montelukast treatment than placebo, but this finding did not achieve statistical significance. Adverse experiences were mild and few in number, and the majority occurred off study therapy.

PROTOCOL

Objectives

- To determine the effect of montelukast administered once daily on exercise-induced bronchoconstriction by measuring AUC_{0-60 min} and time to recovery of FEV1 20 to 24 hours postdose
- To determine the effect of montelukast administered once daily on the inhibition of exercise-induced bronchoconstriction by measuring the mean inhibition of the maximal fall in FEV1
- To evaluate the safety and tolerability of montelukast in 6- to 14-year-old Children

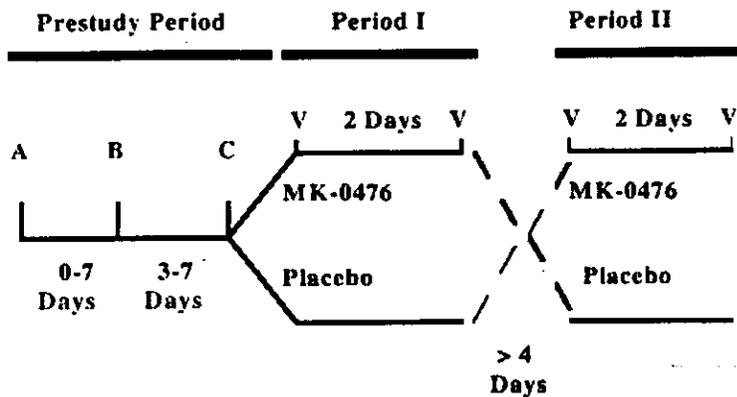
Study Design

This was a three center, randomized, double-blind, placebo-controlled, 2-period, crossover study determining the ability of montelukast (dosed at 5 mg/day with the chewable tablet) to inhibit exercise-induced bronchoconstriction 20 to 24 hours after receiving the last of 2 once-daily doses in 6- to 14-year-old children with asthma. There was at least a 4-day washout interval between periods (Figure 1, below). [91:D-19555]

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Figure 1

Schematic of Study Design



At Prestudy visit A, patients received physical exams, were screened for eligibility, and performed baseline spirometry (FEV1 and FVC). At Prestudy Visit B (which could occur on the same day as Visit A), patients had exercise testing anytime between 8 am and 10 pm. Patients avoided strenuous exercise for 12 hours prior to the exercise challenge. Patients whose averaged FEV1 from two preexercise measurements was $\geq 70\%$ were exercised on a treadmill for 6 minutes to achieve a heart rate of 160-190 bpm; this workload was to be used for subsequent exercise challenges. To qualify for Prestudy visit C, FEV1 had to fall $\geq 20\%$ within 15 minutes of completing the exercise challenge. The same exercise testing protocol was operative for Prestudy visit C, but the testing occurred at 5 pm \pm 2 hours.

Patients whose FEV1 fell $\geq 20\%$ from prechallenge values at Prestudy Visits B and C qualified for entry into the treatment phase. Allocation to Period I occurred on the day of Prestudy Visit C or up to 7 days later.

The treatment phase consisted of 2 periods separated by at least a 4-day washout interval. Each treatment period consisted of 3 days: 2 days of study medication dosing followed by an exercise challenge on the third day. Study medication was taken at 8 pm \pm 1 hour each evening. On Day 3 of both Periods I and II, patients reported to the study center at 5 pm \pm 2 hours for an exercise challenge as conducted during the Prestudy Visits. Serial FEV1 measurements were performed immediately post-exercise, and at 5, 10, 15, 30, 45, and 60 minutes post-exercise. If the patient's FEV1 had not returned to within 5% of post-exercise baseline by 60 minutes post exercise, additional FEV1 measurements were obtained at 75 and 90 minutes.

Rescue therapy was initiated with inhaled/nebulized β -agonists if the patient developed "uncomfortable bronchoconstriction", an FEV1 decrease to $< 40\%$ of predicted at any time during the study, or the FEV1 had not returned to baseline after 90 minutes post-exercise. [89:D-19563]

Patients returned 24 to 48 hours after the last exercise challenge for Poststudy laboratory, spirometry, and other assessments. All Tanner Stage II through V female patients returned 10 to 14 days after the Poststudy Visit for a serum β -hCG pregnancy test. Other patients received telephone follow-up.

Patients may have been discontinued from further participation if any of the following criteria were met: institution of therapy with an excluded study medication; the occurrence of any clinical or laboratory adverse event necessitating discontinuation, worsening of asthma necessitating treatment with oral, intravenous, inhaled, or intramuscular corticosteroids; pregnancy (positive

serum β -hCG); interruption of study medication for more than one dose; rescheduling of exercise challenge more than once during a treatment period; development of an upper respiratory infection.

Key clinical observations and laboratory measurements are summarized in the following table [91:D19425].

Study Procedures

	Prestudy Visit			Period I & II Days			PostStudy or D Visit	14 d. after last challenge
	A	B	C	1	2	3		
Inclusion/exclusion review	x							
Vital signs (sitting BP, HR, RR, and oral temperature)	x	x	x			x	x	
Complete physical exam	x						x	
ECG (12-lead)	x						x	
Exercise challenge on a treadmill		x	x			x		
Pregnancy testing	x	x	x	x		x	x	x

Treatment

Patients were randomly assigned to treatment sequence as Panel A (Group 1) or Panel B (Group 2). Patients received their dose of montelukast (MR-3247) or matching placebo (MR-3250) (1 tablet/day) on Days 1 and 2 of each period. All doses of study drug (montelukast or placebo) were consumed at 8 PM \pm 1 hour.

Group	Period 1	Period 2
1	Placebo	Montelukast
2	Montelukast	Placebo

Patients withheld inhaled albuterol for 6 hours, caffeine-containing foods and beverages for 8 hours, and fasted from all food and liquids (except water and apple juice) for at least 3 hours prior to exercise challenge.

Disallowed respiratory medicines are described under items 3 and 4 of the Exclusion Criteria. Allowed medications included inhaled albuterol, which was used throughout the study "as needed" to treat bothersome asthma symptoms or if a patient developed uncomfortable symptoms after an exercise challenge. Routine and habitual use of inhaled albuterol without symptoms was discouraged. Nasal steroids and nasal cromolyn were allowed if the patient had been on a stable dose for at least 1 month prior to Prestudy Visit A. Patients were allowed to use other airways medications (in monosubstance formulations), namely cough suppressants, expectorants, and nasal decongestants (pseudoephedrine, oxymetazoline). Acetaminophen was the only OTC agent allowed for minor pain relief.

Patients

A total of 27 healthy asthmatics were randomized at 3 study centers.

Inclusion Criteria

1. Male/female between the ages of 6 and 14 years, Tanner Stage I through V.
2. Within 40% of 5th to 95th percentile weight range
3. Nonsmoker
4. In a stable phase of his/her asthma.
5. Patient met all of the following asthma criteria:

- Typical symptoms of asthma, including but not limited to, cough, wheezing, shortness of breath with periodic episodes requiring treatment with bronchodilators.
 - The average FEV1 measured at 20 and 5 minutes pre-exercise was $\geq 70\%$ of predicted on both Prestudy Visits B and C with inhaled β -agonists withheld at least 6 hours.
 - A $\geq 20\%$ decrease after exercise challenge from the average pre-exercise FEV1 values (measured at 20 and 5 minutes pre-exercise) during both Prestudy Visits B and C.
6. Female patients (Tanner Stage II through V) were not pregnant and were taking appropriate precautions against becoming pregnant from 2 weeks prior to treatment until 30 days posttreatment.
 7. Adequate consent
 8. Patient in otherwise in good health, able to perform reproducible pulmonary function testing and PEFr measurements.

Exclusion Criteria

1. Required a visit to the hospital or emergency room due to an asthma exacerbation within 6 months of the Prestudy Visit.
2. Unresolved signs and symptoms of an upper respiratory tract infection (URI) or had a URI within 3 weeks of the Prestudy Visit.
3. Use of any medication other than allowed asthma medications (inhaled β -agonist) within 14 days of the Prestudy Visit.
4. Use of astemizole within 3 months; cromolyn, nedocromil, inhaled, intramuscular, oral, or intravenous steroids within 1 month; theophylline (or like drugs), oral or long-acting β -agonists, antimuscarinic (ipratropium), terfenadine, loratadine, aspirin or nonsteroidal anti-inflammatory agents within 2 weeks of Prestudy Visit A.
5. Consumption of food or medications containing caffeine, chocolate, soda, or cocoa within the 8 hours prior to the start of the treatment period.
6. Excessive intake of caffeine or soda (greater than four caffeinated sodas/day).
7. History of any illness that might confound the results of the study or pose additional risk in administering montelukast to the patient.
8. History of epilepsy or seizures.
9. Significant or unexplained abnormalities on the prestudy physical examination and/or laboratory safety measurements.
10. Females who were pregnant, nursing, or sexually active but unwilling to use effective contraception
11. History of any clinically significant disease of the gastrointestinal, cardiovascular, hepatic, neurological, renal, genitourinary, or hematological systems or had hypertension.
12. Any other pulmonary or thoracic disorder besides asthma that could distort the interpretation of the results, e.g., emphysema, kyphoscoliosis, chronic bronchitis, active tuberculosis, and sarcoidosis.
13. Currently an intermittent or regular user of any illicit drugs or a history of drug or alcohol use.
14. Surgery, blood donation, or participation in another clinical trial within 8 weeks of the Prestudy Visit.

Endpoints

The primary efficacy endpoint was the postexercise values of AUC for the FEV1 percent change from the pre-exercise FEV1 versus time curve (AUC_{0-60 min}). This was calculated as only the area below the pre-exercise FEV1 value and above the percent change from the pre-exercise FEV1 versus time curve. If FEV1 measurements were not available for the entire 60-minute interval (for example, if rescue with albuterol was given), then the last postexercise FEV1 measurement was carried forward for the remaining time points for the calculation of AUC₀₋

Reviewer comment: *If albuterol rescue occurs more commonly during placebo treatment, carrying forward pre-rescue FEV1 measurements will magnify the apparent treatment effect of montelukast.*

Additional efficacy endpoints (described as secondary in the clinical study report) were the maximum FEV1 percent fall from pre-exercise challenge FEV1, and the time since the maximum fall to recovery to within 5% of the pre-exercise FEV1. In the primary analysis of time to recovery, whenever a patient received rescue medication or did not recover within 90 minutes, the time of recovery was defined as 100 minutes. Additional endpoints specified in the clinical study report were rescue medication use after exercise challenge, and percent inhibition of montelukast compared with placebo for each of the exercise challenge endpoints. Methods for their calculation were described [89:D-19431].

Safety endpoints included adverse events, VS, ECG, and blood and urine analyses. Labs included the following: hemoglobin, hematocrit, WBC (total and differential), platelets, BUN, creatinine, total protein, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, glucose, sodium, potassium, chloride, carbon dioxide, phosphate, calcium. Gross and microscopic urinalysis was also done along with laboratory assessments as described in the table under Study Design.

Data Analysis Plan

The null hypothesis, that the mean AUC_{0-60 min} would be equal for the placebo and montelukast groups, required 24 patients to have 90% power to detect (at an $\alpha = 0.05$, two-tailed test) a difference of 615.43 in AUC_{0-60 min} (52% of the placebo AUC_{0-60 min}) between the two treatment groups. The estimation of power was based on the assumption that the AUC_{0-60 min} variability in children was similar to the variability observed in the two previous Phase II adult exercise-induced bronchoconstriction studies.

Efficacy analyses were performed on all randomized patients who had a pre-exercise FEV1 value and postexercise FEV1 measurements for both periods (intention-to-treat population). All patients were included in the safety analysis. An analysis of variance (ANOVA) model for a crossover design was used to compare the primary and secondary efficacy endpoints between the two treatment groups. The model included factors for center, sequence, subject within center-by-sequence, period, and treatment. The treatment-by-center interaction was assessed if center size was adequately large (all treatment-by-center cell sizes ≥ 3). The carryover effect was evaluated for the primary efficacy endpoint using ANOVA with patient, treatment, period, and carryover effects as factors in the model. [89:D-19627-19628].

No multiplicity adjustment was performed since there was only one primary efficacy endpoint. Because of the small study size of approximately 24, no assessment of the interactions between treatment and subgroups was done.

RESULTS

Patient Population

A total of 27 healthy asthmatics were randomized at 3 study centers. There were 20 males and 7 female patients. Compared to the target of 50% participation by children aged 6-10, 11 or 40.7% were in this age group. There was one 6 year old, three 8 year olds, 4 nine year olds, and three 10 year olds. [89:D-19724]

Mean baseline (prerandomization) values for the entire cohort were as follows:

	Mean	SD	Median	Range
Pre-exercise FEV1 (% Predicted)	86.93	12.08	83.72	
AUC0-60 min (% min)	-1072.30	948.64	-838.40	
Maximum % fall in FEV1 (%)	-35.81	11.72	-34.26	
Time to recovery to within 5% of pre-exercise FEV1 (min)	44.97	33.16	36.67	

The mean pre-exercise FEV1 values were virtually identical (~2.5L) for treatment Periods I and II and by treatment assignment to either placebo or montelukast first. [89:D-19439] There were no notable differences in secondary diagnoses, prior drug therapies, and concomitant therapies between the 14 patients who received montelukast first and the 13 that received placebo first. [89:D-19439, D-19731-19735]

One patient allocated to Group 1 (placebo/montelukast), received study medication in the reverse order and so was analyzed as part of the Group 2 (montelukast/placebo) sequence for purposes of the safety and efficacy analyses. Two Group 2 patients discontinued during Period II: one due to a clinical adverse experience and the other for a protocol deviation. Neither patient performed the Period II exercise challenge.

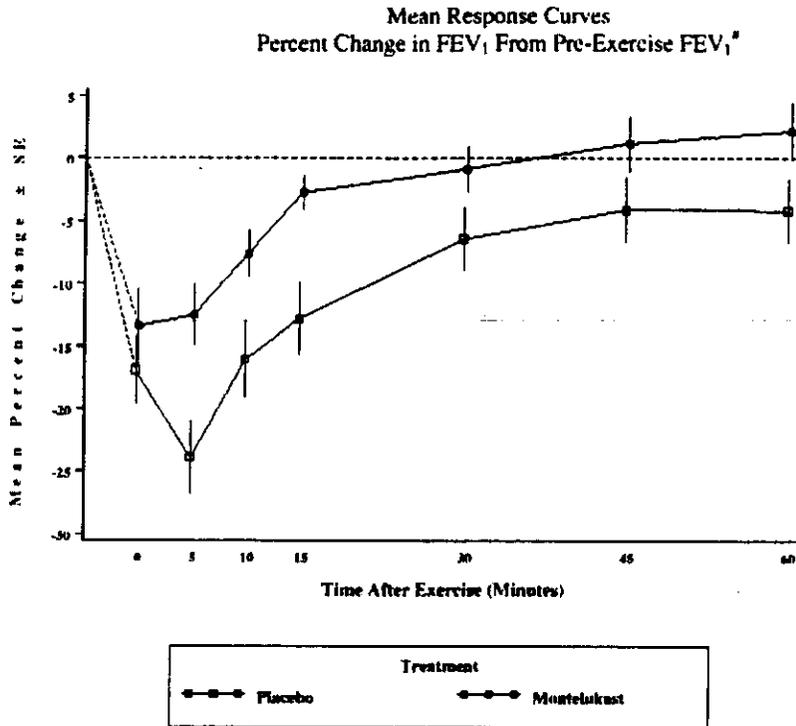
The 25 patients completing both study periods were included in the primary efficacy analysis; the 2 patients who discontinued prior to the Period II challenge were excluded. All 27 patients were included in the safety analysis.

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EFFICACY

Mean Percent Change in FEV₁ from Pre-Exercise FEV₁: This value for each post-exercise time point is displayed below. Statistical testing of individual time points was not done.

Figure 3



* Pre-exercise FEV₁ values were 2.45 and 2.48 liters in the placebo and montelukast treatments, respectively. Dotted line connects pre-exercise FEV₁ to first postexercise FEV₁ value.

AUC_{0-60 min}(Primary Endpoint): Compared with the baseline (prerandomization) value, placebo treatment inhibited FEV₁ AUC_{0-60 min}. Using the sponsor's metric, the medical reviewer calculated that placebo treatment alone was associated with a 45% inhibition of the exercise-induced bronchoconstriction (EIB) seen at baseline.

Compared with placebo, montelukast demonstrated a significant improvement in AUC_{0-60 min} (p = 0.013). The mean AUC_{0-60 min} were -589.72%·min and -264.60%·min for the placebo and the montelukast groups, respectively. Montelukast provided a 58.77% inhibition of EIB compared with placebo with respect to AUC_{0-60 min}.

Medical reviewer inspection of the percent inhibition based on AUC_{0-60 min} by individual patients revealed no age- or sequence-related pattern in EIB improvement as measured by percent inhibition of AUC_{0-60 min}. The range of percent inhibition was from [range] In 8/25 patients, the percent inhibition was negative; in 7/25 of patients, the percentage improvement was 75% or greater. [91:D-19724 and medical reviewer analyses.] A plot of the individual percent inhibition of AUC_{0-60 min} versus age evidenced no age-related pattern, nor was there a statistically significant linear correlation of age and percent inhibition [91:D-19725].

Maximum Percent Fall in FEV1 After Exercise (Secondary Endpoint): Compared with the baseline (prerandomization) value, there was a 27.1% inhibition of the maximum percent fall in FEV1 during placebo treatment. (Medical reviewer calculation)

Compared with placebo, the montelukast group demonstrated a significant improvement in maximum percent fall from pre-exercise FEV1 ($p = 0.009$). The mean maximal percent fall in FEV1 was -26.11% and -18.27% for the placebo and the montelukast groups, respectively. Montelukast provided a 30.78% inhibition of exercise-induced bronchoconstriction compared with placebo with respect to maximal percent fall in FEV1.

Interpolation by the reviewer of the maximum decrement in FEV1 from graphs of percent change from baseline for individual patients [89:D-19697 to D-19723] showed discernible improvement with montelukast over placebo in 4 of 25 patients. In the remaining 21 patients, the maximum percentage fall with montelukast was the same or greater than placebo.

Time to Recovery Within 5% of Pre-Exercise FEV1: Compared with the baseline (prerandomization) value of 44.97 minutes, there was a 37.8% reduction in time to recovery during placebo treatment. (Medical reviewer calculation).

The mean time to recovery was 27.98 minutes and 17.76 minutes for the placebo and the montelukast groups, respectively. This difference was not statistically significant ($p=0.079$).

β -agonist Rescue: Nine patients required β -agonist rescue during one or more prerandomization exercise challenges. Three patients required β -agonist rescue after randomization; 1 patient during both placebo and montelukast treatment, 1 patient during montelukast treatment, and 1 patient during placebo treatment.

There were no period or carryover effects according to the sponsor's statistical analyses of AUC_{0-60 min}, maximum percent fall in FEV1, and time to recovery. [89:D-19440]

Categorical Analyses Done in Adult Study: As with the adult EIB trial, mean values for the post-exercise FEV1_{0-60 min} AUC were reported. Details of the maximum percentage fall in FEV1, time to recovery to within 5% of baseline, and need for β -agonist rescue were not provided for individual patients.

SAFETY

All 27 patients were included in the safety analyses. A total of 14 clinical adverse experiences were reported in 7 patients. All but four of the adverse experiences occurred between study periods while off drug, and so were attributed to the treatment in the last period that the patient completed. Eight of the 14 experiences were attributed to placebo and 6 to montelukast. There were no serious adverse experiences, and no pattern of body system or specific adverse experiences was discernible to the medical reviewer. [89:D-19447]

One patient was discontinued from the study due to an asthma exacerbation that required oral corticosteroid rescue. The last study drug received by this patient was placebo.

The sponsor reported no clinically significant worsenings in physical exams or ECGs.

None of several laboratory values falling outside of the normal range was considered clinically significant by the sponsor. None were attributed to drug therapy by the investigator. Review of all abnormal laboratory values by the medical officer confirmed only minor changes outside the normal range for all laboratory parameters. Abnormal laboratory parameters that appeared unusual or to occur at high incidence were examined more closely for potential association with therapy; these included low hematocrit (16 patients), proteinuria (10 patients), pyuria (1 patient), and hematuria (2 patients). In the opinion of the medical reviewer, none of these appeared related to montelukast treatment. The one case of pyuria consisted of an isolated report of 8 wbc/hpf in a 6 year old male two days after receiving montelukast; subsequent urinalysis was without wbc's.

CONCLUSIONS

In brief, two daily doses of montelukast demonstrated statistically significant end-of-dosing interval improvement in EIB, as measured by post-exercise AUC_{0-60 min} and the maximum percent fall in FEV₁. The clinical significance of these mean changes is not clear; EIB was ameliorated but not ablated in the majority of patients, and about 1/3 of patients worsened on montelukast therapy. Montelukast had an acceptable safety and tolerability profile in this protocol involving limited drug exposure.

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Protocol 039

A Randomized, 2-Period, Multicenter Study to Evaluate the Safety, Tolerability, and Plasma Concentration Profile of MK-0476 Administered as a Chewable Formulation in 6- to 8-Year-Old Children (Tanner Stage 1) With Asthma

This pharmacokinetic study is briefly reviewed here for adverse events associated with montelukast treatment. Details of the protocol and its pharmacokinetic findings are in the Biopharmaceutics review.

SUMMARY AND CONCLUSIONS

In a PK trial of 1 or 15 days exposure to the 5 mg montelukast chewable tablet administered in the morning, children aged 6-8 years experienced no significant clinical adverse experiences. With the exception of decreased serum bicarbonate below the lower limit of normal (seen in 5 children treated with montelukast), there were no notable laboratory abnormalities. The clinical significance of the observed declines in serum bicarbonate in this study is unclear.

PROTOCOL

This randomized, 2-period, two-center study evaluated the safety, tolerability, and plasma concentration profile of a morning 5-mg dose of the MK-0476 chewable tablet formulation in nineteen 6- to 8-year-old children (Tanner Stage I) with mild-to-moderate asthma. On Study Day 1 (Period I), patients were randomized into two groups (A and B): Group A received MK-0476 in Periods I and II and Group B received MK-0476 in Period I and matching placebo in Period II. The periods were sequential with no interval between them, as illustrated below.

Study Design

	Period I	Period II
Group A*	MK-0476	MK-0476
Group B*	MK-0476	Placebo
Duration	1 day (Study Day 1)	14 days (Study Days 2 to 15)
* Patients will be randomized into Group A or Group B at the start of the study		

Period I (Study Day 1) was a single-dose, single-blind period to evaluate the MK-0476 plasma concentration profile. Period II was a double-blind, placebo-controlled, 14-day period (Study Days 2 to 15) evaluating the safety and tolerability of multiple doses of MK-0476.

Patients were between the ages of 6 and 8 years, 18 to 28 kg in weight, had a one year or greater history of asthma with an FEV1 between 60 and 85% of predicted. There were 14 children in Group A and 5 in Group B. Permitted medications included immunotherapy, inhaled β -agonists, inhaled cromolyn, and inhaled corticosteroids. Oral or parenteral corticosteroids were not allowed within 14 days of the treatment period, and restrictions were placed on recent theophylline, oral β -agonists, long-acting antihistamines, and caffeinated product use prior to PK testing.

Safety and tolerability were evaluated by physical examinations, vital signs, laboratory safety tests, electrocardiograms (ECGs), an interim safety visit, and daily phone calls. Physical examinations were conducted at baseline and at discontinuation/ 7 days poststudy, and laboratory safety tests were obtained prestudy, day 8 predose, and day 7 poststudy. Electrocardiograms (ECGs) were obtained at 4-6 hours posttreatment on day 1, and daily phone calls were conducted on study days 3-7, 9-14, and 14 days poststudy. Vital signs were assessed 4, 6, 12, and 24 hours postdose on day 1, and at 2 hours postdose on days 8 and 15.

SAFETY RESULTS

Clinical Adverse Experiences: A total of 15 clinical adverse experiences of mild to moderate severity (12 Group A, 3 Group B) were reported in 9 patients. Four of the clinical adverse experiences associated with montelukast therapy were attributed to the drug although the AE occurred while the patient was off therapy. One child in Group A and one in Group B experienced a headache on treatment day 1, and dyspepsia was noted on two occasions in one child given montelukast. A child who was subsequently diagnosed with sinusitis had 3 episodes of fever while on montelukast.

Discontinuations due to Clinical Adverse Experiences: Two patients on montelukast discontinued from the study due to a clinical adverse experience. [redacted] was discontinued on Study Day 7 (Period II) because of an urinary tract infection. [redacted] was discontinued on Study Day 3 (Period II) because of chicken pox (varicella). In addition, the child with repeated fever and sinusitis [redacted] withdrew from the study after 9 days of drug treatment.

Laboratory Adverse Experience: There was one laboratory adverse experience. [redacted] (Group A, montelukast throughout Periods 1 and 2) had a decreased bicarbonate value of 12.5 mEq/L (normal range 17.0 to 30.6 mEq/L) on Day 8 of montelukast treatment; subsequent measurements on day 15 (on montelukast) and day 20 (off montelukast) were still below the LLN (16.0 and 16.3 mEq/L respectively). A blood test of CO₂ obtained on day 12 at a local laboratory was 24 mEq/L (normal range 22 to 31 mEq/L). The investigator considered this laboratory adverse event as probably not related to study drug.

Other clinical findings: With the exception of otitis media diagnosed on the poststudy physical examination (Day 22 relative to start of study) for [redacted] no other clinically significant changes in ECG parameters, physical examination, or vital signs were observed.

Laboratory Values Outside The Normal Range: The sponsor reported that all laboratory values outside the normal range were without clinical significance. Medical reviewer examination of case report tabulations of all laboratory values outside the normal range revealed serum bicarbonate decreases in a total of 5 patients treated with montelukast and in no patients treated with placebo. These are described in the following paragraph. In addition, 3 patients had minor and transient AST elevations, 2 while on montelukast therapy and one on placebo. These transaminase changes had no apparent clinical significance.

In addition to the decreased bicarbonate classified as a laboratory adverse experience in patient 9048 and discussed in that section, 4 other study subjects had decreased serum bicarbonate levels that were 1-3 mEq/L below the LLN. One of these 4 children had a UTI that necessitated study withdrawal. Another child had a low normal baseline bicarbonate, experienced two clinical adverse experiences of dyspepsia, and did not normalize her serum bicarbonate until after montelukast therapy was discontinued. The remaining 2 children normalized their serum bicarbonate while on montelukast therapy. The potential association of montelukast with decreases in serum bicarbonate is unclear based upon these limited data.

Protocol 036

An Open, Single Oral Dose, 1-Period Study to Evaluate the Plasma Concentration Profile of MK-0476 (Phase III Tablet Formulation) in Adolescents in Early Puberty (Tanner Stages II and III) With Asthma

This pharmacokinetic study is briefly reviewed here for adverse events associated with montelukast treatment. Details of the protocol and its pharmacokinetic findings will be found in the Biopharmaceutics review.

SUMMARY AND CONCLUSIONS

A single, open-label dose of 6 mg or 10 mg montelukast in adolescents aged 9 to 14 years and weighing between 25 and 57 kg was safe as measured by ECG, and laboratory parameters. Headaches were noted in 3/18 (16.7%) of the children.

PROTOCOL

This was an open-label, 1-period, single oral dose study to evaluate the plasma profile of a MK-0476 tablet formulation dosed at 6 or 10 mg, according to body weight, in 18 adolescents. Participants were Tanner Stages II and III, aged 9 to 14 years, with mild-to-moderate asthma. There were equal numbers of patients in each dosage group.

Dosing was with three 2 mg tablets, or one 10 mg tablet as follows:

<u>Weight (kg) with shoes and clothes</u>	<u>Total Dose (mg)</u>	<u>Tablet Dose</u>	<u>Batch No.</u>
≤ 45	6	3 x 2 mg	MR-3189
> 45	10	1 x 10 mg	MR-3165

Patients were asthmatics with FEV1 between 60 and 85% of predicted and weights between 25 and 57 kg. Allowed asthma medications included immunotherapy, inhaled β-agonists, inhaled cromolyn, and inhaled corticosteroids. Oral or parenteral corticosteroids were not allowed within 14 days of the treatment period, and restrictions were placed in recent theophylline, oral β-agonists, long-acting antihistamines, and caffeinated product use prior to PK testing.

Safety assessments consisted of vital sign monitoring during the first 24 hours postdose and ECG monitoring at 4 hours postdose. These tests were repeated at 48 to 72 hours postdose, along with blood and urine laboratory evaluations. If a particular adverse experience was not observed in any of the 16 patients planned for this study, the incidence rate would be less than 0.096 with 80% confidence (0.134 with 90% confidence). In each weight subpopulation, if a particular adverse event was not observed in any of the 8 patients planned, the incidence rate would be less than 0.182 with 80% confidence (0.250 with 90% confidence).

SAFETY FINDINGS

A total of 4 clinical adverse experiences were reported in 4 of the 18 patients treated with montelukast. All were mild in severity. There was one URI that lasted about 6 days and 3 headaches, each of about 1 hour duration. Two headaches occurred with 6 mg of montelukast and one with the 10 mg dose. One headache seen in the 6 mg dose group was considered to be possibly related to drug treatment. No patient discontinued because of a clinical adverse experience.

There were no clinically significant changes in ECG parameters, physical examination, or vital signs. No laboratory adverse experiences were reported. Review of the case report tabulations by the medical officer for all laboratory values outside the normal range found no extreme values. Some mild abnormalities in hematocrit and phosphorus were noted 3 days after montelukast treatment, but no concerning rate or pattern was appreciated by the medical reviewer.

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Integrated Summary of Efficacy

The effect of montelukast (5-mg chewable tablet) on chronic and exercise-induced asthma in pediatric patients (6 to 14 years old) was studied in two protocols, the Chronic Asthma (Protocol 049) and Exercise (Protocol 040) Studies.

OVERALL EFFICACY POPULATION

In the Chronic Asthma (Protocol 049) and Exercise (Protocol 040) Studies, 34.7% of patients were female and 65.3% were male; 80.2% were Caucasian and 19.8% were of other origins. Of these patients, 52.6% were 6 to 11 years old and 47.4% were 12 to 14 years old.

As seen the following table, the Chronic Asthma Study (Protocol 049) cohort had a lower mean predicted FEV₁ than the Exercise Study (Protocol 040) cohort. A subset (36.3%) of patients in Protocol 049 was permitted continued concomitant use of inhaled corticosteroids, while patients in Protocol 040 had near minimal medication use.

Baseline Age and Percent Predicted FEV₁; Pediatric Efficacy Studies

Study	N ¹	Montelukast (Chewable Tablet) Daily Dose (mg)	Treatment Duration	Median Age Years (Range)	FEV ₁ % Predicted (Mean ± SD)
Protocol 049	336	5	8 weeks	11 (6 to 14) ²	71.70 ± 9.55
Protocol 040	27	5	2 days	12 (6 to 14)	86.93 ± 12.08

¹ Number of patients randomized.
² Two patients were 14 years old at Prestudy and turned 15 years old prior to randomization.

TREATMENT OF CHRONIC ASTHMA

The Chronic Asthma Study was a multinational, 8-week, placebo-controlled study with a primary endpoint of FEV₁. Secondary endpoints included daytime symptom score, patient-reported AM PEF, nocturnal asthma score, and "as-needed" β-agonist use. The study was designed to provide 90% power to detect a 7.1 percentage point difference in FEV₁ (the primary endpoint) from baseline between the two treatment groups. A statistically greater percentage increase in mean FEV₁ was found in montelukast patients relative to placebo, as shown in the table below. The magnitude of this increase was less than was seen in the adult program.

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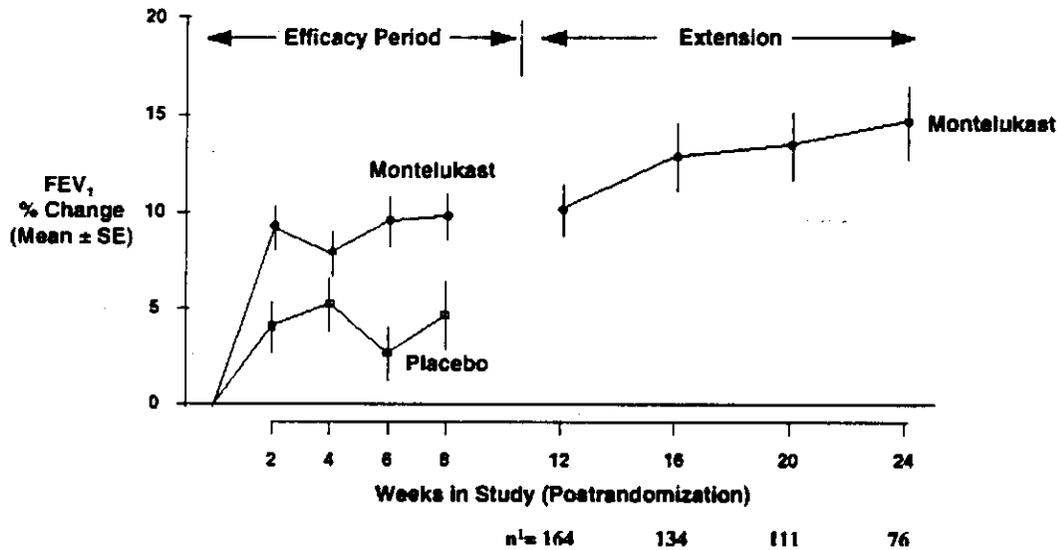
Effect of Montelukast on FEV₁ (Percent Change From Baseline); Pediatric Chronic Asthma Study (Protocol 049)

N ¹		Baseline (L)		% Change (Mean ± SE)	% Change (Mean ± SE)	Difference in LS Mean ² (95% CI)
PBO	MNT	PBO	MNT	PBO	MNT	MNT-PBO
131	196	1.85	1.85	4.16 ± 0.94	8.71 ± 0.90	4.65* (1.92, 7.38)

¹ Number of patients included in intention-to-treat analysis
² Least square mean
 * p < 0.001, compared with placebo
 PBO = Placebo MNT = Montelukast

The following figure shows that the effect of montelukast on FEV₁ was consistent over the 8-week treatment period; the percent change from baseline FEV₁ was statistically greater in the montelukast group at weeks 2, 6, and 8 than in the placebo group (p<0.05) [91:D-20774, -20779, -20784, -20789]. The figure also shows the montelukast effect on FEV₁ for up to 6 months of treatment using FEV₁ data from the open-label extension through 6/24/96. Extension data were available for 164 patients at Week 12 and 76 patients at Week 24 as of the in-house cutoff date.

Effect of Montelukast on FEV₁ (Percent Change From Baseline) in the Pediatric Chronic Asthma Study (Protocol 049); Efficacy Period and Extension



Morning and Evening PEFr: There were no statistically significant between-group differences in patient measured PEFrs, as seen in the following table. Since placebo AM PEFr readings had an unexplained increase over the course of the study, a *post hoc* analysis of AM PEFr measured at clinic visits was done; this analysis showed a statistically significant improvement with montelukast in comparison to placebo.

Reviewer comment: *The magnitude of the clinic visit AM PEFr improvement was about 10 L/min, a change of minimal clinical significance. PM PEFr was the only end-of-dosing interval endpoint in the chronic asthma protocol, and showed no treatment effect of montelukast.*

Effect of Montelukast on AM and PM PEFR (Change From Baseline); Pediatric Chronic Asthma Study (Protocol 049)

Treatment	N ¹		Mean Baseline (L/min)		Change (L/min) (Mean ± SE)	Change (L/min) (Mean ± SE)	Difference in LS Mean ² (95% CI)
	PBO	MNT	PBO	MNT	PBO	MNT	MNT-PBO
AM PEFR							
Clinic Measured	133	197	270.5	264.2	17.8 ± 3.7	27.9 ± 2.8	9.9* (0.9, 19.0)
Patient-Reported (Diary card)	132	197	313.2	311.5	7.1 ± 2.7	9.5 ± 1.8	2.4 (-3.7, 8.5)
PM PEFR							
Patient-Reported (Diary card)	132	197	327.6	325.7	5.7 ± 2.4	5.5 ± 1.6	0.0 (-5.5, 5.5)
¹ Number of patients included in intention-to-treat analysis ² Least square mean * p ≤ 0.050, compared with placebo PBO = Placebo MNT = Montelukast							

Total Daily Beta-Agonist Use (Secondary Endpoint): Mean baseline values for total daily beta-agonist use (3.24 and 3.34 puffs/day for the placebo and montelukast groups, respectively) were low and comparable between the treatment groups. The mean change from baseline was -0.23 and -0.56 puffs/day for the placebo and montelukast groups, respectively. The difference in LS means between the two treatment groups based on change from baseline was -0.36 puffs/day, p=0.08 [91:D-20753].

When analyzed according to the percentage change averaged over the 8-week treatment period, the placebo and montelukast groups had mean percent changes from baseline of 8.20% and -11.66%, respectively, a statistically significant difference of -22.49%. In the placebo group, the paradoxical increase in average mean percentage beta agonist use when compared to the mean decline in absolute use reflects the low baseline values and the magnification of effect by transforming small changes into percentages. [91:D-19825, D-20754].

Reviewer comment: *Although analysis according to percentage change in β-agonist was prespecified, it is misleading in this case since it represents the decline in the placebo group as an increase and also increases the magnitude and statistical significance of the montelukast-placebo difference. The clinical significance of a relative decline of approximately 1/3 puff per day in β-agonist use is small, and product labeling should clearly represent the small magnitude of the mean decrease in β-agonist use with montelukast.*

Asthma-Specific Quality of Life (Tertiary Endpoint claimed in proposed label): The medical reviewer analyzed results from the pediatric asthma quality of life instrument developed by [redacted] and colleagues to determine whether the authors' defined minimally important differences (MID) occurred between montelukast and placebo. This analysis found that montelukast achieved significant MIDs in the overall score and the emotions domain. Symptoms and activity domains were improved but did not achieve the MID above placebo. The sponsor's analysis of statistical differences from placebo without consideration of the MID found a significantly greater improvement than placebo in the 3 domains of symptoms, activity, and emotions, as well as their overall average.

Reviewer comment: *No "win" was prespecified for the quality of life endpoint or its components, and the sponsor's analyses which showed statistical significance in all domains and overall did not follow the minimally important difference interpretation specified by [redacted] and colleagues in their publication concerning the instrument.*

Patient's, Parent's, and Physician's Global Evaluation

At the end of the 8-week treatment period, patients, parents, and physicians independently evaluated the patient's response to study therapy. Compared with placebo, montelukast demonstrated a significant improvement in the parent's global evaluation. The results of the physician's and patient's evaluations favored montelukast but were not statistically significant ($p = 0.058$ and $p = 0.109$, respectively). A predefined analysis of the averaged (parent, patient and physician) global evaluations showed that, compared with placebo, montelukast had a significant improvement in the averaged global evaluations.

Daytime Symptom Score, Nocturnal Asthma, and School Loss

Analysis of entries on a pediatric daily diary card found no statistically significant between-group differences in daytime symptom scores, nocturnal awakenings, or school loss over the treatment period.

Onset of action analysis (claimed in proposed label): Although not a prespecified analysis for the pediatric study, the sponsor modeled the percent change in beta-agonist use, the change in patient-reported PEFR, and the change in daytime symptom scores using repeated measures analysis to determine the onset of treatment effect. The intercept of the regression line for montelukast was statistically improved for total daily β -agonist use and AM PEFR. Daytime symptom scores were improved but not significantly [90:D-19838].

Because the application analyses were modeled and did not make straightforward use of data from the first days of therapy, FDA requested crude daily analyses of the treatment effects of placebo versus montelukast for the first 7 treatment days. Using an ANOVA model with factors for treatment, study center, and stratum, there was a significantly greater percentage change in montelukast patients versus placebo in total daily β -agonist use on treatment days 1 and 2. In contrast, the daytime symptom score and am PEFR of montelukast patients only achieved statistically significant improvement over placebo after 5 days of therapy [Merck response of 11/24/97 to FDA request]. Comparison of daily means for daytime symptom score, am PEFR, and total daily β -agonist use (percentage change) likewise did not evidence any clinically meaningful benefit to montelukast therapy on day 1 of therapy with the exception of the β -agonist use endpoint [91:D-20662ff].

Reviewer comment: *According to the medical reviewer of the adult program, two placebo-controlled adult trials showed montelukast had onset of action at day 1 of therapy as measured by change in symptom scores, β -agonist use, AM PEFR, and nocturnal asthma scores. The pediatric data and modeling done by the sponsor are not convincing for a rapid (within the first day) onset of action; only the percentage change in β -agonist use was statistically significant on the first day of treatment.*

Clinical Control of Asthma (Other Endpoints)

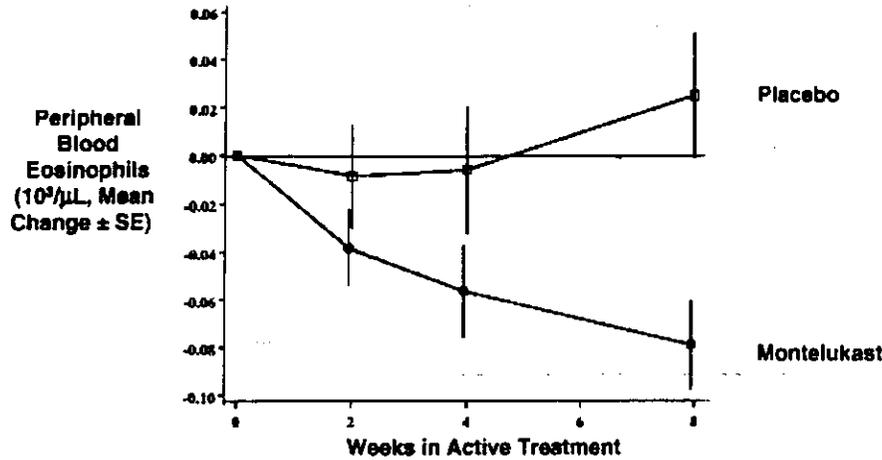
Montelukast demonstrated a significant effect in reducing asthma exacerbations. Over the 8-week treatment period, the mean percent of days with an asthma exacerbation was significantly different between the placebo (25.7%) and montelukast (20.6%) groups ($p < 0.050$). By the medical reviewer's analysis, this translates into about 3 fewer days with an exacerbation in the montelukast group. The percent of patients who experienced at least one asthma exacerbation was 95.5% for the placebo and 84.8% for the montelukast groups ($p < 0.050$). The between-group differences for asthma attacks, asthma-free days, oral corticosteroid rescue, and discontinuations due to asthma were not statistically significant.

Effects of Montelukast on Peripheral Blood Eosinophils (Other Endpoint)

In the Pediatric Chronic Asthma Study (Protocol 049), mean baseline values for eosinophils were 0.47 and 0.44 $\times 10^3$ /mL for placebo and montelukast, respectively. The following figure shows that, compared with placebo, eosinophils decreased in the montelukast patients ($p < 0.050$).

Averaged over the 8-week treatment period, montelukast caused a 13.3% decrease relative to placebo (Figure D-29). The clinical significance of this decrease is unclear.

Effect of Montelukast on Peripheral Blood Eosinophils ($\times 10^3 / \text{mL}$) (Mean Change From Baseline); Pediatric Chronic Asthma Study (Protocol 049)



EXERCISE-INDUCED BRONCHOCONSTRICTION

Effects of Montelukast on Exercise-Induced Bronchoconstriction

A multicenter, 2-period, crossover exercise study was performed in 6- to 14-year-old pediatric asthmatic patients (Protocol 040). EIB challenges were performed 20 to 24 hours after the second of two once-daily doses (5 mg) of montelukast. The ability of montelukast to attenuate EIB was evaluated by three endpoints: (1) $\text{AUC}_{0-60 \text{ min}}$ for percent change from pre-exercise FEV1 versus time curve, (2) maximum percent fall in FEV1 after exercise, and (3) time to recovery of the maximum fall in FEV1 to within 5% of the pre-exercise FEV1.

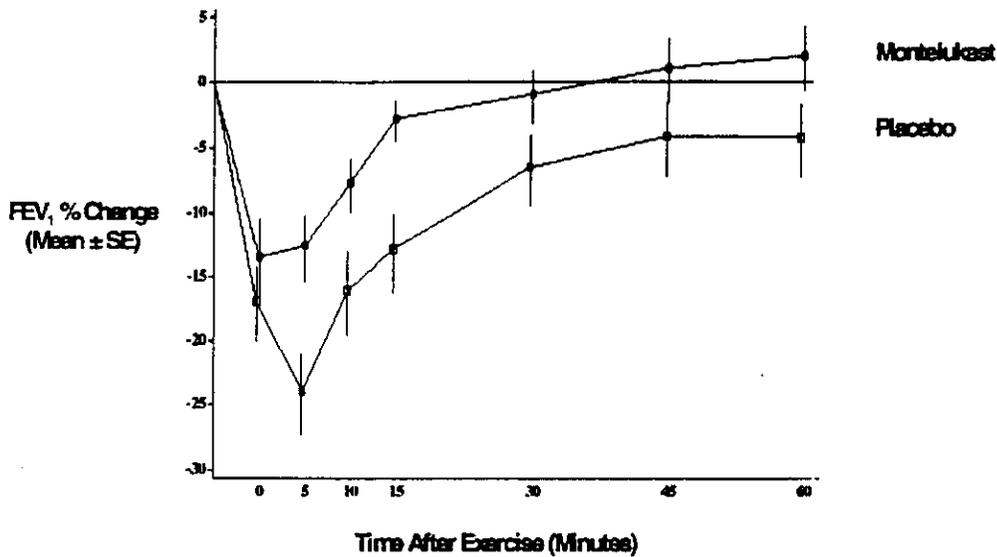
As seen in the following table and figure, montelukast demonstrated significant differences compared with placebo in $\text{AUC}_{0-60 \text{ min}}$ and maximum percent fall in FEV1. A 59% greater inhibition than placebo in $\text{AUC}_{0-60 \text{ min}}$ was seen with montelukast treatment, and the percentage inhibition in maximum percent fall in FEV1 was 31% with montelukast versus placebo. Time to recovery after exercise was improved but not statistically greater than for placebo patients. Medical reviewer analysis of individual patient $\text{AUC}_{0-60 \text{ min}}$ showed EIB was ameliorated but not ablated in the majority of patients; approximately 1/3 of patients had improvements $\geq 75\%$, and approximately 1/3 of patients worsened on montelukast therapy.

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Effect of Montelukast on Exercise-Induced Bronchoconstriction (Mean); Pediatric Exercise Study (Protocol 040)

AUC _(0-60 min) (% Fall FEV ₁ •min) ¹		-Max % Fall in FEV ₁ (%)		Time to Recovery (min)	
PBO	MNT	PBO	MNT	PBO	MNT
-589.72	-264.60*	-26.11	-18.27*	27.98	17.76 [†]
¹ See Figure D-3 * p ≤ 0.050 * p = 0.079 PBO = Placebo (N = 25) MNT = Montelukast (N = 25)					

Postexercise time-response profile (mean percent change in FEV₁ from Pre-exercise FEV₁₀ ; Pediatric Exercise Study (Protocol 040)



POTENTIAL TREATMENT INTERACTIONS

Effects of Age on Chronic Asthma and Exercise-Induced Bronchoconstriction: In Protocol 049, age group interactions analyzed by ANOVA (6 - 11 years versus 12 - 14 years) were not statistically significant. Additional tests of age interaction requested by the FDA for ages 6-8, 9-11, and 12-14 years showed no statistically significant interaction [Merck response of 11/24/97 to FDA request]. Medical reviewer inspection of analyses of FEV₁, daytime symptom score, change in β-agonist use, morning PEF_R, and nocturnal asthma scores stratified by ages 6 - 11, 12 - 14, and 15 years revealed no age-related pattern in efficacy. [91:D-20689ff] Hospitalizations and discontinuations due to asthma occurred in the youngest patients (<11 years) in the study.

Subgroup interaction analyses demonstrated the treatment effect in 6- to 11-year-old and 12- to 14-year-old patients was comparable, as seen in the following table.

Effect of Montelukast on FEV₁ (Percent Change From Baseline) Stratified by Age Group; Pediatric Chronic Asthma Study (Protocol 049)

	Age 6 to 11 Years		Age 12 to 14 Years	
	N	% Change in FEV ₁	N	% Change in FEV ₁
Placebo	70	3.38	61	5.06
Montelukast	102	7.68	94	9.83

In Protocol 040, the EIB study, no significant correlation was seen between age and individual percent inhibition of AUC_{0-60 min}, suggesting comparable effects of montelukast (5 mg) across the 6- to 14-year-old age range. A plot of the individual percent inhibition of AUC_{0-60 min} versus age evidenced no age-related pattern, nor was there a statistically significant linear correlation of age and percent inhibition. Medical reviewer inspection of the percent inhibition based on AUC_{0-60 min} by individual patients revealed no age- or sequence-related pattern in percentage improvement.

Effects of Race, Gender, Tanner Pubertal Stage, Or Concomitant Inhaled Corticosteroid Use in Chronic Asthma: In Protocol 049, prespecified subgroup interactions analyzed by ANOVA and reported by the sponsor were not statistically significant. According to the sponsor, these showed consistent treatment effect regardless of race, gender, Tanner pubertal stage, or concomitant inhaled corticosteroid use. [59:D-136]

The medical reviewer inspected the unadjusted stratified analyses of 5 efficacy measures (FEV₁, daytime symptom score, change in β -agonist use, morning PEF_R, and nocturnal asthma score) by race, gender, Tanner pubertal stage, history of allergic rhinitis, history of EIB, and concomitant inhaled corticosteroid use. Subgroup analyses by **race** revealed that the 24 Black participants on montelukast showed worse or equivalent efficacy to the 18 placebo patients; relative efficacy findings of montelukast compared to placebo among the 263 White patients were much better than for Black patients. [91:D-20694ff]. Data stratified on **gender** showed that females on montelukast had greater improvement in all efficacy endpoints relative to placebo than did males. Variability in efficacy according to individual **Tanner pubertal stage** was seen, but no consistent pattern was seen across the 5 efficacy endpoints. The small number of patients without **allergic rhinitis** (N=20) had a consistently better response to montelukast than the 308 patients with a positive history. Likewise, a small number of patients (N=21) without a history of EIB did somewhat worse than patients with EIB, with the exception of average change in FEV₁. **Concomitant inhaled corticosteroid use** did not have any consistent effect on efficacy parameters.

Reviewer comment: *The race, gender, allergic rhinitis, and EIB patterns seen in the unadjusted stratified subgroup analyses were not seen in the multivariate pediatric models, nor were these factors noted in the adult protocols. As such, these factors are unlikely to play a significant role in any montelukast treatment effect. The observation that the majority of patients in Protocol 049 who were hospitalized or discontinued secondary to asthma were males <11 years of age is provocative, but unsupported by any other data or analyses.*

Protocol 040 examining EIB was a cross-over design of only 25 patients, so subgroup analyses were not done except for age effects (reported in preceding subsection).

CONCLUSIONS

Montelukast administered as 5 mg chewable tablet once-daily improved pulmonary function in children aged 6 -14 years with chronic asthma. Over 8 weeks of therapy, improvement was manifest in a mean FEV1 increase that was approximately 4.5% greater than placebo controls. Although statistically significant, the clinical impact of this small percentage increase is uncertain. The FEV1 improvement seen with montelukast in the double-blind portion of the chronic asthma trial was maintained over 6 months of open-label use.

Secondary efficacy parameters in pediatric chronic asthma trials were generally supportive of montelukast efficacy, although statistical significance was achieved only for reduction in as-needed β -agonist use. This reduction amounted to approximately 1/3 fewer puffs a day than placebo controls, a decline of small clinical impact. The only end-of-dosing interval endpoint, evening PEF, was unchanged in montelukast patients relative to placebo. Onset of action analyses did not demonstrate a first-dose effect in pediatric patients.

End-of-dosing interval efficacy was demonstrated in asthmatic children aged 6 -14 years in the pediatric exercise study. A statistically significant improvement in the mean AUC_{0-60 min} and maximum percentage fall in FEV1 post-exercise was seen after 2 evening doses of 5 mg montelukast as the chewable tablet. Wide individual variability in response (with some patients actually worsening on montelukast) will require careful representation of the pediatric EIB findings in product labeling. Similar limitations were found in the adult EIB studies.

In chronic asthma, the magnitude of the treatment effect seen in children aged 6 -14 years was less than in adults. Furthermore, the pediatric chronic asthma data did not support early onset of action and effectiveness at the end-of-dosing interval for montelukast. The only end-of-dosing interval efficacy data in children were from the exercise study, where comparable efficacy to adults was seen in terms of mean improvements in EIB with montelukast.

In children, the diminished treatment effect relative to adults, the limited end-of-dosing interval evidence for efficacy, and the absence of adequate onset of action data call into question whether once-daily 5 mg montelukast is the optimal pediatric dosage for efficacy. Stratified and multivariate analyses showed no diminished efficacy in older pediatric patients (12 - 14 years) relative to younger patients (6 - 11 years) in the chronic asthma protocol.

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Auditing

Two types of auditing were done for the montelukast pediatric program and are described here. The first was auditing of case report forms and randomization codes done by the medical reviewer, the second a formal audit conducted by FDA Division of Scientific Integrity (DSI). Neither found any important data irregularities. One instance of secondary data reporting occurred with a nonUS investigator, and the sponsor should be advised that such secondary reporting should not be done in the future.

MEDICAL REVIEWER AUDITING AND CHECKING

All clinical protocols (049, 040, 036, and 039) were examined in their original form and compared to their summaries in the study reports. No discrepancies were found. For Protocol 049, only amendment 5 was reviewed on the presumption that it incorporated all previous protocol amendments and so reflected the final plan for the conduct of the chronic asthma study.

Protocol 049

Treatment allocation was checked and is described in the randomization section of the Protocol 049 discussion.

The tabulation of study FEV1 values was scanned for all patients, who satisfied the entry criteria of at least 2 FEV1 values $\geq 50\%$ predicted and $\leq 85\%$ predicted on two occasions prior to the administration of study drug. In addition all abnormal laboratory values for bilirubin, ALT, AST were scanned to enumerate the number of individuals outside the limits of normal for these parameters.

No significant discrepancies were found between the CRFs and tabulations. One non-U.S. investigator's CRFs did not appear in primary form. All case report forms (a total of 2) for Dr. Allan B. Becker of Winnipeg, Manitoba, Canada were entirely done by typewriter/computer; there was no handwriting like the other CRFs reviewed. Even patient diary data responses were typed. Only and laboratory data appeared in the same format as the other CRFs. No explanation was provided in the submission and Merck was asked to explain its occurrence. Item [Merck response to information request, November 7, 1997] explained that Merck's standard operating procedure is to use transcriptions of investigator worksheets for studies that are done outside the U.S. and monitored by the local Merck subsidiary. All transcriptions are corrected and validated by the investigator and returned to the MRL subsidiary. The original CRF (or worksheet) is retained in the subsidiary country. In response to a telephone request to clarify the rationale for this SOP, , replied on November 14, 1997 that the SOP was driven by legibility concerns and restrictions by some foreign countries against transport of confidential patient information (including initials, birth date, etc) across borders. This explanation was considered satisfactory for the purposes of this submission, where the number of patients and centers without primary CRF data were few. However, Merck should be advised that the secondary reporting of patient data from CRFs should be avoided in future submissions to this Division.

Six of the 16 available case report forms were selected at random to compare to the Case Report Tabulations for chemistry, hematology, FEV1 values, concomitant medications, and adverse event reporting. No discrepancies were found. There were potential disagreements on the dose of concomitant medication use during drug treatment; these were minor and may have been the result of a page missing from the CRF.

All abnormal ALT, AST, and bilirubin values were culled from the case report tabulations and compared to the tabulations and calculations prepared by the sponsor. Other than their omission

of a placebo patient with transient elevations in ALT and AST that normalized on study, all numbers and percentages were in agreement.

Protocol 040 —

Only one CRF was available for review and comparison to the case report tabulations. Selected laboratory and PFT values were in full agreement with the case report tabulations and the reasons for this patient's discontinuation from the trial.

REVIEW OF DSI AUDIT

Only one pediatric study site was audited, that of Dr. Galant who participated in Protocol 049, A Multicenter, Double-Blind, Randomized, Parallel-Group Study Comparing MK-0476 to Placebo in 6- to 14-Year-Old Patients With Chronic Asthma. Dr. Galant had previously received a VAI report on a different study conducted in 1994, in which some lab tests were not done according to protocol, and adverse events were not always reported in the final database.

Scope of Investigation

A general inspection was done as well as a special examination comparing the sponsor's tables submitted to FDA with source documents for FEV1 values pre- β -agonist use.

Results of Investigation

General compliance with the requirements of the Bio Research Monitoring Program and regulations was found. Several patient records needed clarification by Dr. Galant, and this was done satisfactorily. Clarifications related to the reporting of Tanner staging and of one patient's prolonged treatment with study drug. One patient was missing records for Visit 3, although the sponsor had measurements for this visit. This occurred due to an error in printing a hard copy for Dr. Galant's records at the time that the data were transmitted electronically to the sponsor (as per protocol). Dr. Galant acknowledged this error by his office staff.

The special examination of FEV1 values pre- β -agonist use found agreement between the sponsor's tables submitted to FDA, and the source documents in Dr. Galant's office.

Conclusions

A few minor study irregularities were found in the spot auditing of one clinical investigator in the pediatric chronic asthma trial. No concerns for data validity were raised.

The DSI Audit found general compliance with the requirements of the Bio Research Monitoring Program and regulations. No FDA 483 was presented at the end of the inspection. A specially requested examination of the investigator's FEV1 records compared to the sponsor's reporting of these values showed full agreement.

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Labeling Review

Since the pediatric indication for Singulair is supported by the more extensive adult program, many labeling points were handled in conjunction with the medical reviewer of the adult program. The comments that follow below are ones that are unique to the pediatric components of the label. A line-by-line editing of the labeling will be provided to the sponsor after detailed review by the entire montelukast evaluation team.

CLINICAL STUDIES, PEDIATRIC PATIENTS 6 TO 14 YEARS OF AGE

1. "Compared with placebo, SINGULAIR, one 5-mg chewable tablet daily at bedtime, significantly decreased the percent of days asthma exacerbations occurred."

This is a tertiary endpoint with a p-value of 0.049; the mean percentage of days with exacerbations for montelukast was 25.67% and for placebo was 20.58%.

This tertiary endpoint should not be positioned as the first efficacy finding in the pediatric clinical section since it makes it appear to be a primary endpoint.

FEV1, the primary efficacy endpoint, is represented later in the labeling as AM FEV1. Since Singulair did not demonstrate efficacy in improving its prespecified secondary AM PEFR, the use of AM in the description of the FEV1 data may be debatable.



Representation of the parents' _____ appears to be cherry-picking from a group of related tertiary endpoints. The parents' _____ is the only one of 3 (including physician and patient) with a statistically significant mean improvement in score over placebo of 0.28, on a scale ranging from -3 to +3. With the physician and patient _____, montelukast improved more than placebo numerically but not statistically. The overall _____ for all three groups was statistically significant and prespecified in the data analysis plan. A clinically meaningful increased score was not predefined.

The _____ claim should not be allowed in labeling, since it did not have a prespecified analysis plan or set of "win" criteria. The sponsor's description of the _____ results does not conform to the instrument's authors' minimally important difference (MID) approach. The sponsor's claims are based on a straight statistical comparison of montelukast versus placebo or baseline, using a more highly powered study than specified by _____

3. "Compared with placebo, there was a significant improvement in morning FEV1 (8.7% versus 4.2% change from baseline in the placebo group, $p < 0.001$)...."

This is a representation of the primary endpoint, the mean percentage change in FEV1 over 8 weeks of double-blinded treatment. The use of AM is accurate since that was the time FEV1 was measured. It should be noted that patient-reported AM PEFR, one of 4 key secondary endpoints, did not show a statistically significant improvement over placebo, but clinic measurements of AM PEFR did show a statistical improvement over placebo.

4. "...and a significant decrease in total "as-needed" β -agonist use (11.7% decrease from baseline versus 8.2% increase from baseline in the placebo group, $p < 0.050$)."

Although technically accurate and a prespecified analytical endpoint, this statement is misleading and should be modified to clarify the magnitude of the treatment effect. Because of the instability of the low baseline beta-agonist use, percentages are inflationary and outliers can significantly affect the mean. It appears as though the placebo group increased use, when in fact, mean beta-agonist use declined. Clarification could be provided with a sentence characterizing the mean declines seen, about 1/2 puff for montelukast and 1/4 puff for placebo.



This claim is not well-supported by the pediatric data and should be eliminated. A complex regression model was used to support onset of action with initiation of therapy. This model was not prespecified in the pediatric analysis plan, and is not convincing of a first dose effect. *Post hoc* daily data analyses that were requested of the sponsor for the first 7 days of montelukast treatment show only the percentage change in beta-agonist use on the first two days was significantly different from controls. Solitary support from that unstable endpoint (see item 4 above) is not sufficient to support a treatment effect after the first dose.

ADVERSE REACTIONS, PEDIATRIC PATIENTS 6 TO 14 YEARS OF AGE

1. "Cumulatively, pediatric patients were treated with SINGULAIR for at least 3 months, for 6 months or longer in clinical trials."

The second safety update report included greater numbers of observations than this, with 169 patients treated for at least 6 months and 121 for a year or longer.

2. "The safety profile of SINGULAIR versus placebo is generally similar to the adult profile."

This should be modified so that adverse experiences that were elevated in children but not in adults should be mentioned, for instance those events that occurred in more than 2% of the children in the double-blinded portion of the clinical trial (viral infection, laryngitis, otitis, sinusitis, diarrhea, and nausea).

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STATISTICAL REVIEW AND EVALUATION CARCINOGENICITY

Date:

AUG 12 1996

IND #:
Applicant: Merck Research Laboratories
Name of Drug: Montelukast Sodium
Documents Reviewed: 2-29-96 Vol 35.20-35.22
5-22-96 Supporting Statistical Analysis Datasets & Documentation
Statistical Reviewer: B Bono, M.S.
Pharmacologist: S Williams, Ph.D.
Key Words: Peto, trend test, adjusted p -values, adjusted α -levels

Text in italics is from the Investigational New Drug Application submitted by the sponsor.

Summary of Review

- There are no statistically significant p -values from the trend test in either of the two animal studies provided that:
 - the α -level of a "rare" tumor is 0.025 and the α -level of a "common" tumor is 0.005, and
 - a pancreatic islet adenoma is a "common" tumor among rats.
- The pairwise comparisons of the control with the low and high dose groups for hepatocellular carcinoma liver tumors among male rats is not statistically significant provided that:
 - the α -level of a "common" tumor is 0.01, and
 - a hepatocellular carcinoma liver tumor is "common" among rats.
- The pairwise comparisons of the control with the middle and high dose groups for pancreatic islet adenoma tumors among male rats is not statistically significant provided that:
 - the α -level of a "common" tumor is 0.01, and
 - a pancreatic islet adenoma tumor is "common" among rats.
- Greater than 50% of the animals in both studies were still alive between weeks 80-90, thus there was adequate exposure of the drug to study tumor incidence.
- Using the log-rank test, the survival rates were not found to be statistically significantly different among the dose groups in either of the two animal studies.

I. Background

Two animal carcinogenicity studies (one in rats, and one in mice) were included in this IND submission. These two studies were intended to assess the oncogenic potential of Montelukast Sodium (MK-0476) in rats and mice when administered orally for two years. The design of these

studies is summarized below.

Study Number	Species	Duration	Doses (mg/kg)
93-110-0	CD-1 (ICR)BR Mouse	92 weeks	0, 0, 25, 50, 200/100*
93-078-0	CD-1 Rat	105 weeks	0, 0, 50, 100, 200

* Due to a treatment-related decrease in body weight gain, the dose level for the high dose group was reduced from 200 to 100 in drug week 10 for both the male and female mice.

In both studies, male and female animals were assigned at random to one of five treatment groups which included two controls and three graded doses of MK-0476 (Mice: 25, 50, 200/100 mg/kg/day; Rats: 50, 100, and 200 mg/kg/day). In the mouse study, due to a treatment-related decrease in body weight gain, the dose level for the high dose group was reduced from 200 to 100 in drug week ten for both the male and female mice. In both studies, the sample size for each sex was 50 for each of two control groups and 50 for each MK-0476 dosage group. The control groups were combined in the analyses to give each study a combined control group size of 100. However, one rat was mis-sexed and excluded from the study in week three resulting in a male rats' combined control group size of 99. Treatment was administered orally (gavage) daily for a period of approximately 92 weeks for the mice and 105 weeks for the rats with terminal necropsy on all remaining animals performed during weeks 92 and 105, respectively, of the mice and rat studies.

Palpable tumors are those which were detected prior to the death or terminal sacrifice of the animal. A nonpalpable tumor was termed "lethal" if classified by the pathologist as a cause of the animal's death (or moribund status leading to an unscheduled sacrifice).

II. Analysis

The sponsor and reviewer analyzed palpable, nonpalpable-lethal and nonpalpable-nonlethal tumors separately, then combined the results using et al. procedures. For a particular tumor type of interest, the incidence data can be summarized in a $2 \times D$ table, where D is the number of dose groups. The first row contains the numbers of animals with the tumor of interest, and the second row contains the numbers of animals without the tumor. However, this summary table can be misleading. If the drug causes animals to die early by some non-cancer related cause, fewer animals will be at risk for tumors in the higher dose groups. Thus, even if the drug also increases the tumor rate, the overall incidence of that tumor in the high dose groups may be smaller than in the control groups. To adjust for the effect that potential differential mortality between the dose groups has on tumor occurrence, the method breaks up study time into several discrete intervals. The intervals used in both studies were: 0-52 weeks, 53-78 weeks, 79-92 weeks, 93-104 weeks, and over 104 weeks. The data can thus be represented by several $2 \times D$ tables, one for each time interval.

The dose groups can also be assigned weights in the statistical analysis to test various hypotheses.

For example, using weights of 0, 1, ... D gives the trend test, which is sensitive to a linear dose effect. Using equal weights (1, 1, 1, 1) gives a test of association between dose and tumor rate without specifying the form of the relationship. Weight can also be made equal to the actual doses given. Finally, choosing weights close to the actual biological effect of the doses will result in the most sensitive test, but in practice this effect is not known. Linear weights or the dose weights are often used.

For the tumor type of interest, each tumor is classified as "fatal", "non-fatal" or "observed before sacrifice or death". This is not a biological classification but a statistical classification. *P*-values are calculated for the three classes separately, and then combined to yield a single *p*-value for the tumor type. Both exact and asymptotic *p*-values can be calculated for tumor type where all of the tumors found were either fatal, non-fatal or observed early. If for a particular tumor type, more than one of the three classes were detected, only asymptotic *p*-values are available. Clearly, when available, the exact *p*-values are preferable.

One-sided *p*-values may be more appropriate than two-sided, since they are more conservative and we are only interested in whether increased doses *increase* tumor incidence.

One hundred forty-one (141) distinct sex/organ/tumor type combinations were found in the two studies. Using an α -level of .05 to determine significance would yield a high false positive rate.

Since so many sex/organ/tumor type combinations are present, a simple application of a .05 decision rule does not appropriately control the overall false positive rate. It has been suggested by Dr. Karl Lin and Dr. Mohammad Rahman¹ that if the tumor is "rare" the cutoff should be .025 and if the tumor is "common" the cutoff should be .005. (Tumors are defined as rare or common using historical control data or the control group in the study being analyzed. The usual practice at FDA is to classify a tumor as common if it occurs in the control group at an incidence of greater than 1%.) Using simulation tests on CD-1 rats and CD(BR) mice, Lin and Rahman found that the overall false positive rate resulting from the use of the α -levels .025 and .005 in the tests for linear trend in a two-species-two-sex study is about 10%. These false-positive rates are judged by the Center for Drug Evaluation and Research as the most appropriate in a regulatory setting.

For pairwise comparisons, the levels of significance are .05 and .01 for a rare and common tumor, respectively.

¹Lin, KK and MA Rahman (1995), "False Positive Rates in Tests for Linear Trends in Tumor Incidences in Animal Carcinogenicity Studies of New Drugs", unpublished report, Division of Biometrics, CDER, FDA, Rockville, MD.

III. Discussion

Dose Weights

As discussed above, it is the usual practice to use either dose weights or linear weights in the analysis of carcinogenicity data. The applicant used dose weights in their analyses. Recall that the mice in the high dose group received 200 mg/kg/day in the first 10 weeks of the study and 100 mg/kg/day after week 10. In the analyses of the mouse study, the applicant selected the 200 mg/kg/day as the highest dose (instead of the 100 mg/kg/day or an intermediate dose). According to the sponsor, the 200 mg/kg/day dose is:

"...the most conservative choice for the male and female mice since it maximizes the differences among the three scales used in the Tukey trend test, and, therefore, will have the greatest chance of obtaining statistical significance..."

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It is assumed that the applicant used the word "conservative" to mean "has the greatest chance of obtaining statistical significance" in the trend tests. Assuming no true tumor trend, the statement is true based on a simulation study conducted by Robert Condon of the Center for Veterinary Medicine at FDA. Additionally, assuming a non-linear tumor trend, the dose weights using the 200 mg dose will also have the greatest chance of obtaining statistical significance. However, assuming a linear tumor trend, the dose weights using the 100 mg dose as the highest dose will have the greatest chance of obtaining statistical significance. Thus, when looking at the Type I error rate, the 200 mg dose is the choice that will have the greatest chance of obtaining statistical significance. However, when looking at power, the most "conservative" choice will depend on the linearity of the true tumor trend.

In the absence of any information about the actual tumor trends for each individual tumor, the p -values in this review reflect a linear dose trend; i.e., the dose groups were given the values (0, 1, 2, 3) in the equations.

Adjusted P -values

As described above, an α -level of .05 is not appropriate because there are 141 unique sex/organ/tumor combinations. Instead of adjusting the α -level at which statistical significance is declared, the applicant adjusted the one-sided p -values using a procedure described by Heyse and Rom² and by Harter³ and then used the usual .05 α -level to determine significance.

Using the adjusted p -values, the applicant found no statistically significant evidence of an

² Heyse, J.F., Rom, D., "Adjusting for Multiplicity of Statistical Tests in the Analysis of Carcinogenicity Studies", *Biometrical Journal* Vol. 30, 1988, 883-896.

³ Harter, H.L., "Error Rates and Sample Sizes for Range Tests in Multiple Comparisons", *Biometrics* Vol. 13, 1957, 511-536.

increasing trend in the incidence of tumor-bearing mice or rats with increasing doses of MK-0476.

Sites In Which Only One Rat Was Observed With Tumor

The applicant's analysis only included sites for which at least two animals were observed with tumor. The applicant argues that statistical significance cannot be achieved for sites in which only one animal was observed with tumor. This is usually true. Since it is possible to find statistical significance, however unlikely, all sites where at least one animal was observed were analyzed in this review.

IV. Reviewer's Analyses and Results

The reviewer's analyses used *et al.* procedures (described above). The results are on pages 7-9. For both male and female animals, an analysis was performed for each organ/tumor type combination even for cases where only one rat was observed with tumor. The first column in the tables is the sex group, followed by the tumor type and organ. Certain tissue types are labeled as "PRSUDETER", which indicates that the primary site of the tumor was undetermined. The column labeled "Class" indicates whether the tumors were classified as fatal (FA), non-fatal (NF), observed before sacrifice or death (OB), or mixed (MI), meaning tumors fall into two or more of the former three classes. The incidence in each of the dose groups is shown, although, as discussed above, these may not always be meaningful because the drug may cause the animals to die early by some non-cancer related explanation. Asymptotic and exact *p*-values are given next, with both one-sided and two-sided *p*-values shown. (These are denoted by "Asymp1", "Exact1" and "Asymp2" and "Exact2".) Unlike the sponsor, the *p*-values presented in this review are the actual *p*-values, not adjusted *p*-values.

Since the highest dose in the mouse study was reduced from 200 mg/kg/day to 100 mg/kg/day during week 10 of the study, linear dose weights were used in the analyses of this study. To be consistent, linear dose weights were also used in the analyses of the rat study.

As described above, Dr. Karl Lin suggested that if the tumor is "rare" the α -level should be 0.025 and if the tumor is "common" the α -level should be 0.005. Using this rule, there are no statistically significant *p*-values from the trend test in either of the two animal studies.⁴ This means that as dose increases linearly, there are no statistically significant increases in incidence of tumor. However, the animals in these studies were fed an "optimized diet" which is a modification of a restricted diet regimen; and according to the reviewing pharmacologist Dr. Shannon Williams, a restricted diet can suppress tumor formation. The applicant was asked to send historical control data from studies using this optimized diet and an ad lib diet to help determine which tumors are rare and which are common in this unusual situation. At the time of this review, the data were not available.

⁴ The one-sided exact *p*-value for the male rats' pancreas islet adenoma tumors is 0.0149. According to the reviewing pharmacologist, this tumor is common, thus the *p*-value would need to be less than .005 to be considered statistically significant.

The pharmacologist requested pairwise comparisons between each dose level and the control group for five tumor type/organ site combinations in the rat study (page 10). Recall, for pairwise comparisons, the α -levels recommended by Lin are .01 and .05 for common and rare tumors, respectively. The only comparisons that may be statistically significant were the low dose versus control and the high dose versus control for the hepatocellular carcinoma in the liver (50 mg: $p=0.0138$; 200 mg: $p=0.0394$). However in this study, the control group's incidence was 2.02%. Recall that the usual practice at FDA is to classify a tumor as common if it occurs in the control group at an incidence of greater than 1%. Thus, the pharmacologist may want to study the historical control data to be submitted by the applicant to decide whether this p -value is statistically significant or not. The p -values of the middle and high dose group comparisons with placebo for Pancreatic Islet Adenoma tumors were .0301 and .0397 respectively. Pancreatic islet adenoma tumors are common, thus the p -values were not statistically significant. All of the other pairwise comparisons requested by Dr. Williams yielded p -values greater than .05.

The pharmacologist considered combining types of tumors within tissue type based on McConnell et al (1986)⁵. However, from inspection after grouping the tumors, it was apparent that there were no increasing tumor trends.

Survival

In the Guidance for Industry draft, it is stated that "a 50% survival rate of the 50 initial animals in the high dose group between weeks 80-90 of a two-year study will be considered as a sufficient number and adequate exposure."⁶ For both the mouse and rat study, plots of survival demonstrate that greater than 50% of the high dose group animals were still alive during weeks 80-90 (page 11).

As discussed above, the trend test used in the applicant's and reviewer's analyses take into account any potential difference in survival rates. Nevertheless, Kaplan-Meier plots and log-rank tests were used to determine if the survival rates among the different dose groups were similar (page 11). Neither the plots nor the log-rank test p -values show any statistically significant evidence of a difference in survival among the dose groups.

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⁵ McConnell, EE, HA Solleveld, JA Swenberg and GA Boorman. "Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies", *Journal of National Cancer Institute* 1986; 76:283-289.

⁶ Guidance For Industry, "On Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies."

P-values from the Trend Test

Mouse Study

Sex Tumor Type	Tissue Class	C	L	M	H	Asymp2	Exact2	Asymp1	Exact1	
F ADENOMA	LUNG	NF	8	9	2	11	0.1116	0.1149	0.0558	0.0671
M HEMANGIOMA	TESTIS	NF	0	0	0	1	0.1204	0.2030	0.0602	0.2030
M HEMANGIOMA	SPLEEN	NF	0	0	0	1	0.1204	0.2030	0.0602	0.2030
M HEMANGIOSARCOMA	LYMPHNODE	NF	0	0	0	1	0.1204	0.2030	0.0602	0.2030
F FIBROSARCOMA	SKIN	OB	0	2	1	2	0.1216	0.1302	0.0608	0.0928
M PAPILLOMA	SKIN	OB	0	0	0	1	0.1227	0.2000	0.0614	0.2000
F ADENOMA	ADRENACORT	NF	0	0	0	1	0.1248	0.2018	0.0624	0.2018
F LYMPHOMA	PRSUDETER	MI	9	3	7	8	0.1628	NA	0.0814	NA
M ADENOMA	LUNG	NF	17	12	10	12	0.2633	0.2735	0.1317	0.1473
M ADENOMA	THYRFOLLIC	NF	0	2	0	1	0.3026	0.4445	0.1513	0.2313
M ADENOMA	PITUITARY	NF	0	0	1	0	0.3156	0.3438	0.1578	0.3438
M LIPOSARCOMA	LIVER	NF	0	0	1	0	0.3156	0.3438	0.1578	0.3438
F ADENOCARCINOMA	SMAINTESTI	NF	0	1	0	1	0.3341	0.4018	0.1671	0.2400
M ADENOMA	PANCREAISL	NF	0	0	1	0	0.4864	0.7871	0.2432	0.3861
M ADENOMA	PROSTATE	NF	0	0	1	0	0.4864	0.7871	0.2432	0.3861
M HEMANGIOMA	PERITONEUM	NF	0	0	1	0	0.4864	0.7871	0.2432	0.3861
M SERTOLICELLTUMOR	TESTIS	NF	0	0	1	0	0.4864	0.7871	0.2432	0.3861
M SQUAMOUSCELLCARCINOMA	EAR	NF	0	0	1	0	0.4864	0.7871	0.2432	0.3861
F HISTIOCYTOMA	SKIN	NF	0	0	1	0	0.4956	0.8073	0.2478	0.4037
F LEIOMYOSARCOMA	SMAINTESTI	NF	0	0	1	0	0.4956	0.8073	0.2478	0.4037
F ADENOMA	PITUITARY	NF	1	2	2	1	0.5282	0.6050	0.2641	0.3221
M ADENOMA	ADRENACORT	NF	5	3	2	4	0.5345	0.5568	0.2673	0.3050
F ADENOMA	OVARY	NF	2	1	0	2	0.7026	0.8502	0.3513	0.4163
M SPINDLECELLTUMOR	ADRENAL	NF	1	0	0	1	0.7046	0.8079	0.3523	0.4767
M HEMANGIOSARCOMA	SKELETMUSC	OB	0	1	1	0	0.7057	0.8038	0.3528	0.4756
F GRANULOSACELLTUMO	OVARY	NF	2	1	2	1	0.7809	0.8644	0.3904	0.4515
F SPINDLECELLTUMOR	ADRENAL	NF	1	2	0	1	0.9340	1.0000	0.4670	0.4601
F ADENOCARCINOMA	MAMMARGLAN	MI	3	5	1	2	0.9588	NA	0.5206	NA
M LYMPHOMA	PRSUDETER	MI	2	3	1	1	0.9484	NA	0.5258	NA
F POLYP	UTERUS	NF	1	3	2	0	0.9407	1.0000	0.5297	0.5485
F HISTIOCYTICSARCOM	PRSUDETER	MI	1	3	1	0	0.9390	NA	0.5305	NA
M POLYP	LARINTESTI	NF	1	0	1	0	0.9364	1.0000	0.5318	0.5947
M ADENOMA	SMAINTESTI	NF	0	1	0	0	0.8719	1.0000	0.5641	0.6139
M NEUROFIBROMA	PLEURA	NF	0	1	0	0	0.8719	1.0000	0.5641	0.6139
M HISTIOCYTICSARCOM	PRSUDETER	FA	0	1	0	0	0.8638	1.0000	0.5681	0.6000
F ADENOCARCINOMA	EHARDERIGL	NF	0	1	0	0	0.8632	1.0000	0.5684	0.5963
F ADENOMA	UTERUS	NF	0	1	0	0	0.8632	1.0000	0.5684	0.5963
F HEMANGIOSARCOMA	UTERUS	NF	0	1	0	0	0.8632	1.0000	0.5684	0.5963
F LEIOMYOSARCOMA	UTERUS	NF	0	1	0	0	0.8632	1.0000	0.5684	0.5963
M HEMANGIOSARCOMA	LIVER	MI	1	1	1	0	0.7661	NA	0.6169	NA
F ADENOMA	THYRFOLLIC	NF	1	1	1	0	0.7643	0.8334	0.6178	0.5034
F HEPATOCELLULARADENOMA	LIVER	NF	4	3	3	1	0.7478	0.7962	0.6261	0.5678
F ADENOCARCINOMA	LUNG	MI	6	3	5	1	0.6215	NA	0.6892	NA
F ADENOMA	EHARDERIGL	NF	8	2	3	3	0.5945	0.6626	0.7028	0.6583
M PHEOCHROMOCYTOMA	ADRENAL	NF	1	1	0	0	0.4030	0.5659	0.7985	0.6688
F SARCOMA	UTENDOMETS	MI	3	0	2	0	0.3985	NA	0.8008	NA
M HEMANGIOSARCOMA	SPLEEN	MI	1	1	0	0	0.3959	NA	0.8021	NA
M ADENOMA	EHARDERIGL	NF	11	7	4	3	0.3656	0.4131	0.8172	0.7898
M ADENOCARCINOMA	LUNG	MI	14	1	5	4	0.3359	NA	0.8321	NA
M ADENOCARCINOMA	EHARDERIGL	NF	1	0	0	0	0.3084	0.6040	0.8458	0.5990
M HEMANGIOMA	LYMPHNODE	NF	1	0	0	0	0.3084	0.6040	0.8458	0.5990
M OSTEOMA	BONE	NF	1	0	0	0	0.3084	0.6040	0.8458	0.5990
M POLYP	GALLBLADDE	NF	1	0	0	0	0.3084	0.6040	0.8458	0.5990
F ADENOCARCINOMA	UTERUS	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F ADENOMA	SMAINTESTI	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F HEMANGIOMA	UTERUS	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F HEMANGIOMA	SKIN	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F HEMANGIOMA	SPLEIN	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F HEMANGIOSARCOMA	LIVER	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F LEIOMYOSARCOMA	OVARY	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963

F MENINGIOMA	BRAIN	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F OSTEOMA	BONE	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F OSTEOSARCOMA	PRSunDETER	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F SEBACEOUSADENOMA	SKIN	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F TERATOMA	OVARY	NF	1	0	0	0	0.3049	0.6055	0.8476	0.5963
F BASALCELLTUMOR	SKIN	OB	1	0	0	0	0.3035	0.6000	0.8483	0.6000
M TRICHOEPITHELIOMA	SKIN	OB	1	0	0	0	0.3035	0.6000	0.8483	0.6000
M HEPATOCELLULARCARCINOMA	LIVER	MI	17	5	5	5	0.2523	NA	0.8738	NA
M HEPATOCELLULARADENOMA	LIVER	NF	14	8	7	3	0.2474	0.2516	0.8763	0.8584
F HEPATOCELLULARCARCINOMA	LIVER	NF	3	1	1	0	0.2462	0.2688	0.8769	0.8255
M FIBROSARCOMA	SKIN	MI	3	1	1	0	0.2184	NA	0.8908	NA
M ADENOCARCINOMA	SMaINTESTI	MI	2	1	0	0	0.1974	NA	0.9013	NA
M LIPOMA	SKIN	OB	2	0	0	0	0.1501	0.2786	0.9250	0.8358
M ADENOMA	TESTLEyDCE	NF	2	0	0	0	0.1487	0.2747	0.9256	0.8404
M LEUKEMIA	PRSunDETER	NF	2	0	0	0	0.1487	0.2747	0.9256	0.8404
M POLYP	URINABLADD	NF	2	0	0	0	0.1487	0.2747	0.9256	0.8404
F POLYP	GALLBLADDE	NF	2	0	0	0	0.1458	0.2837	0.9271	0.8382
F ADENOACANTHOMA	MAMMARGLAN	MI	3	1	0	0	0.1037	NA	0.9481	NA
F LEIOMYOMA	UTERUS	NF	6	1	2	0	0.0917	0.1111	0.9542	0.9417
M HEMANGIOMA	LIVER	NF	4	0	0	0	0.0401	0.0470	0.9799	0.9753

Rat Study

Sex	Tumor Type	Tissue	Class	C	L	M	H	Asymp2	Exact2	Asymp1	Exact1
M	ADENOMA	PANCREAISL	NF	3	4	6	6	0.0212	0.0239	0.0106	0.0149
F	PAPILLOMA	STNONGLANM	NF	0	0	0	2	0.0364	0.0498	0.0182	0.0498
F	ADENOCARCINOMA	UTERUS	MI	0	1	1	2	0.0811	NA	0.0406	NA
F	ADENOMA	KIDNEY	NF	1	0	0	3	0.0897	0.1402	0.0448	0.0755
M	HEPATOCELLULARCARCINOMA	LIVER	MI	2	6	3	5	0.0902	NA	0.0451	NA
M	MESOTHELIOMA	HEART	FA	0	0	0	1	0.1237	0.2008	0.0618	0.2008
M	FIBROADENOMA	MAMMARGLAN	OB	0	0	0	1	0.1237	0.2008	0.0618	0.2008
F	GLIOMA	BRAIN	NF	0	0	0	1	0.1247	0.1923	0.0623	0.1923
M	ADENOCARCINOMA	LAINTESTCO	NF	0	0	0	1	0.1256	0.1964	0.0628	0.1964
M	ADENOMA	MAMMARGLAN	NF	0	0	0	1	0.1256	0.1964	0.0628	0.1964
M	HEMANGIOMA	SKELETMUSC	NF	0	0	0	1	0.1256	0.1964	0.0628	0.1964
M	PAPILLOMA	TONGUE	NF	0	0	0	1	0.1256	0.1964	0.0628	0.1964
F	MESOTHELIOMA	PERITONEUM	NF	0	0	0	1	0.1402	0.2256	0.0701	0.2256
F	SQUAMOUSCELLCARCINOMA	SKIN	NF	0	0	0	1	0.1402	0.2256	0.0701	0.2256
M	KERATOACANTHOMA	SKIN	OB	0	2	3	1	0.1779	0.2242	0.0890	0.1256
M	HISTIOCYTICSARCOM	PRSunDETER	MI	1	0	0	2	0.2354	NA	0.1177	NA
F	POLYP	UTERUS	NF	5	4	8	4	0.2834	0.2867	0.1417	0.1656
F	ADENOMA	PANCREAISL	NF	1	1	1	2	0.2884	0.3523	0.1442	0.1962
M	GLIOMA	BRAIN	NF	0	0	2	0	0.3073	0.4011	0.1536	0.2265
F	ADENOMA	THYRFOLLIC	NF	0	0	2	0	0.3721	0.5661	0.1860	0.2623
F	HISTIOCYTICSARCOM	PRSunDETER	OB	0	0	1	0	0.4927	0.8000	0.2464	0.4000
M	ADENOCARCINOMA	MAMMARGLAN	OB	0	0	1	0	0.4953	0.7992	0.2476	0.4016
M	ADENOMA	PANCREACIN	NF	0	0	1	0	0.5022	0.8095	0.2511	0.4167
M	HEMANGIOMA	LYMPHNODE	NF	0	0	1	0	0.5022	0.8095	0.2511	0.4167
M	THYMOMA	THYMUS	NF	0	0	1	0	0.5022	0.8095	0.2511	0.4167
F	ADENOCARCINOMA	PANCREAISL	NF	0	0	1	0	0.5292	0.7866	0.2646	0.4085
F	ADENOMA	PARATHYROI	NF	0	0	1	0	0.5292	0.7866	0.2646	0.4085
F	ADENOMA	LIVEBILDUC	NF	0	2	0	1	0.5450	0.6305	0.2725	0.3566
M	INTERSTITIALCELLTUMOR	TESTIS	NF	2	4	2	2	0.6150	0.6789	0.3075	0.3552
M	HEPATOCELLULARADENOMA	LIVER	NF	3	5	4	2	0.6336	0.6398	0.3168	0.3570
M	ADENOMA	SKSEBACEGL	OB	0	1	1	0	0.7175	0.8000	0.3587	0.4808
M	PAPILLOMA	SKIN	OB	1	0	0	1	0.7214	0.8000	0.3607	0.4828
M	PAPILLOMA	MOUTHLIP	OB	0	1	1	0	0.7238	0.7971	0.3619	0.4833
F	FIBROMA	SKIN	MI	1	1	0	1	0.7306	NA	0.3653	NA
M	GRANULARCELLTUMOR	BRAIN	NF	1	0	0	1	0.7327	0.7906	0.3664	0.4871
F	MELANOMA	EYEIRIS	NF	0	1	1	0	0.7698	1.0000	0.3849	0.4875
M	FIBROSARCOMA	SKIN	OB	1	0	1	0	0.7949	1.0000	0.3975	0.4878
F	FIBROSARCOMA	SKIN	OB	1	0	1	0	0.8109	1.0000	0.4054	0.4785
F	FIBROADENOMA	MAMMARGLAN	MI	30	14	19	14	0.8674	NA	0.4337	NA
F	PHEOCHROMOCYTOMA	ADRENMEDUL	NF	1	1	0	1	0.9094	1.0000	0.4547	0.4700
M	LIPOSARCOMA	KIDNEY	MI	2	0	1	1	0.9656	NA	0.4828	NA

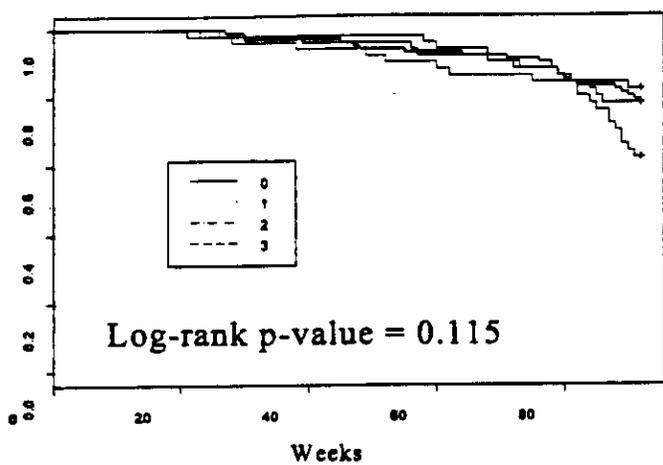
F LYMPHOMA	PRSUNDETER	NF	1	0	1	0	0.9825	1.0000	0.4913	0.3902
M ADENOMA	PARATHYROI	NF	0	1	0	0	0.9194	1.0000	0.5403	0.6667
M HISTIOCYTICSARCOM	PROSTATE	FA	0	1	0	0	0.8606	1.0000	0.5697	0.5984
M MELANOMA	EYE	FA	0	1	0	0	0.8606	1.0000	0.5697	0.5984
M HEMANGIOSARCOMA	SKIN	OB	0	1	0	0	0.8606	1.0000	0.5697	0.5984
M SQUAMOUSCELLCARCINOMA	EAEXTERNAE	OB	0	1	0	0	0.8606	1.0000	0.5697	0.5984
M TRICHOEPITHELIOMA	SKIN	OB	0	1	0	0	0.8606	1.0000	0.5697	0.5984
M ACINAR-ISLETCELLTUMOR	PANCREAS	NF	0	1	0	0	0.8497	1.0000	0.5752	0.5833
M ADENOCARCINOMA	LUNG	NF	0	1	0	0	0.8497	1.0000	0.5752	0.5833
M ADENOMA	LUNG	NF	0	1	0	0	0.8497	1.0000	0.5752	0.5833
M HEMANGIOSARCOMA	SPLEEN	NF	0	1	0	0	0.8497	1.0000	0.5752	0.5833
F ADENOMA	VAGCLITOGL	NF	0	1	0	0	0.8285	1.0000	0.5857	0.5915
M ADENOMA	THYRFOLLIC	NF	1	0	1	0	0.7881	1.0000	0.6060	0.5129
M MESOTHELIOMA	TESTUVAGIN	NF	1	1	1	0	0.7843	0.8205	0.6079	0.5129
F LEIOMYOSARCOMA	UTERUS	MI	0	2	0	0	0.7633	NA	0.6183	NA
M ADENOMA	ADRENACORT	NF	3	0	1	1	0.6679	0.7117	0.6660	0.5815
F ADENOCARCINOMA	PITUITARY	MI	3	1	1	1	0.6017	NA	0.6991	NA
F ADENOCARCINOMA	MAMMARGLAN	MI	19	7	2	10	0.4827	NA	0.7586	NA
M LIPOMA	SKIN	MI	1	2	0	0	0.4271	NA	0.7864	NA
M CARCINOMA	TPARAFOLLIC	NF	4	1	1	1	0.4221	0.5183	0.7890	0.7297
M HISTIOCYTOMA	SKIN	MI	2	1	1	0	0.3983	NA	0.8009	NA
M ADENOCARCINOMA	PANCREAISL	MI	7	2	2	2	0.3848	NA	0.8076	NA
F ADENOMA	MAMMARGLAN	MI	3	2	0	1	0.3844	NA	0.8078	NA
M PHEOCHROMOCYTOMA	ADRENMEDUL	NF	8	3	3	2	0.3595	0.3820	0.8202	0.7867
M ADENOMA	EZYMBALGLA	NF	1	0	0	0	0.3337	0.6111	0.8332	0.5556
M TRANSITIONALCELLCARCINOMA	URINABLADD	NF	1	0	0	0	0.3337	0.6111	0.8332	0.5556
F GRANULARCELLTUMOR	BRAIN	NF	1	0	0	0	0.3112	0.6154	0.8444	0.5769
F HISTIOCYTICSARCOM	LIVER	FA	1	0	0	0	0.3035	0.6000	0.8483	0.6000
F LEIOMYOSARCOMA	LARINTESTA	FA	1	0	0	0	0.3035	0.6000	0.8483	0.6000
F FIBROSARCOMA	EYELID	OB	1	0	0	0	0.3035	0.6000	0.8483	0.6000
F KERATOACANTHOMA	SKIN	OB	1	0	0	0	0.3035	0.6000	0.8483	0.6000
F PAPILOMA	MOUTHLP	OB	1	0	0	0	0.3035	0.6000	0.8483	0.6000
M BASALCELLTUMOR	SKIN	OB	1	0	0	0	0.3015	0.5984	0.8493	0.6024
M FIBROSARCOMA	EARPINNA	OB	1	0	0	0	0.3015	0.5984	0.8493	0.6024
M ADENOMA	KIDNEY	NF	1	0	0	0	0.2937	0.5893	0.8532	0.6071
F ADENOCARCINOMA	KIDNEY	NF	1	0	0	0	0.2880	0.6037	0.8560	0.6220
F CARCINOMA	STNONGLANM	NF	1	0	0	0	0.2880	0.6037	0.8560	0.6220
F FIBROSARCOMA	EARPINNA	NF	1	0	0	0	0.2880	0.6037	0.8560	0.6220
F PAPILOMA	SKIN	NF	1	0	0	0	0.2880	0.6037	0.8560	0.6220
M FIBROMA	SKIN	MI	8	2	0	3	0.2723	NA	0.8638	NA
M PAPILOMA	URINABLADD	NF	2	1	0	0	0.2125	0.3066	0.8937	0.8182
M LYMPHOMA	PRSUNDETER	MI	5	3	0	1	0.1968	NA	0.9016	NA
F GRANULOSACELLTUMOR	OVARY	NF	2	0	0	0	0.1879	0.2821	0.9061	0.7900
F CARCINOSARCOMA	MAMMARGLAN	OB	2	0	0	0	0.1468	0.2786	0.9266	0.8393
M ADENOMA	PITUITARY	MI	40	15	19	13	0.1420	NA	0.9290	NA
F CARCINOMA	TPARAFOLLIC	NF	2	0	0	0	0.1318	0.1913	0.9341	0.8585
F HEPATOCELLULARADENOMA	LIVER	NF	7	3	2	1	0.1289	0.1475	0.9355	0.9202
F ADENOMA	ADRENACORT	NF	4	4	0	0	0.1137	0.1204	0.9432	0.9258
F ADENOMA	PITUITARY	MI	69	30	33	27	0.0696	NA	0.9652	NA
M ADENOMA	TPARAFOLLIC	NF	14	4	2	3	0.0459	0.0473	0.9771	0.9737
F ADENOMA	TPARAFOLLIC	NF	13	3	3	2	0.0282	0.0309	0.9859	0.9840

Pairwise Comparisons of Neoplastic Findings in Rats

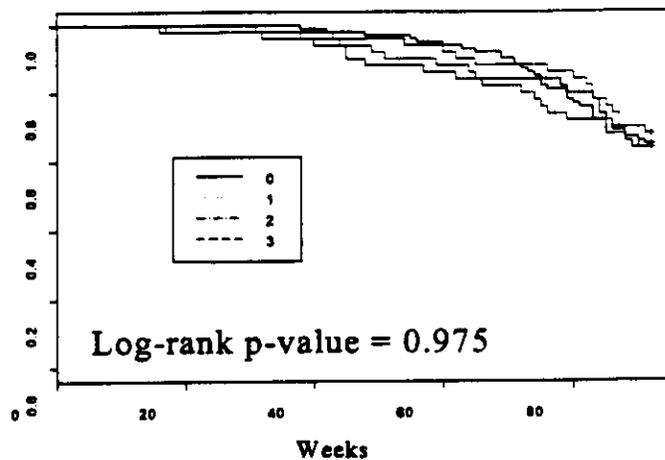
Male Rats				
	Controls 1+2	50 mg	100 mg	200 mg
Total number of animals	99	50	50	50
Number of animals with tumor (<i>p</i> -value of pairwise comparison with control groups)				
<i>Liver</i> : Hepatocellular carcinoma	2	6 (0.0138)	3 (0.2171)	5 (0.0394)
<i>Pancreas</i> : Islet adenoma	3	4 (0.1471)	6 (0.0301)	6 (0.0397)
<i>Brain</i> : Malignant glioma	0	0	2 (0.0958)	0
Female Rats				
	Controls 1+2	50 mg	100 mg	200 mg
Total number of animals	100	50	50	50
Number of animals with tumor (<i>p</i> -value of pairwise comparison with control groups)				
<i>Stomach</i> : Non-glandular mucosa papilloma	0	0	0	2 (0.1401)
<i>Uterus</i> : Adenocarcinoma	0	1 (0.2667)	1 (0.3366)	2
<i>Pancreas</i> : Islet adenoma	1	1 (0.5340)	1 (0.5663)	2 (0.2885)
<i>Brain</i> : Malignant glioma	0	0	0	1 (0.3125)

Kaplan-Meier Plots

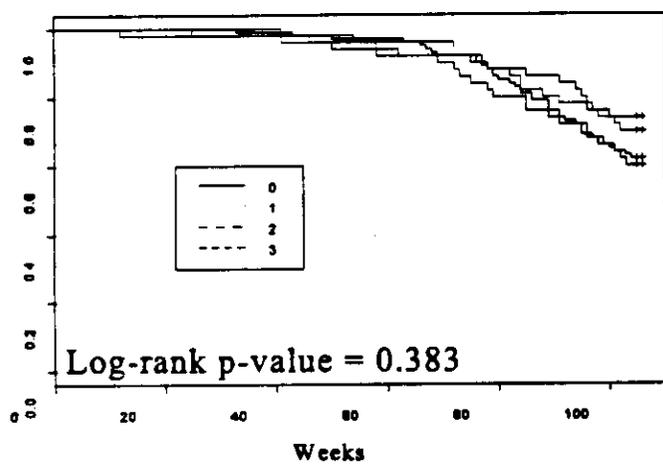
Female Mice



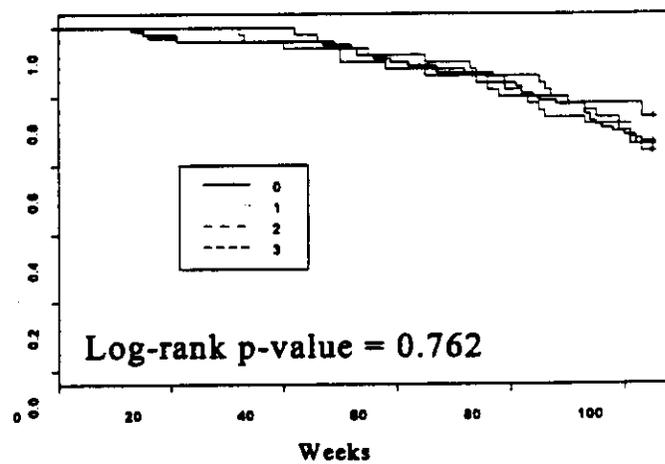
Male Mice



Female Rats



Male Rats



8/12/96

Barbara A. Bono

concur: Dr. Lin
Dr. Nevius

8/12/96
8-12-96

cc:

Orig. IND
HFD-570 / Division File
HFD-570 / BKuzmik
HFD-570 / SWilliams
HFD-570 / JSun
HFD-715 / Division File, Chron
HFD-715 / ENevius, KLin, SWilson, BBono

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