CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

Trade Name: Singulair
Tablet; EQ 10MG Base

Generic Name: (Montelukast Sodium)

Sponsor: Merck and Co., Inc.

Approval Date: 7/27/2005

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

Merck and Co., Inc
P.O. Box 2000, RY32-605
Rahway, NJ 07065-0900

Attention: Frank Seebach, MD, RAC
Director, Regulatory Affairs

Dear Dr. Seebach:

Please refer to your supplemental new drug applications dated September 30, 2004, received September 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules.

We acknowledge receipt of your submissions dated October 11, November 30, and December 3, 2004, and January 18, and 24, June 30, and July 1, 18, 19, and 22, 2005.

These supplemental new drug applications provide for the use of Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules for the relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling [package insert submitted July 19, 2005, (copy enclosed), patient package insert, immediate container and carton labels submitted July 22, 2005].

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submission(s) "**FPL for approved supplements NDA 20-829/S-033, NDA 20-830/S-035 and NDA 21-409/S-012."** Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. A partial waiver for pediatric studies for these applications and this indication was granted for children

less than 6 months of age in the letter dated March 3, 2005. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury

7/27/05 12:39:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

LABELING

MERCK & CO., INC.
Whitehouse Station, NJ 08889, USA

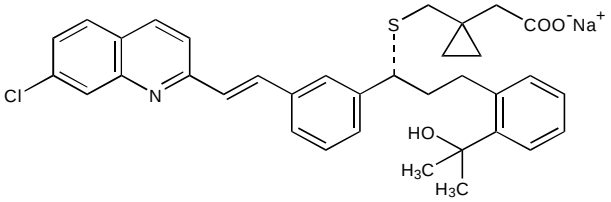
SINGULAIR®
(MONTELUKAST SODIUM)
TABLETS, CHEWABLE TABLETS, AND ORAL GRANULES

DESCRIPTION

Montelukast sodium, the active ingredient in SINGULAIR*, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [*R*-(*E*)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl]cyclopropaneacetic acid, monosodium salt.

The empirical formula is $C_{35}H_{35}ClNNaO_3S$, and its molecular weight is 608.18. The structural formula is:



Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

Each 10-mg film-coated SINGULAIR tablet contains 10.4 mg montelukast sodium, which is equivalent to 10 mg of montelukast, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of: hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red ferric oxide, yellow ferric oxide, and carnauba wax.

Each 4-mg and 5-mg chewable SINGULAIR tablet contains 4.2 and 5.2 mg montelukast sodium, respectively, which are equivalent to 4 and 5 mg of montelukast, respectively. Both chewable tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Each packet of SINGULAIR 4-mg oral granules contains 4.2 mg montelukast sodium, which is equivalent to 4 mg of montelukast. The oral granule formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate.

CLINICAL PHARMACOLOGY

Mechanism of Action

The cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 ($CysLT_1$) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and allergic rhinitis. In asthma, leukotriene-mediated effects include airway

* Registered trademark of MERCK & CO., Inc.

edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis. Intranasal challenge with CysLTs has been shown to increase nasal airway resistance and symptoms of nasal obstruction. SINGULAIR has not been assessed in intranasal challenge studies. The clinical relevance of intranasal challenge studies is unknown.

Montelukast is an orally active compound that binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity.

Pharmacokinetics

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

The 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet when administered to adults in the fasted state. The co-administration of the oral granule formulation with applesauce did not have a clinically significant effect on the pharmacokinetics of montelukast. A high fat meal in the morning did not affect the AUC of montelukast oral granules; however, the meal decreased C_{max} by 35% and prolonged T_{max} from 2.3 ± 1.0 hours to 6.4 ± 2.9 hours.

The safety and efficacy of SINGULAIR in patients with asthma were demonstrated in clinical trials in which the 10-mg film-coated tablet and 5-mg chewable tablet formulations were administered in the evening without regard to the time of food ingestion. The safety of SINGULAIR in patients with asthma was also demonstrated in clinical trials in which the 4-mg chewable tablet and 4-mg oral granule formulations were administered in the evening without regard to the time of food ingestion. The safety and efficacy of SINGULAIR in patients with seasonal allergic rhinitis were demonstrated in clinical trials in which the 10-mg film-coated tablet was administered in the morning or evening without regard to the time of food ingestion.

The comparative pharmacokinetics of montelukast when administered as two 5-mg chewable tablets versus one 10-mg film-coated tablet have not been evaluated.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady state volume of distribution of montelukast averages 8 to 11 liters. Studies in rats with radiolabeled montelukast indicate minimal distribution across the blood-brain barrier. In addition, concentrations of radiolabeled material at 24 hours postdose were minimal in all other tissues.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6 (see *Drug Interactions*). However, *in vitro* studies have shown that montelukast is a potent inhibitor of cytochrome P450 2C8 (see *Drug Interactions*).

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile.

In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations

Gender: The pharmacokinetics of montelukast are similar in males and females.

Elderly: The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race: Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency: Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast area under the plasma concentration curve (AUC) following a single 10-mg dose. The elimination of montelukast was slightly prolonged compared with that in healthy subjects (mean half-life, 7.4 hours). No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Adolescents and Pediatric Patients: Pharmacokinetic studies evaluated the systemic exposure of the 4-mg oral granule formulation in pediatric patients 6 to 23 months of age, the 4-mg chewable tablets in pediatric patients 2 to 5 years of age, the 5-mg chewable tablets in pediatric patients 6 to 14 years of age, and the 10-mg film-coated tablets in young adults and adolescents ≥15 years of age.

The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents ≥15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients ≥15 years of age.

The mean systemic exposure of the 4-mg chewable tablet in pediatric patients 2 to 5 years of age and the 5-mg chewable tablets in pediatric patients 6 to 14 years of age is similar to the mean systemic exposure of the 10-mg film-coated tablet in adults. The 5-mg chewable tablet should be used in pediatric patients 6 to 14 years of age and the 4-mg chewable tablet should be used in pediatric patients 2 to 5 years of age.

In children 6 to 11 months of age, the systemic exposure to montelukast and the variability of plasma montelukast concentrations were higher than those observed in adults. Based on population analyses, the mean AUC (4296 ng•hr/mL [range 1200 to 7153]) was 60% higher and the mean C_{max} (667 ng/mL [range 201 to 1058]) was 89% higher than those observed in adults (mean AUC 2689 ng•hr/mL [range 1521 to 4595]) and mean C_{max} (353 ng/mL [range 180 to 548]). The systemic exposure in children 12 to 23 months of age was less variable, but was still higher than that observed in adults. The mean AUC (3574 ng•hr/mL [range 2229 to 5408]) was 33% higher and the mean C_{max} (562 ng/mL [range 296 to 814]) was 60% higher than those observed in adults. Safety and tolerability of montelukast in a single-dose pharmacokinetic study in 26 children 6 to 23 months of age were similar to that of patients two years and above (see ADVERSE REACTIONS). The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis. Since the 4-mg oral granule formulation is bioequivalent to the 4-mg chewable tablet, it can also be used as an alternative formulation to the 4-mg chewable tablet in pediatric patients 2 to 5 years of age.

Drug Interactions

Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state:

- did not cause clinically significant changes in the kinetics of a single intravenous dose of theophylline (predominantly a cytochrome P450 1A2 substrate).
- did not change the pharmacokinetic profile of warfarin (primarily a substrate of CYP 2C9, 3A4 and 1A2) or influence the effect of a single 30-mg oral dose of warfarin on prothrombin time or the INR (International Normalized Ratio).
- did not change the pharmacokinetic profile or urinary excretion of immunoreactive digoxin.
- did not change the plasma concentration profile of terfenadine (a substrate of CYP 3A4) or fexofenadine, its carboxylated metabolite, and did not prolong the QTc interval following co-administration with terfenadine 60 mg twice daily.

Montelukast at doses of ≥100 mg daily dosed to pharmacokinetic steady state:

- did not significantly alter the plasma concentrations of either component of an oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg.
- did not cause any clinically significant change in plasma profiles of prednisone or prednisolone following administration of either oral prednisone or intravenous prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Montelukast is a potent inhibitor of P450 2C8, but no *in vivo* drug interaction studies have been conducted between montelukast and cytochrome P450 2C8 substrates. Caution should be exercised when concomitantly administering a cytochrome P450 2C8 substrate, such as paclitaxel, rosiglitazone, and repaglinide.

Pharmacodynamics

Montelukast causes inhibition of airway cysteinyl leukotriene receptors as demonstrated by the ability to inhibit bronchoconstriction due to inhaled LTD_4 in asthmatics. Doses as low as 5 mg cause substantial blockage of LTD_4-induced bronchoconstriction. In a placebo-controlled, crossover study (n=12), SINGULAIR inhibited early- and late-phase bronchoconstriction due to antigen challenge by 75% and 57%, respectively.

The effect of SINGULAIR on eosinophils in the peripheral blood was examined in clinical trials. In patients with asthma aged 2 years and older who received SINGULAIR, a decrease in mean peripheral blood eosinophil counts ranging from 9% to 15% was noted, compared with placebo, over the double-blind treatment periods. In patients with seasonal allergic rhinitis aged 15 years and older who received SINGULAIR, a mean increase of 0.2% in peripheral blood eosinophil counts was noted, compared with a mean increase of 12.5% in placebo-treated patients, over the double-blind treatment periods; this reflects a mean difference of 12.3% in favor of SINGULAIR. The relationship between these observations and the clinical benefits of montelukast noted in the clinical trials is not known (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Clinical Studies – Asthma and Allergic Rhinitis (Seasonal and Perennial)

GENERAL

There have been no clinical trials in asthmatics to evaluate the relative efficacy of morning versus evening dosing. The pharmacokinetics of montelukast are similar whether dosed in the morning or evening. Efficacy has been demonstrated for asthma when montelukast was administered in the evening without regard to time of food ingestion. Efficacy was demonstrated for seasonal allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion.

Clinical Studies – Asthma

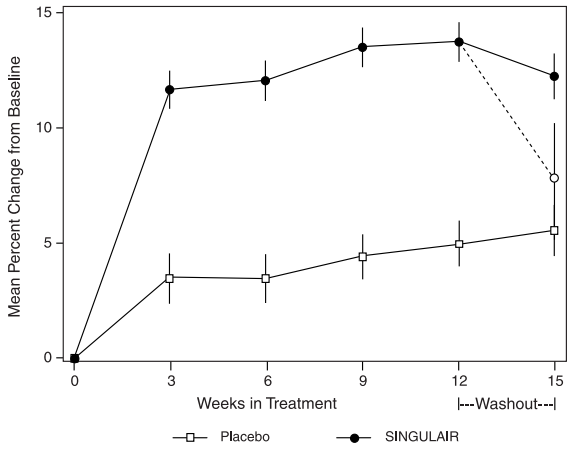
ADULTS AND ADOLESCENTS 15 YEARS OF AGE AND OLDER

Clinical trials in adults and adolescents 15 years of age and older demonstrated there is no additional clinical benefit to montelukast doses above 10 mg once daily. This was shown in two chronic asthma trials

using doses up to 200 mg once daily and in one exercise challenge study using doses up to 50 mg, evaluated at the end of the once-daily dosing interval.

The efficacy of SINGULAIR for the chronic treatment of asthma in adults and adolescents 15 years of age and older was demonstrated in two (U.S. and Multinational) similarly designed, randomized, 12-week, double-blind, placebo-controlled trials in 1576 patients (795 treated with SINGULAIR, 530 treated with placebo, and 251 treated with active control). The patients studied were mild and moderate, non-smoking asthmatics who required approximately 5 puffs of inhaled β-agonist per day on an "as-needed" basis. The patients had a mean baseline percent of predicted forced expiratory volume in 1 second (FEV_1) of 66% (approximate range, 40 to 90%). The co-primary endpoints in these trials were FEV_1 and daytime asthma symptoms. Secondary endpoints included morning and evening peak expiratory flow rates (AM PEFR, PM PEFR), rescue β-agonist requirements, nocturnal awakening due to asthma, and other asthma-related outcomes. In both studies after 12 weeks, a random subset of patients receiving SINGULAIR was switched to placebo for an additional 3 weeks of double-blind treatment to evaluate for possible rebound effects. The results of the U.S. trial on the primary endpoint, FEV_1, expressed as mean percent change from baseline, are shown in FIGURE 1.

FIGURE 1
FEV_1 Mean Percent Change from Baseline
(U.S. Trial)



The effect of SINGULAIR on other primary and secondary endpoints is shown in TABLE 1 as combined analyses of the U.S. and Multinational trials.

TABLE 1
Effect of SINGULAIR on Primary and Secondary Endpoints
in Placebo-controlled Trials
(Combined Analyses - U.S. and Mul inational Trials)

	SINGULAIR		Placebo	
Endpoint	Baseline	Mean Change from Baseline	Baseline	Mean Change from Baseline
Daytime Asthma Symptoms (0 to 6 scale)	2.43	-0.45*	2.45	-0.22
β-agonist (puffs per day)	5.38	-1.56*	5.55	-0.41
AM PEFR (L/min)	361.3	24.5*	364.9	3.3
PM PEFR (L/min)	385.2	17.9*	389.3	2.0
Nocturnal Awakenings (#/week)	5.37	-1.84*	5.44	-0.79

* p<0.001, compared wi h placebo

In adult patients, SINGULAIR reduced “as-needed” β-agonist use by 26.1% from baseline compared with 4.6% for placebo. In patients with nocturnal awakenings of at least 2 nights per week, SINGULAIR reduced the nocturnal awakenings by 34% from baseline, compared with 15% for placebo (combined analysis).

SINGULAIR, compared with placebo, significantly improved other protocol-defined, asthma-related outcome measurements (see TABLE 2).

TABLE 2
Effect of SINGULAIR on Asthma-Related Outcome Measurements
(Combined Analyses - U.S. and Mul inational Trials)

	SINGULAIR	Placebo
Asthma Attack* (% of patients)	11.6†	18.4
Oral Corticosteroid Rescue (% of patients)	10.7†	17.5
Discontinuation Due to Asthma (% of patients)	1.4‡	4.0
Asthma Exacerbations** (% of days)	12 8†	20.5
Asthma Control Days*** (% of days)	38 5†	27.2
Physicians’ Global Evaluation (score)§	1.77†	2.43
Pa ients’ Global Evaluation (score)§§	1.60†	2.15
† p<0.001, compared with placebo ‡ p<0.01, compared with placebo		

* Asthma Attack defined as utilization of health-care resources such as an unscheduled visit to a doctor's office, emergency room, or hospital; or treatment with oral, intravenous, or intramuscular corticosteroid.

** Asthma Exacerbation defined by specific clinically important decreases in PEFR, increase in β-agonist use, increases in day or nighttime symptoms, or the occurrence of an asthma attack.

*** An Asthma Control Day defined as a day without any of the following: nocturnal awakening, use of more than 2 puffs of β-agonist, or an asthma attack.

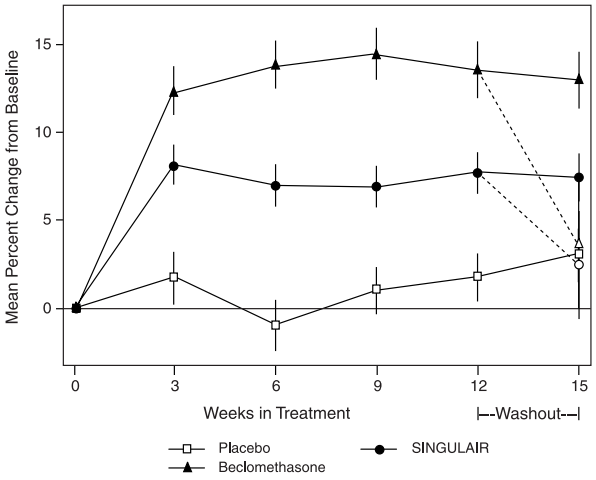
§ Physicians’ evalua ion of he patient’s asthma, ranging from 0 to 6 (“very much better” through “very much worse”, respectively).

§§ Patients’ evaluation of as hma, ranging from 0 to 6 (“very much better” through “very much worse”, respectively).

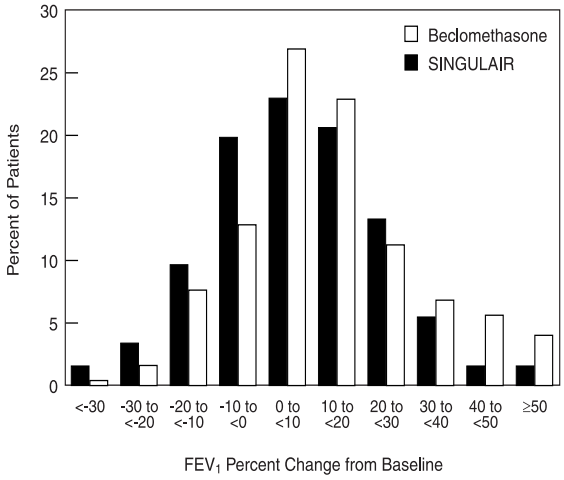
In one of these trials, a non-U.S. formulation of inhaled beclomethasone dipropionate dosed at 200 mcg (two puffs of 100 mcg ex-valve) twice daily with a spacer device was included as an active control. Over the 12-week treatment period, the mean percentage change in FEV_1 over baseline for SINGULAIR and beclomethasone were 7.49% vs 13.3% (p<0.001) respectively, see FIGURE 2; and the change in daytime symptom scores was -0.49 vs -0.70 on a 0 to 6 scale (p<0.001) for SINGULAIR and beclomethasone, respectively. The percentages of individual patients treated with SINGULAIR or beclomethasone achieving any given percentage change in FEV_1 from baseline are shown in FIGURE 3.

FIGURE 2 FIGURE 3

FEV_1
Mean Percent Change From Baseline
(Multinational Trial)



FEV_1
Distribution of Individual Patient Response
(Multinational Trial)



Onset of Action and Maintenance of Benefits

In each placebo-controlled trial in adults, the treatment effect of SINGULAIR, measured by daily diary card parameters, including symptom scores, "as-needed" β-agonist use, and PEFR measurements, was achieved after the first dose and was maintained throughout the dosing interval (24 hours). No significant change in treatment effect was observed during continuous once-daily evening administration in non-placebo-controlled extension trials for up to one year. Withdrawal of SINGULAIR in asthmatic patients after 12 weeks of continuous use did not cause rebound worsening of asthma.

PEDIATRIC PATIENTS 6 TO 14 YEARS OF AGE

The efficacy of SINGULAIR in pediatric patients 6 to 14 years of age was demonstrated in one 8-week, double-blind, placebo-controlled trial in 336 patients (201 treated with SINGULAIR and 135 treated with placebo) using an inhaled β-agonist on an "as-needed" basis. The patients had a mean baseline percent predicted FEV_1 of 72% (approximate range, 45 to 90%) and a mean daily inhaled β-agonist requirement of 3.4 puffs of albuterol. Approximately 36% of the patients were on inhaled corticosteroids.

Compared with placebo, treatment with one 5-mg SINGULAIR chewable tablet daily resulted in a significant improvement in mean morning FEV_1 percent change from baseline (8.7% in the group treated with SINGULAIR vs 4.2% change from baseline in the placebo group, $p<0.001$). There was a significant decrease in the mean percentage change in daily "as-needed" inhaled β-agonist use (11.7% decrease from baseline in the group treated with SINGULAIR vs 8.2% increase from baseline in the placebo group, $p<0.05$). This effect represents a mean decrease from baseline of 0.56 and 0.23 puffs per day for the montelukast and placebo groups, respectively. Subgroup analyses indicated that younger pediatric patients aged 6 to 11 had efficacy results comparable to those of the older pediatric patients aged 12 to 14.

SINGULAIR, one 5-mg chewable tablet daily at bedtime, significantly decreased the percent of days asthma exacerbations occurred (SINGULAIR 20.6% vs placebo 25.7%, $p\leq0.05$). (See TABLE 2 for definition of asthma exacerbation.) Parents' global asthma evaluations (parental evaluations of the patients' asthma, see TABLE 2 for definition of score) were significantly better with SINGULAIR compared with placebo (SINGULAIR 1.34 vs placebo 1.69, $p\leq0.05$).

Similar to the adult studies, no significant change in the treatment effect was observed during continuous once-daily administration in one open-label extension trial without a concurrent placebo group for up to 6 months.

PEDIATRIC PATIENTS 2 TO 5 YEARS OF AGE

The efficacy of SINGULAIR for the chronic treatment of asthma in pediatric patients 2 to 5 years of age was explored in a 12-week, placebo-controlled safety and tolerability study in 689 patients, 461 of whom were treated with SINGULAIR. While the primary objective was to determine the safety and tolerability of SINGULAIR in this age group, the study included exploratory efficacy evaluations, including daytime and overnight asthma symptom scores, β-agonist use, oral corticosteroid rescue, and the physician's global evaluation. The findings of these exploratory efficacy evaluations, along with pharmacokinetics and extrapolation of efficacy data from older patients, support the overall conclusion that SINGULAIR is efficacious in the maintenance treatment of asthma in patients 2 to 5 years of age.

EFFECTS IN PATIENTS ON CONCOMITANT INHALED CORTICOSTEROIDS

Separate trials in adults evaluated the ability of SINGULAIR to add to the clinical effect of inhaled corticosteroids and to allow inhaled corticosteroid tapering when used concomitantly.

One randomized, placebo-controlled, parallel-group trial (n=226) enrolled stable asthmatic adults with a mean FEV_1 of approximately 84% of predicted who were previously maintained on various inhaled corticosteroids (delivered by metered-dose aerosol or dry powder inhalers). The types of inhaled corticosteroids and their mean baseline requirements included beclomethasone dipropionate (mean dose, 1203 mcg/day), triamcinolone acetonide (mean dose, 2004 mcg/day), flunisolide (mean dose, 1971 mcg/day), fluticasone propionate (mean dose, 1083 mcg/day), or budesonide (mean dose, 1192 mcg/day). Some of these inhaled corticosteroids were non-U.S.-approved formulations, and doses expressed may not be ex-actuator. The pre-study inhaled corticosteroid requirements were reduced by approximately 37% during a 5- to 7-week placebo run-in period designed to titrate patients toward their lowest effective inhaled corticosteroid dose. Treatment with SINGULAIR resulted in a further 47% reduction in mean inhaled corticosteroid dose compared with a mean reduction of 30% in the placebo group over the 12-week active treatment period ($p \leq 0.05$). Approximately 40% of the montelukast-treated patients and 29% of the placebo-treated patients could be tapered off inhaled corticosteroids and remained off inhaled corticosteroids at the conclusion of the study (p=NS). It is not known whether the results of this study can be generalized to asthmatics who require higher doses of inhaled corticosteroids or systemic corticosteroids.

In another randomized, placebo-controlled, parallel-group trial (n=642) in a similar population of adult patients previously maintained, but not adequately controlled, on inhaled corticosteroids (beclomethasone 336 mcg/day), the addition of SINGULAIR to beclomethasone resulted in statistically significant improvements in FEV_1 compared with those patients who were continued on beclomethasone alone or those patients who were withdrawn from beclomethasone and treated with montelukast or placebo alone over the last 10 weeks of the 16-week, blinded treatment period. Patients who were randomized to treatment arms containing beclomethasone had statistically significantly better asthma control than those patients randomized to SINGULAIR alone or placebo alone as indicated by FEV_1, daytime asthma symptoms, PEFR, nocturnal awakenings due to asthma, and "as-needed" β-agonist requirements.

In adult asthmatic patients with documented aspirin sensitivity, nearly all of whom were receiving concomitant inhaled and/or oral corticosteroids, a 4-week, randomized, parallel-group trial (n=80) demonstrated that SINGULAIR, compared with placebo, resulted in significant improvement in parameters of asthma control. The magnitude of effect of SINGULAIR in aspirin-sensitive patients was similar to the effect observed in the general population of asthmatic patients studied. The effect of SINGULAIR on the bronchoconstrictor response to aspirin or other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients has not been evaluated (see PRECAUTIONS, *General*).

EFFECTS ON EXERCISE-INDUCED BRONCHOCONSTRICTION (ADULTS AND PEDIATRIC PATIENTS)

In a 12-week, randomized, double-blind, parallel group study of 110 adult and adolescent asthmatics 15 years of age and older, with a mean baseline FEV_1 percent of predicted of 83% and with documented exercise-induced exacerbation of asthma, treatment with SINGULAIR, 10 mg, once daily in the evening, resulted in a statistically significant reduction in mean maximal percent fall in FEV_1 and mean time to

recovery to within 5% of the pre-exercise FEV_1. Exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose). This effect was maintained throughout the 12-week treatment period indicating that tolerance did not occur. SINGULAIR did not, however, prevent clinically significant deterioration in maximal percent fall in FEV_1 after exercise (i.e., ≥20% decrease from pre-exercise baseline) in 52% of patients studied. In a separate crossover study in adults, a similar effect was observed after two once-daily 10-mg doses of SINGULAIR.

In pediatric patients 6 to 14 years of age, using the 5-mg chewable tablet, a 2-day crossover study demonstrated effects similar to those observed in adults when exercise challenge was conducted at the end of the dosing interval (i.e., 20 to 24 hours after the preceding dose).

SINGULAIR should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist (see PRECAUTIONS, *General* and *Information for Patients*).

Clinical Studies – Seasonal Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of seasonal allergic rhinitis was investigated in 5 similarly designed, randomized, double-blind, parallel-group, placebo- and active-controlled (loratadine) trials conducted in North America. The 5 trials enrolled a total of 5029 patients, of whom 1799 were treated with SINGULAIR tablets. Patients were 15 to 82 years of age with a history of seasonal allergic rhinitis, a positive skin test to at least one relevant seasonal allergen, and active symptoms of seasonal allergic rhinitis at study entry.

The period of randomized treatment was 2 weeks in 4 trials and 4 weeks in one trial. The primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing) as assessed by patients on a 0-3 categorical scale.

Four of the five trials showed a significant reduction in daytime nasal symptoms scores with SINGULAIR 10-mg tablets compared with placebo. The efficacy results of one trial are shown below; the remaining three trials that demonstrated efficacy showed similar results. The mean changes from baseline in daytime nasal symptoms score in the treatment groups that received SINGULAIR tablets, loratadine and placebo are shown in TABLE 3.

TABLE 3
Effects of SINGULAIR on Daytime Nasal Symptoms Score* in a Placebo- and Active-controlled Trial in Patients with Seasonal Allergic Rhinitis

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (344)	2.09	-0.39	-0.13‡ (-0.21, -0.06)
Placebo (351)	2.10	-0.26	N.A.
Active Control† (Loratadine 10 mg) (599)	2.06	-0.46	-0.24‡ (-0.31, -0.17)

* Average of individual scores of nasal congestion, rhinorrhea, nasal itching, sneezing as assessed by patients on a 0-3 categorical scale.
† The study was not designed for statistical comparison between SINGULAIR and the active control (loratadine).
‡ Statistically different from placebo ($p \leq 0.001$).

Clinical Studies – Perennial Allergic Rhinitis

The efficacy of SINGULAIR tablets for the treatment of perennial allergic rhinitis was investigated in 2 randomized, double-blind, placebo-controlled studies conducted in North America and Europe. The two

studies enrolled a total of 3357 patients, of whom 1632 received SINGULAIR 10-mg tablets. Patients 15 to 82 years of age with perennial allergic rhinitis as confirmed by history and a positive skin test to at least one relevant perennial allergen (dust mites, animal dander, and/or mold spores), who had active symptoms at the time of study entry, were enrolled.

In the study in which efficacy was demonstrated, SINGULAIR 10-mg tablets once daily was shown to significantly reduce symptoms of perennial allergic rhinitis over a 6-week treatment period (TABLE 4); in this study the primary outcome variable was mean change from baseline in daytime nasal symptoms score (the average of individual scores of nasal congestion, rhinorrhea, and sneezing).

TABLE 4
Effects of SINGULAIR on Daytime Nasal Symptoms Score** in a Placebo-controlled Trial
in Patients with Perennial Allergic Rhinitis

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08‡ (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

** Average of individual scores of nasal conges ion, rhinorrhea, sneezing as assessed by patients on a 0-3 categorical scale.
‡ Statistically different from placebo ($p \leq 0.001$).

The other 6-week study evaluated SINGULAIR 10 mg (n=626), placebo (n=609), and an active-control (cetirizine 10 mg; n=120). The primary analysis compared the mean change from baseline in daytime nasal symptoms score for SINGULAIR vs. placebo over the first 4 weeks of treatment; the study was not designed for statistical comparison between SINGULAIR and the active-control. The primary outcome variable included nasal itching in addition to nasal congestion, rhinorrhea, and sneezing. The estimated difference between SINGULAIR and placebo was -0.04 with a 95% CI of (-0.09, 0.01). The estimated difference between the active-control and placebo was -0.10 with a 95% CI of (-0.19, -0.01).

INDICATIONS AND USAGE

SINGULAIR is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

SINGULAIR is indicated for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older).

CONTRAINDICATIONS

Hypersensitivity to any component of this product.

PRECAUTIONS

General

SINGULAIR is not indicated for use in the reversal of bronchospasm in acute asthma attacks, including status asthmaticus.

Patients should be advised to have appropriate rescue medication available. Therapy with SINGULAIR can be continued during acute exacerbations of asthma.

While the dose of inhaled corticosteroid may be reduced gradually under medical supervision, SINGULAIR should not be abruptly substituted for inhaled or oral corticosteroids.

SINGULAIR should not be used as monotherapy for the treatment and management of exercise-induced bronchospasm. Patients who have exacerbations of asthma after exercise should continue to use their usual regimen of inhaled β-agonists as prophylaxis and have available for rescue a short-acting inhaled β-agonist.

Patients with known aspirin sensitivity should continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR. Although SINGULAIR is effective in improving airway function in asthmatics with documented aspirin sensitivity, it has not been shown to truncate bronchoconstrictor response to aspirin and other non-steroidal anti-inflammatory drugs in aspirin-sensitive asthmatic patients (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Eosinophilic Conditions

In rare cases, patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see ADVERSE REACTIONS).

Information for Patients

- Patients should be advised to take SINGULAIR daily as prescribed, even when they are asymptomatic, as well as during periods of worsening asthma, and to contact their physicians if their asthma is not well controlled.
- Patients should be advised that oral SINGULAIR is not for the treatment of acute asthma attacks. They should have appropriate short-acting inhaled β-agonist medication available to treat asthma exacerbations.
- Patients should be advised that, while using SINGULAIR, medical attention should be sought if short-acting inhaled bronchodilators are needed more often than usual, or if more than the maximum number of inhalations of short-acting bronchodilator treatment prescribed for a 24-hour period are needed.
- Patients receiving SINGULAIR should be instructed not to decrease the dose or stop taking any other anti-asthma medications unless instructed by a physician.
- Patients who have exacerbations of asthma after exercise should be instructed to continue to use their usual regimen of inhaled β-agonists as prophylaxis unless otherwise instructed by their physician. All patients should have available for rescue a short-acting inhaled β-agonist.
- Patients with known aspirin sensitivity should be advised to continue avoidance of aspirin or non-steroidal anti-inflammatory agents while taking SINGULAIR.

Chewable Tablets

- *Phenylketonurics:* Phenylketonuric patients should be informed that the 4-mg and 5-mg chewable tablets contain phenylalanine (a component of aspartame), 0.674 and 0.842 mg per 4-mg and 5-mg chewable tablet, respectively.

Drug Interactions

SINGULAIR has been administered with other therapies routinely used in the prophylaxis and chronic treatment of asthma with no apparent increase in adverse reactions. In drug-interaction studies, the recommended clinical dose of montelukast did not have clinically important effects on the pharmacokinetics of the following drugs: theophylline, prednisone, prednisolone, oral contraceptives (norethindrone 1 mg/ethinyl estradiol 35 mcg), terfenadine, digoxin, and warfarin.

Although additional specific interaction studies were not performed, SINGULAIR was used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of clinical adverse interactions. These medications included thyroid hormones, sedative hypnotics, non-steroidal anti-inflammatory agents, benzodiazepines, and decongestants.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the area under the plasma concentration versus time curve (AUC) for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

Montelukast demonstrated no evidence of mutagenic or clastogenic activity in the following assays: the microbial mutagenesis assay, the V-79 mammalian cell mutagenesis assay, the alkaline elution assay in rat hepatocytes, the chromosomal aberration assay in Chinese hamster ovary cells, and in the *in vivo* mouse bone marrow chromosomal aberration assay.

In fertility studies in female rats, montelukast produced reductions in fertility and fecundity indices at an oral dose of 200 mg/kg (estimated exposure was approximately 70 times the AUC for adults at the maximum recommended daily oral dose). No effects on female fertility or fecundity were observed at an oral dose of 100 mg/kg (estimated exposure was approximately 20 times the AUC for adults at the maximum recommended daily oral dose). Montelukast had no effects on fertility in male rats at oral doses up to 800 mg/kg (estimated exposure was approximately 160 times the AUC for adults at the maximum recommended daily oral dose).

Pregnancy, Teratogenic Effects

Pregnancy Category B:

No teratogenicity was observed in rats at oral doses up to 400 mg/kg/day (estimated exposure was approximately 100 times the AUC for adults at the maximum recommended daily oral dose) and in rabbits at oral doses up to 300 mg/kg/day (estimated exposure was approximately 110 times the AUC for adults at the maximum recommended daily oral dose). Montelukast crosses the placenta following oral dosing in rats and rabbits. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, SINGULAIR should be used during pregnancy only if clearly needed.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to SINGULAIR while pregnant. Healthcare providers are encouraged to report any prenatal exposure to SINGULAIR by calling the Pregnancy Registry at (800) 986-8999.

Nursing Mothers

Studies in rats have shown that montelukast is excreted in milk. It is not known if montelukast is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINGULAIR is given to a nursing mother.

Pediatric Use

Safety and efficacy of SINGULAIR have been established in adequate and well-controlled studies in pediatric patients with asthma 6 to 14 years of age. Safety and efficacy profiles in this age group are similar to those seen in adults. (See *Clinical Studies* and ADVERSE REACTIONS.)

The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.

The safety of SINGULAIR 4-mg chewable tablets in pediatric patients 2 to 5 years of age with asthma has been demonstrated by adequate and well-controlled data (see ADVERSE REACTIONS). Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma and is based on similar pharmacokinetic data, as well as the assumption that the

disease course, pathophysiology and the drug's effect are substantially similar among these populations. Efficacy in this age group is supported by exploratory efficacy assessments from a large, well-controlled safety study conducted in patients 2 to 5 years of age.

The safety of SINGULAIR 4-mg oral granules in pediatric patients 12 to 23 months of age with asthma has been demonstrated in an analysis of 172 pediatric patients, 124 of whom were treated with SINGULAIR, in a 6-week, double-blind, placebo-controlled study (see ADVERSE REACTIONS). Efficacy of SINGULAIR in this age group is extrapolated from the demonstrated efficacy in patients 6 years of age and older with asthma based on similar mean systemic exposure (AUC), and that the disease course, pathophysiology and the drug's effect are substantially similar among these populations, supported by efficacy data from a safety trial in which efficacy was an exploratory assessment.

The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile (see ADVERSE REACTIONS). The safety of SINGULAIR 4-mg oral granules in pediatric patients as young as 6 months of age with perennial allergic rhinitis is supported by extrapolation from safety data obtained from studies conducted in pediatric patients 6 months to 23 months of age with asthma and from pharmacokinetic data comparing systemic exposures in patients 6 months to 23 months of age to systemic exposures in adults.

The safety and effectiveness in pediatric patients below the age of 12 months with asthma and 6 months with perennial allergic rhinitis have not been established. Long-term trials evaluating the effect of chronic administration of SINGULAIR on linear growth in pediatric patients have not been conducted.

Geriatric Use

Of the total number of subjects in clinical studies of montelukast, 3.5% were 65 years of age and over, and 0.4% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Adults and Adolescents 15 Years of Age and Older with Asthma

SINGULAIR has been evaluated for safety in approximately 2600 adult and adolescent patients 15 years of age and older in clinical trials. In placebo-controlled clinical trials, the following adverse experiences reported with SINGULAIR occurred in greater than or equal to 1% of patients and at an incidence greater than that in patients treated with placebo, regardless of causality assessment:

Adverse Experiences Occurring in ≥1% of Patients
wi h an Incidence Greater than that in Patients Treated with Placebo,
Regardless of Causality Assessment

	SINGULAIR 10 mg/day (%) (n=1955)	Placebo (%) (n=1180)
Body As A Whole		
As henia/fatigue	1.8	1.2
Fever	1.5	0.9
Pain, abdominal	2.9	2.5
Trauma	1.0	0.8
Digestive System Disorders		
Dyspepsia	2.1	1.1
Gastroenteritis, infectious	1.5	0.5
Pain, dental	1.7	1.0
Nervous System/Psychiatric		
Dizziness	1.9	1.4
Headache	18.4	18.1
Respiratory System Disorders		
Congestion, nasal	1.6	1.3
Cough	2.7	2.4
Influenza	4.2	3.9
Skin/Skin Appendages Disorder		
Rash	1.6	1.2
*Laboratory Adverse Experiences**		
ALT increased	2.1	2.0
AST increased	1.6	1.2
Pyuria	1.0	0.9

* Number of patients tested (SINGULAIR and placebo, respectively): ALT and AST, 1935, 1170; pyuria, 1924, 1159.

The frequency of less common adverse events was comparable between SINGULAIR and placebo.

Cumulatively, 569 patients were treated with SINGULAIR for at least 6 months, 480 for one year, and 49 for two years in clinical trials. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 6 to 14 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 321 pediatric patients 6 to 14 years of age. Cumulatively, 169 pediatric patients were treated with SINGULAIR for at least 6 months, and 121 for one year or longer in clinical trials. The safety profile of SINGULAIR in the 8-week, double-blind, pediatric efficacy trial was generally similar to the adult safety profile. In pediatric patients 6 to 14 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: pharyngitis, influenza, fever, sinusitis, nausea, diarrhea, dyspepsia, otitis, viral infection, and laryngitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo. With prolonged treatment, the adverse experience profile did not significantly change.

Pediatric Patients 2 to 5 Years of Age with Asthma

SINGULAIR has been evaluated for safety in 573 pediatric patients 2 to 5 years of age in single- and multiple-dose studies. Cumulatively, 426 pediatric patients 2 to 5 years of age were treated with SINGULAIR for at least 3 months, 230 for 6 months or longer, and 63 patients for one year or longer in clinical trials. SINGULAIR 4 mg administered once daily at bedtime was generally well tolerated in clinical trials. In pediatric patients 2 to 5 years of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: fever, cough, abdominal pain, diarrhea, headache, rhinorrhea, sinusitis, otitis, influenza, rash, ear pain, gastroenteritis, eczema, urticaria, varicella, pneumonia, dermatitis, and conjunctivitis.

Pediatric Patients 6 to 23 Months of Age with Asthma

Safety and effectiveness in pediatric patients younger than 12 months of age with asthma have not been established.

SINGULAIR has been evaluated for safety in 175 pediatric patients 6 to 23 months of age. The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. SINGULAIR administered once daily at bedtime was generally well tolerated. In pediatric patients 6 to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.

Adults and Adolescents 15 Years of Age and Older with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated for safety in 2199 adult and adolescent patients 15 years of age and older in clinical trials. SINGULAIR administered once daily in the morning or in the evening was generally well tolerated with a safety profile similar to that of placebo. In placebo-controlled clinical trials, the following event was reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: upper respiratory infection, 1.9% of patients receiving SINGULAIR vs. 1.5% of patients receiving placebo. In a 4-week, placebo-controlled clinical study, the safety profile was consistent with that observed in 2-week studies. The incidence of somnolence was similar to that of placebo in all studies.

Pediatric Patients 2 to 14 Years of Age with Seasonal Allergic Rhinitis

SINGULAIR has been evaluated in 280 pediatric patients 2 to 14 years of age in a 2-week, multicenter, double-blind, placebo-controlled, parallel-group safety study. SINGULAIR administered once daily in the evening was generally well tolerated with a safety profile similar to that of placebo. In this study, the following events occurred with a frequency ≥2% and at an incidence greater than placebo, regardless of causality assessment: headache, otitis media, pharyngitis, and upper respiratory infection.

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

SINGULAIR has been evaluated for safety in 3357 adult and adolescent patients 15 years of age and older with perennial allergic rhinitis of whom 1632 received SINGULAIR in two, 6-week, clinical studies. SINGULAIR administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.

Pediatric Patients 6 Months to 14 Years of Age with Perennial Allergic Rhinitis

The safety in patients 2 to 14 years of age with perennial allergic rhinitis is supported by the established safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 to 23 months of age is supported by data from pharmacokinetic and safety and efficacy studies in asthma in this pediatric population and from adult pharmacokinetic studies.

Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing use: hypersensitivity reactions (including anaphylaxis, angioedema, pruritus, urticaria, and very rarely, hepatic eosinophilic infiltration); dream abnormalities and hallucinations, drowsiness, irritability, agitation including aggressive behavior, restlessness, insomnia, paraesthesia/hypoesthesia, and very rarely seizures; arthralgia, myalgia including muscle cramps; increased bleeding tendency, bruising; palpitations; edema; nausea, vomiting, dyspepsia, diarrhea, and very rarely pancreatitis. Rare cases of cholestatic hepatitis, hepatocellular liver-injury, and mixed-pattern liver injury have been reported in patients treated with SINGULAIR. Most of these occurred in combination with other confounding factors, such as use of other medications, or when SINGULAIR was administered to patients who had underlying potential for liver disease such as alcohol use or other forms of hepatitis.

In rare cases, patients with asthma on therapy with SINGULAIR may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between SINGULAIR and these underlying conditions has not been established (see PRECAUTIONS, *Eosinophilic Conditions*).

OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 335 and 210 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 and 145 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose).

No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, montelukast has been administered at doses up to 200 mg/day to adult patients for 22 weeks and, in short-term studies, up to 900 mg/day to patients for approximately a week without clinically important adverse experiences. In the event of overdose, it is reasonable to employ the usual supportive measures; e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

There have been reports of acute overdosage in pediatric patients in post-marketing experience and clinical studies of up to at least 150 mg/day with SINGULAIR. The clinical and laboratory findings observed were consistent with the safety profile in adults and older pediatric patients. There were no adverse experiences reported in the majority of overdosage reports. The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain.

It is not known whether montelukast is removed by peritoneal dialysis or hemodialysis.

DOSAGE AND ADMINISTRATION

General Information

SINGULAIR should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualized to suit patient needs.

Patients with both asthma and allergic rhinitis should take only one tablet daily in the evening.

Adults and Adolescents 15 Years of Age and Older with Asthma or Allergic Rhinitis

The dosage for adults and adolescents 15 years of age and older is one 10-mg tablet daily.

Pediatric Patients 6 to 14 Years of Age with Asthma or Allergic Rhinitis

The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily. No dosage adjustment within this age group is necessary.

Pediatric Patients 2 to 5 Years of Age with Asthma or Allergic Rhinitis

The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules daily.

Pediatric Patients 12 to 23 Months of Age with Asthma

The dosage for pediatric patients 12 to 23 months of age is one packet of 4-mg oral granules daily to be taken in the evening.

Pediatric Patients 6 to 23 Months of Age with Perennial Allergic Rhinitis

The dosage for pediatric patients 6 to 23 months of age is one packet of 4-mg oral granules daily.

Safety and effectiveness in pediatric patients younger than 6 months of age with perennial allergic rhinitis and in patients less than 12 months of age with asthma have not been established.

Administration of SINGULAIR Oral Granules

SINGULAIR 4-mg oral granules can be administered either directly in the mouth, dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (with or without mixing with baby formula, breast milk, or food) must be administered within 15 minutes. If mixed with baby formula, breast milk, or food, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. SINGULAIR oral granules are not intended to be dissolved in any liquid other than baby formula or breast milk for administration. However, liquids may be taken subsequent to administration. SINGULAIR oral granules can be administered without regard to the time of meals.

HOW SUPPLIED

No. 3841 — SINGULAIR Oral Granules, 4 mg, are white granules with 500 mg net weight, packed in a child-resistant foil packet. They are supplied as follows:

NDC 0006-3841-30 unit of use carton with 30 packets.

No. 3796 —SINGULAIR Tablets, 4 mg, are pink, oval, bi-convex-shaped chewable tablets, with code MRK 711 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0711-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and two silica gel desiccant canisters

NDC 0006-0711-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0711-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

No. 3760 — SINGULAIR Tablets, 5 mg, are pink, round, bi-convex-shaped chewable tablets, with code MRK 275 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0275-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and two silica gel desiccant canisters

NDC 0006-0275-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0275-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister packs of 100.

No. 3761 — SINGULAIR Tablets, 10 mg, are beige, rounded square-shaped, film-coated tablets, with code MRK 117 on one side and SINGULAIR on the other. They are supplied as follows:

NDC 0006-0117-31 unit of use high-density polyethylene (HDPE) bottles of 30 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0117-54 unit of use high-density polyethylene (HDPE) bottles of 90 with a polypropylene child-resistant cap, an aluminum foil induction seal, and a silica gel desiccant canister

NDC 0006-0117-28 unit dose paper and aluminum foil-backed aluminum foil peelable blister pack of 100

NDC 0006-0117-80 bulk packaging high-density polyethylene (HDPE) bottles of 8000 with a non-child-resistant white plastic closure with a wax paper/pulp liner, an aluminum foil induction seal, and 25 silica gel desiccant canisters.

Storage

Store SINGULAIR 4-mg oral granules, 4-mg chewable tablets, 5-mg chewable tablets and 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in original package.

Storage for Bulk Bottles

Store bottle of 8000 SINGULAIR 10-mg film-coated tablets at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture and light. Store in

original container. When product container is subdivided, repackage into a well-closed, light-resistant container.

MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Issued XXXXXX 2005
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

OFFICE DIRECTOR MEMO

DIVISION DIRECTOR'S MEMORANDUM

Date: July 27, 2005

To: NDA 20-829, NDA 20-830, NDA 21-409

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary and Allergy Drug products, HFD-570

Product: Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules

Applicant: Merck Research Laboratories

Administrative and Introduction

Merck Research Laboratories submitted supplements to Singulair (montelukast sodium) Tablets NDA 20-829 (SE 1, 033), Chewable Tablets NDA 20-830 (SE 1, 035), and Oral Granules 21-409 (SE 1, 012) on September 30, 2004 (CDER stamp date), to add perennial allergic rhinitis (PAR) indication to the currently approved asthma and seasonal allergic rhinitis (SAR) indications for these products. The regulatory pathway of this application is 505(b)(1). The PDUFA due date on this application is July 31, 2005. Montelukast is currently approved for treatment of asthma in adults and pediatric patients 12 months of age and older, and for the relief of symptoms of SAR in adults and pediatric patients 2 years of age and older. Since leukotrienes are known to be involved in the pathophysiology of allergic rhinitis, and montelukast has been shown to be safe and effective for the relief of symptoms of SAR, it is plausible that montelukast would also be effective in PAR. The Division has held the position that in such a circumstance one successful clinical study would be adequate to support a PAR indication. Merck submitted results from two clinical studies in support of this application, one of which supported efficacy of montelukast. The overall data support approval of this application.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Singulair Tablets, Chewable Tablets, and Oral Granules are marketed products. There are no new major CMC data in this application. Merck has submitted new packaging for trade and complimentary distribution to reflect the addition of the PAR indication. The new packaging has labels for trays, cartons, blister packages, and oral granules packets, etc. CMC reviewer Dr. Peri has reviewed these and has suggested changes in the wording and language on the packaging labels, and I concur with those suggestions. Merck has committed to incorporate the suggested changes. All manufacturing facilities related to this application have acceptable EER status.

Clinical and Statistical

Merck submitted results from two clinical studies (studies 246 and 265) to support efficacy and safety of Singulair in PAR. Although one study would have been adequate to support this application, Merck conducted two studies, because study 246, which was conducted first, failed to show efficacy. Guided by the results of the first study, Merck conducted a second study, Study 265, which was successful in showing efficacy of montelukast for PAR. These two studies and other supporting data are reviewed in detail in Dr. Purohit-Sheth's medical review and Ms. Feng's statistical review. Brief comments on these studies are made in the subsequent sections.

Study 246 was double-blind, double-dummy, multi-center, placebo- and active-controlled, parallel group in design conducted in the United States in patients 15 to 85 years of age with PAR. The study had a 5-7 day placebo run-in period, followed by 6 weeks double-blind treatment period. The treatment arms were montelukast 10 mg, cetirizine 10 mg, and placebo, all dosed in the evening. Efficacy was assessed by morning and evening reflective patient scoring of four nasal symptoms (nasal congestion, rhinorrhea, sneezing, and nasal itching) on a four point scale (0=none, 1=mild, 2=moderate, and 3=severe), and several other measures, such as global patient rating of allergic rhinitis symptoms, rhinitis QOL questionnaire, and PAR questionnaire. The primary efficacy endpoint was the change from baseline in the Daytime Nasal Symptom Score (DNSS) averaged over the first 4 weeks of treatment. DNNS was the pre-dose evening reflective patient scoring of the four nasal symptoms mentioned above. The sample size of the study was calculated based on the results of the montelukast SAR program. The montelukast and placebo treatment arms were designed to have 500 evaluable patients to give an 88% power to detect a 0.1 difference in the primary efficacy endpoint at a two-sided alpha-level of 0.05. The study was not designed to compare between montelukast and cetirizine. Safety assessments included recording of adverse events, vital signs, physical examinations, ECG, and clinical laboratory measures.

A total of 1365 patients were randomized to the three treatment arms of which 1198 (88%) completed the study. There no preferential drop outs in any treatment arm. Montelukast and cetirizine were well tolerated in the study. Results of the primary efficacy endpoint as well as the individual symptoms that form the primary endpoint are shown in Table 1. Montelukast failed to show statistically significant difference from placebo in the primary efficacy endpoint, whereas cetirizine was statistically significantly different from placebo. Results of the secondary efficacy variables (data not shown) generally tracked the results of the primary variable.

Table 1. Efficacy Data from Study 246

Treatment Groups	n	Mean Baseline Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI)
Primary Efficacy Endpoint *				
Daytime Nasal Symptom Score (Nasal Congestion, Rhinorrhea, Sneezing, and Nasal Itching) †				
Montelukast 10 mg	626	2.08	- 0.39	- 0.04 (- 0.09, 0.01)
Cetirizine 10 mg	120	2.13	- 0.45	- 0.10 (- 0.19, - 0.01)
Placebo	609	2.07	- 0.36	

Treatment Groups	n	Mean Baseline Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI)
Individual Symptoms				
Nasal Congestion				
Montelukast 10 mg	626	2.44	- 0.37	- 0.04
Cetirizine 10 mg	120	2.49	- 0.40	- 0.08
Placebo	609	2.42	- 0.33	
Rhinorrhea				
Montelukast 10 mg	626	2.12	- 0.41	- 0.06
Cetirizine 10 mg	120	2.18	- 0.44	- 0.09
Placebo	609	2.15	- 0.35	
Sneezing				
Montelukast 10 mg	626	1.84	- 0.42	- 0.06
Cetirizine 10 mg	120	1.89	- 0.50	- 0.14
Placebo	609	1.78	- 0.36	
Nasal Itching				
Montelukast 10 mg	626	1.93	- 0.38	0.00
Cetirizine 10 mg	120	1.97	- 0.46	- 0.03
Placebo	609	1.94	- 0.39	

[*] Change from baseline in the Daytime Nasal Symptom Score averaged over 4-week period
[†] Symptoms of nasal congestion, rhinorrhea, sneezing, and nasal itching, each scored by patients on 0-3 scale in the evening before taking study medication.

Study 265 was conducted by Merck in follow-up to the study 246, which failed to show efficacy of montelukast in PAR. The design and conduct of this study was similar to study 246 with four notable differences. First, Merck decided to drop nasal itching from the DNSS because in study 246 there was no numerical effect on nasal itching score by montelukast. Second, the primary efficacy endpoint was assessed over 6 weeks of treatment as opposed to 4 weeks in study 246. Third, no active comparator was included in this study. Fourth, the study had centers in the United States, as well as in Canada, and Europe, as opposed to study 246 only having centers in the United States. Merck changed the primary efficacy endpoint with the Agency's agreement. The sample size of this study was calculated based on the difference between the montelukast and placebo treatment arms of study 246. The montelukast and placebo treatment arms were designed to have 800 evaluable patients to give a 90% power to detect a 0.075 difference in the primary efficacy endpoint at a two-sided alpha-level of 0.05. This study therefore was notably larger than the study 246. A total of 1922 patients were randomized to the two treatment arms of which 1813 (91%) completed the study. There no preferential drop outs in any treatment arm. Montelukast was well tolerated in the study. Results of the primary efficacy endpoint as well as the individual symptoms that form the primary endpoint and the symptom of nasal itching are shown in Table 2. Montelukast was statistically significantly superior to placebo for the primary efficacy endpoint. Interestingly, the numerical difference between montelukast and placebo for nasal itching was numerically large. Results of the secondary efficacy variables (data not shown) generally tracked the results of the primary variable.

Table 2. Efficacy Data from Study 265

Treatment Groups	n	Mean Baseline Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI)
Primary Efficacy Endpoint *				
Daytime Nasal Symptom Score (Nasal Congestion, Rhinorrhea, Sneezing, and Nasal Itching) †				
Montelukast 10 mg	1000	2.09	- 0.42	- 0.08 (- 0.12, - 0.04)
Placebo	980	2.10	- 0.35	
Individual Symptoms				
Nasal Congestion				
Montelukast 10 mg	1000	2.38	- 0.38	- 0.05
Placebo	980	2.40	- 0.34	
Rhinorrhea				
Montelukast 10 mg	1000	2.11	- 0.44	- 0.08
Placebo	980	2.15	- 0.37	
Sneezing				
Montelukast 10 mg	1000	1.79	- 0.44	- 0.10
Placebo	980	1.76	- 0.33	
Nasal Itching				
Montelukast 10 mg	1000	1.82	- 0.39	- 0.10
Placebo	980	1.80	- 0.29	

* Change from baseline in the Daytime Nasal Symptom Score averaged over 6-week period
† Symptoms of nasal congestion, rhinorrhea, and sneezing, each scored by patients on 0-3 scale in the evening before taking study medication. Nasal Itching was scored, but was not part of the Daytime Nasal Symptom Score.

The clinical program as summarized above support efficacy and safety of montelukast in the treatment of PAR. In study 265, montelukast was statistically significantly superior to placebo for the primary efficacy endpoint. In study 246, montelukast failed to separate from placebo statistically, but the numerical trend was in favor of montelukast compared to placebo. The secondary efficacy variables also generally favored montelukast over placebo. The two studies did not show any new safety signal for montelukast.

The effect size of montelukast in this program was small, as was seen for montelukast in the SAR program. In the SAR program, the effect size of montelukast numerically tended to be less than loratadine. In this PAR program, in study 246, montelukast failed to statistically separate from placebo, but cetirizine statistically separated from placebo with a smaller sample size. In both the SAR and PAR programs, the studies were not designed to compare motelukast to an active comparator; therefore, definitive comparative conclusion cannot be made. Nevertheless, to better guide the prescriber, results of study 265 and study 246, including effect size from the cetirizine arm, will be described in the product label, as was done for the SAR, where effect size from the loratadine arm is described in the product label along with the montelukast effect size.

Clinical Pharmacology and Biopharmaceutics

There are no outstanding clinical pharmacology and biopharmaceutics issues. No specific clinical pharmacology studies were conducted for montelukast in support of this application. The pharmacokinetic properties of montelukast in adults and pediatric

patients 6 months and older were extensively evaluated and reviewed by the Agency previously as part of the original and supplemental NDAs for all formulations of montelukast, and the data are reflected in the current package insert of montelukast.

There is one point that is worth noting in reference to this application. The current lowest approved age of montelukast use for any indication is 1 year, which is for asthma. With this approval the lowest age of montelukast use will be 6 months, which will be for PAR. The dose of montelukast for patients 6 months to 5 years of age will be 4 mg, as compared to 5 mg for patients 6 to 14 years of age and 10 mg for patients 15 years of age and older. It is known that systemic exposure to montelukast, as reflected by AUC, in children 6 to 12 months of age is about 62% higher compared to historical adult controls, and there is about 6-fold variability in the AUC values in this age group. In children 1 to 2 years of age, the systemic exposure to montelukast is about 34% higher compared to historical adult controls, but there is less variability. Although the systemic exposure in children 2 years and younger are higher compared to adults, there is adequate safety data to support the high exposure. Also, because of the high variability in young children a slightly higher dose is appropriate so that patients in the lower spectrum of the variability range will be still within the efficacy window.

Pharmacology and Toxicology

There are no outstanding preclinical issues. The applicant did not conduct any new preclinical studies specifically for this application. Due to increased exposure levels at the younger age groups, the Pharmacology and Toxicology review team recommended changes in animal to human exposure levels to the relevant label sections, and I concur with the recommended changes.

Data Quality, Integrity, and Financial Disclosure

No DSI audit for the clinical study sites were conducted because montelukast is not a new molecular entity, montelukast is already approved for a related indication, and during review of the submission no irregularities were found that would raise concerns regarding data integrity. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. The applicant provided adequate disclosure of financial interest of the clinical investigators. In study 246, 26 investigators (3.7%) and in study 265, 15 investigators (3.1%) had a significant equity interest in Merck. That interest contributed a small number of patients to the whole clinical program. Review of the efficacy and safety data of the particular investigators' site did not show any suspicious trends.

Pediatric Considerations

The PAR efficacy studies for montelukast were conducted in adults and adolescents 15 years of age and older. Merck is proposing that efficacy of montelukast in PAR be extrapolated to a younger age, which is reasonable. The demonstrated efficacy of montelukast in adults and adolescents in PAR can be extrapolated to children because the

disease is similar in adults and children and the outcome of montelukast treatment is likely to be similar in PAR in both adults and children. The same rationale was applied in granting pediatric indications for montelukast for SAR and for asthma. The lower age of extrapolating efficacy for montelukast in PAR is 6 months, because there is no clear evidence that PAR occurs below 6 months of age. The Division has taken the position that PAR occurs in children 6 months of age and older and SAR occurs in children 2 years of age and older. Although the lower age cut-off is somewhat arbitrary, there is literature support on the lower age bound (J Allergy Clin Immunol 2000; 106:832). Merck requested a waiver of pediatric studies below 6 months of age. The waiver was granted because as stated above there is no clear evidence that PAR occurs below 6 months of age.

Product Name
The trade name Singulair is approved and used by Merck for the product line containing montelukast. The suffix Tablets, Chewable Tablets, and Oral Granules, are also approved and have been previously determined by the Agency as appropriate for the dosage forms.

Labeling
Merck submitted labeling with major changes and additions to the Clinical Trials, Indications and Usage, Adverse Reactions, Dosage and Administration, and Pediatric Use sections of the label. These changes and additions were reviewed by various disciplines of this Division, particularly by the clinical and statistical disciplines, and consults were obtained from DDMAC and DSRCS of ODS. The Division and Merck have agreed on the final version of the label. The Clinical Trials section briefly describes the two studies that were conducted by Merck to assess the efficacy and safety of montelukast in PAR. The Indication and Usage section language is changed to include the PAR indication. The Dosage and Administration section contains age appropriate dosage recommendation for all three presentations of montelukast. The Pediatric Use subsection contains language that explains that the approval in pediatric patients is based on extrapolation from the adult data. The Adverse Reactions section contains relevant safety findings from the new clinical studies.

Action
Merck has submitted adequate rationale and clinical efficacy and safety data to support approval of Singulair Tablets, Chewable Tablets, and Oral Granules for the relief of symptoms of PAR in adults and pediatric patients 6 months of age and older. Therefore, the action on this application will be APPROVAL.

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/s/

Badrul Chowdhury
7/27/05 09:26:46 AM
MEDICAL OFFICER
Div Dir Memo - Singulair for PAR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

MEDICAL REVIEW(S)

Medical Team leader Review memorandum

Memorandum to File:
NDA 20-829/SE1/033; NDA 20-830/SE1/035; NDA 21-409/SE1/012
Drug Products: Singulair (montelukast sodium) film-coated tablets (NDA 20-829); Singluair (montelukast sodium) Chewable tablets (NDA 20-830); Singulair (montelukast sodium) Granules (NDA 21-409)

Applicant: Merck Research Laboratories
Memo Date: July 20, 2005
Memo From: Lydia I. Gilbert-McClain, MD, FCCP, Medical Team Leader

This memorandum provides a summary of the development program for Singulair for the treatment of the symptoms of perennial allergic rhinitis. This Memorandum documents the secondary review of Dr. Tejashri Purohit-Sheth's primary review of the application and my recommendations on approvability.

Background and Administrative

Singulair (montelukast) 10 mg film-coated tablets and 5 mg chewable tablets were approved on February 20, 1998 for the maintenance treatment of asthma in patients 15 years of age and older (10 mg tablets) and 6 to 14 years of age (5 mg chewable tablet). A 4-mg chewable tablet was approved on March 3, 2000 in children 2 to 5 years of age and Singulair 4 mg Oral Granules was approved on July 26, 2000 in children 12 months to 5 years of age for the maintenance treatment of asthma. An approval for the treatment of the symptoms of seasonal allergic rhinitis was obtained on December 31, 2002 for all the Singulair products for patients 2 years of age and older. The Applicant submitted an efficacy supplement to support marketing of Singulair for the treatment of symptoms of Perennial Allergic Rhinitis on September 30, 2004 and the PDUFA due date for this application is July 30, 2005. The Applicant had one teleconference with the Division on May 30, 2003 where the design of the pivotal study for PAR was discussed and agreed upon. Given that Singulair had already received an approval for the treatment of the symptoms of seasonal allergic rhinitis (SAR), approval for the PAR indication could be supported with efficacy data from one pivotal trial.

Clinical Development Program

The clinical development Program for PAR was based on 2 pivotal studies. The 2 studies were conducted in patients aged 15 to 82 years of age with a history of PAR for at least 2 years. Patients had to have had positive skin tests results to relevant perennial allergens such as dust mites, animal dander, and mold spores. Both studies were similarly designed in that they were randomized, double-blind, and placebo-controlled studies. The first study (Study 246) was different in that it also included an active comparator (cetirizine 10 mg) and the primary efficacy variable (Daytime Nasal Symptom Score [DNSS]) comprised 4 nasal symptoms (running nose, itching, sneezing, and nasal congestion) whereas, in the second study (study 265) the primary efficacy variable did not include nasal itching, and there was no active comparator arm. The overall development program included 3,357 patients, of whom 1,632 were treated with Singulair. The two efficacy studies are briefly described.

Study P246 was the first study conducted. A total of 1,356 subjects were enrolled in this study. At randomization, 630 patients were in the Singulair arm, 613 were placed on placebo, and 122 received cetirizine. Although the study duration was 6 weeks, the primary efficacy outcome measure (mean change from baseline in DNSS between Singulair and placebo) was determined at 4 weeks. The study was not designed for statistical comparison between montelukast and cetirizine. The study was powered to detect a treatment difference of 0.10 in the change from Baseline in DNSS over 4 weeks with a two-side test $\alpha = 0.05$. However, at 4 weeks, the LS mean difference between Singulair and placebo for the DNSS was only -0.04 and was not statistically significant (CI -0.09; 0.01). Whereas, cetirizine was statistically superior to placebo for the TNSS (LS mean difference -0.10; CI -0.19; -0.01). The individual daytime nasal symptom scores were analyzed separately as secondary efficacy outcome measures. Singulair showed numerical improvement compared to placebo for congestion, rhinorrhea, and sneezing, but not nasal itching over the first 4 weeks of treatment. In a post hoc analysis, using these 3 nasal symptoms to form the primary efficacy variable (DNSS = nasal congestion, sneezing, and rhinorrhea), the results favored Singulair compared to placebo (LS mean difference –0.06; CI -0.12,-0.01). To confirm this finding, in the second study (Study 265), the Applicant excluded nasal itching from the DNSS.

Study 265 enrolled 1980 subjects (Singulair n = 1000; placebo n = 980) and was conducted for 6 weeks. The primary efficacy endpoint was measured at Week 6. The study was powered to detect a treatment difference of 0.075 between Singulair and placebo with a two-sided test $\alpha = 0.05$. At Week 6, the LS mean difference between Singulair and placebo for the DNSS was -0.08 (CI -0.12, -0.04). Evaluation of the treatment effect by each week showed that efficacy was demonstrated during the first week and was maintained throughout the 6-week treatment period.

Although one pivotal study is enough to support approval of the product for the PAR indication, it should be noted that the efficacy demonstrated in this development program is very small. Statistical significance aside, it should be underscored that the statistical threshold for efficacy was achieved in a study where the applicant doubled the size of the patient population and decreased the effect size to ~ ¾ of what it was in the first study. Therefore, although statistically significant, and supportive of approval from a regulatory standpoint, these data are anything but robust.

There were no new safety findings in the PAR study. Studies in pediatric patients under 15 years of age were not conducted because efficacy could be extrapolated from the efficacy data in the adults given that the disease course and the drug effects are similar in adults and children (Pediatric Rule 21CFR 201.57 (iv)). Therefore, safety in patients 6 months to 14 years of age was supported by safety data from asthma and seasonal allergic rhinitis trials and pharmacokinetic (PK) data. Safety in children under 1 year of age was supported primarily from pharmacokinetic data since there were no asthma or SAR studies in this age group. The PK data indicated that the exposure (AUC) to Singulair was higher (AUC values up to 48% higher) and more variable in patients $\geq$ 6 months to < 1year of age following administration of 4 mg granules compared to adults following administration of the 10 mg tablet. However, this higher exposure does not appear to be a safety concern since adults have been exposed to systemic exposures $\geq$ 7 times higher than that seen in children without any safety concerns.

Interdisciplinary Issues

Apart from the PK data mentioned above as it relates to safety, there were no other interdisciplinary issues with this application. The drug products under evaluation for the new indication are approved and marketed in the U.S.

Data Integrity/DSI Audit

There were no integrity concerns with the data and given that the drug products are not new and an indication for SAR has already been obtained a DIS audit was deemed unnecessary.

Pediatric considerations

The Applicant requested a partial waiver of pediatric studies for patients under 6 months of age. This is appropriate given that there is no clear evidence of perennial allergic rhinitis in patients under 6 months. This argument is reasonable and I recommend that the Applicant be granted a partial waiver for PAR studies for patients under 6 months of age.

Labeling

Labeling consultations were sent to DDMAC and DSRCS (Division of Surveillance, Research and Communication Support – ODS) and their labeling recommendations were taken into account with the labeling changes made to the PI, Patient Instructions for Use, and sample cartons, blisters and trays. At the time of this writing, labeling discussions have been conducted with the Applicant. The main changes to the PI are in the Clinical Trials, Indication and Usage, Precautions, Adverse Reactions, Dosage and Administration, and Pediatric Use sections. These sections have been updated to incorporate relevant information about the perennial allergic rhinitis clinical trials, the age for which the products are approved for that indication, and relevant safety and dosing information. The Applicant has agreed to all the Division's labeling recommendations for the PI.

Of note is that for the change from baseline in Table 4 of the PI, the Applicant uses the mean values (0.42 [Singulair] and 0.35 [placebo]) whereas, in the Primary Medical Officer review, the LS mean values are used (0.44 [Singulair] and 0.37 [placebo]) throughout the review instead. Both values are correct. It is noted that in Table 3 of the PI that displays the SAR study results, the Applicant uses mean values and not LS means. Therefore, for consistency it is appropriate to report the results as mean values for the PAR study. The difference from placebo and the confidence intervals remain the same whether mean or LS mean values are used.

Conclusions and Recommendations on Approvability

The data support the efficacy (albeit small) of Singulair for the treatment of the symptoms of perennial allergic rhinitis and I recommend that the application be given and APPROVAL action.

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/s/

Lydia McClain
7/26/05 12:07:41 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	20-829, 20-830, 21-409
Submission Code	SE1/033, SE1/035, SE1/012
Letter Date	9/30/04
Stamp Date	10/5/04
PDUFA Goal Date	7/31/05
Reviewer Name	Tejashri Purohit-Sheth
Review Completion Date	7/11/05
Established Name	Montelukast Sodium
(Proposed) Trade Name	Singulair™
Therapeutic Class	Leukotriene Antagonist
Applicant	Merck Research Laboratories
Priority Designation	S
Formulation	Tablets, Chewable Tablets, Granules
Dosing Regimen	Once daily
Indication	Perennial Allergic Rhinitis
Intended Population	6 months and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends an "Approval" action for this NDA.

The clinical trials submitted in this application support the efficacy and safety of the applicant's product for the treatment of the symptoms of perennial allergic rhinitis PAR in patients 15 years of age and older. As the pathophysiology of PAR is similar in adults and children, the efficacy in PAR is extrapolated to children 6 months of age and older. Safety data from clinical and pharmacology studies previously submitted to NDA 21-409 (Singulair™ Oral Granules) and NDA 21-829 (Singulair™ 10-mg Film Coated Tablets), support the safety in patients 6 months of age and older.

1.2 Recommendation on Postmarketing Actions

No postmarketing actions are needed for this already marketed product.

1.3 Summary of Clinical Findings

1.3.1 BRIEF OVERVIEW OF CLINICAL PROGRAM

Merck Research Laboratories' (MRL) product SINGULAIR™ (montelukast sodium) is currently indicated for the prophylaxis and treatment of symptoms of asthma in adults and pediatric patients 12 months of age and older, and for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older. It is currently available as 10-mg film-coated tablets, 4-mg and 5-mg chewable tablets, and 4-mg oral granules. The applicant submits this supplemental application to all of the previously approved New Drug Applications (NDAs) for all of these formulations for the treatment of symptoms of perennial allergic rhinitis in adults and children 6 months and older.

This supplemental application for Singulair is intended to support a new indication for prescription marketing. The proposed indication is for the symptoms of perennial allergic rhinitis in adults and children 6 months of age and older. The proposed dosage in patients 6 to 23 months of age is 4-mg oral granules once daily (b) (4) The proposed dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules daily. The proposed dosage in patients 6 to 14 years of age and in patients 15 years of age and older is one 5-mg chewable tablet and one 10-mg tablet daily, respectively.

This clinical program consisted of two clinical studies; however, the applicant considers only one as pivotal (265) and the other as supportive (264), although both were Phase 3 studies. This reviewer considers both studies as pivotal. Both trials were multicenter, randomized, double-blind, placebo controlled 4-week safety and efficacy studies evaluating the efficacy of Singulair for the relief of symptoms of PAR in patients 15 years of age and older. However, there were some notable differences in the design of these trials.

Study 246 was conducted first, and also included an active comparator, cetirizine. In this study, the applicant was unable to show a statistically significant difference between Singulair and placebo for the primary efficacy endpoint, Daytime Nasal Symptom Score (DNSS), which was a composite of nasal congestion, sneezing, rhinorrhea, and nasal pruritus. The sponsor attributed this lack of efficacy to the individual symptom of pruritus, for which Singulair did not show benefit, whereas benefit was noted in the other individual symptoms. Thus, for the second study (265), considered "pivotal" by the applicant, the applicant based the primary efficacy endpoint, (Daytime Nasal Symptom Score), on only nasal congestion, rhinorrhea, and sneezing and excluded pruritus.

To utilize the results of Study 246 in a supportive manner, the applicant conducted a post-hoc analysis. The applicant re-analyzed the results using the identical DNSS as defined in Study 265, excluding nasal pruritus. Although post-hoc analyses have their limitations, this analysis demonstrated that Singulair was superior to placebo with respect to the primary efficacy endpoint used in Study 265. These results are considered supportive for the efficacy of Singulair.

Although both pivotal studies were conducted in patients 15 years of age and older, efficacy can be extrapolated to younger children as the pathophysiology of disease is similar in adults and children. This ability to extrapolate data is based on previously conducted pharmacokinetic studies demonstrating similar or greater systemic exposure in children and adults.

As Singulair is currently approved in patients 12 months of age and older, safety findings from the previously approved Singulair applications may be referenced to provide for safety in patients with PAR down to 12 months of age. However, safety of the proposed 6 months to < 12 months of age population needed to be addressed in this sNDA.

The applicant states that previously submitted information in NDA 21-409 Singulair™ Oral Granules is sufficient to support the safety in the 6 to < 12 months of age population. In NDA 21-409, the applicant submitted results of two studies containing data in patients with asthma ages 6 to < 24 months of age. One study was a pharmacokinetic study comparing systemic exposure in this pediatric age group to adults and children 2 to < 5 years of age. Also, a safety and efficacy study was conducted in the 6 to < 24 month age group. Theses studies were previously reviewed in-depth by the medical officer [Dr. Peter Starke, Medical Officer Review, NDA 21-409, N-000, 9/28/01] and the clinical pharmacology reviewer [Dr. Sandra Suarez, Clinical Pharmacology Review, NDA 21-409].

Based on re-evaluation of these reviewed data, safety is supported in the 6 to < 12 months of age group.

1.3.2 EFFICACY

The applicant conducted two phase III multicenter, randomized, double-blind, placebo-controlled trials in patients 15 years of age and older to support the efficacy of Singulair for the relief of symptoms associated with perennial allergic rhinitis. Although the first study failed to demonstrate a statistically significant improvement in the pre-specified primary efficacy endpoint, a post hoc analysis using an efficacy endpoint comprised of 3 nasal symptoms (congestion, rhinorrhea, and sneezing) favored Singulair over placebo.

In the first study, Study 246, the pre-specified primary efficacy endpoint was the change from baseline in DNSS, which comprised the average of nasal congestion, rhinorrhea, sneezing and pruritus. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.39 (95% CI: -0.43, -0.36), -0.45 (95% CI: -0.54, -0.37) in the cetirizine group, and -0.36 (95% CI:-0.39, -0.32) in the placebo group. The LS Mean difference between montelukast and placebo was -0.04 (95% CI: -0.09, 0.01), which was not statistically significant (p=0.150). However, the LS Mean difference between cetirizine and placebo of -0.10 (95% CI: -0.19, -0.01) was statistically significant (p=0.038). A trend favoring montelukast was noted in three of the four individual nasal symptoms and other secondary endpoints.

To explore this trend, a post-hoc analysis was performed defining the primary efficacy endpoint using three symptom excluding pruritus, since efficacy was not demonstrated for this individual symptom. The LS Mean changes from Baseline for montelukast, cetirizine, and placebo using 3 symptoms in the DNSS averaged over the first 4-week period were -0.40 (95% CI: -0.44, -0.36), -0.45 (95% CI: -0.54, -0.36), and -0.34 (95% CI: -0.38, -0.30), respectively, with a corresponding LS Mean difference between montelukast and placebo of -0.05 (95% CI: -0.11, 0.00). The exclusion of nasal pruritus from the primary efficacy endpoint did increase the effect size.

If the DNSS defined with 3 symptoms is averaged over the entire 6week study period, the corresponding LS Mean changes from Baseline for montelukast, cetirizine, and placebo were -0.46 (95% CI: -0.50, -0.42), -0.48 (95% CI: -0.57, -0.39), and -0.40 (95% CI; -0.44, -0.36), respectively. In this case, the LS Mean difference between montelukast and placebo was -0.06 (95% CI: -0.12, -0.01).

For Study 265, the DNSS was defined using only three symptoms: nasal congestion, rhinorrhea, and sneezing. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.44 with a 95% CI of {-0.48,-0.41} and in the placebo group was -0.37 with a 95% CI of {-0.40,-0.35}. The difference between treatment groups was -0.08, with a 95% CI of {-0.12; -0.04}. This difference between montelukast and placebo was statistically significant at a $p \leq 0.001$. All secondary endpoints also favored montelukast compared to placebo. Of note, in this study, montelukast was noted to show numerical improvement in the individual symptom of nasal pruritus, in contrast to Study 246. When the secondary endpoint of DNSS + pruritus (the pre-specified primary in Study 246), is evaluated, the results are consistent with those noted for the pre-specified primary efficacy endpoint.

Therefore, although Study 246 failed to demonstrate efficacy of Singulair for the treatment of symptoms of perennial allergic rhinitis, Study 265 did demonstrate that Singulair was superior to placebo for the primary efficacy endpoint as well as for secondary endpoints. Not only did the second study demonstrate improvements in the DNSS when defined as the average of 3 nasal symptoms, but also when the DNSS was defined as the average of 4 nasal symptoms as defined in the initial study.

The applicant has met the minimum regulatory requirements to obtain approval in PAR, since only one pivotal PAR study showing efficacy is necessary to support an approval if an indication already exists in SAR. The results of the initial study are supportive of the second study which demonstrated the efficacy of montelukast in the treatment of symptoms of PAR. Overall, the submitted data support the modest efficacy of Singulair for the relief of symptoms of perennial allergic rhinitis.

1.3.3 SAFETY

The safety of montelukast for patients 6 months of age and older with perennial allergic rhinitis is supported by the Applicant's clinical studies, the Agency's previous determination of safety in patients 12 months of age and older with asthma and 2 years of age and older with SAR, the Agency's previous evaluation of systemic exposures with montelukast in adults and children 6 months of age and older, the Applicant's literature search, and summary of post-marketing experience.

The safety in patients 15 years of age and older with perennial allergic rhinitis is supported by the two pivotal studies (246 and 265) submitted with this sNDA. Both studies demonstrated that montelukast was generally well tolerated. A total of 1632 patients were exposed to montelukast in the two pivotal studies for a mean of 39.2 days. No deaths were reported in either study. The types and frequencies of reported serious adverse events and adverse events were generally similar to placebo, and consistent with previous experience in asthma and SAR studies and post-marketing experience.

The safety in pediatric patients 2 years of age to 14 years of age with perennial allergic rhinitis is supported by the established safety in children 2 years of age and older with seasonal allergic rhinitis. In the pediatric population 12 to 23 months of age with perennial allergic rhinitis, safety is supported by the established safety in previously conducted asthma studies in this age group.

For patients ages 6 months to < 12 months of age, safety is supported by previously conducted pharmacokinetic studies in both pediatric (Study 136) and adult (Study 003) patients and safety studies conducted in patients 6 to 23 months of age with asthma (Study 171 and 232). Study 136 demonstrated that systemic exposures in children 6 to < 12 months of age were 48% greater than noted for adults at currently prescribed doses. However, results from Study 003 suggest that this 48% greater systemic exposure does not raise any specific safety concerns. Adults had systemic exposures that were more than 7 times the exposure noted in these children without any corresponding safety concerns. Additionally, montelukast was evaluated in children 6 months to 23 months of age with asthma in a 12 week safety study (171) followed by an open-label

extension phase (232), and was generally well tolerated. Therefore, the pharmacokinetic and safety studies in children 6 to 23 months of age with asthma, previously evaluated by the Agency, lend support for the safety in children 6 to <12 months of age.

The Applicant's review of the literature and review of postmarketing experience did not reveal any new safety issues; the types and frequencies of reported adverse events are consistent with previous experience.

1.3.4 DOSING REGIMEN AND ADMINISTRATION

This application does not alter the currently approved dosing regimen with respect to asthma or seasonal allergic rhinitis. For PAR in patients 12 months and older, the currently approved dosing regimen is identical to that currently approved for asthma and seasonal allergic rhinitis. This application provides for the (b) (4) to patients 6 months to < 12 months of age. The proposed dosage in patients 6 to 23 months of age is 4-mg oral granules once daily (b) (4). The proposed dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules daily. The proposed dosage in patients 6 to 14 years of age is one 5-mg chewable tablet and in patients 15 years of age is one 10-mg tablet daily.

1.3.5 DRUG-DRUG INTERACTIONS

Information about drug-drug interaction was not required for this application and none was provided.

1.3.6 SPECIAL POPULATIONS

The applicant did not conduct any new investigations specifically targeted towards any special population as part of this supplemental NDA.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Montelukast sodium is an orally active cysteinyl leukotriene type ($CysLT_1$) receptor antagonist. It is currently approved in the United States as well as numerous countries in the European Union and world-wide for the relief of symptoms of seasonal allergic rhinitis (SAR) in adults and pediatric patients 2 years of age and older. Montelukast is also approved in 83 countries for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

2.2 Currently Available Treatment for Indications

Currently, the major pharmaceutical therapies available are anti-histamines (oral and intranasal) and intranasal corticosteroids. Singulair is an additional option for patients with SAR. Since the underlying pathophysiology for SAR and PAR is similar, and patients with SAR have shown modest benefits with Singulair, it can be expected that blockade of the $CysLT_1$ receptor in patients with PAR will have some clinical benefit as well.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, montelukast sodium, is currently approved for and is marketed in the United States as Singulair ™ 10-mg film-coated tablets (NDA 20-829), 4-mg and 5-mg chewable tablets(NDA 20-830), and 4-mg oral granules (NDA-21-409).

2.4 Important Issues with Pharmacologically Related Products

No relevant issues.

2.5 Presubmission Regulatory Activity

The original marketing applications for Singulair 10-mg film coated tablets (NDA 20-829) and 5-mg chewable tablets (NDA 20-830) were approved on February 20, 1998. A supplemental application for 4-mg chewable tablets was approved on March 3, 2000 (NDA 20-830/S-008). An application for Singulair Oral Granules (NDA 21-409) was approved July 26, 2000. The above applications were submitted for the treatment of asthma. A supplemental application was filed to all of the above NDAs for the treatment of symptoms of seasonal allergic rhinitis and approved on December 31, 2002.

The sponsor now submits this efficacy supplement in support of the treatment of symptoms of perennial allergic rhinitis in pediatric patients 6 months and older and adults. Prior to the submission of this NDA, a teleconference was held at the sponsor's request on May 30, 2003 when concurrence on the registration with one pivotal PAR study and concurrence on the proposed study design for said pivotal study were requested and obtained.

2.6 Other Relevant Background Information

Since allergic rhinitis (seasonal and perennial) is a similar disease in adults and children, and therefore can be treated with similar medications, any demonstrated efficacy for PAR in adults can be extrapolated to pediatric patients. This is consistent with the approach accepted for approval of Singulair for SAR. Therefore, the pivotal studies for PAR were done in adults and adolescents 15 years of age and older.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

Since Singulair is an approved product, there are no Chemistry, Manufacturing, and Control, Pharmacology/Toxicology/Microbiology sections submitted with this application, nor were they

required. Significant findings from Clinical Pharmacology are summarized in Section 5, Clinical Pharmacology.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The evaluation of safety and efficacy for the treatment of PAR in patients 15 years of age and older was based on the review of two safety and efficacy studies submitted in this application, Studies 265 and 246. The safety and efficacy for children 12 months to 14 years of age for the treatment of PAR was supported by the established safety and effectiveness in patients with seasonal allergic rhinitis and asthma. To support the safety in pediatric patients 6 months to < 12 months of age, an age group for whom Singulair is not approved, previously conducted evaluations by Dr. Sandra Suarez, Clinical Pharmacology Reviewer (Study 136) and Dr. Peter Starke, Medical Reviewer (Studies 171) for NDA 21-409 were consulted. Additionally, Clinical Study Reports (Studies 136, 171, and 232) and Synopses (Study 003) submitted by the applicant as a part of this submission were briefly re-evaluated.

4.2 Tables of Clinical Studies

Data from a total of 6 studies are summarized in this application. The 2 pivotal studies submitted in this application, Studies 265 and 246 are reviewed in-depth in the appendix. Data from pharmacokinetic studies, Studies 136 and 003, are briefly summarized in Section 5, *Clinical Pharmacology*, and data from two safety studies in pediatric patients 6 months to < 12 months of age, Studies 171 and 232, are briefly summarized in Section 7, *Integrated Review of Safety*. The clinical studies reviewed in-depth and consulted from previously conducted reviews are summarized in tabular format in the following section.

Table 1. Summary of Pivotal Studies Submitted with this Supplemental NDA

Study	Design	Duration	Dosage	Patients	Evaluations
P246	Phase III, 6-week, multicenter, randomized, parallel group, double-blind, placebo and active- controlled trial in PAR patients ages 15-82 yrs	*6 weeks	Montelukast 10 mg Cetirizine 10 mg Placebo	1356 M*=630 C=122 P=613	Primary Efficacy Daytime Nasal Sx Score (nasal congestion, sneezing, rhinorrhea, nasal pruritus)
P265	Phase III, 6-week, multicenter (16), randomized, double-blind, parallel, placebo controlled trial in PAR patients ages 15-81 yrs	6 weeks	Montelukast 10 mg Placebo	1992 M=1002 P=990	Safety: AEs Lab AEs Exploratory efficacy

*Primary efficacy measure at 4 weeks

Table 2. Summary of Studies Previously Reviewed by the Agency that Were Consulted in Review of this Supplemental NDA

Study	Design	Treatment Groups	Duration	Dosage	Subjects n / Sex	Evaluations /
P136	Multi-center, open-label, randomized, single-dose PK study	Boys and girls, ages ≥6 to <24 months, between 6kg and 15 kg, with a history of asthma or "asthma-like" symptoms who might benefit from controller therapy	1 single dose	4 mg oral granules in applesauce	Total: 26 evaluable 14 M 18 F 6-11m: 14 12-23m: 18	Pop PK: AUC_{pop} C_{max} T_{max} $t_{1/2}$ C_{24hr} Cl/F Safety
P176	Multi-center, randomized, double-blind, placebo-controlled, parallel group safety and tolerability study	Boys and girls, ages ≥6 to <24 months, with a history of 3 episodes of asthma or "asthma-like" symptoms after 8 weeks of age and within 6 months of the study	6 weeks	4 mg oral granules Placebo mixed in applesauce QD at night	Total 256 175/169 * M: 116 F: 59 81/74 *	Safety: AEs Lab AEs Exploratory efficacy:
232	Extension study for 171; Multi-center, randomized, open-label, parallel group, active controlled extension study	Boys and girls, ages ≥6 to <24 months, between 6kg and 15 kg, with a history of asthma or "asthma-like" symptoms who might benefit from controller therapy	52 weeks	4 mg oral granules Usual care group (beta agonists, steroids)	Total 113	Safety AEs Labs
P003	Single-center, randomized, double-blind, placebo-controlled, multiple-dose, time-lagged, serial panel, pharmacokinetic study	Healthy adult males ages 18-45 years of age	9 days	Singulair tablets: 50, 100, and 300 mg dosed three times daily	24 males	PK: AUC_{0-8} $AUC_{0-\infty}$ C_{max} T_{max} $t_{1/2}$ Safety
* Enrolled/Completed number of patients						

4.3 Review Strategy

The applicant submitted two pivotal studies in this NDA to support the safety and efficacy in patients 15 years of age and older with PAR, Studies 065 and 246. Both of these studies were reviewed in-depth in the Appendix and summary data provided in other applicable portions of this review. The efficacy for children 6 months to 14 years of age is extrapolated for the results in adults and the safety is supported by previously submitted and reviewed data.

The safety in pediatric patients 2 years of age and older with perennial allergic rhinitis was supported by the established safety of montelukast in children 2 years of age and older with

seasonal allergic rhinitis and asthma. In the pediatric population 12 to 23 months of age with perennial allergic rhinitis, safety was supported by the established safety in previously conducted asthma studies in this age group.

For patients ages 6 months to < 12 months of age, safety was supported by re-evaluation of previously conducted pharmacokinetic studies in both pediatric (Study 136) and adult (Study 003) patients and safety studies conducted in patients 6 to 23 months of age with asthma (Study 171 and 232). Previously conducted evaluations by Dr. Sandra Suarez, Clinical Pharmacology Reviewer and Dr. Peter Starke, Medical Reviewer for NDA 21-409 were consulted. Additionally, Clinical Study Reports and Synopses of the previously reviewed data were re-evaluated briefly.

4.4 Data Quality and Integrity

No DSI audits were requested for this NDA. Singulair is not a new molecular entity. No irregularities necessitating review by DSI were raised during the review process.

4.5 Compliance with Good Clinical Practices

The protocols were reviewed by the Independent Ethics Committee (IEC) or the Institutional Review Board (IRB) of each study site. IEC and IRB approval letters were received and verified before the shipment of study drug.

The studies was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. The studies were in compliance with Good Clinical Practices.

4.6 Financial Disclosures

Studies 246 and 265 had 705 and 489 total investigators per protocol, respectively. In Study 246 26 investigators (3.7%) had financial disclosures, and in Study 265, 15 investigators (3.1%) had financial disclosures. The percentage of investigators that had financial disclosures were quite low, and it is unlikely that this would affect the interpretation of the final results [NDA 20,829, SE1-033-C, 11/18/04].

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetic properties of montelukast were extensively evaluated and reviewed by the Agency previously as part of the original and supplemental NDAs for all formulations approved thus far. The reader is referred to the current package insert for the pharmacokinetic

characteristics and to previous Agency reviews of NDA 20-829, 20-830 and 21-409 for in-depth reviews of the data.

However, to support the safety of montelukast in pediatric patients ages 6 months to < 12 months of age, a population for which montelukast is currently not approved, previously reviewed pharmacokinetic data were revisited. Results of Study 136 (a PK study in children 6 to < 24 months of age) and Study 003 (an adult PK study) will be briefly summarized. The reader is referred to Clinical Pharmacology Reviews of NDAs 20-829 (Study 003) and 21-409 (Study 136) for in-depth reviews.

The systemic exposure data from the pediatric and adult studies will be compared. In both of these studies, montelukast was generally well tolerated, without any new clinical concerns raised. The safety information will be briefly summarized in the *Other Studies* section under the *Integrated Review of Safety,* Section 7.2.2.1.

5.1.1 STUDY 136

Relevant to the pediatric population of interest, the applicant conducted one pharmacokinetic study in patients ages 6 months to < 24 months of age, with data stratified according to age group: 6 months to < 12 months of age and 12 months to < 24 months of age. This study was previously submitted as part of NDA 21-409 for Singulair ™ Oral Granules and was extensively reviewed by Dr. Sandra Suarez, Clinical Pharmacology Reviewer.

Study 136 was an open label, single dose, multicenter pharmacokinetic study evaluating the safety, tolerability, and plasma concentration profiles of Singulair Oral Granules in children 6 months to <24 months of age. This study evaluated and compared montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax) obtained from the 6 to <24-month-old children after administration of a 4-mg dose of the sprinkle formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the film-coated tablets of montelukast using a population PK approach.

The results of these analyses showed that in children 6 months to < 1 year of age, AUC values ranged from 1200 ng*hr/mL to 7153 ng*hr/mL and the geometric mean value was 48% higher than that observed in adults. Cmax ranged from 465.1 to 1057.8 ng/ml and the mean value increased by 79% compared to adults. The systemic exposure in the 1 year to <2 year olds was less variable, but still higher compared to that in adults. The mean AUC was 34% higher and the mean Cmax was 58% higher that those observed in adults (Table 3). No correlation was found between the pharmacokinetic parameters clearance and volume of distribution and weight or age. These results are summarized in the table below which was excerpted from Dr. Suarez's review.

Table 3. Mean montelukast population PK parameters following single administration of Singulair sprinkles 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets 4-mg to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM [excerpted from Clinical Pharmacology Review, Dr. Sandra Suarez, NDA 21-409].

	Montelukast formulations: sprinkles, chewable tablets, film-coated tablets				
PK Parameter	**Children ≥6m to <1y**	**Children ≥1y to <2y**	**Children ≥6m to <2y**	**Children ≥2y to <6y**	**Adults**
AUC_{pop} (ng*hr/mL)[a]	4298.2±542.1	3573.4±907.1	3907 ±286.4	2761.1±200.7*	2644.8±154.1
$Cmax_{pop}$ (ng/mL) [a]	666.6±77.9	561.9±47.4	610.2 ±44.4	504.4±46.1*	352.6±25.53**
CL_{pop} (ml/min) [a]	20.47±4.1	19.59±1.33	19.96±1.86	25.7±1.58*	66.7±18.75
Tmax (hr) [b]	1.5±0.2	1.52±0.16	1.51±0.18	1.81±0.78	3.87±1.36**
T1/2[b]	3.39±1.5	3.37±0.97	3.38±1.22	2.36±0.9	1.94±0.33[c]

[a] mean ± SE; [b]mean±SD; *Data estimated using NONMEM from protocol no. 066; **calculated using non-compartmental methods; [c]based on 2CBM parameters

Source: Clinical Pharmacology Review, Dr. Sandra Suarez, NDA 21-409

Dr. Suarez concluded that high variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 year of age. A lower dose of Singulair Oral Granules for this population would give a similar systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target AUC of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, a dose of 4-mg Oral Granules was recommended for the 6 months to < 12 months of age group with respect to efficacy. However, it was recommended that the medical officer evaluate the safety of 48% greater systemic exposure in children 6 months to < 12 months of age as compared to adults.

5.1.2 STUDY 003

To evaluate the safety of a 48% greater systemic exposure (based on geometric mean AUC data), this reviewer consulted a pharmacokinetic study (003) previously conducted in adults, where systemic exposures noted in adults far exceeded what was noted in the pediatric patients in Study 136. This was a randomized, double-blind, placebo-controlled, pharmacokinetic study in healthy male volunteers to investigate the safety and tolerability of multiple oral doses of montelukast. The study was conducted as part of the original NDA application for montelukast 10-mg tablets and was previously reviewed by the Agency. These results are briefly summarized.

A total of 24 healthy males ages 18 to 45 years were enrolled. Montelukast 50 mg, 100 mg, and 300 mg capsules or matching placebo were dosed three times daily for 8 and 1/3 days. Pharmacokinetic profiles were assessed. The geometric mean ratios (GMR) for AUC for day 1 ($AUC_{0-\infty}$) and Day 9 (AUC_{0-8}) were compared. The following table summarizes these results [taken from Reference R11 submitted as part of this sNDA].

Geometric Mean Ratio (GMR) Comparing Day 1 $AUC_{(0-\infty)}$ and Day 9 $AUC_{(0-8)}$ [µg•hr/mL] for Doses of MK-0476

Dose:Day	N	Geometric Mean	GMR of Day 9 to Day 1	90% CI For GMR of Day 9 to Day 1	p-Value#
50 mg					
Day 1	6	8.30	1.51	(1.07, 2.12)	0.061
Day 9	6	12.50			
100 mg					
Day 1	6	23.24	1.87	(1.08, 3.24)	0.071
Day 9	6	43.41			
300 mg					
Day 1	6	58.74	2.49	(1.51, 4.08)	0.014
Day 9	6	146.04			
# p-Values based on paired t-test on log scale					

Source: Clinical Overview, Reference R11

If the AUC geometric means are converted to ng*hr/mL to be able to compare AUC data from the pediatric study discussed above (136), the AUC varies from 8030 ng*hr/mL to 58,740 ng*hr/mL following single doses ranging from 50 mg to 300 mg. The exposure is even higher when Day 9 results are reviewed (12,500 to 146,040 ng*hr/mL). The applicant concluded that with multiple dosing, plasma concentrations of montelukast accumulate to a greater extent than predicted by the single-dose plasma profiles and that the pharmacokinetics of montelukast may be dose dependent, and that the drug was generally well tolerated.

5.1.3 CONCLUSIONS FROM STUDIES 136 AND 003

The results of these studies were presented to support the safety of montelukast oral granules in children 6 months to < 12 months of age. The results of Study 136 demonstrated that following single doses of 4 mg oral granules in children 6 to < 12 months of age, the systemic exposure (based on geometric mean AUC data) was about 48% higher in these children as compared to historical adult controls who received 10 mg doses in previously conducted studies. However, safety evaluation demonstrated that 4mg oral granules were generally well tolerated [see section 7.2.2.1].

Study 003 provided exposure data from single and multiple dosing in adults, where systemic exposures far exceeded the highest exposure in the children noted in Study 136. In study 136, the systemic exposure in children 6 to < 12 months of age ranged from 1200 ng*hr/mL to 7153 ng*hr/mL. From Study 003, following single oral doses of 50 to 300 mg in adults, the exposure ranged from 8000 ng*hr/mL to 146,040 ng*hr/mL. This study evaluated the safety and tolerability in adults with exposures up to 6 times higher than those noted in children 6 to < 12 months of age. In general, even at such high exposures in adults, there were no safety concerns [see section 7.2.2.1].

Therefore, although Study 136 demonstrated systemic exposures in children 6 to < 12 months of age that were 48% greater than noted for adults at currently prescribed doses, results from 003 suggest that this 48% greater systemic exposure does not raise any specific safety concerns. The safety in children 6 to < 12 months of age is supported by the safety noted in adults with systemic exposures 7 or more times higher than the highest exposure noted in children 6 to < 12 months of age. Since both studies demonstrated that montelukast was generally well tolerated, this is supportive of the safety in children 6 months to < 12 months.

5.2 Pharmacodynamics

Other than the two pivotal phase III clinical trials submitted in this application, which will be summarized in the following section and reviewed in detail in the Appendices, no other specific clinical pharmacodynamic studies were conducted or reviewed in support of this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

This application is submitted to support the use of montelukast tablets, chewable tablets, and oral granules for the relief of symptoms associated with perennial allergic rhinitis in adults and pediatric patients 6 months of age and older.

6.1.1 METHODS

Studies 246 and 265 were the phase III studies submitted to support the new indication and constituted the primary basis in this review to support the efficacy in patients 15 years of age and older with perennial allergic rhinitis. Each of these two studies was reviewed in detail and the individual reviews are found in Section 10-*Appendices*.

It should be noted that the applicant only considered one of the phase III studies as pivotal support for the efficacy in perennial allergic rhinitis, Study 265. The Agency had previously agreed with the applicant that one pivotal study would be acceptable to provide the basis for efficacy for the treatment of symptoms associated with perennial allergic rhinitis [Meeting Minutes for 5/3/2003 meeting with Industry]. This is consistent with regulatory guidance that states that when accompanied by substantial evidence in seasonal allergic rhinitis, a single pivotal study demonstrating efficacy in perennial allergic rhinitis may be considered substantial evidence for product labeling [Guidance for Industry: Allergic Rhinitis: Clinical Development Programs for Drug Products; DRAFT GUIDANCE April 2000]. Since montelukast is already approved for the treatment of symptoms associated with seasonal allergic rhinitis, this approach was considered acceptable and consistent with previous regulatory decisions. However, as the applicant conducted two trials it was deemed important to evaluate both and consider them pivotal, although the decision to approve may rest on the substantial finding of efficacy from one trial.

Study 246 was the study conducted initially to support the proposed indication; however, for the pre-specified primary efficacy endpoint (DNSS using 4 nasal symptoms), the applicant was unable to show a statistically significant difference between montelukast and placebo. For study 265, the applicant changed the primary efficacy endpoint to exclude one of the 4 nasal symptoms. Since this study was able to demonstrate a statistically significant difference between montelukast and placebo, the applicant considered this study as the pivotal study to support the efficacy for montelukast in the treatment of symptoms associated with perennial allergic rhinitis. This reviewer evaluated both studies in detail considering them both as pivotal in the evaluation of efficacy.

Both of these studies were conducted in patients 15 years of age and older with perennial allergic rhinitis. Since the pathophysiology of the disease is similar in adults and children, efficacy is extrapolated down to children 6 months of age and older. This is consistent with the Pediatric Rule that states that the Agency may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the Agency would have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult population to permit extrapolation from the adult efficacy data to pediatric patients [(21CFR 201.57 (9) (iv)].

6.1.2 GENERAL DISCUSSION OF ENDPOINTS

The primary efficacy endpoint for both trials was the change from Baseline in the Daytime Nasal Symptoms Score (DNSS). However, the DNSS was defined differently for each study. Study 246 was initially conducted, with the DNSS representing the average of each of the following nasal symptoms: congestion, rhinorrhea, pruritus, and sneezing. When this trial failed to demonstrate a statistically significant difference between montelukast and placebo for this primary efficacy endpoint, the applicant conducted a second trial, Study 265. Based on results from Study 246 where efficacy was not noted for nasal pruritus, the applicant changed the DNSS to comprise the average of the following three nasal symptoms, excluding pruritus: congestion, rhinorrhea, and sneezing. The Draft Guidance for Allergic Rhinitis recommends using DNSS as the primary efficacy endpoint which could comprise either three or four nasal symptoms. The use of either three or four symptoms in the DNSS is acceptable.

Additionally, the applicant conducted a post-hoc analysis redefining the DNSS in Study 246 to include the same three nasal symptoms used to define the DNSS in Study 265: nasal congestion, rhinorrhea, and sneezing. Although this was a post-hoc analysis, this analysis was considered useful to support the efficacy as it allowed for cross-study comparisons using the same primary efficacy endpoint.

The major secondary endpoints for both studies included the following:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Daily Rhinitis score
- Daytime Nasal Symptoms + Itching score

- End-of-Day Nasal Symptoms + Itching score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Rhinoconjunctivitis Quality-of-Life score

The selected secondary endpoints were acceptable. The main focus from the secondary endpoints was on the individual symptom scores as well as the post-hoc analysis using the redefined DNSS in Study 246.

6.1.3 STUDY DESIGN

The two pivotal studies, 246 and 265 were adequate, well-controlled studies and provided a reasonable assessment for the nasal symptoms associated with perennial allergic rhinitis. The two studies were generally similar in design with a few exceptions, the major ones being the definition of the primary efficacy endpoint, and the inclusion of an active control (cetirizine) in study 246. These studies are summarized in tabular format below and in text following the table.

Table 4. Summary of Pivotal Phase III Trials

Study	Design	Duration	Dosage	Patients	Evaluations
P246	Phase III, 6-week, multicenter, randomized, parallel group, double-blind, placebo and active- controlled trial in PAR patients ages 15-82 yrs	*6 weeks	Montelukast 10 mg Cetirizine 10 mg Placebo	1356	Primary Efficacy Daytime Nasal Sx Score (nasal congestion, sneezing, rhinorrhea, nasal pruritus)
P265	Phase III, 6-week, multicenter (16), randomized, double-blind, parallel, placebo controlled trial in PAR patients ages 15-81 yrs	6 weeks	Montelukast 10 mg Placebo	1992	Safety: AEs Lab AEs Exploratory efficacy

*Primary efficacy endpoint measured at 4 weeks

Both studies were multicenter, randomized, double-blind, placebo controlled, parallel group trials in patients 15 years of age and older with perennial allergic rhinitis. Both consisted of a 6-week active treatment period preceded by a single-blind, placebo run-in period to establish eligibility for randomization and to establish baseline efficacy endpoint values. However, the primary efficacy endpoint was at Week 4 for study 246. Patients who were selected for study had active PAR, based on documented clinical history/diagnosis, active symptoms, and allergen skin testing. The allergenic extracts used for skin testing assessed allergens known to be associated with PAR (e.g., dust mites, animal dander [cat and dog antigens], cockroach, and mold spores [perennial fungi of Penicillium and Aspergillus species]).

In Study 246, patients were randomized to montelukast 10 mg once daily, cetirizine 10 mg once daily, or placebo. In Study 265, patients were randomized to either montelukast 10 mg once daily or to placebo.

The primary endpoint and several other secondary endpoints were based on patient self-rated symptom scores, from 0 (none) to 3 (severe), that were collected twice daily (morning and evening). The primary efficacy endpoint was change from baseline in the Daytime Nasal Symptoms Score, which was defined as the average of 3 or 4 nasal symptoms. In study 246, the DNSS comprised the average of 4 nasal symptoms: congestion, rhinorrhea, pruritus and sneezing. In Study 265, the DNSS comprised the average of 3 nasal symptoms: congestion, rhinorrhea, and sneezing.

The major secondary endpoints for both studies included the following:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Daily Rhinitis score
- Daytime Nasal Symptoms + Itching score
- End-of-Day Nasal Symptoms + Itching score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Rhinoconjunctivitis Quality-of-Life score

Additionally Study 246 included the following secondary endpoints: Composite Symptoms Score, average of the DNSS and Nighttime Symptoms Score, Daytime Eye Symptoms Score, Daytime Throat Symptoms Score, Rhinoconjunctivitis Quality-of-Life score, and Perennial Allergic Rhinitis score based on Perennial Allergic Rhinitis Questionnaire.

6.1.4 EFFICACY FINDINGS

6.1.4.1 Patient Disposition

In both studies, the majority of the patients, 87 – 92% completed the study. The percentage of patients discontinuing from the studies ranged from 8 to 14%. In general, the percentage of patients discontinuing secondary to an adverse event was low (3 to 5%). The patient disposition for both studies is summarized in the following table.

Table 5. Patient Disposition for Studies 246 and 265

	Study 246			Study 265	
Status	**Montelukast** n (%)	**Cetirizine** n (%)	**Placebo** n (%)	**Montelukast** n (%)	**Placebo** n (%)
Number of patients randomized	630	122	613	1002	990
ITT for efficacy	626 (99.4)	120 (98.4)	609 (99.3)	1000 (99.8)	980 (99.0)
Number of patients completing study	562 (89.2)	106 (86.9)	530 (86.5)	913 (91.1)	906 (91.5)

	Study 246			Study 265	
Status	Montelukast n (%)	Cetirizine n (%)	Placebo n (%)	Montelukast n (%)	Placebo n (%)
Number of patients discontinued	68 (10.8)	16 (13.1)	83 (13.5)	89 (8.9)	84 (8.5)
Adverse event*	29 (4.6)	4 (3.3)	24 (3.9)	32 (3.2)	35 (3.5)
Protocol Deviation	13 (2.5)	4.9 (3.3)	18 (2.9)	25 (2.5)	23 (2.3)
Treatment failure	3 (0.5)	2 (1.6)	9 (1.5)	14 (1.4)	12 (1.2)
Withdrawal of Consent	14 (2.2)	5 (4.0)	16 (2.6)	10 (1.0)	4 (0.40)
Lost to follow-up	2 (0.3)	1 (0.8)	2 (0.3)	3 (0.30)	4 (0.40)
Other	5 (0.8)	0	11 (1.8)	5 (0.50)	6 (0.60)

*Includes 1 patient in Study 246 who discontinued after randomization due to an AE that began prior to randomization

Source: Vol. 4, p. 74; clinstat/studies/p264.pdf/appendix 4.5.1/1335; Vol. 5, p. 58-59

6.1.4.2 Demographics/Baseline Characteristics with Respect to Allergy Related Characteristics for Studies 246 and 265

In general, treatment groups were comparable with respect to gender, race, age, weight, height, and duration of allergic rhinitis. The majority of patients were female for both studies (64 to 70%). The mean age ranged from 35 to 37 years. The majority of patients were between 18 to 64 years of age (90 to 93%). The majority of patients were White (73 to 84%). The duration of allergic rhinitis ranged from 18 to 19 years. [Vol. 4, p. 79-80; Vol. 5, p. 62-63].

Treatment groups were comparable with respect to baseline allergy- related disease characteristics. The majority of patients (79% to 83%) had perennial allergic rhinitis with seasonal flare-ups and the majority (85 -96%) had perennial allergic rhinitis exacerbated by dust mite antigen. Cat allergen was the next common perennial allergen (in 60-67% of patients). A total of 59-72% of patients had seasonal allergic rhinitis exacerbated by tree, grass, or weed exposure. Approximately 94-97% of patients had symptoms of nasal congestion, 92-95% had sneezing, 91-94% had rhinorrhea, and 86-87% had symptoms of itchy nose at baseline. The percentage of patients receiving immunotherapy was low (3.2-6.2%). Approximately 83-85% of patients had concomitant allergic conjunctivitis and 24-29% of patients had concomitant asthma. Thus, treatment groups were fairly well matched with respect to baseline characteristics [Vol. 4, p. 83; Clinstat/studies/ P264.pdf/Appendix 4.4.2., p. 1320-1321 and Appendix 4.3.2, p. 2202; Vol. 5, p. 64; Clinstat/studies/ P265.pdf/Appendix 4.4.2., p. 1032-1034 and Appendix 4.21, p. 1226] Baseline nasal symptom scores were also comparable between treatment groups for each study.

6.1.4.3 Compliance

Compliance was assessed by comparing the number of days that study drug was taken with the patient-specified number of days in the active treatment period. Mean compliance in both studies was reported as greater than 98% for all treatment groups, which is quite adequate to assess for efficacy.

6.1.4.4 Efficacy Outcomes

6.1.4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint was the change from baseline in the Daytime Nasal Symptoms Score (DNSS) averaged over a 4-week period (Study 246) or over a 6-week period (Study 265). The DNSS comprised the average of nasal congestion, rhinorrhea, and sneezing for both studies; however, the DNSS for Study 246 included nasal pruritus. The results will be summarized for each study individually and then will be compared between studies.

For Study 246, the Baseline DNSS (average of rhinorrhea, sneezing, congestion, and nasal pruritus) were 2.08, 2.13, and 2.07 in the montelukast, cetirizine, and placebo groups, respectively. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.39 (95% CI: -0.43, -0.36), -0.45 (95% CI: -0.54, -0.37) in the cetirizine group, and -0.36 (95% CI:-0.39, -0.32) in the placebo group. The LS Mean difference between montelukast and placebo was -0.04 (95% CI: -0.09, 0.01), which was not statistically significant (p=0.150). However, the LS Mean difference between cetirizine and placebo of -0.10 (95% CI: -0.19, -0.01) was statistically significant (p=0.038). Thus, montelukast failed to demonstrate a statistically significant difference compared to placebo for the pre-specified primary efficacy endpoint in this trial. Although the sponsor failed to show a statistically significant improvement in the pre-specified primary comparison for the primary efficacy endpoint, there was a trend favoring montelukast compared to placebo.

To explore this trend, a post-hoc analysis was performed defining the primary efficacy endpoint using three nasal symptoms to comprise the primary efficacy endpoint. The LS Mean changes from Baseline for montelukast, cetirizine, and placebo averaged over the first 4-week period were -0.40 (95% CI: -0.44, -0.36), -0.45 (95% CI: -0.54, -0.36), and -0.34 (95% CI: -0.38, -0.30), respectively, with a corresponding LS Mean difference between montelukast and placebo of -0.05 (95% CI: -0.11, 0.00). If the DNSS defined with 3 symptoms is averaged over the entire 6week study period, the corresponding LS Mean changes from Baseline for montelukast, cetirizine, and placebo were -0.46 (95% CI: -0.50, -0.42), -0.48 (95% CI: -0.57, -0.39), and -0.40 (95% CI; -0.44, -0.36), respectively. In this case, the LS Mean difference between montelukast and placebo was -0.06 (95% CI: -0.12, -0.01).These results are summarized in the following table.

Table 6. Study 246, Summary of Pre-Specified and Post-Hoc Primary Analyses

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)	Delta (p-value) {95% CI}	Delta (p-value) {95% CI}
Pre-specified Primary Efficacy Variable: DNSS with 4 symptoms					
Baseline	2.08	2.13	2.07	----------	----------
Change from Baseline *	-0.39 (-0.43, -0.36)	-0.45 (-0.54, -0.37)	-0.36 (-0.39, -0.32)	0.04 (0.150) {-0.09,0.01}	0.10 (0.038) {-0.19,-0.01}
Change from Baseline†	-0.46 (-0.50, -0.42)	-0.48 (-0.57, -0.39)	-0.41 (-0.45, -0.37)	0.05 (0.086) {-0.10,0.01}	0.07 (0.133) {-0.17,0.02}

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)	Delta (p-value) {95% CI}	Delta (p-value) {95% CI}
Post-Hoc specified Primary Efficacy Variable: DNSS with 3 symptoms (Excluding Nasal Pruritus)					
Baseline	2.13	2.19	2.12	----------	----------
Change from Baseline*	-0.40 (-0.44,-0.36)	-0.45 (-0.54,-0.36)	-0.34 (-0.38,-0.30)	0.05 (0.049) {-0.11,0.00}	0.11 (0.028) (-0.20,-0.01}
Change from Baseline†	-0.46 (-0.50,-0.42)	-0.48 (-0.57,-0.39)	-0.40 (-0.44,-0.36)	0.06 (0.024) {-0.12,-0.01}	0.09 (0.082) {-0.18,0.01}

*pre-specified endpoint: DNSS averaged over the first 4-week period
†DNSS averaged over the entire 6-week period
Source: Vol. 4, p. 97, 99, 144, 163

For Study 265, the mean DNSS at Baseline was 2.09 and 2.10 in the montelukast and placebo groups, respectively. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.44 with a 95% CI of {-0.48,-0.41} and in the placebo group was -0.37 with a 95% CI of {-0.40,-0.35}. The difference between treatment groups was -0.08, with a 95% CI of {-0.12; -0.04}. This difference between montelukast and placebo was statistically significant at a $p \leq 0.001$. This study, considered pivotal by the applicant, did demonstrate efficacy for the pre-specified primary efficacy endpoint.

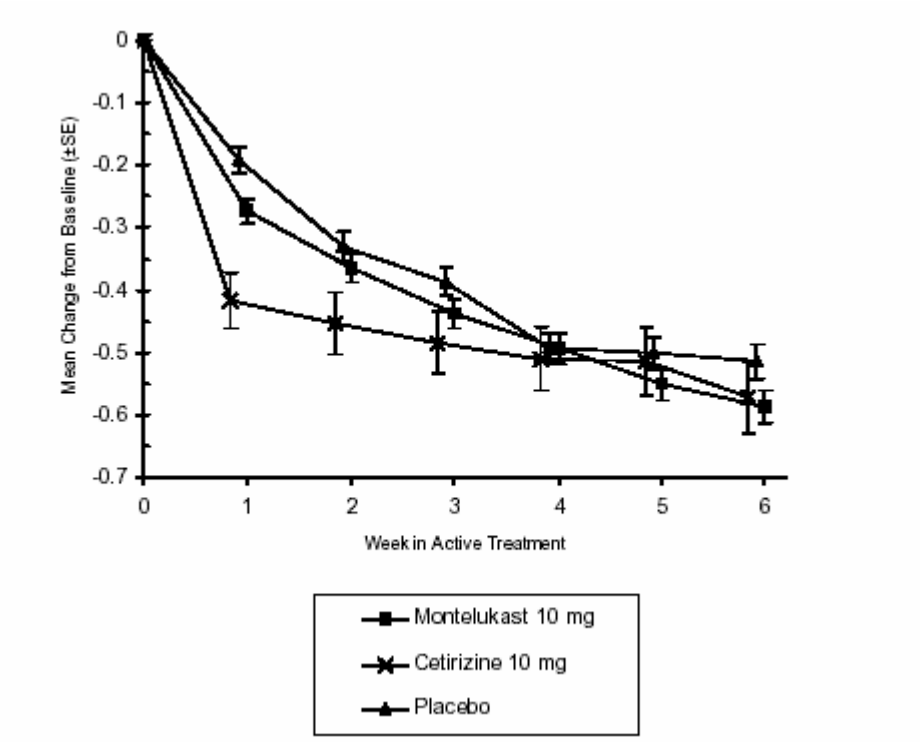
Table 7. Study 265, Summary of Primary Efficacy Analysis

	Montelukast N=1000	Placebo n = 980	Outcomes	
			Montelukast vs. Placebo	
	LS mean * (SD) {95% CI}		Delta (95% CI)	P value
Baseline †	2.09	2.10	----------	----------
Average change from Baseline	-0.44 (0.51) {-0.048,-0.41}	-0.37 (0.48) {-0.40,-0.34}	-0.08 (-0.12,-0.04)	$\leq$ 0.0010

Source: Vol. 5, p. 67; clinstat/studies/p265.pdf/Table 15, p. 60

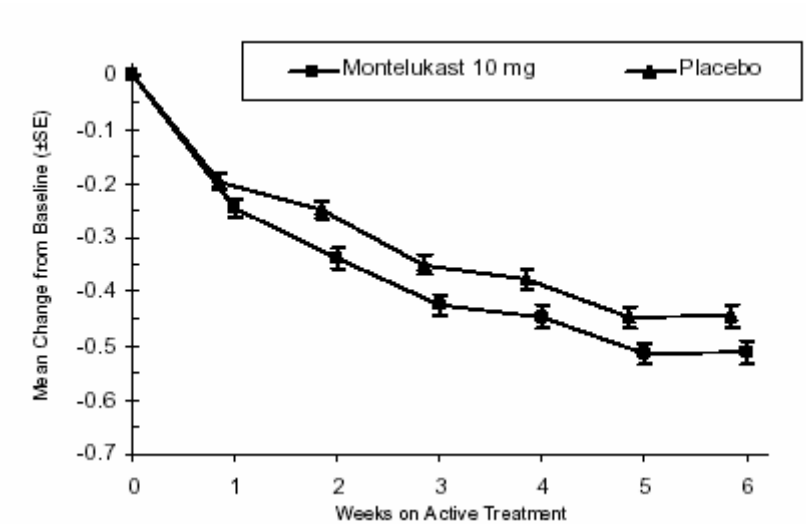
If the DNSS as defined as the average of three symptom scores (congestion, rhinorrhea, and sneezing) average over 6 weeks, the change from baseline for this endpoint was similar for montelukast for both studies (-0.46 for Study 246 and -0.44 for Study 265). The delta for the DNSS change from baseline compared to placebo for Studies 246 and 265 was 0.06 and 0.08, respectively. The mean change from baseline over time for both studies is depicted in the following two figures.

Figure 1. Study #246, Mean Change from Baseline (± Standard Error) in Daytime Nasal Symptoms Score (Modified Intention-to-Treat Approach)



Source: clinsat/studies/p246.pdf./p.100

Figure 2. Mean Change from Baseline (± Standard Error) in Daytime Nasal Symptoms Score by Week of Active Treatment (Modified Intention-to-Treat Approach)



Source: clinsat/studies/p265.pdf./p.100

Although the initial study failed to demonstrate a statistically significant difference for the pre-specified primary efficacy endpoint, there was a trend favoring montelukast compared to placebo. This trend for efficacy was confirmed in a second study, 265, where there was a statistically significant difference compared to placebo for the pre-specified primary efficacy endpoint ($p \leq 0.001$)

6.1.4.4.2 Secondary Efficacy Outcomes

In general, for both studies, there were trends favoring montelukast compared to placebo for most secondary endpoints, although the effect size was larger in Study 265 as compared to Study 246.

6.1.4.4.2.1 Individual Symptoms

6.1.4.4.2.1.1 Study 246

Results of the individual nasal symptoms of congestion, rhinorrhea, and sneezing averaged over the first 4 weeks of treatment, favored improvement in the montelukast group compared to placebo; this favorable effect was not noted with the individual symptom of nasal itching. The LS Mean changes from Baseline for these four symptoms ranged from -0.37 to -0.42, -0.40 to -0.50, and -0.33 to -0.39 in the montelukast, cetirizine, and placebo groups respectively. The LS Mean differences between montelukast and placebo ranged from -0.04 to -0.06 for the symptoms of congestion, rhinorrhea, and sneezing. For nasal itching, the LS Mean difference was only 0.01. This relative lack of efficacy in the treatment of the individual symptom of nasal pruritus was not noted when treatment effect of cetirizine was compared to placebo; LS Mean differences between cetirizine and placebo for all four of the nasal symptoms ranged from 0.06 to 0.14. Clearly, the lack of efficacy noted with montelukast in the individual symptom of nasal pruritus, skewed the primary efficacy endpoint unfavorably with respect to the primary comparison of montelukast to placebo. Similar results were observed when the data were averaged over the entire 6 weeks of therapy, although slightly greater improvements were noted from Baseline in all treatment groups. The results of the individual symptoms are summarized in the following table.

Table 8. Study #246, Summary Results for Individual Nasal Symptom Scores, Averaged Over First 4 Weeks and Over the Entire 6-Week Study Period

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean	LS Mean	LS Mean	Delta	Delta
Nasal Congestion					
Baseline	2.44	2.49	2.42	----------	----------
Change from Baseline *	-0.37	-0.40	-0.33	-0.04	-0.08
Change from Baseline†	-0.43	-0.44	-0.37	-0.05	-0.07

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean	LS Mean	LS Mean	Delta	Delta
Rhinorrhea					
Baseline	2.12	2.18	2.15	----------	----------
Change from Baseline*	-0.41	-0.44	-0.35	-0.06	-0.09
Change from Baseline†	-0.047	-0.46	-0.41	0.07	0.06
Nasal Itching					
Baseline	1.93	1.97	1.94		
Change from Baseline*	-0.38	-0.46	-0.39	0.01	0.07
Change from Baseline†	-0.44	-0.47	-0.44	0.00	0.03
Sneezing					
Baseline†	1.84	1.89	1.78		
Change from Baseline*	-0.42	-0.50	-0.36	0.06	0.14
Change from Baseline†	-0.47	-0.53	-0.41	0.06	0.12

*pre-specified endpoint: Scores averaged over the first 4-week period
†Scores averaged over the entire 6-week period
Source: Vol. 4, p. 97, 99, 144, 163 /clinstat/studies/p246.pdf/appendix 4.10.4/1380-1398

6.1.4.4.2.1.2 Study 265

Results of the individual nasal symptoms of congestion, rhinorrhea, sneezing, and itching favored improvement in the montelukast group compared to placebo. The mean change from Baseline in the individual symptom scores ranged from -0.38 to -0.44 in the montelukast group and -0.29 to -0.37 in the placebo group. The LS Mean difference between treatment ranged between -0.05 to -0.10. Of the four symptoms, the least improvement was noted in nasal congestion. The other three symptoms demonstrated similar improvements, and the improvement noted in the primary endpoint does not appear to be skewed favorably by any one individual symptom. On the contrary, it appears that the decreased improvement noted in congestion, may diminish the average composite score.

It is interesting to note that in the study, there was a favorable effect on nasal pruritus, with an LS mean difference between montelukast and placebo of -0.08, the same numerical difference noted with the primary efficacy endpoint. The results of the other secondary endpoints and the individual symptoms are summarized in the following table.

Table 9. Study #265, Summary Results for Individual Nasal Symptoms

	Montelukast N=1000	Placebo n = 980	Outcomes	
			Montelukast vs. Placebo	
	LS mean * (SD)		Delta	P value
Congestion				
Baseline	2.38	2.40		
Change from Baseline	-0.38 (0.58)	-0.34 (0.53)	-0.05	N/A
Rhinorrhea				
Baseline	2.11	2.15		
Change from Baseline	-0.44 (0.63)	-0.37 (0.60)	-0.08	N/A
Sneezing				
Baseline	1.79	1.76		
Change from Baseline	-0.44 (0.63)	-0.33 (0.62)	-0.10	N/A
Itching				
Baseline	1.82	1.80		
Change from Baseline	-0.39 (0.63)	-0.29 (0.61)	-0.10	N/A
Source: Vol. 5, p. 67; clinstat/studies/p265.pdf/Table 15, p. 60				

6.1.4.4.2.2 Other Secondary Endpoints

In Study 246, for most of the symptom score based secondary endpoints, the LS mean difference between treatment groups ranged from -0.03 to -0.05, favoring montelukast. However, there was no numerical difference between montelukast and placebo for the Daytime Eye Symptom score. With respect to the Rhinoconjunctivitis Quality of Life Score and Global Evaluation by Patient and Physician, there was trend favoring montelukast as well. It should be pointed out that for most of the endpoints in this study, cetirizine demonstrated greater numerical improvements in the parameters compared to montelukast. No meaningful differences were noted in the change from baseline in the Eosinophil count for any treatment group.

In Study 265, for all of the symptom score based secondary endpoints, the LS mean difference between treatment groups ranged from -0.06 to -0.08, favoring montelukast. It should be noted that the secondary endpoint *Daytime Nasal Symptoms + Itching score* in Study 265 represents the primary efficacy endpoint used in Study 246. Although a statistically significant difference between montelukast and placebo was not noted in Study 246 for this endpoint, in Study 265, montelukast shows greater improvements for this endpoint compared to placebo. In fact in Study 265, similar differences between montelukast and placebo were noted for this secondary endpoint as were noted for the pre-specified primary efficacy endpoint (-0.07 and -0.08, respectively). Montelukast also was noted to provide greater improvement in symptoms based on subjective non-symptom score endpoints, Rhinoconjunctivitis Quality of Life Score and Global Evaluation by Patient; the LS mean differences between treatments were -0.15 for both endpoints.

6.1.4.4.3 Subgroup Analyses

For both studies, subgroup analyses based on gender, age, race, history of SAR, history of allergic conjunctivitis, history of asthma, recent symptoms of asthma, and baseline congestion did not demonstrate any meaningful differences between treatment groups. Dr. Feng Zhou, the Biostatistician Reviewer confirmed that there were no meaningful treatment-by-subgroup interactions.

6.1.5 EFFICACY CONCLUSIONS

Studies 246 and 265 were two adequate and well controlled studies intended to support the efficacy of Singulair for the relief of symptoms associated with perennial allergic rhinitis in patients 15 years of age and older. Although the first study failed to demonstrate statistically significant improvements in Daytime Nasal Symptoms Score, a trend favoring montelukast was noted. This trend towards efficacy was confirmed in a second pivotal study, where the applicant was able to demonstrate statistically significant improvements in the Daytime Nasal Symptom Score.

The applicant has met the minimum regulatory requirements to obtain approval in PAR, since only one pivotal PAR study showing efficacy is necessary to support an approval if an indication already exists in SAR. Although the results of the initial study alone would not be enough to obtain an approval, they are supportive of the second study which demonstrated the efficacy of montelukast in the treatment of symptoms of PAR. No clinical studies were conducted in patients younger than 15 years of age; however, efficacy can be extrapolated to children 6 months of age and older since the pathophysiology of the disease is similar in adults and children. Overall, the submitted data support the modest efficacy of Singulair for the relief of symptoms of perennial allergic rhinitis.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety of montelukast in perennial allergic rhinitis was assessed mainly by evaluating the two clinical studies submitted in this sNDA. Additional sources of safety information included: the Agency's previous determination of safety in patients 12 months of age and older with asthma and 2 years of age and older with SAR, the Agency's previous evaluation of systemic exposures in children and adults following montelukast, the Applicant's literature search, summary of post-marketing experience, and the safety update.

The review of safety in patients 15 years of age and older was based on the pivotal studies submitted in this application, 246 and 265. The safety in pediatric patients 2 to 14 years of age with perennial allergic rhinitis is supported by the established safety in children 2 years of age and older with seasonal allergic rhinitis and asthma. In the pediatric population of 12 to 23

months of age with perennial allergic rhinitis, safety is supported by the established safety in previously conducted asthma studies in this age group.

For patients ages 6 months to < 12 months of age, safety is supported by data from previously conducted pharmacokinetic studies in both pediatric (Study 136) and adult (Study 003) patients and safety studies conducted in patients 6 to 23 months of age with asthma (Study 171 and 232). Previously conducted evaluations by Dr. Sandra Suarez, Clinical Pharmacology Reviewer and Dr. Peter Starke, Medical Reviewer for NDA 21-409 were consulted to provide evidence of support in this pediatric population. Additionally, Clinical Study Reports and Synopses of these previously reviewed data were re-evaluated briefly.

This section, 7.1, will primarily focus on the integrated summary of findings from the two pivotal studies which comprised the basis for support of the PAR indication. This reviewer will primarily focus on the comparisons between montelukast and placebo, since the number of patients randomized in the pooled studies was comparable for these two treatment groups. There were too few patients enrolled in the cetirizine group to allow for any meaningful comparisons (cetirizine: 122; montelukast and placebo: over 1600 patients each groups) to montelukast and placebo, although cetirizine information will be summarized in tabular format where possible. Safety from other sources will be briefly summarized in section 7.2 as well, to include safety summaries from studies previously reviewed by the Agency. The safety information from these supportive studies will be summarized individually, and not integrated, as the designs were varied; these can be found in section 7.2.2, *Description of Secondary Clinical Data Sources Used to Evaluate Safety and Findings*.

7.1.1 DEATHS

There were no deaths in any of the pivotal studies.

7.1.2 OTHER SERIOUS ADVERSE EVENTS

A total of 10 serious adverse events (SAEs) were reported in the two PAR studies, of which 3 were pregnancies which were reported in Study 246 (1 in the montelukast group, 2 in the placebo group). As pregnancies, by definition per FDA regulations [21 CFR 314.80(a)], are not serious adverse events, the narratives of these will not be summarized further in this section. The remaining 7 are summarized in the table below.

Table 10. Number of Patients with SAEs in the Pooled Pivotal Studies

Serious Adverse Event	Montelukast n=1632	Placebo n=1603
Any Serious Adverse Event	5 (0.31)	2 (0.12)
Angina/unstable	0	1
Anxiety disorder	1 (0.06)	0
Asthma	1 (0.06)	0
Dehydration	1 (0.06)	0
Joint Injury	1 (0.06)	0

Laceration	1 (0.06)	0
Myocardial Infarction	0	1

Source: Vol. 2/2.7.4/p. 26

Although a greater percentage of patients in the montelukast group reported SAEs compared to placebo, the incidence was still quite low (montelukast 0.31% vs. 0.12%). The Applicant's narratives were reviewed and summarized in the individual study reviews in the Appendix. There is no clear safety signal from the types and frequencies of SAEs reported for the pooled pivotal studies. In this reviewer's opinion, the SAEs reported in the montelukast group are probably not related to therapy due to nature of the SAE (dehydration, joint injury, and laceration) or represent a pre-existing disease (anxiety disorder and asthma). It should be noted that the patient with dehydration was pregnant who experienced severe intermittent vomiting, leading to the dehydration. Therefore, review of the SAEs for the pooled pivotal does not raise any new concerns in terms of safety.

7.1.3 DROPOUTS AND OTHER SIGNIFICANT ADVERSE EVENTS

7.1.3.1 Overall profile of dropouts

In both pivotal studies, the majority of patients completed the trials (89% or greater for montelukast and placebo and 87% for cetirizine). In general, the number of dropouts and reasons for discontinuation were comparable among treatment groups. A total of approximately 10% of patients discontinued from each of the montelukast and placebo groups, compared to 13% from the cetirizine group. The most common reason for discontinuation for all treatment groups was adverse event (2.7% for each of the montelukast and placebo treated group; 3.3% for the cetirizine group). The adverse events leading to discontinuation will be summarized in the following section. The overall profile of dropouts is summarized in the following table, the incidences of which reveal no meaningful differences between montelukast and placebo.

Table 11. Summary of Disposition from Pooled Studies

	Pooled Studies 246 and 265		
Status	**Montelukast** n (%)	**Cetirizine** n (%)	**Placebo** n (%)
Number of patients randomized	1632	122	1603
Number of patients completing study	1475 (90.4)	106 (86.9)	1436 (89.6)
Number of patients discontinued	157 (9.6)	16 (13.1)	167 (10.4)
Adverse event*	61 (3.7)	4 (3.3)	59 (3.7)
Protocol Deviation	38 (2.3)	4.9 (3.3)	41 (2.6)
Treatment failure	17 (1.0)	2 (1.6)	21 (1.3)
Withdrawal of Consent	24 (1.5)	5 (4.0)	20 (1.2)
Lost to follow-up	5 (0.3)	1 (0.8)	6 (0.4)
Other	10 (0.6)	0	17 (1.1)

*Includes 1 patient in Study 246 who discontinued after randomization due to an AE that began prior to randomization

Source: Vol. 4, p. 74; clinstat/studies/p264.pdf/appendix 4.5.1/1335; Vol. 5, p. 58-59

7.1.3.2 Adverse events associated with dropouts

A total of 120 patients discontinued from the pooled pivotal studies secondary to adverse events: 58 patients each from the montelukast and placebo groups, and 4 patients from the cetirizine. The percentage of patients discontinuing from any treatment group for any given adverse events was low (≤ 1%). The most common reasons for discontinuation from the studies were: respiratory tract infection, influenza, nasopharyngitis, and pharyngitis. Other adverse events leading to study discontinuation were rare and occurred in one patient or less. The adverse events occurring in one or more patients in the montelukast group at a greater frequency than in the placebo group are summarized in the following table.

Table 12. Summary of All Adverse Events in Patients Leading to Discontinuation from the Montelukast Group Occurring at a Greater Frequency than Placebo

	Pooled Studies 246 and 265		
Adverse Event	**Montelukast n=1632** n (%)	**Cetirizine n=122** n (%)	**Placebo n=1603** n (%)
Respiratory Tract Infection (to include URI)	17(1.0)	1 (0.8)	9 (0.6)
Sinusitis	11 (0.7)	0	9 (0.6)
Influenza	3 (0.2)	0	2 (0.2)
Nasopharyngitis	2 (0.1)	0	0
Pharyngitis (all causes)	2 (0.1)	0	0
Atopic Dermatitis	1(0.1)	0	0
Back Pain	1(0.1)	0	0
Bacterial Infection	1 (0.1)	0	0
Bursitis	1 (0.1)	0	0
Diarrhea	1 (0.1)	0	0
Exanthem	1 (0.1)	0	0
GI Discomfort	1 (0.1)	0	0
Infective Conjunctivitis	1 (0.1)	0	0
Migraine	1 (0.1)	0	0
Otitis Media	1 (0.1)	0	0
Pregnancy	1 (0.1)	0	0
Somnolence	1 (0.1)	0	0
Tachypnea	1 (0.1)	0	0
Tooth Abscess	1 (0.1)	0	0

Source: Vol. 4, p. 74; clinstat/studies/p264.pdf/appendix 4.5.1/1335; Vol. 5, p. 58-59; Vol.2/2.74/p.28-30

Review of these adverse events does not raise any new concerns, as more commonly reported adverse events leading to discontinuation from montelukast therapy were previously reported and summarized in the package insert.

7.1.3.3 Other significant adverse events

Adverse events that led to dose reduction or significant additional concomitant therapy, but not to discontinuation of treatment, were not reported.

7.1.4 COMMON ADVERSE EVENTS

7.1.4.1 Eliciting adverse events data in the development program

Adverse events were elicited by open-ended questioning (assumed as no specific checklists were used) by study personnel. These were assessed every week during the double-blind treatment period, in clinic at Weeks 2, 4, and 6, and by phone at Weeks 1, 3, and 5. Therefore, weekly assessments of adverse events were made by study personnel. All adverse event data were recorded and evaluated for their seriousness, severity, and relationship to study medication. Adverse event data were recorded on site by the clinical staff on case report forms [clinstat/studies/p265/appendix 3.3/p. 542-45; 555-560].

7.1.4.2 Appropriateness of adverse event categorization and preferred terms

An adverse experience was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR'S product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR'S product, is also an adverse experience. Adverse events were categorized using MedDRA (Medical Dictionary for Regulatory Activities) Version 7.0 and serious adverse events were recorded based on CFR regulations, both of which are acceptable [clinstat/studies/p265/appendix 3.3/p. 542-45; 555-560].

7.1.4.3 Incidence of common adverse events

In general, the types and frequencies of reported adverse events were low and comparable among treatment groups. Adverse events were reported in 31%, 35%, and 32% of patients receiving montelukast, cetirizine, and placebo, respectively. The most commonly reported adverse events in the montelukast group were upper respiratory tract infection, headache, nasopharyngitis, pharyngolaryngeal pain, sinusitis, nausea, cough, and epistaxis (in > 1% of patients in the montelukast group). Of these, only upper respiratory tract infection, sinusitis, cough, epistaxis, and sinus headache were reported in a greater percentage of patients in the montelukast group compared to placebo.

In general, the types of adverse events reported in the pooled pivotal studies are consistent with current labeling in the package insert, although some of the adverse events were not listed under the adult asthma studies, but under pediatric studies sections.

7.1.4.4 Common adverse event tables

The most commonly reported adverse events reported in $\geq$ 0.5% of patients in the montelukast group are summarized in the following table. The information in this table forms the basis for the PAR subsection in the Adverse Reactions in the proposed label.

Table 13. Adverse Events Reported in $\geq$ 0.5% of Patients Receiving Montelukast Therapy in Pooled Pivotal Studies

Adverse Event	Montelukast (n=1632) n (%)	Cetirizine (n=122) n (%)	Placebo (n=1603) n (%)

Adverse Event	Montelukast (n=1632) n (%)	Cetirizine (n=122) n (%)	Placebo (n=1603) n (%)
Patients with Adverse Events	**511 (31.3)**	**43 (35.2)**	**519 (32.4)**
Digestive System Disorders			
Diarrhea	15 (0.9)	3 (2.5)	13 (0.8)
Dry Mouth	14 (0.9)	3 (2.5)	2 (0.1)
Nausea	19 (1.2)	0	22 (1.4)
Vomiting	9 (0.6)	0	8 (0.5)
General Disorders			
Pyrexia	9 (0.6)	2 (1.6)	17 (1.1)
Infections and Infestations			
Bronchitis	10 (0.6)	0	9 (0.6)
Gastroenteritis	8 (0.5)	0	5 (0.3)
Influenza	14 (0.9)	0	9 (0.6)
Nasopharyngitis	47 (2.9)	0	51 (3.2)
Pharyngitis	10 (0.6)	3 (2.5)	6 (0.4)
Sinusitis	26 (1.6)	0	21 (1.3)
Upper Respiratory Tract Infection (to include Viral URI)	65 (4.0)	8 (6.6)	53 (3.3)
Urinary Tract Infection	11 (0.7)	1 (0.8)	11 (0.7)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	8 (0.5)	0	6 (0.4)
Back Pain	15 (0.9)	0	9 (0.6)
Nervous System Disorders			
Dizziness	11 (0.7)	2 (1.6)	8 (0.5)
Headache	61 (3.7)	8 (6.6)	72 (4.5)
Insomnia	10 (0.6)	0	14 (0.9)
Sinus Headache	18 (1.1)	0	13 (0.8)
Respiratory Disorders			
Cough	20 (1.2)	2 (1.6)	12 (0.7)
Epistaxis	19 (1.2)	0	16 (1.0)
Pharyngolaryngeal Pain	31 (1.9)	0	30 (1.9)
Skin			
Rash	13 (0.8)	1 (0.8)	12 (0.7)
Source: Vol. 4, p. 175-181; Vol. 2/2.2.4/p.18-20			

7.1.4.5 Identifying common and drug-related adverse events

The incidence of adverse events judged to be drug-related by the investigator was low, 4.6% and 4.9% in the montelukast and placebo groups, respectively. Headache was the only adverse event

judged to be drug-related that occurred at an incidence of ≥1% (montelukast: 1.2%; placebo: 1.5%); however, it was reported in a greater percentage of placebo patients. Adverse events judged by the investigator to be drug-related and reported in a greater percentage of patients in the montelukast group include: dry mouth, dizziness, somnolence, and nasal dryness. With the exception of dry mouth, the other adverse events were fairly comparable between treatment groups. Dry mouth was noted in 0.6% of patients in the montelukast group compared to 0% in the placebo group. This adverse should be listed in the adverse events section as an adverse event that was reported in a greater percentage of montelukast treated patients compared to placebo treated patients. The following table summarizes these results.

Table 14. Adverse Events Reported in a Greater Percentage of Montelukast Patients Which Were Judged by the Investigator to be Related to Therapy in Pooled Pivotal Studies

Adverse Event	Montelukast (n=1632) n (%)	Placebo (n=1603) n (%)
Patients with Adverse Events	**75 (4.6)**	**79 (4.9)**
Dry Mouth	10 (0.6)	0
Dizziness	5 (0.3)	1 (0.1)
Somnolence	5 (0.3)	4 (0.2)
Nasal Dryness	4 (0.2)	0
Source: Vol. 2/2.7.4/21		

7.1.4.6 Additional analyses and explorations

As somnolence may be an adverse event associated with antihistamines, the Applicant conducted an additional analysis for the adverse event of somnolence. In the pooled PAR studies, somnolence-related–fatigue, tiredness, poor concentration, hypersomnia, lethargy, drowsiness, groggy, or somnolence–adverse events were reported in 0.5%, 4.1%, and 0.6% percentage of patients in the montelukast, cetirizine, and placebo groups, respectively. Since sedation is a commonly reported adverse event of cetirizine and montelukast is not an antihistamine, the results are not surprising [Vol. 2/2.7.4/22-23].

7.1.5 LESS COMMON ADVERSE EVENTS

Other less frequently reported adverse events in the montelukast group which were reported in a greater percentage of patients compared to placebo included: diarrhea, dry mouth, vomiting, gastroenteritis, influenza, pharyngitis, arthralgia, back pain, dizziness, and rash. However, these were reported in <1% of patients, and were fairly comparable between treatment groups, with the exception of dry mouth. Dry mouth was reported in 0.9% of patients in the montelukast group (note that this event was judged by the investigator to be related to treatment in 0.06% of patients; see section 7.1.4.5) but in only 0.1% of patients in the placebo group. Interestingly, this was one adverse event that was actually judged by the investigator to be related to therapy in 0.6% of patients treated with montelukast and in no patients treated with placebo. No specific new safety concerns were raised with the review of these adverse events.

7.1.6 LABORATORY FINDINGS

7.1.6.1 Overview of laboratory testing in the development program

Standardized laboratory safety tests (hematology, serum chemistry, and urinalysis) were specified to be performed pre-and post-randomized treatment in only 1 of the pivotal studies, Study 246. In the other study, Study 265, laboratory tests were only performed at screening, and then on a case-by-case basis as needed to follow up clinical or laboratory findings. A centralized laboratory facility analyzed all laboratory specimens, with the exception of a few sites where in was not practical to use the central laboratory.

7.1.6.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The large majority of laboratory safety data in the PAR studies were from Study 246, since only 10 patients in Study 265 had post-randomization laboratory results. Therefore, this section will focus on Study 246 and then briefly summarize the results from Study 265.

7.1.6.3 Standard analyses and explorations of laboratory data

Study 246

Of the 1365 randomized patients, 1343 (98.4%) had at least one post-treatment laboratory test result and 30 patients (2.2%) had laboratory adverse events. Sixteen patients (2.6%), 4 patients (3.4%), and 10 patients (1.7%) in the montelukast, cetirizine, and placebo groups had laboratory AEs. Five patients discontinued due to laboratory AEs, 3 from the montelukast group, and 2 from the placebo group.

The majority of patients with laboratory AEs had AEs reported for serum chemistry, whereas 1 or less patients with laboratory AEs were reported for hematology or urinalysis. Of the laboratory tests routinely performed, elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were the most commonly reported, although the incidence was low (1.3% in the active treated group). These elevations are notable since none were reported in the placebo group. Eight patients (1.3%) in the montelukast group, 1 patient (0.8%) in the cetirizine group, and none in the placebo group had elevations in ALT. Three patients (0.5%) in the montelukast group, 1 patient (0.8%) in the cetirizine group, and none in the placebo group had elevations in AST. Note that these patients could have both had increases in ALT and AST and therefore the same patient could be listed as having elevations in ALT and AST. These elevations will be further explored in the following section. The incidences and types of other laboratory AEs were similar across treatment groups and occurred in one or less patients in the active treatment groups, the review of which did not raise any specific concerns. These results are presented in the following table.

Table 15. Study #246: Number (%) of Patients with Specific Laboratory Adverse Events

Adverse Event	Montelukast (n=630) n/m*	Cetirizine (n=122) n/m* (%)	Placebo (n=613) n/m* (%)
Total with Laboratory AEs	**16/620 (2.6)**	**4/119 (3.4)**	**10/604 (604)**
Serum Chemistry	**13/619 (2.1)**	**3/119 (2.5)**	**5/600 (0.8)**

Adverse Event	Montelukast (n=630) n/m*	Cetirizine (n=122) n/m* (%)	Placebo (n=613) n/m* (%)
Alanine aminotransferase increased	8/619 (1.3)	1/119 (0.8)	0
Aspartate aminotransferase increased	3/612 (0.5)	1/119 (0.8)	0
Creatine phosphokinase increased†	1/24 (4.2)	1/6 (16.7)	2/12 (16.7)
Gamma-glutamyl transpeptidase increased	1/10 (10)	0	0
Hyperbilirubinemia	1/619 (0.2)	1/119 (0.8)	0
Hypercalcemia	1/619 (0.2)	0	0
Hyperglycemia	1/619 (0.2)	0	1/599 (0.2)
Nonfasting blood glucose decreased	1/619 (0.2)	0	0
Nonfasting blood glucose increased	1/619 (0.2)	0	1/599 (0.2)
Hematology	**1/616 (0.2)**	**0**	**1/599 (0.2)**
Hemoglobin decreased	0	0	1/599 (0.2)
Leukocytes decreased	1/616 (0.2)	0	0
Lymphocytes decreased	1/616 (0.2)	0	0
Neutrophils decreased	1/616 (0.2)	0	0
Urinalysis	**3/615 (0.5)**	**1/119 (0.8)**	**4/602 (0.7)**
Glycosuria	1/615 (0.2)	0	0
Hematuria	1/615 (0.2)	0	4/602 (0.7)
Leukocyturia	1/615 (0.2)	0	0
Proteinuria	0	1/119 (0.8)	0

*Total in whom particular lab results were measured

†Creatine phosphokinase (CPK) was not routinely measured; however, in individuals with LFT elevations, CPK was evaluated as well

Source: Vol.4, p. 190-191

Study 265

Although comparative laboratory analyses were not performed, 10 patients had at least 1 laboratory test performed post-baseline, 6 in the montelukast group and 4 in the placebo group. However, no significant laboratory abnormalities were reported in the montelukast group. Two patients in the placebo group had abnormalities: 1 had an elevated carbohydrate antigen 125 and another had elevated AST and ALT. No hepatic enzyme abnormalities were reported in any montelukast patients.

7.1.6.4 Additional analyses and explorations

7.1.6.4.1.1.1.1 Increases in Liver Function Tests

Review of laboratory abnormalities did not reveal any concerns, with the exception of liver function tests. Although there did not appear to be any clinically important changes from Baseline in the Mean ALT or AST, some patients did have increases in ALT and AST in the study, at a greater incidence compared to placebo. Treatment groups were comparable for mean ALT and AST values at Baseline. There did not appear to be any clinically important changes from Baseline in the mean ALT or AST. The mean ALT at Baseline was 21.7, 20.3, and 21.5 IU/L for the montelukast, cetirizine, and placebo groups, respectively. The mean AST at Baseline was 21.9, 21.1, and 22.3, for the montelukast, cetirizine, and placebo groups, respectively. The mean change from Baseline in ALT was 0.2 or less in all treatment groups. The mean change from Baseline in AST was 0 or less [clinstat/studies/p246.pdf/appendix 4.26.1/p. 1576].

Although the incidences of increases in ALT and AST were quite low (1.3% or less), the fact that they were noted in the active treatment groups, and not in the placebo treatment group (see reviewer's comment below), is suggestive of a possibility that they are drug related. Note that only one patient in the cetirizine had elevations in LFTs, compared to the montelukast treatment group. Since the study population is much larger in the montelukast group compared to cetirizine, conclusions regarding inter-treatment differences between these groups are difficult to make. Nonetheless, these results are suggestive that montelukast may possibly cause increases in ALT/AST.
Reviewer's comments: As defined by the sponsor, Dr. Feng Zhou printed out data illustrating increases in ALT and AST. Her printout also demonstrated that 2 patients had increases in ALT and 1 in AST. This was not noted in the table above by the sponsor. However, reviewing the results of these placebo patients, it was noted that all of these patients clearly had increases in ALT or AST prior to randomization. It is assumed that this is the reason the sponsor did not include these as laboratory adverse experiences.

As this reviewer was interested in the number of patients with increases in ALT or AST compared to Baseline, this reviewer requested Dr. Feng Zhou to summarize this data. These results were individually reviewed, with pre and post comparison data, obtained from Dr. Feng Zhou. Evaluation of these results reveals that the majority of patients had minor elevations in ALT and AST when pre and post-treatment comparisons were made. Of the nine patients with increases in ALT and/or AST in the montelukast group, three had increases noted from screening to the pre-randomized period. Since the increases in these parameters occurred prior to receiving montelukast, it is unlikely that this may represent a drug effect. Of the remaining six patients, four patients had decreases after discontinuation of therapy, suggestive of a potential drug effect, although two did have an increased value at the final post-treatment value. Given the small number of patients reported with these increases, it is difficult to draw any definitive conclusions as to the causality of these increases in ALT/AST. These results are summarized in the following table.

Table 16. Study #246, ALT and AST Increases in Patients Noted as Laboratory Adverse Experiences

	ALT			AST		
Patient Number	Pre (day)	Post (day)	Final (day)	Pre (day)	Post (day)	Final (day)

Montelukast						
AN 4742†	26 (1)	81 (42)	78 (94)	25 (1)	52 (42)	48 (94)
AN 4763†	48 (1)	127 (9)	28 (37)	34 (1)	52 (9)	27 (37)
AN 5272	33 (1)	28 (12)	26 (28)	27 (-12)*	45 (1)	39 (28)
AN 5274	38 (1)	66 (40)	47 (49)	25 (1)	36 (40)	None
AN 5447	17 (1)	40 (40)	78 (57)	21 (1)	31 (40)	50 (57)
AN 5452†	48 (1)	65 (12)	50 (41)	35 (1)	None	28 (41)
AN 5578†	21 (1)	60 (43)	63 (57)	14 (1)	31 (43)	37 (57)
AN 5844†	26 (-35)	70 (1)*	47 (42)	25 (-35)*	51 (1)	33 (42)
AN 5873	23 (-16)	106 (8)*	100 (40)	23 (-16)	76 (8)	60 (40)
Cetirizine						
AN5592	11 (1)	55 (43)	15 (67)	12 (1)	59 (43)	22 (67)

*Note that these patients had normal screening laboratories; however, increases in ALT and/or AST were noted prior to randomized treatment period. For these patients, only the highest post-treatment value is listed; however, initial increases were noted prior to taking study drug.

†Note that patients AN 4742, 4763, 5452, 5578, and 5844 were taking concomitant acetaminophen, although only patient 4763 was taking 1-4 grams/day of acetaminophen, doses that could potentially lead to elevations in LFTs. [Vol. 4, p. 200]

Source: SAFETY.sas created by Dr. Feng Zhou on 15 March 2005 where data was created for individuals with increases in ALT and AST as defined as laboratory AEs by the sponsor

The sponsor also provided results based on the percentage of patients with ALT or AST elevations separated based on interval of elevations above the upper limits of normal, regardless of pre-randomization values. This data was not helpful, as it did not identify whether these values were increased, decreased, or changed from Baseline. Nonetheless, this reviewer requested that Dr. Zhou print out all patients with post-randomization elevated values. These were perused, and a total of 112 (18%), 25 (21%), and 86 patients (14%) in the montelukast, cetirizine, and placebo groups, respectively had elevations in ALT and/or AST. The majority of elevated values were less than 75 IU/L in all treatment groups. Only 3 (0.5%), 2 (1.7%), and 3 (0.5%), patients respectively, had values of $\geq$75 and < 100 IU/L. Similarly, a very small percentage had values of 100 IU/L or greater in each of the treatment groups (montelukast, 5 patients (0.8%); cetirizine, 1 patient (0.8%); placebo, 4 patients (0.7%). These results show that, generally, the types and frequencies of elevations in ALT and/or AST were similar across groups and did not raise any particular concerns, and are consistent with current labeling [Vol. 4, p. 207].

7.1.7 VITAL SIGNS

Vital signs were assessed at screening in both studies; however, only Study 246 pre-specified pre- and post-randomization vital sign assessments. Therefore, any change with treatment with respect to vital signs could only be assessed with Study 246. Review of pre- and post-randomization vital sign changes from baseline did not reveal any clinically meaningful differences. No specific safety concern was raised from review of vital signs.

7.1.8 ELECTROCARDIOGRAMS (ECGS)

EKGs were only performed for screening purposes in both studies and were not repeated post-randomization. Therefore, there is no comparative data with respect to EKGs.

7.1.9 HUMAN REPRODUCTION AND PREGNANCY DATA

The use of montelukast in pregnancy and lactation was not specifically evaluated in this marketing application. However, seven patients had a positive pregnancy test in the pooled pivotal studies, 2 in the montelukast treatment group, and 5 in the placebo treatment group.

Of the two patients, one each from Study 246 and 265, that became pregnant while receiving montelukast therapy, one was delivered of three healthy girls via cesarean section. The other patient was still being followed at the time of the study report and no additional information regarding the outcome her pregnancy is available [Vol. 2/2.7.4/p. 39-40].

7.1.10 WITHDRAWAL PHENOMENA AND/OR ABUSE POTENTIAL

No special studies to investigate withdrawal phenomena and/or abuse potential were provided or warranted for this efficacy supplement.

7.1.11 OVERDOSE EXPERIENCE

In the pivotal studies, there were no adverse events of overdose in any patient receiving montelukast; however, 10 patients did inadvertently take an additional 10 mg tablet for 1 or 2 days during the 6-week treatment period. No untoward effects were reported as a result of these actions.

The following information was obtained from the currently approved package insert. No specific information is available on the treatment of overdosage with SINGULAIR. In chronic asthma studies, SINGULAIR has been administered at doses up to 200 mg/day to adult patients for 22 weeks and in short-term studies, up to 900 mg/day to patients for approximately one week without clinically important adverse experiences.

There have been reports of acute overdosage in children in postmarketing experience and clinical studies of up to at least 150 mg/day with SINGULAIR. The clinical and laboratory findings observed were consistent with the safety profile in adults and older pediatric patients. There were no adverse experiences reported in the majority of overdosage reports. The most frequent adverse experiences observed were thirst, somnolence, mydriasis, hyperkinesia, and abdominal pain [Product Circular: Worldwide product circular, Singulair ™, tablets/chewable tablets/oral granules: 2004].

7.1.12 POSTMARKETING EXPERIENCE

From 31-Jul-1997 (market introduction) through 30-Jun-2004, approximately (b) (4) (10-mg film-coated tablet, 5-mg chewable tablets, 4-mg chewable tablets, and 4-mg oral granules sachets) have been distributed worldwide; equivalent to approximately (b) (4) patient-years

of treatment. Per the applicant, overall, no age- or dose-related safety and tolerability concerns have been identified with the FCT, CT, or oral granules formulations. The safety profile of montelukast in the clinical studies of asthma and of SAR, along with marketed use for both indications in adult and pediatric patients, remains very favorable [Vol. 1, Clinical Overview, p. 22].

The following side effects have been reported in postmarketing use: hypersensitivity reactions (including anaphylaxis, angioedema, rash, pruritus, urticaria and, very rarely, hepatic eosinophilic infiltration); dream abnormalities and hallucinations, drowsiness, irritability, agitation including aggressive behavior, restlessness, insomnia, paraesthesia/hypoesthesia, and very rarely seizure; nausea, vomiting, dyspepsia, diarrhea, increased ALT and AST, and very rarely cholestatic hepatitis; arthralgia, myalgia including muscle cramps; increased bleeding tendency, bruising; palpitations; and edema [Product Circular: Worldwide product circular, Singulair ™, tablets/chewable tablets/oral granules: 2004].

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 DESCRIPTION OF PRIMARY CLINICAL DATA SOURCES (POPULATIONS EXPOSED AND EXTENT OF EXPOSURE) USED TO EVALUATE SAFETY

7.2.1.1 Study type and design/patient enumeration

The pivotal studies were both multicenter, randomized, double-blind, placebo-controlled parallel group trials in patients with perennial allergic rhinitis, ages 15 years of age and older. A total of 1356 patients were enrolled in Study 246 and a total of 1992 patients were enrolled in Study 265. Pooling both studies, 1632 patients were randomized to receive montelukast, 122 were randomized to receive cetirizine, and 1603 were randomized to receive placebo. The design and patient enumeration is summarized in the following table.

Table 17. Summary of Study Design and Enumeration of Patients in Pivotal Studies

Study	Design	Duration	Dosage	Patients	Evaluations
P246	Phase III, 6-week, multicenter, randomized, parallel group, double-blind, placebo and active- controlled trial in PAR patients ages 15-82 yrs	6 weeks	Montelukast 10 mg Cetirizine 10 mg Placebo	1356 M*=630 C=122 P=613	Primary Efficacy Daytime Nasal Sx Score (nasal congestion, sneezing, rhinorrhea, nasal pruritus)
P265	Phase III, 6-week, multicenter (16), randomized, double-blind, parallel, placebo controlled trial in PAR patients ages 15-81 yrs	6 weeks	Montelukast 10 mg Placebo	1992 M=1002 P=990	Safety: AEs Lab AEs Exploratory efficacy

7.2.1.2 Demographics

In general, the demographics at baseline were similar among treatment groups. The majority of patients were female for both studies (64 to 70%). The mean age ranged from 35 to 37 years. The majority of patients were between 18 to 64 years of age (90 to 93%). The majority of patients were White (73 to 84%). The duration of allergic rhinitis ranged from 18 to 19 years. [Vol. 4, p. 79-80; Vol. 5, p. 62-63]. The pooled demographics are summarized in the following table for the montelukast and placebo groups.

Table 18. Summary of Demographics for Pooled Pivotal Studies

	Montelukast n=1632 n(%)	**Cetirizine n=122** n(%)	**Placebo n=1603** n(%)	**Total n=3357** n(%)
Gender				
Female	1063 (65.1)	85 (69.7)	1050 (65.5)	2198 (65.5)
Male	569 (34.9)	37 (30.3)	553 (34.5)	1159 (34.5)
Age				
Mean	35.9	36.3	36.1	36.0
Range	15-81	15-75	15-82	15-82
Age Distribution				
15-17 years	114 (7.0)	4 (3.3)	93 (5.8)	211 (6.3)
18-64 years	1481 (90.7)	113 (92.6)	1474 (92.0)	3068 (91.4)
Over 64 years	37 (2.3)	5 (4.1)	73 (2.3)	115 (3.4)
Race				
White	1338 (82.0)	89 (73.0)	1306 (81.5)	2733 (81.4)
Black	139 (8.5)	11 (9.0)	138 (8.6)	288 (8.6)
Hispanic	98 (6.0)	13 (10.7)	93 (5.8)	204 (6.1)
Other	57 (3.5)	9 (7.4)	55 (3..4)	121 (3.6)

Source: Vol. 2, 2.74/p.8; Vol. 4, p. 79-80

7.2.1.3 Extent of exposure (dose/duration)

In the pooled studies, 1632, 1603, and 122 patients ages 15 years and older received montelukast, cetirizine, and placebo, respectively. The mean exposure for montelukast 10 mg was 39.2 days (range 1-56), for cetirizine 10 mg was 38.6 (range 1-50), and for placebo was 38.8 (range 1-56). The extent of exposure for montelukast is summarized in the following table, which was comparable to the other treatment groups.

Table 19. Extent of Exposure for Patients Randomized to Montelukast in Pooled Pivotal Studies

Extent of Exposure (Weeks)	**Montelukast 10 mg n**	**Montelukast 20 mg n**
< 2	47	10
≥ 2 to < 3	36	0

≥ 3 to < 4	32	0
≥ 4 to < 5	94	0
≥5 to < 6	492	0
≥ 6	931	0
Total ≥5	1423	0
Mean Number of Days on Drug	39.2	1.1
Range of Days on Drug	1-56	1-2
Source: Vol. 2/2.74/p.7		

7.2.2 DESCRIPTION OF SECONDARY CLINICAL DATA SOURCES USED TO EVALUATE SAFETY AND FINDINGS

7.2.2.1 Other studies

Three previously reviewed studies were re-evaluated from study reports, synopses, and previous reviews of these studies conducted by Agency reviewers: Study 136, Study 003, Study 171, Study 232, and Study 009. The safety of these studies is briefly summarized in this section.

7.2.2.1.1 Study 136

This study was described in Section 5.1.1 with respect to pharmacokinetic endpoints. The safety of this study will be summarized here.

Study 136 was an open label, single dose, multicenter pharmacokinetic study evaluating the safety, tolerability, and plasma concentration profiles of Singulair Oral Granules in children 6 months to <24 months of age. This study evaluated and compared montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax) obtained from the 6 to <24-month-old children after administration of a 4-mg dose of the sprinkle formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the film-coated tablets of montelukast using a population PK approach.

The results of these analyses showed that in children 6 months to < 1 years of age, AUC values ranged from 1200 ng*hr/mL to 7153 ng*hr/mL and the geometric mean AUC value was 48% higher than that observed in adults.
In terms of safety, no deaths were reported in this study. One patient reported a serious adverse event: 20-month old who was hospitalized with dehydration. One patient discontinued from the study secondary to nausea/vomiting. A total of 22 adverse events were reported in 13 patients. The most commonly reported AEs were diarrhea (noted in 6 patients), nausea/vomiting and "common cold" (each noted in 3 patients). In the 6 to < 12 month age group, 6 patients had AEs, of which influenza like symptoms (reported in 2 patients) was the most commonly reported. No specific safety concerns were raised by this study.

Although the systemic exposure for a single 4-mg oral dose in 6 months to < 12 months of age was 48% greater than in adult historical controls dosed single doses of 10 mg, safety evaluations do not raise any specific safety concerns.

7.2.2.1.2 Study 003

The sponsor previously conducted a randomized, double-blind, placebo-controlled, pharmacokinetic study in healthy male volunteers to investigate the safety and tolerability of multiple oral doses of montelukast (Study 003). Per the submitted synopsis, 24 healthy males ages 18 to 45 years were enrolled. Montelukast 50 mg, 100 mg, and 300 mg capsules or matching placebo were dosed three times daily for 8 and 1/3 days. Pharmacokinetic profiles were assessed. The geometric mean ratios (GMR) for AUC for day 1 ($AUC_{0-\infty}$) and Day 9 (AUC_{0-8}) were compared. The following table summarizes these results [taken from Reference R11 submitted as part of this sNDA].

Geometric Mean Ratio (GMR) Comparing Day 1 $AUC_{(0-\infty)}$ and Day 9 $AUC_{(0-8)}$ [µg•hr/mL] for Doses of MK-0476

Dose:Day	N	Geometric Mean	GMR of Day 9 to Day 1	90% CI For GMR of Day 9 to Day 1	p-Value#
50 mg					
Day 1	6	8.30	1.51	(1.07, 2.12)	0.061
Day 9	6	12.50			
100 mg					
Day 1	6	23.24	1.87	(1.08, 3.24)	0.071
Day 9	6	43.41			
300 mg					
Day 1	6	58.74	2.49	(1.51, 4.08)	0.014
Day 9	6	146.04			
# p-Values based on paired t-test on log scale					

The applicant concluded that with multiple dosing, plasma concentrations of montelukast accumulate to a greater extent than predicted by the single-dose plasma profiles and that the pharmacokinetics of montelukast may be dose dependent.

In terms of safety, it was reported that these doses were well tolerated. In the 23 (out of 24) subjects that completed the study, there were 23 and 10 adverse events reported in the montelukast and placebo groups, respectively. Note that 18 subjects received montelukast, 6 at each dose level, and 6 subjects total received placebo. A total of 7 laboratory AEs were reported, 6 in the montelukast group, and 1 in the placebo group. One patient discontinued from the montelukast group secondary to an AE. The most commonly reported AE was headache, reported in 4 montelukast treated subjects, compared to 1 placebo treated subject. Flatulence, catarrh, and chest tightness were each reported in 2 montelukast subjects and 1 placebo treated subject. No dose ordering of AEs was noted. Other AEs occurred in one or less subject in each group. The applicant concluded that no dose-related AEs were observed in as much as 90 times the recommended dose of montelukast and it was well tolerated. As three times as many subjects received montelukast compared to placebo and types and frequencies of adverse events were generally similar between groups, this reviewer concurs with the applicant. Note that this study is currently referenced in the approved package insert which states that *in short-term studies, up to 900 mg/day [were tolerated] without clinically important adverse experiences.*

7.2.2.1.3 Study 171

As this study was previously reviewed in-depth as part of NDA 21-409 by Dr. Peter Starke, relevant sections have been taken from this review to describe this study and its results.

This was a six-week, multicenter, double-blind, randomized, parallel-group safety and tolerability study comparing montelukast 4 mg oral granules with placebo in 256 pediatric patients ages 6 to 23 months with recurrent wheezing (defined as "at least 3 episodes of asthma or 'asthma-like' symptoms (including but not limited to cough, wheezing, and shortness of breath), all occurring after 8 weeks of age"). The primary objective was to evaluate the safety and tolerability of montelukast compared with placebo over the 6-week treatment period. Safety measurements included clinical evaluations, physical examinations, vital signs, adverse event monitoring, and laboratory safety tests. Laboratory tests included CBC and serum chemistries (ALT, AST, bilirubin, BUN, creatinine, glucose, calcium, total protein, electrolytes). The primary safety endpoint was the overall incidence of adverse experiences and incidences of adverse experiences by body system reported by the parents/guardians. The safety results of Study P176 are briefly summarized below. The reader is referred to Dr. Peter Starke's Medical Officer Review of NDA 21-409 where this study is reviewed in-depth.

The study was conducted at 65 study centers, 29 in US and 36 ex-US including 22 countries in Africa, Asia, Europe, North American, and South America. The study enrolled 256 patients (randomized 2:1, montelukast: placebo), 175 to the montelukast group and 81 to placebo. Mean age of enrollment was 14.6 months, with 84 patients (32.8%) less than 12 months at randomization. A greater percentage of males compared to females were enrolled in both treatment groups (for the 6-11 month group, 69-72% were males). Patient demographics were similar for height and weight. Mean compliance rates were 94-95% for both treatment groups. The extent of exposure was comparable between treatment groups; 97% of patients in the montelukast group compared to 91% in the placebo group completed the study. [Medical Officer Review, Dr. Peter Starke, NDA 21-409]

A total of 132 patients (75%) treated with montelukast and 62 patients (77%) treated with placebo reported adverse events. In general, the types and frequencies of reported adverse events were comparable between treatment groups. The most commonly reported AEs in the montelukast group were: upper respiratory tract infection (montelukast: 32%; placebo: 17%), asthma (montelukast: 19%; placebo: 22%), diarrhea (montelukast: 11%; placebo: 12%), otitis media (montelukast: 9%; placebo: 6%), and pharyngitis (montelukast: 8%; placebo: 7%). There were no deaths in this study. Eight patients experienced serious adverse events in this study, 7 in the montelukast group compared to 1 in the placebo group. These events spanned a wide variety of clinically unrelated areas. Four events related to the respiratory tract: one patient with worsening asthma 4 days after ending montelukast (11 month BF, AN6139), one patient with pneumonia associated with wheezing on Day 11 of montelukast (18 month multi-racial M, AN6525), one patient with bronchiolitis on Day 30 of placebo (17 month WM, AN6172), and one patient with aspiration of a walnut while on montelukast (18 month WM, AN6711). Other events included Shigella infection related dehydration, inguinal hernia, and urinary tract infection. Close review by Dr. Starke revealed no relationship between the pattern of these serious clinical adverse events and use of montelukast. Two percent of patients in the montelukast group and 4% of patients in the placebo group discontinued due to an adverse event.

The reasons for discontinuation in the montelukast group were: worsening asthma (concomitant URI and OM), rash, and vomiting. In the placebo group, the reasons for discontinuation were: asthenia/fatigue, bronchitis, and sleep disorder. [Medical Officer Review, Dr. Peter Starke, NDA 21-409]

Eight patients (3.2%) had at least one laboratory adverse event (7 montelukast {4.1%}, 1 placebo {1.3%}). There were no serious laboratory adverse events, and no patients were discontinued due to a laboratory adverse event. While there was a trend toward more frequent drug-related laboratory adverse events in the montelukast group several patients experienced other clinical adverse events that may have influenced the results. Therefore no clear picture emerged.

Dr. Starke's findings from reviewing the adverse events data were as follow. There was a difference in the number of laboratory AEs, with a higher number in the montelukast group and almost none in the placebo group. Several patients in the montelukast group experienced mild, transient changes in laboratory values, including elevations in serum transaminases (2 AST, 3 AST), decreased white blood cell counts (2 leukocytes, 1 lymphocytes, 1 neutrophil), or decreased platelet counts (2). Most of these laboratory adverse events, including the elevations in serum transaminases, occurred in patients with other clinical adverse events that may have been associated with those laboratory events (one patient with +EB virus, and one patient with a urinary tract infection, and one patient with an upper respiratory infection).

There were no clinically meaningful differences between treatment groups in change from baseline related to vital signs or physical examinations. It was concluded that montelukast was generally well tolerated in the age group and no specific new safety concerns were raised, although the trend for elevated transaminases was noted.

7.2.2.1.4 Study 232 [from p232 submitted with this sNDA as reference]

Study 232 was a 52-week open-label, randomized, controlled (usual care) study to provide extended safety in patients using the montelukast oral granule formulation. The sponsor submitted a clinical study report for an interim analysis of 3-month safety data. As the study was done in 2002, it is unclear why the sponsor submitted only the interim analyses. Nonetheless, the safety information from the submitted report will be summarized. Only patients who completed Protocol 176 (see above) were allowed into this study. In Study 176, patients received either the 4 mg montelukast oral granule formulation or placebo. A minimum of 2 months after successful completion of the last visit of Study 176, patients entered Study 232 and were randomly allocated to receive either montelukast sprinkles 4 mg or usual care (defined as inhaled/nebulized cromolyn or nedocromil or inhaled/nebulized corticosteroids according to the investigators usual practice). A total of 113 patients entered the study, 94 in the montelukast group and 19 in the usual care group. Two patients discontinued from the study in the montelukast group (lost to follow up and withdrew consent) and none from the placebo group. None of the patients discontinued secondary to adverse events.

Clinical adverse experiences were reported by 85 (75.2%) of the 113 randomized patients. The clinical adverse experience profile is summarized by treatment group in Table 18. Clinical

adverse experiences occurred in 73 patients (77.7%) in the montelukast treatment group and 12 patients (63.2%) in the usual care treatment group. Overall, there were no clinically meaningful differences between treatment groups in the incidence of clinical adverse experiences. The most commonly reported adverse events were upper respiratory infection, asthma, pharyngitis and fever. There were no deaths reported in this study. Four SAEs were reported in the montelukast group (none in the placebo): pneumonia, asthma, adenoidal hypertrophy and seizures.

Laboratory adverse experiences were infrequent, and there were no clinically meaningful differences in the frequency of laboratory adverse experiences. Of note, no patients had elevations in transaminases in this interim analysis. There were no serious laboratory adverse experiences. No patients discontinued study therapy due to a laboratory adverse experience. No clinically meaningful differences were reported for vital signs or physical examination.

The sponsor concluded that overall, montelukast 4-mg oral granules were well tolerated in asthmatic patients in this age range. This reviewer concurs with this after reviewing the interim analysis submitted with this sNDA.

7.2.2.1.5 Study 009

The applicant previously conducted a multicenter, open-uncontrolled extension study in adults whose synopsis was submitted with this sNDA (Study 009) where 73 patients with chronic asthma received decreasing doses of montelukast once nightly (200 mg for 22 weeks, followed by 100 mg for 12 weeks and 50 mg for 38 weeks). The applicant concluded that no safety or tolerability concerns were raised during this extension study [clinical overview/Reference R4]. The applicant further states that safety findings with drug overdose confirm the excellent tolerability profile with montelukast and are consistent with the safety data in adults where doses substantially higher than the 10-mg dose were generally well tolerated.

7.2.2.2 Postmarketing experience

The following side effects have been reported in postmarketing use: hypersensitivity reactions (including anaphylaxis, angioedema, rash, pruritus, urticaria and, very rarely, hepatic eosinophilic infiltration); dream abnormalities and hallucinations, drowsiness, irritability, agitation including aggressive behavior, restlessness, insomnia, paraesthesia/hypoesthesia, and very rarely seizure; nausea, vomiting, dyspepsia, diarrhea, increased ALT and AST, and very rarely cholestatic hepatitis; arthralgia, myalgia including muscle cramps; increased bleeding tendency, bruising; palpitations; and edema [Product Circular: Worldwide product circular, Singulair ™, tablets/chewable tablets/oral granules: 2004].

7.2.2.2.1 Worldwide Adverse Experience System (WAES)

The Applicant reviewed all of the serious spontaneous adverse experiences reported in patients using montelukast for an indication of allergic rhinitis with or without concomitant asthma. The WAES was searched from 7/31/97 to 6/30/04 and 22 non-fatal reports were elicited. Twelve were consistent with labeled events in the product circular, and 10 were considered unexpected with montelukast therapy. Of these 10, there were 3 reports of allergic granulomatous angiitis (AGA). The Applicant concluded that there was insufficient data from these reports to allow an

assessment of AGA and no consistent trends were noted in the remaining 7 adverse events [Vol. 2. 2.7.4/p.56-67].

The current product labeling does contain a section in the Precautions describing eosinophilic conditions to include Churg-Strauss (aka AGA). No new specific information is revealed from this marketing application to warranting adjustment to the currently approved labeling.

7.2.2.3 Literature

The applicant conducted a literature review of over 66 published articles through 6/30/2004 regarding the safety of montelukast in the treatment of allergic rhinitis. This reviewer also reviewed the abstracts of said literatures submitted, and concurs with the applicant, that the safety findings reported in published literature are consistent with the safety information provided in current product labeling [Clinical Overview, 2.5.5.5, p. 22].

7.2.3 ADEQUACY OF OVERALL CLINICAL EXPERIENCE

As montelukast is an approved product, this application was not intended to or required to re-establish the overall safety of the drug. Safety information from the two pivotal studies submitted with this sNDA were integrated and discussed earlier in this document. Given that 1632 patients with PAR were evaluated in the pooled pivotal studies, the overall clinical experience is adequate for the intended purpose: evaluation of safety and efficacy in patients with perennial allergic rhinitis.

7.2.4 ADEQUACY OF ROUTINE CLINICAL TESTING

The Applicant only conducted routine clinical testing in the initial PAR study, Study 246. There was a signal for elevations in ALT and AST in this study, and it would have been useful to have had laboratory data to review for Study 265. However, since the current label does mention elevations in ALT and AST based on post-marketing experience, and the number of patients evaluated in the initial study was fairly large for an allergic rhinitis study, routine clinical testing of study patients was adequate.

7.2.5 ADEQUACY OF METABOLIC, CLEARANCE, AND INTERACTION WORKUP

These areas of evaluation were not necessary for this application.

7.2.6 ADEQUACY OF EVALUATION FOR POTENTIAL ADVERSE EVENTS FOR ANY NEW DRUG AND PARTICULARLY FOR DRUGS IN THE CLASS REPRESENTED BY THE NEW DRUG; RECOMMENDATIONS FOR FURTHER STUDY

As montelukast is not a new molecular entity or a new drug, this section is not applicable to this efficacy supplement.

7.2.7 ASSESSMENT OF QUALITY AND COMPLETENESS OF DATA

The quality of data available for a safety review was generally adequate. Narratives, CRTs, and CRFs were available, accessible, and complete.

7.2.8 SAFETY UPDATE [SE1-033-SU, 1/24/05]

The Applicant provides a brief safety update on relevant information from 6/30/04 to 11/30/04, which includes updated safety information received for the PAR studies after the studies were completed and safety data from post-marketing use after 7/1/04.

7.2.8.1 Updated Information Relevant to Pivotal PAR Studies

The Applicant received updated information for 3 pregnancies that were ongoing at the time the pivotal studies were completed, 1 of the pregnancies was in a patient randomized to montelukast, and 2 in patients randomized to the placebo. The outcome of all three pregnancies was the same: the term delivery of normal children weighing over 7 lbs each.

7.2.8.2 Updated Post-Marketing Experience

Safety data from post-marketing experience covering the period of the safety update did not reveal any new safety concerns. A search of the WAES database revealed 5 new serious adverse events, 4 were labeled and 1 was unexpected. The labeled events included: angioedema/urticaria, throat tightness/pruritus/rash, cholestatic jaundice, and urticaria. The patient with the unexpected events had pharyngolaryngeal pain, cough, and nasal congestion. The Applicant was unable to draw any conclusions from these unexpected adverse events.

The Applicant concluded that the serious adverse events reported were already listed in current labeling or represented situations for which specific conclusions as to causality can not be determined. This reviewer concurs with the Applicant.

7.2.8.3 Conclusions from Safety Update

The safety update did not reveal any new safety concerns and it was reassuring to learn that the pregnant patient who received montelukast therapy was delivered of a healthy baby.

7.3 General Methodology

7.3.1 POOLING DATA ACROSS STUDIES TO ESTIMATE AND COMPARE INCIDENCE

The Applicant submitted two pivotal studies as part of this marketing application. Since both studies were similarly designed, safety was assessed via pooling the data. For other supportive

studies that were previously reviewed by the Agency, these studies were summarized separately, as their designs were not similar, preventing pooling.

7.3.1.1 Pooled data vs. individual study data

For the pivotal studies, exposure data, adverse event data, serious adverse event data, and discontinuations from studies due to adverse events were pooled to compare the incidence. However, since pre- and post-randomization data only existed for Study 246 with respect to laboratory testing data and vital signs, the results of this study were summarized separately.

Since this reviewer also evaluated findings from data previously reviewed by the Agency for studies that were not similar in design, the safety information from these studies was described separately.

7.3.1.2 Combining data

Combining exposure and adverse event data from the two pivotal studies was appropriate as the studies were of similar design.

7.3.2 EXPLORATIONS FOR PREDICTIVE FACTORS

Other than attempting to evaluate drug-demographic interactions, the Applicant did not perform any additional explorations for predictive factors (i.e. dose and time dependency of adverse events, drug-drug interactions, drug-disease interactions). As montelukast is an approved product with extensive previous experience, these explorations were not warranted for this marketing application.

7.3.2.1 Explorations for drug-demographic interactions

The Applicant investigated demographic characteristics with respect to age, gender, and race in the PAR studies to determine potential interaction with montelukast. In general no drug-demographic interactions were noted, and where variability in response was noted, the number of patients was too small to make any definitive conclusions. The Division's Statistician and this reviewer concur with the Applicant that no meaningful drug-demographic interactions were noted.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

This application does not alter the currently approved dosing regimen with respect to asthma or seasonal allergic rhinitis. For PAR in patients 12 months and older, the currently approved dosing regimen is identical to that currently approved for asthma and seasonal allergic rhinitis.

This application provides for the (b) (4) to patients 6 months to < 12 months of age. The proposed dosage in patients 6 to 23 months of age is 4-mg oral granules once daily (b) (4). The proposed dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules daily. The proposed dosage in patients 6 to 14 years of age and in patients 15 years of age and older is one 5-mg chewable tablet and one 10-mg tablet daily, respectively.

Since montelukast is not currently approved in children 6 months to < 12 months of age, the dose selection for this group is important. Data from previously reviewed clinical pharmacology data demonstrate that mean systemic exposures in children this age are variable following single oral administration of 4-mg granules; however, exposures are similar or up to 48% greater in this pediatric population as compared to adults. This supports the efficacy for the use of the 4-mg oral granules in this pediatric population. The safety of the 4-mg oral granules in this pediatric population is supported by comparing systemic exposures in adults dosed 90 times the current approved dose of montelukast. The findings from this study demonstrated that when adults have greater than 7 times the exposures noted in patients 6 months to < 12 months of age following 4-mg oral granules, no specific safety concerns were raised. Therefore, re-evaluation of previously reviewed clinical pharmacology data by the Agency supports the dose of 4-mg oral granules for use in children 6 months to < 12 months of age.

8.2 Drug-Drug Interactions

The Applicant did not evaluate for drug-drug interactions in this application, as the current label describes previously conducted studies for evaluation of drug-drug interactions.

8.3 Special Populations

Since montelukast is an approved product, and this application relied on the Agency's previous determination of the safety of montelukast in the original application, studies to assess the use in special populations were not conducted.

8.4 Pediatrics

Since montelukast is currently approved in patients 12 months of age and older, the use of montelukast in children 6 months to < 12 months of age became an issue. As the pathophysiology of the disease is similar in adults and children, and the exposures in this age group are similar to or greater than that of adults, efficacy can be extrapolated to this pediatric population. However, the evaluation of safety became important since the systemic exposures in this young pediatric population were greater than 7 times those noted in adults.

To address the safety in this pediatric population, previously reviewed data was consulted. For patients ages 6 months to < 12 months of age, safety is supported by pharmacokinetic studies previously reviewed in both pediatric (Study 136) and adult (Study 003) patients and safety studies conducted in patients 6 to 23 months of age with asthma (Study 171 and 232). Study 136 demonstrated that systemic exposures in children 6 to < 12 months of age were 48% greater than

noted for adults at currently prescribed doses. However, results from Study 003 suggest that this 48% greater systemic exposure does not raise any specific safety concerns. Adults had systemic exposures that were more than 7 times the exposure noted in these children without any corresponding safety concerns. Additionally, montelukast was evaluated in children 6 months to 23 months of age with asthma in a 12 week safety study (171) followed by an open-label extension phase (232), and was generally well tolerated. Therefore, the pharmacokinetic and safety studies in children 6 to 23 months of age with asthma, previously evaluated by the Agency, lend support for the safety in children 6 to <12 months of age. Additional support of safety in this population is solicited from a safety and efficacy study conducted in patients 6 months to < 23 months of age with asthma (Study 171).

8.5 Literature Review

The Applicant performed a literature search to support the safety of montelukast. Review of these data does not raise and specific safety concerns. Findings were consistent with current labeling.

8.6 Postmarketing Risk Management Plan

Since montelukast is an approved product with extensive marketing worldwide, no specific postmarketing risk management plan is warranted.

9 OVERALL ASSESSMENT

9.1 Conclusions

The data submitted in this application are adequate from a clinical perspective to support the approval of this marketing application with labeling changes. The applicant conducted two phase III multicenter, randomized, double-blind, placebo-controlled trials in support of the efficacy of Singulair for the relief of symptoms associated with perennial allergic rhinitis in patients 15 years of age and older. Although the first study failed to demonstrate statistically significant improvements in the pre-specified primary efficacy endpoint Daytime Nasal Symptoms Score (comprised of four nasal symptoms), a trend favoring montelukast was noted. This trend towards efficacy was confirmed in a second pivotal study, where the applicant was able to demonstrate statistically significant improvements in the primary efficacy endpoint, Daytime Nasal Symptoms Score (consisting of three nasal symptoms excluding nasal pruritus). As montelukast is already approved in SAR, the submitted data are sufficient to establish efficacy in patients 15 years of age and older with PAR. Efficacy in patients 6 months to 14 years of age is extrapolated from the demonstrated efficacy in patients 15 years of age and older as the pathophysiology of PAR is similar in adults and children.

In general, review of the safety data from the pivotal studies does not reveal any new safety concerns that are not consistent with current labeling. The pivotal studies support the safety of

montelukast in patients 15 years of age and older with PAR. Safety in patients 12 months to 14 years of age is supported by previous experience in patients 12 months of age and older with asthma and patients 2 years of age and older with seasonal allergic rhinitis and asthma. Safety in patients 6 months to < 12 months of age is supported by previously reviewed clinical pharmacology studies and safety and efficacy studies in patients 6 months of age to 23 months of age with asthma.

9.2 Recommendation on Regulatory Action

From a clinical perspective, the data submitted in this NDA provide adequate support for approval.

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are needed for this already marketed product.

9.4 Line-by-Line Labeling Review

The applicant proposes changes to the following sections based on information provided in this submission: Package Circular Footnote, Clinical Pharmacology, Indications and Usage, Precautions, Adverse Reactions and Dosage and Administration. The proposed changes will be provided with reviewer comments for each of these sections. Note that any deleted language from the current label or any proposed added language will be bolded.

9.4.1 PACKAGE CIRCULAR FOOTNOTE

The applicant will include a revised copyright date.

9.4.2 PACKAGE CIRCULAR FOOTNOTE

The applicant will include a revised copyright date.

Reviewer's comments: This is acceptable.

9.4.3 CLINICAL PHARMACOLOGY

The applicant proposes changes to two subsections in this section: Adolescents and Pediatric Patients and Clinical Studies.

9.4.3.1 Adolescent and Pediatric Patients

The applicant provides language to differentiate age for use for the 4-mg oral granules formulation in asthma and perennial allergic rhinitis. The second to the last sentence in the last paragraph is amended to include this information.

Currently approved language: *The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma.*

Proposed language: *The 4-mg oral granule formulation should be used for pediatric patients 12 to 23 months of age for the treatment of asthma**, or for pediatric patients 6 to 23 months of age for the treatment of perennial allergic rhinitis**.*

Reviewer's comments: The addition of this language is acceptable.

9.4.3.2 Clinical Studies

The applicant proposes to revise this section heading, revise the last sentence under "GENERAL" for clarity, and adds the "Clinical Studies-Perennial Allergic Rhinitis" with study results from the PAR trials.

9.4.3.2.1 Revision of Section Heading

Currently, this section is titled, *Clinical Studies-Asthma and **Seasonal** Allergic Rhinitis*.

The applicant proposes to change it to, *Clinical Studies-Asthma and Allergic Rhinitis **(Seasonal and Perennial)***.

Reviewer's comments: These changes are acceptable.

9.4.3.2.2 GENERAL

In this section, the sponsor proposes to amend the last sentence for clarity.

This last sentence currently states, *Efficacy was demonstrated for **seasonal** allergic rhinitis when montelukast was administered in the morning or the evening without regard to time of food ingestion.*

The proposed change is, *Efficacy was demonstrated for allergic rhinitis when montelukast was administered in the morning or evening without regard to time of food ingestion* (b) (4)

Reviewer's comments: This reviewer recommends maintaining the statement as is in the current label. This reviewer feels that the proposed statement is not as clear to the reader as is the statement in the currently approved label.

9.4.3.2.3 Clinical Studies-Perennial Allergic Rhinitis

This subheading was added to reflect the results from the PAR trials submitted in this sNDA. The proposed new section is as follows:

(b) (4)

TABLE 4
Effects of SINGULAIR on Daytime Nasal Symptoms Score** in a Placebo-controlled Trial
in Patients with Perennial Allergic Rhinitis

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08‡ (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

** Average of individual scores of nasal congestion, rhinorrhea, sneezing as assessed by patients on a 0-3 categorical scale.
‡ Statistically different from placebo (p≤0.001).

Reviewer's comments: This reviewer has a few issues with this section. First, the applicant states that the efficacy was investigated in (b) (4) *patients 15 to 82 years of age with perennial allergic rhinitis…," the total number of* (b) (4) *reflecting patients from both phase III trials submitted in this sNDA. Additionally, the applicant correctly lists the total number of patients (1632) who received Singulair in both of these trials.* (b) (4) *Study 265, where the applicant was able to show statistically significant improvements in the pre-specified primary efficacy endpoint.* (b) (4) *where the applicant was unable to demonstrate statistically significant improvements for the pre-specified primary efficacy endpoint. Additionally, this study also provided important comparative data to cetirizine.* (b) (4)

Additionally, the total number of patients evaluated in both trials was not (b) (4) *but 3357; a total of 1365 were enrolled in Study 246 and 1992 were enrolled in Study 265. The number* (b) (4) *is misleading as* (b) (4) *The applicant should include the total number of patients enrolled* (b) (4) *as 3357.*

Also, the table lists 1000 patients in the Singulair group and 980 patients in the placebo group. This does not represent the total number of patients randomized to the trial (1002 and 990

patients were randomized to the Singulair and placebo groups, respectively). Rather, these numbers represent the number of patients who had data that could be analyzed for efficacy. The inclusion of the number of patients evaluable for efficacy as proposed in the table is acceptable.

This reviewer recommends amending this section to:

The efficacy of SINGULAIR tablets for the treatment of perennial allergic rhinitis was investigated in 2 randomized, double-blind, placebo-controlled (active-controlled with cetirizine in one trial) trials conducted in North America and Europe. The two trials enrolled a total of 3357 patients, of whom 1632 were treated with Singulair Tablets. Patients 15 to 82 years of age with perennial allergic rhinitis as confirmed by history and a positive skin test to at least one relevant perennial allergen (dust mites, animal dander, and mold spores), who had active symptoms at time of study entry, were enrolled.

The primary outcome variable was the mean change from baseline in Daytime Nasal Symptom Score (DNSS) which represented the average of individual scores of nasal congestion, rhinorrhea, sneezing, and ± nasal itching (depending on the study). Individual symptoms were assessed by patients on a 0-3 categorical scale.

One of the two trials showed a significant reduction in Daytime Nasal Symptom Score with Singulair 10-mg tablets over a 6-week treatment period compared to placebo. In this study, the Daytime Nasal Symptom Score comprised the average of three individual symptoms (nasal congestion, rhinorrhea, and sneezing). The results of this trial are shown below.

TABLE 4
Effects of SINGULAIR on Daytime Nasal Symptoms Score** in a Placebo-controlled Trial
in Patients with Perennial Allergic Rhinitis

Treatment Group (N)	Baseline Mean Score	Mean Change from Baseline	Difference Between Treatment and Placebo (95% CI) Least-Squares Mean
SINGULAIR 10 mg (1000)	2.09	-0.42	-0.08‡ (-0.12, -0.04)
Placebo (980)	2.10	-0.35	N.A.

** Average of individual scores of nasal congestion, rhinorrhea, sneezing as assessed by patients on a 0-3 categorical scale.
‡ Statistically different from placebo ($p \leq 0.001$).

In the other trial, Singulair was not shown to significantly reduce the DNSS over a 6-week treatment period, which comprised the average of four individual symptoms (nasal congestion, rhinorrhea, sneezing, and nasal itchiness), although there was a numerical trend favoring Singulair compared to placebo. The mean changes from baseline in the DNSS for Singulair, cetirizine, and placebo were -0.46, -0.50, and -0.39, respectively.

9.4.4 INDICATIONS AND USAGE

The applicant proposes to revise this section to include perennial allergic rhinitis.

The current label states, *Singulair is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older.*

The proposed label is, *Singulair is indicated for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older**, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older***.

Reviewer's comments: This is acceptable.

9.4.5 PRECAUTIONS

In this section under *Pediatric Use,* the applicant proposes to add patient information for perennial allergic rhinitis, revise wording to collectively refer to seasonal and perennial allergic rhinitis as *allergic rhinitis*, and revise the age range for pediatric safety and efficacy.

Second Paragraph
The current label states, *The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with **seasonal** allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.*

The proposed label states, *The efficacy of SINGULAIR for the treatment of seasonal allergic rhinitis in pediatric patients 2 to 14 years of age **and for the treatment of perennial allergic rhinitis in pediatric patients 6 months to 14 years of age** is supported by extrapolation from the demonstrated efficacy in patients 15 years of age and older with allergic rhinitis as well as the assumption that the disease course, pathophysiology and the drug's effect are substantially similar among these populations.*

Reviewer's comments: These changes are acceptable.

Fifth and Sixth Paragraphs

The current label states, *The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile (see ADVERSE REACTIONS).*

The safety and effectiveness in pediatric patients below the age of 12 months have not been established.

The proposed label states, *The safety of SINGULAIR 4-mg and 5-mg chewable tablets in pediatric patients aged 2 to 14 years with allergic rhinitis is supported by data from studies conducted in pediatric patients aged 2 to 14 years with asthma. A safety study in pediatric*

patients 2 to 14 years of age with seasonal allergic rhinitis demonstrated a similar safety profile (see ADVERSE REACTIONS). (b) (4) .

Reviewer's comments: The last sentence in the second to last paragraph should be amended to reflect that the safety of oral granules in pediatric patients 6 months to 23 months of age is supported by data from studies conducted in pediatric patients 6 months to 23 months of age with asthma, and by pharmacokinetic data comparing systemic exposures between this pediatric population and adults.

9.4.6 ADVERSE REACTIONS

A section titled Adolescents and Adults 15 years of Age and Older with Perennial Allergic Rhinitis and study results were added. Also the subsection Pediatric Patients 12 to 23 months of age was changed to 6 to 23 months of age and relocated to the end of the section.

9.4.6.1 Adolescents and Adults 15 years of Age and Older with Perennial Allergic Rhinitis

The applicant proposes to add the following subsection and results,

Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

(b) (4) *SINGULAIR administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.*

Reviewer's comments: This reviewer recommends changing the first sentence, as this sentence implies that Singulair was administered (b) (4) *It may be clearer to state, "The safety of Singulair in adult and adolescent patients 15 years of age and older with perennial allergic rhinitis was evaluated in two, 6-week clinical trials enrolling a total of 3357 patients, of whom 1632 received Singulair." The description of adverse events are accurate.*

9.4.6.2 Change in "Pediatric Patients 12 to 23 Months of Age"

The sponsor currently has a subsection titled *Pediatric Patients 12 to 23 Months of Age with Asthma* under the ADVERSE REACTIONS section which is currently located under the section titled *Pediatric Patients 2 to 5 years of Age with Asthma.*

This section currently states, *Pediatric Patients **12** to 23 Months of Age **with Asthma***
SINGULAIR has been evaluated for safety in 124 pediatric patients 12 to 23 months of age. The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. SINGULAIR administered once daily at bedtime was generally well tolerated. In pediatric patients 12 to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.

The proposed wording changes are as follows:
(b) (4)
*SINGULAIR has been evaluated for safety in **175** pediatric patients **6** to 23 months of age. The safety profile of SINGULAIR in a 6-week, double-blind, placebo-controlled clinical study was generally similar to the safety profile in adults and pediatric patients 2 to 14 years of age. SINGULAIR administered once daily at bedtime was generally well tolerated. In pediatric patients **6** to 23 months of age receiving SINGULAIR, the following events occurred with a frequency ≥2% and more frequently than in pediatric patients who received placebo, regardless of causality assessment: upper respiratory infection, wheezing; otitis media; pharyngitis, tonsillitis, cough; and rhinitis. The frequency of less common adverse events was comparable between SINGULAIR and placebo.*

Reviewer's comments: (b) (4) *This reviewer recommends leaving the section as is in the current label.*

To address the safety in the 6 months of age and older with perennial allergic rhinitis, this reviewer recommends adding a subheading titled "Pediatric Patients 6 Months to 14 Years of Age with Perennial Allergic Rhinitis," stating the following:

"SINGULAIR has not been evaluated in patients 6 months to 14 years of age with perennial allergic rhinitis. However, the safety in patients 2 to 14 years of age with perennial allergic rhinitis is extrapolated from the established safety in patients 2 to 14 years of age with seasonal allergic rhinitis. The safety in patients 6 months of age to 23 months of age is extrapolated by data from pharmacokinetic and safety and efficacy studies in asthma in this population and adult pharmacokinetic studies.

9.4.7 DOSAGE AND ADMINISTRATION

The applicant revised wording and section headings for each age group to collectively refer to seasonal and perennial allergic rhinitis as *allergic rhinitis* and added dosage instructions for pediatric patients with perennial allergic rhinitis. The applicant also revised the safety and effectiveness statement and revised oral granule administration instructions to include the option to mix in baby formula or breast milk.

This section in the current label is as follows (applicable allergic rhinitis sections):

*Adults and Adolescents 15 Years of Age and Older with Asthma or **Seasonal** Allergic Rhinitis*
The dosage for adults and adolescents 15 years of age and older is one 10 mg tablet daily.

*Pediatric Patients 6 to 14 Years of Age with Asthma or **Seasonal** Allergic Rhinitis*
The dosage for pediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily. No dosage adjustment within this age group is necessary.

*Pediatric Patients 2 to 5 Years of Age with Asthma or **Seasonal** Allergic Rhinitis*
The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet or one packet of 4 mg oral granules daily.

Pediatric Patients 12 to 23 Months of Age with Asthma
The dosage for pediatric patients 12 to 23 months of age is one packet of 4-mg oral granules daily to be taken in the evening. ***Safety and effectiveness in patients younger than 12 months of age have not been established.***

Administration of SINGULAIR Oral Granules
SINGULAIR 4 mg oral granules can be administered either directly in the mouth, or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (with or without mixing food) must be administered within 15 minutes. If mixed food, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. SINGULAIR oral granules are not intended to be dissolved in liquid for administration. However, liquids may be taken subsequent to administration. SINGULAIR oral granules can be administered without regard to the time of meals.

The proposed label for this section is as follows:

Adults and Adolescents 15 Years of Age and Older with Asthma or Allergic Rhinitis
The dosage for adults and adolescents 15 years of age and older is one 10 mg tablet daily.

Pediatric Patients 6 to 14 Years of Age with Asthma or Allergic Rhinitis
The dosage for pediatric patients 6 to 14 years of age is one 5 mg chewable tablet daily. No dosage adjustment within this age group is necessary.

Pediatric Patients 2 to 5 Years of Age with Asthma or Allergic Rhinitis
The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet or one packet of 4 mg oral granules daily.

Pediatric Patients 12 to 23 Months of Age with Asthma
The dosage for pediatric patients 12 to 23 months of age is one packet of 4-mg oral granules daily to be taken in the evening.

Pediatric Patients 6 to 23 Months of Age with Perennial Allergic Rhinitis
The dosage for pediatric patients 6 to 23 months of age is one packet of 4-mg oral granules daily. (b) (4)

Administration of SINGULAIR Oral Granules
SINGULAIR 4 mg oral granules can be administered either directly in the mouth, ***dissolved in 1 teaspoonful (5 mL) of cold or room temperature baby formula or breast milk,*** *or mixed with a spoonful of cold or room temperature soft foods; based on stability studies, only applesauce, carrots, rice, or ice cream should be used. The packet should not be opened until ready to use. After opening the packet, the full dose (****with or without mixing with baby formula, breast milk, or*** *food) must be administered within 15 minutes. If mixed with* ***baby formula, breast milk, or*** *food, SINGULAIR oral granules must not be stored for future use. Discard any unused portion. SINGULAIR oral granules are not intended to be dissolved in* ***any*** *liquid* ***other than baby formula or breast milk*** *for administration. However, liquids may be taken subsequent to administration. SINGULAIR oral granules can be administered without regard to the time of meals.*

Reviewer's comments: the changes made to this section are acceptable.

10 APPENDICES

10.1 Review of Individual Study Reports

This efficacy supplement presents evidence from two US clinical trials in adults and adolescents to support the safety and efficacy of Singulair™ for the indication of perennial allergic rhinitis. Based upon discussions with the Agency, the sponsor submits one pivotal study, P265, and one supporting study, P246. Although the sponsor refers to the studies in these terms, for review purposes, both studies are considered pivotal. These two studies are described in detail in this section of the review.

10.1.1 STUDY P265: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY INVESTIGATING THE CLINICAL EFFECTS OF MONTELUKAST IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Protocol #:	P265
Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Investigating the Clinical Effects of Montelukast in Patients with Perennial Allergic Rhinitis
Study Dates:	Initiated October 27, 2003. Completed May 3, 2004.
Sites:	117 sites in Canada, Europe, and United States
Investigators:	117 Investigators
IRB:	The protocol was reviewed by the Independent Ethics Committee (IEC) or the Institutional Review Board (IRB) of each study site. IEC and IRB approval letters were received and verified before the shipment of study drug.
Ethical Considerations:	This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Source: Vol. 5, p. 19, 27

10.1.1.1 Study Design

10.1.1.1.1 Objectives

Primary Objective

The primary objective of the study was to asses the treatment effect of montelukast 10 mg versus placebo on the primary endpoint of Daytime Nasal Symptoms score (average of scores of congestion, rhinorrhea, and sneezing) over a 6-week treatment period, in patients with PAR and to determine the tolerability profile of montelukast 10 mg in patients with PAR. **[Vol. 5, p. 3]**

Secondary Objectives

The secondary objectives were to assess the treatment effect of montelukast 10 mg versus placebo, over a 6-week treatment period in patients with PAR, on the secondary endpoints of: Global Evaluation of allergic rhinitis by patient, and overall rhinoconjunctivitis Quality-of-Life score, in addition to other endpoints. **[Vol. 5, p. 3]**

10.1.1.1.2 Study Description

This was an international, multicenter, 6-week, 2-period, randomized, double-blind, placebo-controlled study investigating the safety and efficacy of montelukast 10 mg versus placebo in 1992 patients 15 to 85 years of age with perennial allergic rhinitis, conducted during the winter season.

10.1.1.1.3 Population

Approximately 1600 patients were planned for enrollment, 3401 were screened, and 1992 non-smoking males and females ages 15-85 years of age, with at least a 2-year documented clinical history of PAR symptoms, a positive skin test to two or more perennial allergens, and a minimum predefined level of Daytime Nasal Symptoms were randomized. **[Vol. 2, 2.7.6, p. 8]**

10.1.1.1.4 Inclusion Criteria

Patients were eligible for study entry if they fulfilled the following:

1. Patient understood the study procedures and had agreed to participate by signing the appropriate informed consent form (with assent, as applicable).

2. Patient was a man or woman between the ages of 15 years and 85 years (inclusive) at Visit 1. Women had to have used appropriate contraceptives (hormonal and/or barrier) beginning at least 7 days before Visit 1 and continuing with uninterrupted use of appropriate contraceptives until at least 14 days after study completion (or Discontinuation Visit). Women had to have demonstrated a urine β-human chorionic gonadotropin (β-hCG) level consistent with a nongravid state at Visit 1.

3. Patient had a documented clinical history (at least 2 years) of perennial allergic rhinitis symptoms.

4. Patient fulfilled the following signs and symptoms of perennial allergic rhinitis by Visit 3, prior to having been randomized and enrolled into Period II:

    a. Two or more positive skin tests: a positive skin test (wheal ≥3 mm greater than saline control) to ≥2 of the relevant perennial allergens.

For patients that had 2 positive skin tests only (i.e., remainder of panel was negative):
• One test must have indicated sensitivity to non-animal antigen.
• Those who reacted to an animal antigen must have had daily exposure to that animal as a constant indoor pet.
b. A minimal predefined level of Daytime Nasal Symptoms score (i.e., a 5-day score of at least 23) as derived from the patient diary cards during Period I (between Visit 2 and Visit 3).

5. Patient was a nonsmoker and had been a nonsmoker for at least 6 months prior to Visit 1, with a cumulative smoking history of no more than 20 pack-years (i.e., 1 pack [20 cigarettes] per day for 20 years).

6. Patient was judged to be in good, stable physical and mental health (except for his/her allergic rhinitis) based on medical history, physical examination, and review of electrocardiogram and routine laboratory data, and the patient appeared able to successfully complete this study.

10.1.1.1.5 Exclusion Criteria

Patients were excluded from study entry if they met any of the following:

1. Patient was under the age of legal consent and consent (assent, as applicable) could not be obtained from parent or guardian.

2. Patient was, in the opinion of the investigator, mentally or legally incapacitated, preventing informed consent from being obtained, or could not read or comprehend written material.

3. Patient was hospitalized.

4. Patient was a woman who was <8 weeks postpartum or was breast-feeding an infant.

5. Patient intended to move or to vacation away from home during the study.

6. Patient had undergone any major surgical procedure within 4 weeks prior to Visit 1.

7. Patient was a current or recent past abuser (within the past 10 years) of alcohol or was currently a user or recent past abuser (within the past 10 years) of illicit drugs.

8. Patient had participated in a clinical study involving an investigational or marketed drug within 4 weeks prior to Visit 1.

9. Patient required treatment other than inhaled short-acting β-agonist for asthma (e.g., inhaled or oral corticosteroids, theophylline, nedocromil, cromolyn, oral or long-acting inhaled β-agonist, leukotriene receptor antagonist, leukotriene synthesis inhibitor, or ipratropium bromide) and/or used more than 8 puffs per day of inhaled short-acting β-agonist.

10. Patient had been treated in an emergency room for asthma within 1 month or had been hospitalized for asthma within 3 months prior to Visit 1.

11. Patient had an upper respiratory tract infection, chronic and/or purulent sinusitis, infectious rhinitis (with symptoms such as sore throat, fever, thick purulent rhinorrhea), ocular infection, otitis media, or history of any of these within 3 weeks prior to Visit 1 or any time between Visits 1 and 3.

12. Other than asthma, patient had any active, acute, or chronic pulmonary disorder that was documented by history, physical examination, or chest x-ray.

13. Patient had rhinitis medicamentosa or nonallergic rhinitis.

14. Patient had a dependency on nasal, oral, or ocular decongestants as determined by the investigator.

15. Patient had evidence of significant nasal obstruction due to structural causes (e.g., markedly deviated nasal septum, severe nasal polyposis) that significantly interfered with nasal airflow, as determined by the investigator.

16. Patient had a recent history (within 3 months prior to study start) of a clinically significant psychiatric disorder other than mild depression (which did not interfere with work or social activities).

17. Patient had a history of an anaphylactic allergic reaction related to administration of either a marketed or investigational drug or was otherwise hypersensitive to montelukast, or one of its components.

18. Patient had a clinically significant, active disease of the gastrointestinal, cardiovascular, hepatic, neurological, renal, genitourinary, or hematologic systems or had uncontrolled hypertension (>160/95 mm Hg).

19. Patient had a history of any illness that would require treatment with an excluded medication, could have been immediately life-threatening (ventricular arrhythmia, neoplasia [incompletely cured or treated in the 3 months prior to study start], “brittle” diabetes mellitus), would have posed restriction on participation or successful completion of the study, or would have posed an additional risk to the patient on administration of the study

drug.

20. Patient had significant and unexplained abnormalities on Visit 1 laboratory measurements.

21. Patient was 50% over or under normal weight for height and body build.

22. Patient had taken the following medications before Visit 1. These therapies were also not allowed during the study, unless otherwise specified:
    a. Antihistamines:
        1) Short-acting, within 24 hours;
        2) Long-acting, within 72 hours (e.g., loratadine, desloratadine, fexofenadine, cetirizine, meclizine, or azelastine);
    b. Ophthalmic corticosteroids within 2 weeks;
    c. Nasal corticosteroids within 3 weeks;
    d. Inhaled, oral, intravenous, rectal, or high-potency topical corticosteroids within 1 month;
    e. Intramuscular or intra-articular corticosteroids within 3 months;
    f. Nasal, ophthalmic, or inhaled cromolyn, or nedocromil within 2 weeks;
    g. Oral leukotriene receptor antagonists (e.g., zafirlukast or montelukast) or leukotriene synthesis inhibitors (e.g., zileuton) within 2 weeks;
    h. Oral or long-acting inhaled β-adrenergic agonists or inhaled anticholinergic agents within 1 week;
    i. Theophylline therapy within 1 week;
    j. Tricyclic antidepressants within 1 month.

23. Patient had started immunotherapy within 3 months prior to Visit 1. If patient was using immunotherapy, patient should be on a maintenance or stable dose during the 3 months prior to Visit 1 and throughout the course of the study. Immunotherapy was not to be performed within 24 hours preceding a study visit. It could be administered immediately after study visits.

24. Patient had taken any specifically excluded medication within 14 days prior to Visit 1.

25. Patient was unable or unwilling to comply with the study procedures as determined during Period I, including adequate completion of the diary card and medication compliance.

10.1.1.2 Therapies

10.1.1.2.1 Study Treatments

All eligible patients were randomized to receive montelukast or placebo in a 1:1 ratio.

Montelukast 10 mg or a montelukast matching-image placebo were to be taken once daily at bedtime. All treatments were manufactured and provided by MRL. The formulation number for montelukast was MR-4847 and for matching placebo was MR-4309. **[Vol. 5, p. 31]**

10.1.1.2.2 Allowed Therapies

The sponsor allowed certain therapies during the course of the study.

- Acetaminophen for minor pain relief

- Medications on a stable regimen used to treat concurrent disorders that did not affect nasal symptoms and were not specifically excluded, were allowed, if they were initiated one month prior to study onset.

- Short-acting β_2 agonists (up to 8 puffs per day) were allowed for the treatment of asthma symptoms prior to onset of active treatment phase; no allergic rhinitis or asthma rescue medications were allowed during the study.

- Appropriate contraceptive drugs were allowed.

- Immunotherapy was allowed if the patients were on a stable regimen

Reviewer's comments: immunotherapy was allowed if the patient was on a stable regimen; however, any benefits noted in the study could potentially be attributable to immunotherapy. However, if there is an improvement from baseline in individuals currently on immunotherapy, then this improvement may be attributable to study drug.

10.1.1.2.3 Excluded Therapy

All excluded therapies and respective exclusionary periods are shown in the following table.

Table 20. Study 265, Excluded Therapies and Respective Exclusionary Periods

Therapy	Exclusionary Period
Intramuscular or intra-articular corticosteroids	3 months
Tricyclic Antidepressants	1 month
Inhaled, intravenous, rectal, or high-potency topical corticosteroids	1 month
Intranasal corticosteroids	3 weeks
Nasal, ophthalmic, or inhaled cromolyn, or nedocromil	2 weeks
Oral leukotriene receptor antagonists	2 weeks
Ophthalmic corticosteroids	2 weeks
Oral or long-acting inhaled β_2-agonists or inhaled anticholinergic agents	1 week
Theophylline	1 week
Long-acting antihistamines	72 hours
Short-acting antihistamines	24 hours

Source: Vol. 5, p. 29

10.1.1.2.4 Compliance

Compliance was evaluated by counting tablets upon return of dispensed medication bottles. **[Vol. 5, p. 34]**

10.1.1.2.5 Withdrawal Criteria [Vol. 5, p. 545]

Patients were to be discontinued from the trial if they:

- required therapy with any excluded medication
- missed any study medication on 5 or more days between visits during the randomized, double-blind treatment phase
- experienced a clinical or laboratory adverse event that would jeopardize their health or that would preclude them from completing the study
- withdraw consent for any reason at any point in time

10.1.1.3 Conduct

The study was a multicenter, randomized, double-blind, 2-period, 6-week placebo-controlled study evaluating the clinical benefit of Montelukast 10 mg in the treatment of PAR and the safety and tolerability in this patient population. The study was divided into two periods and 6 visits. Visit I was the screening visit where medical history, physical examination, laboratory investigations, EKG, and informed consent were obtained. During this visit the patient received a diary where symptoms scores were to be recorded. At Visit 2, the diary was reviewed, and if patients continued to meet eligibility criteria, they then started Period I, a 5-7 day, single-blind, placebo run-in period. At Visit 3, eligible patients entered Period II, the 6-week, randomized, double-blind active treatment phase, when they were randomized to receive either montelukast 10 mg or placebo. Patients returned every two weeks for follow-up visits (Visits 4-6).

Table 21. Study 265, Study Procedure Assessments and Schedules

	Screening	Period I		Period II		
Visit	**1**	**2**	**3**	**4**	**5**	**6**
Week	**-2**	**-1**	**0**	**2**	**4**	**6**
Procedure						
Informed Consent	√					
Medical History	√					
Physical Examination	√					
Inclusion/Exclusion Criteria	√	√	√			
Prior/Concomitant Therapy	√	√	√	√	√	√
Adverse Event Review	√	√	√	√	√	√
Height/Weight	√					
Vital Signs	√					
EKG	√					
Skin Test	√					
Laboratory Tests	√					
Urine Pregnancy Test	√		√			√
Diary, Questionnaire, dosing schedule Review	√	√	√	√	√	√
Dispense Diaries	√	√	√	√		
Dispense Study Medication		√	√	√	√	
Collect Study Medication			√	√	√	√
Genetic Analysis in consenting patients			√			
Rhinoconjunctivitis QOL Questionnaire			√			√
Patient Global Evaluation of Allergic Rhinitis						√

Source: vol. 5, p. 23

Reviewer's comments: It is noted that the sponsor did not check post-treatment labs, vitals, physical examinations, or EKGs. As montelukast has been extensively studied in the past without safety concerns for laboratory or EKG adverse events, this lack of post-treatment assessments is not too concerning.

10.1.1.4 Efficacy Assessments

The following measurements were assessed during the trial to support efficacy:

- Patient Diary dependent assessments: patients completed the allergic rhinitis diary daily containing 3 sections requesting information on daytime, end-of-day, and nighttime allergic rhinitis symptoms.
    - Daytime Allergic Rhinitis Symptoms: these symptoms were reflectively evaluated each evening before taking study medication. The nasal symptoms of stuffy nose, runny nose, sneezing, and itchy nose were evaluated on a 4-point scale, with 0 corresponding to no symptoms and 3 corresponding to severe symptoms that were defined as symptoms bothersome most of the time and/or very bothersome some of the time
    - End-of-Day Allergic Rhinitis Symptoms: the same four symptoms were evaluated on a 4-point scale, 0 being (not noticeable right now) to 3 (symptoms very bothersome right now); these were instantaneous scores recorded prior to daily evening dosing
    - Nighttime Allergic Rhinitis Symptoms: these symptoms were assessed upon arising in the morning and they were based on nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings; these symptoms were also evaluated on a 4-point scale
- Global Evaluation of Allergic Rhinitis by Patient: At Visit 6, all patients evaluated their allergic rhinitis symptoms compared to when they started the study based on whether they were:
    - Very much better
    - Moderately better
    - A little better
    - Unchanged
    - A little worse
    - Moderately worse
    - Very much worse
- Rhinoconjunctivitis Quality-of-Life Questionnaire: patients completed a self-administered questionnaire at Visits 3 and 6; this questionnaire contained 28 questions relating to activity, sleep, non-nasal symptoms, non-ocular symptoms, nasal symptoms, ocular symptoms, practical problems, and emotions. Each question was rated on a 7-point scale ranging from best response (0) to worst response (6).

10.1.1.5 Safety Assessments

Safety assessments included

- Adverse events
- Physical examination
- Vital signs
- EKG

- Laboratory examinations (serum chemistries and complete blood count)
- Urine β-hCG

10.1.1.6 Statistical Plan

The primary objective of the study was to evaluate the efficacy of Singulair 10 mg once daily in the evening compared to placebo in the treatment of perennial allergic rhinitis. There were no changes to the planned analyses, nor were there any interim analyses.

10.1.1.6.1 Definition of Study Population

The primary analyses were performed using a modified intent-to-treat population. This population included all patients with efficacy measurements at baseline and during the treatment period. **[Vol. 5, p. 47]**

Reviewer's comments: It is assumed that the above means that the sponsor includes those that have a baseline measurement, and received at least one dose of study medication with efficacy evaluations, and not referring to a completer analysis population. The primary study population should be the ITT population, and if the sponsor modifies this to include individuals who at least have one post-baseline efficacy evaluation, then this appears reasonable. Clarification on this issue was requested from Dr. Feng Zhou, and she will verify if the assumption is correct.

The sponsor also performed a per-protocol analysis. This population comprised all individuals who did not have clinically important deviations from prespecified criteria.
Reviewer's comments: This reviewer will primarily focus on the modified ITT population.

10.1.1.6.2 Definition of Baseline

For the primary efficacy endpoint and the secondary endpoints, with the exception of the Rhinoconjunctivitis Quality-of-Life Score, baseline was defined as the daily average values during the pretreatment placebo period (average period I scores). For the Rhinoconjunctivitis Quality-of-Life Score, Baseline was defined as the Visit 3 value (at the start of the randomization period). **[Vol. 5, p. 40-41]**

10.1.1.6.3 Sample Size Considerations

The sample size determination was based on the difference between the montelukast and placebo treatment estimates obtained from the supporting study, #246, where the power estimates were made assuming a two-sided test with an alpha of 0.05. For the primary comparison of Daytime Nasal Symptoms score over 6 weeks, a sample size of 800 patients per treatment arm was chosen to have a 90% power to detect a treatment difference of 0.075 between montelukast and placebo, assuming a standard deviation of 0.075. **[Vol. 5, p. 45, 567]**

10.1.1.6.4 Handling of Dropout or Missing Data

Since the primary analyses was based on average values over the 6-week period, no data points were carried forward, which appears reasonable. For secondary analyses where data was collected weekly, a particular data point was carried forward if the latter was missing. **[Vol. 5, p. 49]**

10.1.1.6.5 Primary Efficacy Analyses

The primary efficacy analyses were performed using an ANCOVA model with the corresponding baseline values as covariates. Treatment differences were estimated through the differences it the least-squares (LS) means obtained from the ANCOVA model.

The primary efficacy endpoint was the change from baseline Daytime Nasal Symptom Score (DNSS) averaged over 6 weeks. The DNSS was a combined score of the individual components of congestion, rhinorrhea, and sneezing.

10.1.1.6.6 Secondary Efficacy Analyses [Vol. 5, p. 40]

The secondary efficacy endpoints included the following presented as change from baseline:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Daily Rhinitis score
- Daytime Nasal Symptoms + Itching score
- End-of-Day Nasal Symptoms + Itching score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Rhinoconjunctivitis Quality-of-Life score

Additionally, the Global Evaluation of Allergic Rhinitis was performed. This was not performed at Baseline, but was an assessment of how the patient felt at the end of the study.

10.1.1.6.7 Subgroup Analyses

The sponsor examined the following subgroups to determine if the treatment effect was consistent across different study centers:

- Gender
- Race
- Age
    - < 18 years
    - ≥ 18 years
    - < 65 years
    - ≥ 65 years
- Reported history of SAR
- Reported history of allergic conjunctivitis
- Reported history of asthma
- Active asthma at the start of study as defined by recent symptoms noted during 2 weeks prior to study onset
- Baseline congestion scores
    - <2
    - ≥ 2
- Baseline Daytime Nasal Symptom scores

- Number of positive skin tests

10.1.1.7 Results

10.1.1.7.1 Patient Disposition

A total of 1922 patients were randomized to 117 study centers in the U.S., Canada, and Europe, of which 1819 (91.3%) completed the randomized study treatment period. Of the 1002 and 990 patients randomized to montelukast and placebo, respectively, 913 (91.1%) and 906 (91.5%) completed the study.

A total of 173 patients, 89 (8.9%) and 84 (8.5%), discontinued from the study, from the montelukast and placebo groups, respectively. The most common reason for discontinuation was adverse events, noted in 32 patients (3.2%) and 35 patients (3.5%), in the montelukast and placebo groups, respectively. A total of 25 patients (2.5%) from the montelukast group and 23 patients (2.3%) discontinued due to protocol violations. The percentage of patients discontinuing due to treatment failure was comparable between treatment groups (montelukast, 1.4%; placebo, 1.2%). Other reasons for discontinuation were noted in ≤1% of individuals. These results are summarized in the following table.

Table 22. Study #265, Patient Disposition

Status	Montelukast n (%)	Placebo n (%)	Total n (%)
Number of patients randomized	1002	990	1992
ITT for efficacy	1000 (99.8)	980 (99.0)	1980 (99.0)
Number of patients completing study	913 (91.1)	906 (91.5)	1813 (91.3)
Number of patients discontinued	89 (8.9)	84 (8.5)	173 (8.7)
Adverse event*	32 (3.2)	35 (3.5)	67 (3.4)
Protocol Deviation	25 (2.5)	23 (2.3)	48 (2.4)
Treatment failure	14 (1.4)	12 (1.2)	26 (1.3)
Withdrawal of Consent	10 (1.0)	4 (0.40)	14 (0.70)
Lost to follow-up	3 (0.30)	4 (0.40)	7 (0.35)
Other	5 (0.50)	6 (0.60)	11 (0.55)

*Includes 3 patients who discontinued after randomization that began prior to randomization

Source: Vol. 5, p. 58-59

10.1.1.7.2 Protocol Deviations

The sponsor does not have an in-depth section on protocol deviations where protocol deviations are summarized. However, the sponsor states that patients with significant protocol deviations were excluded from the Per-Protocol population. Examining the reasons for exclusion from the Per-Protocol population provides some idea as to the types of protocol deviations that were considered major. The three most common protocol deviations were study discontinuation prior

to Week 6, insufficient number of data points, and compliance lower than 75%. These results are summarized in the following table.

Table 23. Study #265, Major Protocol Deviations

Protocol Deviation	Montelukast n=1002	Placebo n=990
Insufficient number of data points	35 (3.5)	28 (2.8)
Baseline Daytime Nasal Symptoms Condition Not Satisfied	4 (0.4)	6 (0.6)
No positive skin test	3 (0.3)	1 (0.1)
Immunotherapy started < 1 month before Visit 1 or change in dose	5 (0.5)	3 (0.3)
Discontinued before start of treatment week 6	75 (7.5)	65 (6.6)
Compliance lower than 75% at Baseline	2 (0.2)	2 (0.2)
Compliance lower than 75% during therapy	34 (3.4)	22 (2.2)
Source: Vol. 5, p. 59; clinstat appendix 4.5.1, p. 1040		

10.1.1.7.3 Demographic and Baseline Characteristics

10.1.1.7.3.1 Demographics

Patients were fairly similar at baseline with respect to gender, age, race, height and weight. The majority of patients in the study were female (64%), which was comparable between treatment groups. The mean age of the study population was 36.4 years, with the majority of patients in the 18-64 age group (92.0%). The predominant race evaluated was White (83.2%), although 8.1% of the study populations were black. A few other races were evaluated but not in significant numbers to allow for subgroup analyses with respect to race. The mean height and weight of the study population were 169.6 cm and 76.1 kg, respectively, which were quite comparable between treatment groups. The mean duration of allergic rhinitis was 18.3 years, with a range of 0-66 years. The following table summarizes these results.

Table 24. Study #265, Summary of Demographics at Baseline

	Montelukast n (%)	Placebo n (%)	Total n (%)
Gender			
Female	644 (64.3)	632 (63.8)	1276 (64.1)
Male	358 (35.7)	358 (36.2)	716 (35.9)
Age (years)			
Mean	36.3	36.6	36.4
Range	15-81	15-79	15-81
Age Distribution			
15-17 years	60 (6.0)	46 (4.6)	106 (5.3)
18-64 years	912 (91.0)	921 (93.0)	1833 (92.0)
Over 64 years	30 (3.0)	23 (2.3)	53 (2.7)

	Montelukast n (%)	Placebo n (%)	Total n (%)
Race			
White	839 (83.7)	818 (82.6)	1657 (83.2)
Black	84 (8.4)	78 (7.9)	162 (8.1)
Hispanic	52 (5.2)	56 (5.7)	108 (5.4)
Asian	20 (2.0)	26 (2.6)	46 (2.3)
Native American	4 (0.4)	6 (0.6)	10 (0.5)
Indian	1 (0.1)	3 (0.3)	4 (0.2)
Polynesian	1 (0.1)	2 (0.2)	3 (0.2)
Multi-Racial	1 (0.1)	1 (0.1)	2 (0.1)
Height (cm)			
Mean	169.4	169.8	169.6
Range	137-198	142-203	137-203
Weight (kg)			
Mean	76.2	76.0	76.1
Range	34-151	39-141	34-151
Duration of Allergic Rhinitis (years)			
Mean	18.0	18.6	18.3
Range	0-66	1-60	0-66

Source: Vol. 5, p. 62-63

10.1.1.7.3.2 Baseline Characteristics

This section summarizes baseline allergy- related disease characteristics, which were comparable between treatment groups. The majority of patients (82%, montelukast; 81%, placebo) had perennial allergic rhinitis with seasonal flare-ups. The majority of patients, (96% of patients in both montelukast and placebo treated groups) had perennial allergic rhinitis exacerbated by dust mite antigen. A total of 63-72% of patients had seasonal allergic rhinitis exacerbated by tree, grass, or weed exposure. Greater than 94% of patients had symptoms of nasal congestion, rhinorrhea, and sneezing, whereas 86% or greater had symptoms of itchy nose. The percentage of patients receiving immunotherapy was low, 4.4 and 3.2 % in the montelukast and placebo groups, respectively. This is reassuring as this makes it more likely that any efficacy noted is attributable to the study drug and not to the concomitant immunotherapy. Approximately 83% of patients had concomitant allergic conjunctivitis and 27-29% of patients had concomitant asthma. These results are summarized in the following table.

Table 25. Study #265, Summary of Baseline Patient Characteristics

Baseline Patient Characteristics	Montelukast n=1002 n (%)	Placebo n=990 n (%)
Type of Allergic Rhinitis		
Perennial with seasonal flare-ups	823 (82.1)	805 (81.3)

Perennial	179 (17.9)	185 (18.7)
Allergic Rhinitis Exacerbated by		
Dust Mites	959 (95.7)	949 (95.9)
Cat	650 (64.9)	630 (63.6)
Dog	378 (37.7)	376 (38.0)
Mold	561 (56.0)	576 (58.2)
Cockroach	275 (27.4)	254 (25.7)
Grass	722 (72.1)	705 (71.2)
Tree	639 (63.8)	622 (62.8)
Weed	657 (65.6)	668 (67.5)
Allergic Rhinitis Nasal Symptoms		
Nasal Congestion	967 (96.5)	961 (97.1)
Itchy Nose	861 (85.9)	859 (86.8)
Rhinorrhea	945 (94.3)	929 (93.8)
Sneezing	958 (95.6)	945 (95.5)
Concomitant Immunotherapy	44 (4.4)	32 (3.2)
History of Allergic Conjunctivitis	831 (82.9)	835 (84.3)
History of Asthma	274 (27.3)	288 (29.1)
Recent Asthma Symptoms*	79 (7.9)	87 (8.8)
*defined as asthma symptoms reported within 2 weeks prior to study start Source: Vol. 5, p. 64; Clinstat/studies/ P265.pdf/Appendix 4.4.2., p. 1032-1034 and Appendix 4.21, p. 1226		

Reviewer's comments: The sponsor aims to assess the efficacy of montelukast in the treatment of PAR; however, the majority of patients had perennial allergic rhinitis with seasonal exacerbations. Given that many patients have concomitant PAR and SAR, and the difficulty in finding a large population with PAR alone, to include patients with both PAR and SAR is reasonable. However, the sponsor needs to assure that the study is conducted during a time when the symptoms can be attributable to perennial allergens and not seasonal. The study was conducted between 27 October 2003 and 03 May 2004. For most of the United States where seasonal changes occur, weed allergy will probably not be a problem during the time when the study was initiated, as winter weather will have begun; however, tree allergen (and grass allergen in some areas as well) is prevalent prior to 03 May 2004. Since this was an international study, and the prevalence of the various seasonal allergens depends on the region, the fact that there is an overlap of the U.S. tree allergen season (East Coast), this may not affect the interpretation of results. However, the sponsor may need to assure the agency that patients were evaluated for perennial allergic symptoms outside of the season that triggers their symptoms.

This issue was brought up with the Statistical reviewer, Dr. Feng Zhou. It was requested that she perform some subpopulation analyses to determine if there is a difference. Since the majority of the patients were from the United States, it was agreed that performing a differential analysis on efficacy with respect to time of enrollment, either prior to March 1 or after March 1, 2004, would be useful in supporting claims to efficacy in perennial symptoms. Additionally, Dr. Zhou

will attempt to identify what percentage of the US population was enrolled during the winter months, when symptoms would mainly be attributable to perennial allergens, and what percentage were enrolled during the spring months.

10.1.1.7.3.3 Concomitant Medical Diagnoses and Medications.

Line listings of secondary medical diagnoses were reviewed. **[Clinstat/studies/p265.pdf/Appendix 4.20/p. 1183-1220]** The incidences of concomitant medical diagnoses were fairly similar between treatment groups at Baseline. Minor differences in incidences or types of secondary diagnoses were not deemed clinically relevant. Similarly, no clinically important differences were noted in reviewing line listings of concomitant medications at Baseline between treatment groups. **[Clinstat/studies/p265.pdf/Appendix 4.21/p. 1221-1272]**

10.1.1.7.3.4 Baseline Nasal Symptoms Scores

Nasal Symptoms scores were comparable between treatment groups at Baseline. For the primary efficacy variable, Daytime Nasal Symptoms Score (DNSS), the mean score was 2.09 and 2.10 for montelukast and placebo, respectively. The mean End-of-Day Nasal Symptom Scores and Daily Rhinitis Scores were identical, 1.83 and 1.85 for montelukast and placebo, respectively. In general, the Nighttime Symptom scores were lower at Baseline, 1.56 for montelukast and 1.59 for placebo. These results are summarized below.

Table 26. Study #265, Summary of Baseline Symptoms Scores for Nasal Symptom Scores

Baseline Symptom Scores	Montelukast n=1002 n (SD)	Placebo n=990 n (SD)
Daytime Nasal Symptoms Score (Scale 0-3)		
Mean	2.09 (0.40)	2.10 (0.41)
Range	1.1-3.0	0.6-3.0
End-of-Day Nasal Symptoms Score (Scale 0-3)		
Mean	1.83 (0.56)	1.85 (0.59)
Range	0.1-3.0	0.0-3.0
Nighttime Symptoms Score (Scale 0-3)		
Mean	1.56 (0.60)	1.59 (0.62)
Range	0.0-3.0	0.2-3.0
Daily Rhinitis Score (0-3)		
Mean	1.83 (0.43)	1.85 (0.45)
Range	0.8-3.0	0.9-3.0
Source: Vol. 5, p. 65		

10.1.1.7.4 Compliance

Compliance was assessed by comparing the number of days that study drug was taken with the patient-specified number of days in the active treatment period. Mean compliance was 98.9% in the montelukast group and 98.8% in the placebo group. Although the sponsor did not provide a breakdown of compliance by Week in the study, since the compliance was close to 100% for the

patients throughout the study, the lack of compliance by Week does not need to be further addressed.

10.1.1.7.5 Efficacy Outcomes

The modified ITT will be summarized for all efficacy analyses.

10.1.1.7.5.1 Primary Efficacy Analyses

Analyses of efficacy were based on daily patient diary symptoms scores and the modified ITT sample was the primary analysis sample. The primary efficacy endpoint was the change from Baseline in the Daytime Nasal Symptoms Score (DNSS) averaged over the 6-week period. The DNSS was calculated as the average of the 3 individual scores: nasal congestion, rhinorrhea, and sneezing, rated on a 0-3 scale.

The mean DNSS at Baseline was 2.09 and 2.10 in the montelukast and placebo groups, respectively. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.44 with a 95% CI of {-0.48,-0.41} and in the placebo group was -0.37 with a 95% CI of {-0.40,-0.35}. The difference between treatment groups was -0.08, with a 95% CI of {-0.12; -0.04}. This difference between montelukast and placebo was statistically significant at a $p \leq 0.001$.

Reviewer's comments: With respect to the DNSS, subgroup analyses were performed to evaluate the effects of improvements in the confounding variable of concomitant seasonal allergic rhinitis, since the study period includes October 27, 2003 to May 3, 2004. Since spring usually starts in late February in the US and Canada, subgroup analyses were performed to determine the differences in efficacy when patient results were compared with study termination prior to the median (2/2/04), 3/1/04, and 3/15/04. These three groups were evaluated since the onset of Spring can vary from region to region in the US and Canada as well. These two countries were chosen since the majority of the study population came from these two countries, and the seasons are well known. The results demonstrate that if the median is used as the cut off for comparisons, there was no significant difference noted between the two treatment groups. If results were compared using 3/1/04 or 3/15/04 as the cutoff, significant differences were noted between treatment groups.
These results were reviewed with Dr. Zhou, and she stated that the lack of clinically significant results with the median as the cut-off, is not too concerning since the numbers are so low. Looking at the ending date of 3/1/04, there is a statistically significant difference between the treatment groups. This supports the idea that efficacy results are not favorably skewed by results from the SAR component of the symptoms. The fact that the mean difference between treatments is greater in this subpopulation supports efficacy in PAR. The results of the primary efficacy analysis and the subgroup analyses in the US and Canadian population with different cut offs are presented in the following table.

Table 27. Study #265, Summary of Primary Efficacy Analyses in the Total Population and in the US and Canadian Population with Respect to Differential Cutoffs with Respect to Seasons

	Montelukast N=1000	Placebo n = 980	Outcomes Montelukast vs. Placebo	
	LS mean * (SD) {95% CI}		Delta (95% CI)	P value
Baseline †	2.09	2.10		
Average change from Baseline	-0.44 (0.51) {-0.048,-0.41}	-0.37 (0.48) {-0.40,-0.34}	-0.08 (-0.12,-0.04)	≤ 0.0010
Subgroup Analyses in Population* prior to February 2nd (median)				
	n=414	**n=423**		
Average change from Baseline	-0.44 (0.59)	-0.36 (0.60)	0.06	0.0915
Subgroup Analyses in Population* prior to March 1				
	n=439	**n=441**		
Average change from Baseline	-0.44 (0.58)	-0.34 (0.59)	0.10	0.0030
Subgroup Analyses in Population* prior to March 15th				
	n=597	**n=580**		
Average change from Baseline	-0.47 (0.55)	-0.37 (0.57)	-0.10	0.0004

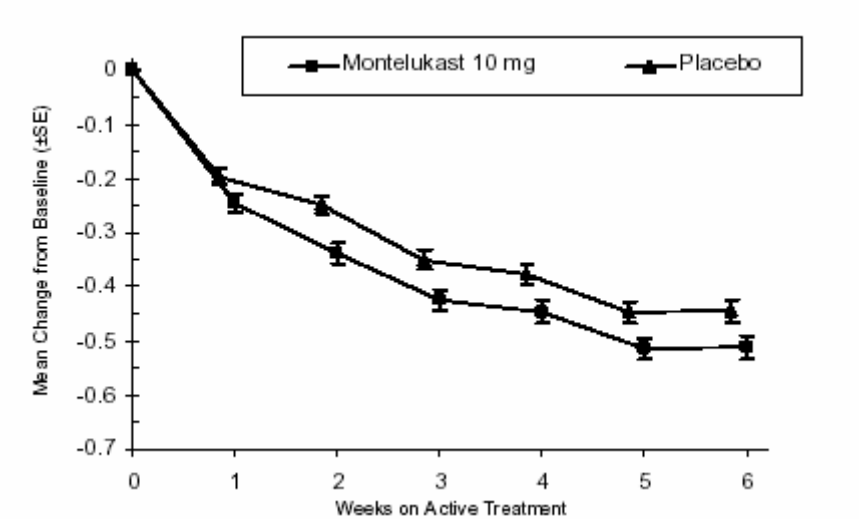
*This subgroup analysis was performed in the US and Canadian population (the subgroup analyses were performed by Dr. Feng Zhou at this reviewer's request)

Source: Vol. 5, p. 67; clinstat/studies/p265.pdf/Table 15, p. 60

10.1.1.7.5.1.1 Treatment Effect by Week

Evaluating the change from Baseline in the DNSS over the 6 weeks shows that the treatment effect was consistent from week to week. The data show that separation in the mean change from Baseline in DNSS between the montelukast and placebo treatment groups was noted before the end of the first Week, this effect remained fairly constant throughout the 6-week treatment period. This demonstrates constancy of effect without evidence of tolerance to montelukast over the 6 weeks of treatment. See the figure below for illustration.

Figure 3. Mean Change from Baseline (± Standard Error) in Daytime Nasal Symptoms Score by Week of Active Treatment (Modified Intention-to-Treat Approach)



10.1.1.7.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints included the following presented as change from baseline:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Daily Rhinitis score
- Daytime Nasal Symptoms + Itching score
- End-of-Day Nasal Symptoms + Itching score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Rhinoconjunctivitis Quality-of-Life score

Additionally, the Global Evaluation of Allergic Rhinitis was performed. This was not performed at Baseline, but was an assessment of how the patient felt at the end of the study.

10.1.1.7.5.2.1 End-of-Day Nasal Symptoms Score

The End-of-Day Nasal Symptoms Score was based on the instantaneous recall of the average of congestion, rhinorrhea, and sneezing. Baseline scores were comparable between montelukast and placebo, 1.83 and 1.85, respectively. Mean changes from Baseline were -0.35 and -0.30 for the montelukast and placebo groups, respectively. The LS Mean changes from Baseline were -0.37 and -0.31 for montelukast and placebo, respectively, with a difference in LS Mean scores of 0.06.

10.1.1.7.5.2.2 Nighttime Symptoms Score

Results for this endpoint were based on the average of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings. Baseline scores for the montelukast group compared to placebo were1.56 and 1.59, respectively. Mean changes from Baseline were -0.30 and -0.25 in the montelukast and placebo groups, respectively. LS Mean changes from Baseline were -0.32 and -0.26 in the montelukast and placebo groups, respectively, with a mean difference of 0.06.

10.1.1.7.5.2.3 Daily Rhinitis Symptoms Score

The Daily Rhinitis Symptoms Score comprised the average of the Daytime Nasal Symptoms Score and the Nighttime Symptoms score. Baseline scores were 1.83 and 1.85 for the montelukast and placebo groups, respectively. The mean changes from Baseline in the montelukast and placebo groups were -0.36 and -0.30 (LS Mean changes: -0.38 and -0.32, respectively). The LS Mean difference between treatment groups was -0.06.

10.1.1.7.5.2.4 Daytime Nasal Symptoms + Itching Score

These results included the average of nasal congestion, rhinorrhea, sneezing, and nasal itching, the primary efficacy endpoint in the supporting study P246. Baseline scores were 2.02 and 2.03 in the montelukast and placebo groups, respectively. The mean change from Baseline was -0.41 in the montelukast group and -0.33 in the placebo group (LS Mean change of -0.38 for montelukast and -0.32 for placebo). The LS Mean difference between treatment groups was -0.07.

10.1.1.7.5.2.5 End-of-Day Nasal Symptoms + Itching Score

These results included the average of nasal congestion, rhinorrhea, sneezing, and nasal itching. Baseline scores were 1.78 and 1.80 in the montelukast and placebo groups, respectively. The mean change from Baseline was -0.35 in the montelukast group and -0.30 in the placebo group (LS Mean change of -0.37 for montelukast and -0.31 for placebo). The LS Mean difference between treatment groups was -0.08.

10.1.1.7.5.2.6 Individual Symptoms Scores

Results of the individual nasal symptoms of congestion, rhinorrhea, sneezing, and itching favored improvement in the montelukast group compared to placebo. The mean change from Baseline in the individual symptom scores ranged from -0.38 to -0.44 in the montelukast group and -0.29 to -0.37 in the placebo group. Of the four symptoms, the least improvement was noted for nasal congestion. The other three symptoms demonstrated similar improvements, and the improvements noted in the primary endpoint do not appear to be skewed favorably by any one individual symptom. On the contrary, it appears that the decreased improvement noted in congestion, may diminish the efficacy in the average composite score. The results of the other secondary endpoints and the individual symptoms are summarized in the following table.

Table 28. Study #265, Summary Results for Secondary Endpoints

	Montelukast N=1000	Placebo n = 980	Outcomes Montelukast vs. Placebo	
	LS mean * (SD)		Delta	P value
End-of Day Symptoms Score				
Baseline †	1.83	1.85	------	-------
Average change from Baseline	-0.37	-0.31	0.06	N/A
Nighttime Symptoms Score				
Baseline	1.56	1.59	-------	-------
Average change from Baseline	-0.32	-0.26	-0.06	N/A
Daily Rhinitis Score				
Baseline	1.83	1.85	-------	-------
Average change from Baseline	-0.36	-0.30	-0.07	N/A
Daytime Nasal Symptoms + Itching Score				
Baseline	2.02	2.03	-------	-------
Average change from Baseline	-0.41	-0.33	-0.08	N/A
End-of-Day Nasal Symptoms + Itching Score				
Baseline	1.78	1.80	-------	------
Average change from Baseline	-0.37	-0.31	-0.06	N/A
Individual Nasal Symptom Scores				
Congestion				
Baseline	2.38	2.40		
Change from Baseline	-0.38 (0.58)	-0.34 (0.53)	-0.05	N/A
Rhinorrhea				
Baseline	2.11	2.15		
Change from Baseline	-0.44 (0.63)	-0.37 (0.60)	-0.08	N/A
Sneezing				
Baseline	1.79	1.76		
Change from Baseline	-0.44 (0.63)	-0.33 (0.62)	-0.10	N/A
Itching				
Baseline	1.82	1.80		
Change from Baseline	-0.39 (0.63)	-0.29 (0.61)	-0.10	N/A
Source: Vol. 5, p. 67; clinstat/studies/p265.pdf/Table 15, p. 60				

10.1.1.7.5.2.7 Quality-of-Life Questionnaire

The questionnaire Rhinoconjunctivitis Quality-of-Life Questionnaire: patients completed a self-administered questionnaire at Visits 3 and 6; this questionnaire contained 28 questions relating to

activity, sleep, non-nasal symptoms, non-ocular symptoms, nasal symptoms, ocular symptoms, practical problems, and emotions. Each question was rated on a 7-point scale ranging from best response (0) to worst response (6). The results of the QOL questionnaire were summarized in 7 domains: activity domain, sleep domain, non-nose/non-eye domain, practical problems domain, nasal domain, eye domain, and emotions domain.

The Baseline values for each of the domains ranged between 2.45 to 3.72 in the montelukast group and 2.53 to 3.73 for the placebo group. For each of the domains, the Baseline values were fairly comparable. The LS mean change from Baseline for each domain in the montelukast group, ranged from -0.73 to -1.03 and -0.59 to -0.81 in the placebo group. The LS Mean difference between treatment groups for the domains ranged from -0.12 to -0.20.

If the domain scores are averaged, the Baseline mean scores were 2.94 and 2.97 in the montelukast and placebo groups, respectively. The LS Mean changes from Baseline were -0.84 and -0.69 in the montelukast and placebo groups, respectively, with a between group difference in the LS Mean of -0.15.

10.1.1.7.5.2.8 Global Evaluation of Rhinitis by Patient

After the end of 6-weeks of therapy (or at time of discontinuation from the study), patients completed a Global Evaluation of Rhinitis, when all patients evaluated their allergic rhinitis symptoms compared to when they started the study based on whether they were:

- Very much better
- Moderately better
- A little better
- Unchanged
- A little worse
- Moderately worse
- Very much worse

For this endpoint, montelukast treated patients noted greater improvements compared to placebo. The LS Mean scores were 2.27 and 2.42 in the montelukast and placebo groups, respectively (the greater the score, the worse they felt). The LS Mean difference between groups was -0.15.

10.1.1.7.5.3 Other Analyses

There were no treatment-by-center or treatment-by-baseline interactions noted for any of the primary or secondary endpoints, [vol. 5, p. 87; clinstat/p265.pdf/Table 4.7.1/p. 1044]
Review of the line-listings for the mean change from Baseline in DNSS demonstrated a wide range of effects, ranging from 0.25 to -1.47 for the montelukast group and 0.15 to -0.91 in the placebo group.

10.1.1.7.5.3.1 Subgroup Analysis

Subgroup analyses based on gender, age, race, history of SAR, history of allergic conjunctivitis, history of asthma, recent symptoms of asthma, baseline congestion and skin test results demonstrated that the treatment effect was variable dependent on the group evaluated.

Subgroup Analysis based on gender revealed that numerically, females had a greater improvement in symptoms compared to males in both montelukast and placebo treated groups (montelukast, -0.44 and -0.39; placebo, -0.37 and -0.31). With respect to age, in the montelukast group, the ≥65 years of age group, manifested greater improvements in symptoms compared to the <18 year age group and the 18-64 year age group, although the improvement in the ≥ 65 year olds was greater compared to the < 18 age group. In the placebo group, the ≥65 year group also demonstrated greater improvement in symptoms compared to the < 18 age group while the < 18 and 18-64 year group had comparable results to placebo. In terms of race, the treatment effect was similar between Whites, Hispanics and Other group; the Black race demonstrated greater improvements compared to the other groups. In the placebo group, these effects were not noted.

With respect to subgroup analyses based on disease characteristics/concomitant diseases, the results were also somewhat variable. In both the montelukast and placebo treated groups, there was a greater numerical improvement in those patients without concomitant seasonal allergic rhinitis (montelukast group, without SAR: -0.48; with SAR, -0.41). Similar results were noted with respect to history of allergic conjunctivitis. History of asthma did not seem to affect the results for the primary efficacy endpoint; however, recent symptoms of asthma showed that those without recent symptoms had greater improvements in symptoms compared to those with a history of recent asthma. Also, it appears that patients with more severe disease demonstrated greater improvements in the montelukast and placebo groups. In the montelukast group, if the Baseline DNSS was <1.86, the improvement was -0.32 compared to -0.44 and -0.49 in the 1.86-2.29 and >2.29 group, respectively. In the montelukast group, patients with 3 or more positive skin tests had numerically greater improvements compared to those less than 3.

The following table summarizes these results.

Table 29. Study #265, Subgroup Analyses Results with Respect to Mean Change from Baseline in the DNSS

	Montelukast		Placebo	
	n	Mean (SD)	n	Mean (SD)
Gender				
Female	642	-0.44 (0.52)	626	-0.37 (0.49)
Male	358	-0.39 (0.50)	354	-0.31 (0.48)
Age				
< 18	60	-0.26 (0.51)	44	-0.34 (0.50)
≥ 18 to < 65	910	-0.43 (0.51)	913	-0.35 (0.49)
≥ 65	30	-0.58 (0.59)	23	-0.47
Race				
White	838	-0.41 (0.51)	810	-0.34 (0.47)
Black	84	-0.52 (0.56)	77	-0.38 (0.58)
Hispanic	51	-0.38 (0.49)	56	0.40 (0.53)
Other	27	-0.39 (0.54)	37	-0.35 (0.41)
History of Seasonal Allergic Rhinitis				
No	179	-0.48 (0.55)	184	-0.44 (0.51)
Yes	821	-0.41 (0.51)	796	-0.33 (0.48)

	Montelukast		Placebo	
	n	Mean (SD)	n	Mean (SD)
History of Allergic Conjunctivitis				
No	170	-0.50 (0.56)	154	-0.43 (0.50)
Yes	830	-0.40 (0.50)	826	-0.33 (0.480
History of Asthma				
No	727	-0.42 (0.50)	697	-0.36 (0.47)
Yes	273	-0.41 (0.56)	283	-0.32 (0.53)
Recent Symptoms of Asthma				
No	920	-0.43 (0.52)	895	-0.36 (0.48)
Yes	79	-0.35 (0.49)	85	-0.26 (0.53)
Baseline Congestion Score				
< 2	175	-0.31 (0.53)	142	-0.24 (0.5)
≥ 2	825	-0.44 (0.51)	838	-0.37 (0.49)
Baseline DNSS				
< 1st tertile (1.86)	312	-0.32 (0.52)	320	-0.26 (0.45)
Between first and second tertile (between 1.86 and 2.29, exclusive)	379	-0.44 (0.49)	312	-0.36 (0.49)
> second tertile (2.29)	309	-0.49 (0.53)	348	-0.42 (0.50)
Number of Positive Skin Tests (out of 6)				
≤2	158	-0.37 (0.50)	158	-0.33 (0.43)
3	306	-0.44 (0.52)	276	-0.34 (0.47)
≥4	536	-0.43 (0.52)	546	-0.36 (0.50)
Source: clinstat/studies/p265.pdf/Appendix 4.14.2/p. 1118-1119				

Reviewer's comments: The subgroup analyses reveal that females had a greater improvement in symptoms compared to males, patients greater than 65 years of age had greater improvements compared to their younger counterparts, and Blacks had greater improvements compared to other races studied. The results suggest that there may be a gender, age, and race effect with respect to treatment; however, discussions with Dr. Feng Zhou reveal that the numbers are not sufficient in each group with respect to age and race to draw any definitive conclusions. With respect to gender effect, there were a greater number of females in the study and this disparity may be favoring efficacy in females. It may be difficult to draw any definitive conclusions from the subgroup analyses. Dr. Feng Zhou will attempt to reanalyze the subgroup data and notify me of any significant interactions.

These results also suggest that patients with solely perennial disease, more severe PAR, and 3 or more positive skin tests, had greater improvements in symptoms. This is not surprising as this confirms that patients with more severe disease respond to therapy compared to those with milder disease. Additionally, it is not surprising that patients with PAR and SAR did not respond as well as those with PAR alone, since symptoms may be worse in patients with both perennial and seasonal components of symptoms. This is actually supported by the fact that when subgroup

analyses are performed in patients starting after 3/1/04 (US and Canadian population), when tree pollens are starting to appear, there does not appear to be a differentiation in effect size between the two treatment groups.

10.1.1.7.5.4 Efficacy Conclusions

The sponsor demonstrated that there was a statistically significant difference between montelukast and placebo in the treatment of PAR in this 6-week randomized, double-blind, placebo-controlled trial. Furthermore, the secondary efficacy endpoints favored montelukast in compared to placebo as well.

10.1.1.7.6 Safety Outcomes

10.1.1.7.6.1 Extent of Exposure

The extent of exposure was comparable between treatment groups and was adequate to allow for a safety analysis. The mean number of days on drug in the montelukast group was 39.1 and 38.8 in the placebo treatment group. The number of days on treatment ranged from 1-56 for both treatment groups. The majority of patients (86% in the montelukast group and 85% in the placebo group) were exposed to treatment for 5 weeks and greater. The recommended trial duration for PAR is a minimum of 4 weeks. In both treatment groups, 93-94% of patients received at least 4 weeks of treatment. The extent of exposure is summarized in the following table.

Table 30. Study #265, Extent of Exposure

Extent of Exposure (Weeks)	Montelukast (n=1002) n (%)	Placebo (n=990) n (%)
< 2	21 (21)	23 (23)
≥ 2 to < 3	25 (25)	25 (25)
≥ 3 to < 4	19 (19)	22 (22)
≥ 4 to < 5	80 (80)	76 (76)
≥5 to < 6	306 (31)	294 (30)
≥ 6	551 (55)	550 (55)
Total ≥ 4	937 (94)	920 (93)
Total ≥5	857 (85)	844 (86%)
Mean Number of Days on Drug	39.1	38.8
Range of Days on Drug	1-56	1-56
Source: Vol. 5, p. 91		

10.1.1.7.6.2 Adverse Events

Adverse events were reported in 557 patients (28%), 269 (27%) in the montelukast group and 288 (29%) in the placebo group. There were no deaths in this study and 5 SAEs, 4 in the montelukast group, and 1 in the placebo group. A total of 64 patients (3.2%) discontinued from the study due to adverse events, 30 (3%) in the montelukast group and 34 (3.4%) in the placebo group.

Generally, the incidence of any particular adverse event was low and fairly comparable between treatment groups with a few exceptions. The most commonly reported AEs in the montelukast group were nasopharyngitis (montelukast, 3.6%; placebo 3.7%), URI (montelukast, 3.3%; placebo 2.5%), and headache (montelukast, 2.9%; placebo 4.7%). Other less commonly reported adverse events, but occurring at an incidence of 1% of greater in the montelukast group included pharyngolaryngeal pain (montelukast, 1.9%; placebo 1.6%), epistaxis (montelukast, 1.6%; placebo 1.2%), sinusitis (montelukast, 1.1%; placebo 0.7%), influenza (montelukast, 1.0%; placebo, 0.9%), and nausea (montelukast, 1.0%; placebo, 1.1%). A few adverse events reported with lower incidences, but noted in a much greater percentage of montelukast patients included dry mouth (montelukast, 0.9%; placebo, 0.2%) and cough (montelukast, 0.9%; placebo 0.4%). Other adverse events were fairly comparable between treatment groups. Since the incidences of these adverse events were so low, it is difficult to draw any definitive conclusions regarding any noted differences.
These results are summarized in the following table.

Table 31. Study #265, Adverse Events Reported in 0.5% or greater in the Montelukast Treatment Group

Adverse Event	Montelukast (n=1002) n (%)	Placebo (n=990) n (%)
Patients with Adverse Events	**269 (26.8)**	**288 (29.1)**
Gastrointestinal Disorders		
Diarrhea	9 (0.9)	6 (0.6)
Dry Mouth	9 (0.9)	2 (0.2)
Nausea	10 (1.0)	11 (1.1)
Vomiting	6 (0.6)	4 (0.4)
General Disorders		
Fatigue	6 (0.6)	8 (0.8)
Pain	5 (0.5)	2 (0.2)
Pyrexia	5 (0.5)	8 (0.8)
Infections and Infestations		
Gastroenteritis Viral	5 (0.5)	7 (0.7)
Influenza	10 (1.0)	9 (0.9)
Nasopharyngitis	36 (3.6)	37 (3.7)
Pharyngitis	5 (0.5)	1 (0.1)
Sinusitis	11 (1.1)	7 (0.7)
Upper Respiratory Tract Infection	33 (3.3)	25 (2.5)
Viral Infection	5 (0.5)	3 (0.3)
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	6 (0.6)	3 (0.3)
Back Pain	8 (0.8)	5 (0.5)
Myalgia	5 (0.5)	2 (0.2)
Nervous System Disorders		
Dizziness	5 (0.5)	4 (0.4)

Adverse Event	Montelukast (n=1002) n (%)	Placebo (n=990) n (%)
Headache	29 (2.9)	47 (4.7)
Sinus Headache	5 (0.5)	2 (0.2)
Psychiatric Disorders		
Insomnia	5 (0.5)	9 (0.9)
Respiratory Disorders		
Cough	9 (0.9)	4 (0.4)
Epistaxis	16 (1.6)	2 (1.2)
Pharyngolaryngeal pain	19 (1.9)	16 (1.6)
Source: Vol. 5, p. 94-95		

Reviewer's comments: Adverse events judged to be treatment related will not be summarized as these were only in the opinion of the investigator. However, it will be stated that the incidence of these adverse events was quite low, all in less than 1% of patients, and the only notable AE reported more frequently in the montelukast group (as judged by the investigator) was dry mouth. This was reported in 6 patients in the montelukast group and in 0 in the placebo treated group.

10.1.1.7.6.3 Deaths

There were no deaths reported in this study.

10.1.1.7.6.4 Serious Adverse Events

Five Serious Adverse Events were reported for this study, 4 in the montelukast group and 1 in the placebo group. These are briefly summarized below.

10.1.1.7.6.4.1 Montelukast

Four SAEs were reported in the montelukast group: dehydration, anxiety disorder, joint injury, and asthma. Their narratives are briefly presented in the following bullets.

- Dehydration: 31 year old female with allergic rhinoconjunctivitis, gastroesophageal reflux disease who started randomized drug therapy (montelukast) on 1/6/04. On 2/10/04, patient experienced nausea/vomiting and on 2/11/04 home pregnancy revealed positive pregnancy. Patient was subsequently discontinued from the study. (b) (6) patient was hospitalized for severe dehydration due to sever intermittent vomiting. Patient recovered, and per last follow-up (6/28/04), pregnancy was progressing well.
- Anxiety Disorder: 72-year old female with a history of anxiety disorder was admitted five days after initiating therapy with montelukast for cardiac testing/rule out myocardial infarction, which was subsequently ruled out. The patient was discharged from the hospital 2 days later with a diagnosis of anxiety and exhaustion. The patient remained on therapy for the prescribed study duration and did not have any further problems.
- Joint Injury: 22 year old male with a history of a knee injury in 12/03, initiated study therapy on 2/11/04. Approximately (b) (6), he had worsening of knee pain, for which he underwent an arthroscopy and was treated with NSAIDs. The patient recovered and continued receiving study drug.

- Asthma: 51 year old male without previous history of asthma initiated study drug on 2/18/04. (b) (6) he was hospitalized for "allergic asthma" and chronic bronchitis and sinopulmonary syndrome. The patient was said to have recovered; there is no further information available for this patient.

Reviewer's comments: Review of the narratives demonstrates that it is doubtful that these SAEs were caused by study drug.

10.1.1.7.6.4.2 Placebo

The placebo patient was a 49 year old male who initiated randomized therapy on 1/22/04. A couple of weeks later, he was hospitalized for an anteroseptal MI for which he underwent a PTCA. This will not be further discussed as this occurred in the placebo arm, and therefore not attributable to montelukast.

10.1.1.7.6.5 Discontinuations Secondary to Adverse Events

A total of 64 patients (3.2%) discontinued from the study due to adverse events, 30 (3%) in the montelukast group and 34 (3.4%) in the placebo group. The most common reasons for study discontinuation in the montelukast group were upper respiratory tract infection (9 patients, 0.9%), sinusitis (3 patients, 3%), respiratory tract infection (2 patients, 0.2%), nasopharyngitis (2 patients, 0.2%), and influenza (2 patients, 0.2%). The rates were comparable to placebo for URI and sinusitis. The other AEs were not listed as reasons for study discontinuation in the placebo group. Other listed AEs occurred in 1 patient or less in the montelukast group. The AEs resulting in discontinuation in 2 or more patients in the montelukast group are summarized in the following table.

Table 32. Study #265, Discontinuations Due to Adverse Events in 2 or More Patients in the Montelukast Treatment Group

Adverse Event	Montelukast (n=1002) n (%)	Placebo (n=990) n (%)
Upper Respiratory Tract Infection	9 (0.9)	7 (0.7)
Sinusitis	3 (0.3)	4 (0.4)
Respiratory Tract Infection	2 (0.2)	0
Influenza	2 (0.2)	0
Nasopharyngitis	2 (0.2)	0
Source: Vol. 5, p. 102		

10.1.1.7.6.6 Laboratory, Vital Signs, EKGs

Laboratory analyses, vital signs, physical examinations, and EKG were all performed during Screening and were not repeated following the treatment period. Therefore, there is no comparative data with respect to these parameters for the end of the study. Since montelukast has been extensively studied in the past, this is not too concerning.

However, it must be noted that post-marketing experience has revealed a possible signal for elevation of hepatic enzymes. It was anticipated that this study would provide further data;

however, as laboratory analyses were not performed for comparative purposes, this is not to be the case.

Although comparative laboratory analyses were not performed, 10 patients had at least 1 laboratory test performed post-baseline, 6 in the montelukast group and 4 in the placebo group. However, no significant laboratory abnormalities were reported in the montelukast group. Two patients in the placebo group had abnormalities: 1 had an elevated carbohydrate antigen 125 and another had elevated AST and ALT. No hepatic enzyme abnormalities were reported in any montelukast patients.

10.1.1.8 Conclusion

The study P265 is the pivotal study supporting safety and efficacy of montelukast for the treatment of symptoms of perennial allergic rhinitis conducted from 10/27/03 to 5/3/04. This was a randomized, double-blind, placebo-controlled, parallel group study in 1992 patients age 15 years and older. Following a 1 week placebo-run period, patients were randomized to receive either montelukast 10 mg once daily in the evening or placebo for 6 weeks.

A total of 1992 patients were randomized, 1002 to the montelukast group and 990 to the placebo group. Greater than 91% of patients completed the study with 98% or greater compliance to with treatment. Demographics and baseline characteristics were fairly comparable between treatment groups. The majority of patients were female, White and were in the 18 to 64 year age group.

The primary efficacy endpoint was the change from baseline in the Daytime Nasal Symptoms Score averaged over 6 weeks. Although the effect size was small, there was a statistically significant difference between montelukast and placebo for the prespecified primary efficacy endpoint. The LS mean changes from Baseline for the DNSS in the montelukast and placebo groups were -0.44 and -0.37, respectively, with a LS mean difference between treatments of -0.08. The primary efficacy variable included assessment of symptoms of sneezing, rhinorrhea and nasal congestion. In the supporting study, P246, which is to be reviewed in the following section, the primary efficacy variable included four symptoms: sneezing, congestion, rhinorrhea and pruritus. If this same variable is looked at in this study, statistically significant differences are noted between the treatment groups. The LS mean changes from Baseline in the montelukast and placebo groups were -0.43 and -0.35, respectively, with a LS mean difference between treatments of -0.08. Results from secondary efficacy analyses also favored montelukast, and it did not appear that any one individual symptom skewed the results toward favoring montelukast. Also, the data show that patients had greater improvements in symptoms with montelukast therapy if they had higher baseline DNSS, positive skin testing to 3 or more allergens, and did note have concomitant SAR.

Additional analyses were performed by the Division attempting to resolve a noted discrepancy. The study was conducted from 10/27/03 to 5/3/04, during which time a seasonal overlap occurred. Analyses were performed to determine if patients ended the study prior to March 1 (US and Canada were used as the subpopulation for analyses since the seasons are well known in this region and the majority of the patients were from these two countries). Evaluating the primary efficacy endpoint in those patients ending the study prior to March 1, it can be

reasonably assumed that any symptoms noted in these patients were from perennial allergens and not seasonal. These analyses showed similar results to the primary analysis sample for the primary efficacy endpoint, namely that montelukast was statistically significant compared to placebo.

In terms of safety, the majority of safety is from review of adverse events as the sponsor did not routinely perform comparative physical examinations, vital signs, EKGs or laboratory analyses. In general the incidence of any specific adverse event was low and fairly comparable between treatment groups with few exceptions. A total of 27% and 29% of patients experienced adverse events in this study. There were no reported deaths. Five SAEs were reported, of which one was a pregnancy. None of these appeared attributable to montelukast. A fairly small percentage of patients discontinued from the study due to adverse events, 3.0 % and 3.4% in the montelukast and placebo groups respectively. The most commonly reported adverse events included nasopharyngitis, upper respiratory tract infection, and headache, which were comparable or reported at a lower incidence to placebo. Review of the submitted safety information did not raise any concerns for any new or unexpected adverse events.

In conclusion, this study supports the efficacy and safety of montelukast for the treatment of symptoms of perennial allergic rhinitis.

10.1.2 STUDY P246: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY INVESTIGATING THE CLINICAL EFFECTS OF MONTELUKAST IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS

Protocol #:	246
Title:	A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Investigating the Clinical Effects of Montelukast in Patients with Perennial Allergic Rhinitis
Study Dates:	Initiated November 27, 2001. Completed May 5, 2002.
Sites:	74 sites in United States
Investigators:	74 Investigators
IRB:	The protocol was reviewed by the Institutional Review Board (IRB) of each study site; the chairperson of each IRB is listed by study center in [3.6]. IRB approval letters were received and verified before the shipment of study drug; copies are on file with MRL.
Ethical Considerations:	This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research.

Source: Vol. 4, p. 2, 19, 25

10.1.2.1 Study Design

This was the initial study Merck performed to support an indication in PAR. The pivotal study (P265 reviewed above) was conducted subsequently. Both studies are nearly identical in design with the major difference in P246 being that it had an additional treatment arm, cetirizine 10 mg as an active control. The differences in study design, conduct, assessments will be outlined where applicable; however, similar study elements will not be repeated and further information regarding these will be referenced to Study P265.

10.1.2.1.1 Objectives

Primary Objective

To assess the treatment effect of montelukast 10 mg versus placebo on the primary, secondary, and other/exploratory endpoints, over the first 4 weeks of a 6-week treatment period, in patients with perennial allergic rhinitis. 2. To determine the tolerability profile of montelukast 10 mg in patients with perennial allergic rhinitis. **[Vol. 4, p. 26]**

Secondary Objectives **[Vol. 4, p. 27]**

- To assess the treatment effect of montelukast 10 mg versus placebo on the primary, secondary, and other/exploratory endpoints, over a 6-week treatment period in patients with perennial allergic rhinitis. 2.
- To assess the treatment effect of cetirizine 10 mg versus placebo on the primary, secondary, and other/exploratory endpoints, over the 4-week and 6-week treatment periods in patients with perennial allergic rhinitis.
- To estimate the efficacy of montelukast 10 mg versus cetirizine 10 mg on the primary, secondary, and other/exploratory endpoints, over the 4-week and 6-week treatment periods in patients with perennial allergic rhinitis.

10.1.2.1.2 Study Description

This was a multicenter, US, 6-week, 2-period, randomized, double-blind, double-dummy, placebo- and active-controlled study investigating the safety and efficacy of montelukast 10 mg versus placebo and cetirizine 10 mg in 1365 patients 15 to 85 years of age with perennial allergic rhinitis, conducted during the winter season.
Reviewer's comments: Merck states that both studies were performed in the winter season; however, when study ends in May, the spring season is well under way, and any improvements noted in those individuals enrolled from March to May may be attributable to improvements in SAR. As with the pivotal study, subgroup analyses with cut off dates for patients completing the study prior to March 1 and post-March 1 will be requested to be conducted.

10.1.2.1.3 Population

Approximately 1600 patients were planned for enrollment, 3401 were screened, and 1992 non-smoking males and females ages 15-85 years of age, with at least a 2-year documented clinical history of PAR symptoms, a positive skin test to two or more perennial allergens, and a minimum predefined level of Daytime Nasal Symptoms were randomized. **[Vol. 2, 2.7.6, p. 8]**

10.1.2.1.4 Entry Criteria

Patients ages 15 to 85 years of age, using adequate contraception, were enrolled into the study if they had a documented clinical history (at least 2 years) of perennial allergic rhinitis symptoms. Many of the inclusion and exclusion criteria are identical to those of the pivotal study reviewed earlier. Only differences in the Inclusion/Exclusion Criteria from the pivotal study are elaborated below.

In contrast to Study P265, patients were only required to have documented skin test positivity to one perennial allergen, and should have only had a 10-pack year history of smoking; otherwise, the inclusion criteria were identical.

In terms of exclusion criteria, in comparison to Study P265, only a couple of minor differences were noted. In this study, patients with a history of hypersensitivity to cetirizine or hydroxyzine were excluded and patients had to have withheld cetirizine for 1 week prior to study entry. Otherwise, all other exclusion criteria are identical to those reviewed in the previous study.

10.1.2.2 Therapies

10.1.2.2.1 Study Treatments

All eligible patients were randomized to receive montelukast, cetirizine or placebo in a 1:1 ratio. The treatment arms were as follows:

- Montelukast 10 mg: Formulation Number MR-4380
- Cetirizine 10 mg: Formulation Number MR-4584
- Montelukast matching Placebo: Formulation Number: MR-4309
- Cetirizine matching Placebo: Formulation Number: MR: 4568

Patients received 2 bottles of study medication: 1 bottle of montelukast or matching-image placebo and 1 bottle of cetirizine or matching-image placebo. Patients were instructed to take 1 tablet from each bottle once daily at bedtime, irrespective of food intake. **[Vol. 4, p. 37-38]**

10.1.2.2.2 Allowed Therapies, Excluded Therapies, Compliance, and Study Withdrawal Criteria

These were identical to Study P265. Refer to above sections 10.1.1.2 for these elements.

10.1.2.3 Conduct

The study was a multicenter, randomized, double-blind, double-dummy, 2-period, 6-week placebo- and active-controlled study evaluating the clinical benefit of Montelukast 10 mg in the treatment of PAR and the safety and tolerability in this patient population compared to placebo and cetirizine 10 mg. The study was divided into two periods and 6 visits. Visit I was the screening visit where medical history, physical examination, laboratory investigations, EKG, and informed consent were obtained. During this visit the patient received a diary where symptoms scores were to be recorded. At Visit 2, the diary was reviewed, and if patients continued to meet eligibility criteria, they then started Period I, a 5-7 day, single-blind, placebo run-in period. At Visit 3, eligible patients entered Period II, the 6-week, randomized, double-blind active treatment phase, when they were randomized to receive either montelukast 10 mg or placebo. Patients returned every two weeks for follow-up visits (Visits 4-6).

The procedures in this study were quite similar to study P265 and similarities will not be further elaborated. One major difference in this study was the fact that the sponsor performed pre and post baseline laboratory, vital sign, and physical examination assessments.

10.1.2.4 Efficacy Assessments

The efficacy assessments were nearly identical to the pivotal study and are summarized below. Note that there is one assessment that was not performed in the pivotal study: Perennial Allergic Rhinitis Questionnaire.
The following measurements were assessed during the trial to support efficacy:

- Patient Diary dependent assessments: patients completed the allergic rhinitis diary daily containing 3 sections requesting information on daytime, end-of-day, and nighttime allergic rhinitis symptoms.
    - Daytime Allergic Rhinitis Symptoms: these symptoms were reflectively evaluated each evening before taking study medication. The nasal symptoms of stuffy nose, runny nose, sneezing, and itchy nose were evaluated on a 4-point scale, with 0 corresponding to no symptoms and 3 corresponding to severe symptoms that were defined as symptoms bothersome most of the time and/or very bothersome some of the time. Throat and eye symptoms were also evaluated. Throat symptoms evaluated by patients corresponded to the endpoints of mucus dripping down throat/postnasal drip and clearing of throat. Eye symptoms evaluated by patients corresponded to the endpoints of Tearing and Itchy Eyes.
    - End-of-Day Allergic Rhinitis Symptoms: the same four symptoms were evaluated on a 4-point scale, 0 being (not noticeable right now) to 3 (symptoms very bothersome right now); these were instantaneous scores recorded prior to daily evening dosing
    - Nighttime Allergic Rhinitis Symptoms: these symptoms were assessed upon arising in the morning and they were based on nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings; these symptoms were also evaluated on a 4-point scale
- Global Evaluation of Allergic Rhinitis by Patient: At Visit 6, all patients evaluated their allergic rhinitis symptoms compared to when they started the study based on whether they were:
    - Very much better
    - Moderately better
    - A little better
    - Unchanged
    - A little worse
    - Moderately worse
    - Very much worse
- Rhinoconjunctivitis Quality-of-Life Questionnaire: patients completed a self-administered questionnaire at Visits 3 and 6; this questionnaire contained 28 questions relating to activity, sleep, non-nasal symptoms, non-ocular symptoms, nasal symptoms, ocular symptoms, practical problems, and emotions. Each question was rated on a 7-point scale ranging from best response (0) to worst response (6).

- Perennial Allergic Rhinitis Questionnaire: Patients completed a self-administered Perennial Allergic Rhinitis Questionnaire at Visit 3 and Visit 7 (or upon discontinuation). Patients were asked about allergy symptoms over the past 7 days that were due to indoor allergens. The patient was specifically asked to evaluate his/her own perennial allergic rhinitis symptoms (itchy or irritated throat, fullness or pressure in sinuses, breathing through mouth, headache, cough, and trouble breathing due to chest tightness). Note that this was not assessed in the pivotal study.

10.1.2.5 Safety Assessments

Safety assessments were similar to the previous study and included:

- Adverse events: the MEDRA dictionary was used to code adverse events
- Physical examination
- Vital signs
- EKG
- Laboratory examinations (serum chemistries and complete blood count)
    - Hematology: CBC; peripheral blood eosinophil count was performed and changes from Baseline Week 6 were analyzed.
    - Serum Chemistry
        - Alanine aminotransferase (ALT), Alkaline phosphatase, Aspartate aminotransferase (AST) Bicarbonate, Blood sugar, Blood urea nitrogen, Calcium, Chloride, Creatinine, Phosphate, Potassium, Sodium, Total bilirubin
    - Urinalysis
    - Urine β-hCG

An important difference in this study in terms of safety assessments was that laboratory, vital sign, and physical examination assessments were repeated at the end of study treatment.

10.1.2.6 Statistical Plan

The primary objective of the study was to evaluate the efficacy of Singulair 10 mg once daily in the evening compared to placebo in the treatment of perennial allergic rhinitis. There were no changes to the planned analyses, nor were there any interim analyses.

10.1.2.6.1 Definition of Study Population

The primary analyses were performed using a modified intent-to-treat population. This population included all patients with efficacy measurements at baseline and at least one post-treatment measurement. **[Vol. 4, p. 58]**

The sponsor also performed a per-protocol analysis. This population comprised all individuals who did not have clinically important deviations from prespecified criteria.
Reviewer's comments: This reviewer will primarily focus on the modified ITT population.

10.1.2.6.2 Definition of Baseline

For the primary efficacy endpoint and the secondary endpoints, with the exception of the Rhinoconjunctivitis Quality-of-Life Score and Perennial Allergic Rhinitis Questionnaire, baseline was defined as the daily average values during the pretreatment placebo period (average

period I scores). For the Rhinoconjunctivitis Quality-of-Life Score and Perennial Allergic Rhinitis Questionnaire, Baseline was defined as the Visit 3 value (at the start of the randomization period). **[Vol. 4, p. 50-51]**

10.1.2.6.3 Sample Size Considerations

The sample size determination was based on the difference between the montelukast and placebo treatment estimates obtained from the seasonal allergic rhinitis studies used to gain approval in SAR. A sample size of 500 in the montelukast and placebo groups was selected to have an 88% power to detect, a treatment difference of 0.10 in the change from Baseline in Daytime Nasal Symptoms Score over 4 weeks with a two-side test at an alpha of 0.05 . For the cetirizine group, a sample of size of 100 was selected to have an 89% power to detect a 0.18 difference between cetirizine and placebo over 4 weeks of treatment. **[Vol. 4, p. 58]**

10.1.2.6.4 Handling of Dropout or Missing Data

Since the primary analyses was based on average values over the first 4-weeks of treatment, no data points were carried forward, which appears reasonable. For secondary analyses where data were collected weekly, a particular data point was carried forward if the latter was missing. **[Vol. 4, p. 63]**

10.1.2.6.5 Primary Efficacy Analyses

The primary efficacy analyses were performed using an ANCOVA model with the corresponding baseline values as covariates. Treatment differences were estimated through the differences in the least-squares (LS) Means obtained from the ANCOVA model.

The primary efficacy endpoint was the change from baseline Daytime Nasal Symptom Score (DNSS) averaged over the first 4 weeks of the entire 6 week treatment period. In contrast to Study P265, the DNSS in this study was a combined score of the individual components of congestion, rhinorrhea, nasal pruritus, and sneezing. **[Vol. 4, p. 52, 58]**

10.1.2.6.6 Secondary Efficacy Analyses [Vol. 4, p. 52-55, 58]

The secondary efficacy endpoints included the following presented as change from baseline averaged over the entire 6-week treatment period:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Daily Rhinitis score
- Daytime Nasal Symptoms + Itching score
- End-of-Day Nasal Symptoms + Itching score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Composite Symptoms Score: average of the DNSS and Nighttime Symptoms Score
- Daytime Eye Symptoms Score
- Daytime Throat Symptoms Score

- Rhinoconjunctivitis Quality-of-Life score
- Perennial Allergic Rhinitis score based on Perennial Allergic Rhinitis Questionnaire

Additionally, the Global Evaluation of Allergic Rhinitis was performed. This was not performed at Baseline, but was an assessment of how the patient felt at the end of the study.

10.1.2.6.7 Subgroup Analyses

The sponsor examined the following subgroups to determine if the treatment effect was consistent across different study centers:

- Gender
- Race
- Age
  - < 18 years
  - ≥ 18 years
  - < 65 years
  - ≥ 65 years
- Reported history of SAR
- Reported history of allergic conjunctivitis
- Reported history of asthma
- Active asthma at the start of study as defined by recent symptoms noted during 2 weeks prior to study onset
- Baseline congestion scores
  - <2
  - ≥2
- Baseline Daytime Nasal Symptom scores

10.1.2.7 Results

10.1.2.7.1 Patient Disposition

A total of 1365 patients were randomized to 74 study centers in the U.S., of which 1199(87.8%) completed the randomized study treatment period. Of the 630, 122, and 195 patients randomized to montelukast, cetirizine, and placebo, respectively, 562 (89.2%), 106 (86.9%), and 530 (86.5%) completed the study.

A total of 165 patients discontinued from the study, 68 (10.8%), 16 (13.1%) and 83 (13.5%), in the montelukast, cetirizine, and placebo groups, respectively. The most common reason for discontinuation was adverse events, noted in 57 patients, 29 patients (4.6%), 4 patients (3.3%), and 24 patients (3.9%) in the montelukast, cetirizine, and placebo groups, respectively. A total of 13 patients (2.5%) from the montelukast group, 4 patients (3.3%), and 18 patients (2.9%) discontinued due to protocol violations. The percentage of patients discontinuing due to treatment failure was comparable between the cetirizine and placebo groups (cetirizine, 1.6%; placebo, 1.5%), and lower in the montelukast group (0.5%). These results and other reasons for discontinuation are summarized in the following table.

Table 33. Study #246, Patient Disposition

Status	Montelukast n (%)	Cetirizine n (%)	Placebo n (%)
Number of patients randomized	630	122	613
ITT for efficacy	626 (99.4)	120 (98.4)	609 (99.3)
Number of patients completing study	562 (89.2)	106 (86.9)	530 (86.5)
Number of patients discontinued	68 (10.8)	16 (13.1)	83 (13.5)
Adverse event*	29 (4.6)	4 (3.3)	24 (3.9)
Protocol Deviation	13 (2.5)	4.9 (3.3)	18 (2.9)
Treatment failure	3 (0.5)	2 (1.6)	9 (1.5)
Withdrawal of Consent	14 (2.2)	5 (4.0)	16 (2.6)
Lost to follow-up	2 (0.3)	1 (0.8)	2 (0.3)
Other	5 (0.8)	0	11 (1.8)

*Includes 1 patient who discontinued after randomization due to an AE that began prior to randomization

Source: Vol. 4, p. 74; clinstat/studies/p264.pdf/appendix 4.5.1/1335

10.1.2.7.2 Protocol Deviations

The sponsor does not have an in-depth section on protocol deviations where protocol deviations are summarized. However, the sponsor states that patients with significant protocol deviations were excluded from the Per-Protocol population. Examining the reasons for exclusion from the Per-Protocol population provides some idea as to the types of protocol deviations that were considered major. The three most common protocol deviations were study discontinuation prior to Week 4, insufficient number of data points, and compliance lower than 75%. These results are summarized in the following table.

Table 34. Study #246, Major Protocol Deviations

Protocol Deviation	Montelukast n=630	Cetirizine n= 122	Placebo n=613
Excluded from the Per-Protocol Analysis	97 (15.4)	19 (15.6)	114 (18.6)
Insufficient number of data points	45 (7.1)	6 (4.9)	59 (9.6)
Baseline Daytime Nasal Symptoms Condition Not Satisfied	1 (0.2)	0	2 (0.3)
Immunotherapy started < 1 month before Visit 1 or change in dose	2 (0.3)	0	1 (0.2)
Discontinued before start of treatment week 4	40 (6.3)	11 (9.0)	44 (7.2)
Compliance lower than 75% at Baseline	1 (0.2)	0	0
Compliance lower than 75% during therapy	8 (1.3)	2 (1.6)	5 (0.8)
No positive skin test	0	0	3 (0.5)
Source: clinstat/studies/p264.pdf/appendix 4.5.1/p 1335			

10.1.2.7.3 Demographic and Baseline Characteristics

10.1.2.7.3.1 Demographics

Patients were fairly similar at baseline with respect to gender, age, race, height and weight. The majority of patients in the study were female (67.5%), which was comparable between treatment groups. The mean age of the study population was 35.4 years, with the majority of patients in the 18-64 age group (90.5%). The predominant race evaluated was White (78.8%), although 9.2% of the study population was black. A few other races were evaluated but not in significant numbers to allow for subgroup analyses with respect to race. The mean height and weight of the study population were 168.8 cm and 75.1 kg, respectively, which were quite comparable between treatment groups. The mean duration of allergic rhinitis was 17.9 years, with a range of 0-66 years. The following table summarizes these results for the individual treatment groups.

Table 35. Study #246, Summary of Baseline Demographics

	Montelukast n=630 n (%)	**Cetirizine n=122** n (%)	**Placebo n=613** n (%)
Gender			
Female	419 (66.5)	85 (69.7)	418 (68.2)
Male	211 (33.5)	37 (30.3)	195 (31.8)
Age			
Mean (SD)	35.3 (12.87)	36.3 (13.67)	35.3 (13.17)
Range	15-76	15-75	15-82
Age Distribution			
15-17 years	54 (8.6)	4 (3.3)	47 (7.7)
18-64 years	569 (90.3)	113 (92.6)	553 (90.2)
Over 64 years	7 (1.1)	5 (4.1)	13 (2.1)
Race			
White	499 (79.2)	89 (73.0)	488 (79.6)
Black	55 (8.7)	11 (9.0)	60 (9.8)
Hispanic	46 (7.3)	13 (10.7)	37 (6.0)
Other	30 (4.8)	9 (7.4)	28 (4.6)
Weight (kg)			
Mean (SD)	75.0 (16.4)	76.7 (16.1)	74.9 (16.7)
Range	44-133	50-127	33-129
Height (cm)			
Mean (SD)	168.8 (9.6)	168.6 (10.4)	168.8 (9.6)
Range	135-211	147-198	140-198

	Montelukast n=630 n (%)	Cetirizine n=122 n (%)	Placebo n=613 n (%)
Duration of Allergic Rhinitis (years)			
Mean (SD)	18.0 (12.3)	18.4 (12.9)	17.7 (12.6)
Range	0-63	2-56	0-66

Source: Vol. 4, p. 79-80

10.1.2.7.3.2 Baseline Characteristics

This section summarizes baseline allergy related disease characteristics, which were comparable between treatment groups, for the most part. The majority of patients (79%, montelukast; 83%, cetirizine; 80%, placebo) had perennial allergic rhinitis with seasonal flare-ups. The majority of patients had perennial allergic rhinitis exacerbated by dust mite antigen, 85-90% of patients depending on the treatment group. Cat allergen was the next common perennial allergen (in 60-67% of patients). A total of 59-70% of patients had seasonal allergic rhinitis exacerbated by tree, grass, or weed exposure. Approximately 97% of patients had symptoms of nasal congestion, 92-95% had sneezing, 91-92% had rhinorrhea, and 86-87% had symptoms of itchy nose. The percentage of patients receiving immunotherapy was low, 6.2%, 6.6%, and 3.4 % in the montelukast, cetirizine, and placebo groups, respectively. Although the percentage of patients receiving immunotherapy is higher in the two active groups compared to placebo, it is doubtful that this difference will affect final outcomes as the percentages are fairly low. Approximately 85% of patients had concomitant allergic conjunctivitis and 24% of patients had concomitant asthma. Thus, treatment groups were fairly well matched for the most part with respect to baseline characteristics and these results are summarized in the following table.

Table 36. Study #246, Summary of Baseline Patient Characteristics

Baseline Patient Characteristics	Montelukast n=630 n (%)	Cetirizine n=122 n (%)	Placebo n=613 n (%)
Type of Allergic Rhinitis			
Perennial with seasonal flare-ups	497 (79.0)	101 (82.8)	490 (80.3)
Perennial	132 (21.0)	21 (17.2)	120 (19.7)
Allergic Rhinitis Exacerbated by			
Dust Mites	567 (90.0)	104 (85.2)	544 (88.7)
Cat	422 (67.0)	80 (65.6)	371 (60.5)
Dog	241 (38.3)	43 (35.2)	220 (35.9)
Mold	385 (61.1)	70 (57.4)	353 (57.6)
Cockroach	122 (19.4)	20 (16.4)	128 (20.9)
Grass	433 (68.7)	85 (69.7)	416 (67.9)
Tree	390 (61.9)	83 (68.0)	361 (58.9)
Weed	412 (65.4)	72 (59.0)	410 (66.9)
Allergic Rhinitis Nasal Symptoms			

Nasal Congestion	610 (96.8)	119 (97.5)	596 (97.2)
Itchy Nose	545 (86.5)	106 (86.9)	528 (86.1)
Rhinorrhea	574 (91.1)	112 (91.8)	564 (92.0)
Sneezing	587 (93.2)	116 (95.1)	566 (92.3)
Concomitant Immunotherapy	39 (6.2)	8 (6.6)	21 (3.4)
History of Allergic Conjunctivitis	538 (85.5)	99 (81.1)	515 (84.2)
History of Asthma	148 (23.5)	32 (26.2)	151 (24.7)
Recent Asthma Symptoms*	49 (7.8)	11 (9.0)	38 (6.2)
*defined as asthma symptoms reported within 2 weeks prior to study start Source: Vol. 4, p. 83; Clinstat/studies/ P264.pdf/Appendix 4.4.2., p. 1320-1321 and Appendix 4.3.2, p. 2202			

Reviewer's comments: The sponsor aims to assess the efficacy of montelukast in the treatment of PAR; however, the majority of patients had perennial allergic rhinitis with seasonal exacerbations, as was noted in the study P265. Given that many patients have concomitant PAR and SAR, and the difficulty in finding a large population with PAR alone, to include patients with both PAR and SAR is reasonable. However, the sponsor needs to assure that the study is conducted during a time when the symptoms can be attributable to perennial allergens and not seasonal. As with the previously reviewed study, P265, this study was also conducted during a time frame when seasonal and perennial allergens overlap (ended in the beginning of May). The statistical reviewer, Dr. Feng Zhou was requested to perform a differential analysis on efficacy with respect to time of enrollment, either prior to March 1 or after March 1, 2004, to attempt to reasonably separate perennial and seasonal allergen triggered symptoms.
These results will be summarized in the following efficacy sections.

10.1.2.7.3.3 Concomitant Medical Diagnoses and Medications.

Line listings of secondary medical diagnoses were reviewed. **[Clinstat/studies/p265.pdf/appendix 4.30/p. 2138-2168]** The incidences of concomitant medical diagnoses were fairly similar between treatment groups at Baseline. Minor differences in incidences or types of secondary diagnoses were not deemed clinically relevant. Similarly, no clinically important differences were noted in reviewing line listings of concomitant medications at Baseline between treatment groups. **[Clinstat/studies/p265.pdf/appendix 4.3.2/p. 2191-2211]**

10.1.2.7.3.4 Baseline Nasal Symptoms Scores [Vol. 4, p. 83-84]

Nasal Symptoms scores were fairly comparable between treatment groups at Baseline, with few exceptions. For the primary efficacy variable, Daytime Nasal Symptoms Scores (DNSS), the mean scores were comparable between montelukast (2.08) and placebo (2.07); the mean scores for the cetirizine group (2.13) at baseline suggest that this treatment group had more severe nasal symptoms at Baseline. Cetirizine treated patients also had greater End-of-Day Nasal Symptoms Scores at Baseline (1.87) compared to montelukast (1.84) and placebo (1.81) In general, the Nighttime Symptom scores were lower at Baseline for each group; however, cetirizine had the highest score at Baseline compared to the other two treatment groups. These results and results of Baseline Eye and Throat Symptoms Scores are summarized below.

Table 37. Study #246, Summary of Baseline Symptoms Scores for Nasal Symptom Scores

Baseline Symptom Scores	Montelukast n=630 n (SD)	Cetirizine n=122 n (SD)	Placebo n=613 n (SD)
Daytime Nasal Symptoms Score (Scale 0-3)			
Mean	2.08 (0.40)	2.13 (0.37)	2.07 (0.40)
Range	1.4-3.0	1.5-3.0	1.0-3.0
End-of-Day Nasal Symptoms Score (Scale 0-3)			
Mean	1.84 (0.58)	1.87 (0.55)	1.81 (0.59)
Range	0.1-3.0	0.6-3.0	0-3.0
Nighttime Symptoms Score (Scale 0-3)			
Mean	1.63 (0.62)	1.65 (0.61)	1.58 (0.62)
Range	0-3.0	0.5-3.0	0.2-3.0
Composite Symptoms Score (0-3) (average of Daytime and Nighttime Symptoms Score)			
Mean	1.86 (0.44)	1.89 (0.43)	1.82 (0.45)
Range	0.8-3.0	1.1-3.0	0.7-3.0
Daytime Eye Symptoms			
Mean	1.49 (0.84)	1.63 (0.86)	1.48 (0.85)
Range	0-3.0	0.-3.0	0-3.0
Daytime Throat Symptoms			
Mean	2.10 (0.71)	2.16 (0.67)	2.04 (0.76)
Range	0-3.0	0-3.0	0-3.0

Source: Vol. 4, p. 83-84

Reviewer's comments: The Baseline symptoms scores for the primary efficacy variable and most of the secondary variables suggest that the cetirizine treated subjects had more severe symptoms compared to montelukast and placebo, and the latter two groups were fairly comparable in this respect. As seen in the previous study, the more severe patients had better efficacy, it may be anticipated that the cetirizine-treated patients may demonstrate better treatment effect. However, since the montelukast and placebo groups were similar for the most part, support of efficacy will rely on the primary comparison of montelukast and placebo. The more severe montelukast-treated patients may also demonstrate differential efficacy as compared to the milder patients.

10.1.2.7.4 Compliance

Compliance was assessed by comparing the number of days that study drug was taken with the patient-specified number of days in the active treatment period. Mean compliance was 99.4%, 99.5%, and 99.4% in the montelukast, cetirizine, and placebo groups, respectively. Although the sponsor did not provide a breakdown of compliance by Week in the study, since the compliance was close to 100% for the patients throughout the study, the lack of compliance by Week does not need to be further addressed. It should be noted that 11%, 13%, and 14% of montelukast, cetirizine, and placebo treated patients, respectively, were listed as "missing" for information in the line listings under compliance. Since the majority of the compliance data available demonstrates 100% compliance, and the frequency of missing data was fairly comparable between treatment groups, it is doubtful that this will pose a problem with interpretation of efficacy. **[clinstat/studies/p246.pdf/appendix/4.24/p.1516-1533]**

10.1.2.7.5 Efficacy Outcomes

The modified ITT will be summarized for all efficacy analyses.

10.1.2.7.5.1 Efficacy Analyses of Primary Endpoint

10.1.2.7.5.1.1 Pre-Specified Analyses of Primary Efficacy Endpoint

Analyses of efficacy were based on daily patient diary symptoms scores and the modified ITT sample was the primary analysis sample. The primary efficacy endpoint was the change from Baseline in the Daytime Nasal Symptoms Score (DNSS) averaged over the 4-week period. The DNSS was calculated as the average of the 4 individual scores: nasal congestion, rhinorrhea, sneezing, and nasal pruritus rated on a 0-3 scale.

The Baseline DNSS were 2.08, 2.13, and 2.07 in the montelukast, cetirizine, and placebo groups, respectively. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.39 (95% CI: -0.43, -0.36), -0.45 (95% CI: -0.54, -0.37) in the cetirizine group, and -0.36 (95% CI:-0.39, -0.32) in the placebo group. The LS Mean difference between montelukast and placebo was -0.04 (95% CI: -0.09, 0.01), which was not statistically significant (p=0.150). However, the LS Mean difference between cetirizine and placebo of -0.10 (95% CI: -0.19, -0.01) was statistically significant (p=0.038). A trend favoring montelukast was noted in three of the four individual nasal symptoms and other secondary endpoints. Thus, montelukast failed to demonstrate a statistically significant difference compared to placebo for the pre-specified primary efficacy endpoint in this trial.

10.1.2.7.5.1.2 Post-Hoc Analyses of Primary Efficacy Endpoint

Although the sponsor failed to show statistically significant improvement in the pre-specified primary comparison on the primary efficacy endpoint, there was a trend favoring montelukast compared to placebo. To explore this trend toward improvement, a few post-hoc analyses were performed defining the primary efficacy endpoint using the same criteria as were done in Study P265.

If the DNSS is defined as in Study P265 (the average of three nasal symptom scores, excluding nasal pruritus) and the results are averaged over the 6-week period, a "statistically significant" difference is seen between montelukast and placebo. Since this is a post-hoc analysis, the meaning of a p-value or the term "statistically significant" is not valid. These results do suggest an improved change from Baseline when comparing montelukast to placebo. The LS Mean changes from Baseline for montelukast, cetirizine, and placebo using 3 symptoms in the DNSS averaged over the first 4-week period were -0.40 (95% CI: -0.44, -0.36), -0.45 (95% CI: -0.54, -0.36), and -0.34 (95% CI: -0.38, -0.30), respectively, with a corresponding LS Mean difference between montelukast and placebo of -0.05 (95% CI: -0.11, 0.00). The exclusion of nasal pruritus from the primary efficacy endpoint did increase the effect size.

If the DNSS defined with 3 symptoms is averaged over the entire 6week study period, the corresponding LS Mean changes from Baseline for montelukast, cetirizine, and placebo were -

0.46 (95% CI: -0.50, -0.42), -0.48 (95% CI: -0.57, -0.39), and -0.40 (95% CI; -0.44, -0.36), respectively. In this case, the LS Mean difference between montelukast and placebo was -0.06 (95% CI: -0.12, -0.01).which was similar to the statistically significant difference in LS Means between montelukast and placebo noted in Study P265.

10.1.2.7.5.1.3 Summary of Primary Efficacy Analyses and Post-Hoc Analyses of the Primary Efficacy Variable

The results of the primary efficacy analyses and the post-hoc analyses are summarized in the following table. Note that the first section includes the data when the DNSS is defined using the pre-specified criteria of 4 nasal symptoms, and the second section includes the data when the definition of DNSS is changed to include three nasal symptoms excluding nasal pruritus. Additionally, in each section, the change from baseline includes data averaged over 4 and 6 weeks.

Table 38. Study #246, Summary of Baseline DNSS, Change from Baseline in DNSS Averaged Over 4-weeks, Over 6-weeks, and Post-Hoc Analysis of DNSS Excluding Nasal Pruritus

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)	Delta (p-value) {95% CI}	Delta (p-value) {95% CI}
Pre-specified Primary Efficacy Variable: DNSS with 4 symptoms					
Baseline	2.08	2.13	2.07	----------	----------
Change from Baseline *	-0.39 (-0.43, -0.36)	-0.45 (-0.54, -0.37)	-0.36 (-0.39, -0.32)	0.04 (0.150) {-0.09,0.01}	0.10 (0.038) {-0.19,-0.01}
Change from Baseline†	-0.46 (-0.50, -0.42)	-0.48 (-0.57, -0.39)	-0.41 (-0.45, -0.37)	0.05 (0.086) {-0.10,0.01}	0.07 (0.133) {-0.17,0.02}
Post-Hoc specified Primary Efficacy Variable: DNSS with 3 symptoms (Excluding Nasal Pruritus)					
Baseline	2.13	2.19	2.12	----------	----------
Change from Baseline*	-0.40 (-0.44,-0.36)	-0.45 (-0.54,-0.36)	-0.34 (-0.38,-0.30)	0.05 (0.049) {-0.11,0.00}	0.11 (0.028) (-0.20,-0.01}
Change from Baseline†	-0.46 (-0.50,-0.42)	-0.48 (-0.57,-0.39)	-0.40 (-0.44,-0.36)	0.06 (0.024) {-0.12,-0.01}	0.09 (0.082) {-0.18,0.01}

*pre-specified endpoint: DNSS averaged over the first 4-week period
†DNSS averaged over the entire 6-week period
Source: Vol. 4, p. 97, 99, 144, 163

Reviewer's comments: Although this study failed to demonstrate a statistically significant difference between montelukast and placebo for the pre-specified primary efficacy endpoint, the study does suggest a trend favoring montelukast. Using the same pre-specified primary efficacy endpoint as was used in the larger study, P265, similar differences between montelukast and placebo are noted in comparison. Although these results were obtained using a post-hoc analysis

and given the limitations of such analysis, these results are supportive in favoring montelukast, nonetheless.

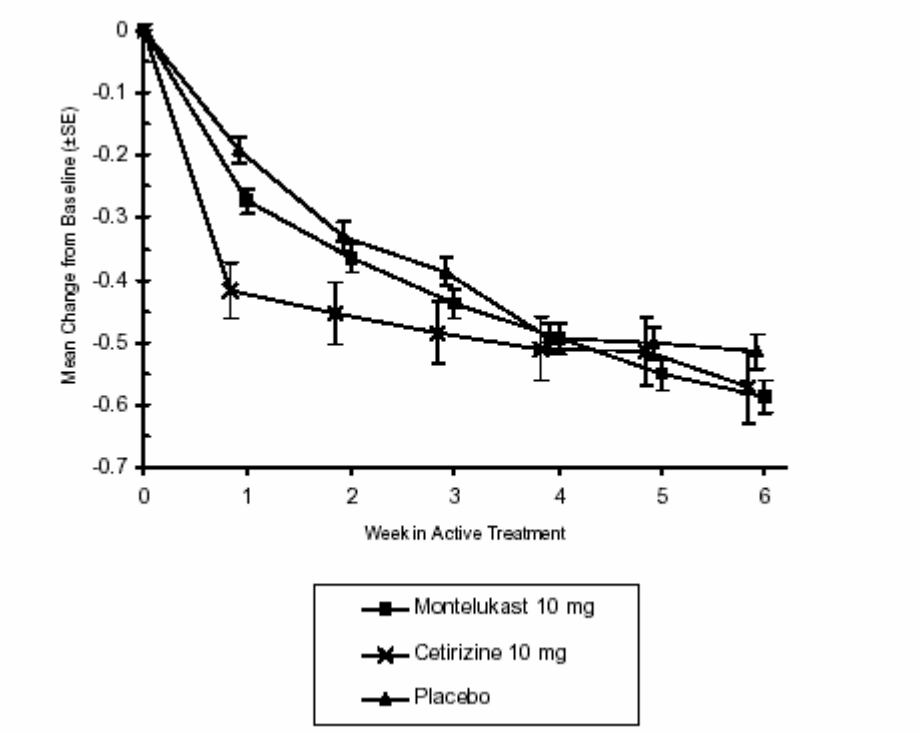
10.1.2.7.5.1.4 Consideration of Timing of Study

Similar to Study 265, this study was conducted during a time period that overlapped with the Spring season. The study was conducted between 27 November 2001 and 05 May 2002. It is unlikely that any seasonal allergens would be prevalent during the start of the study; however, during the last two months of the study, it is likely that symptoms could be attributable to both seasonal and perennial allergens. Since statistical significance was not attained for the primary efficacy endpoint, analysis of the data prior to March 1 compared to the overall data was not done by the Statistics Reviewer. It is unlikely that this comparison would add any additional useful information.

10.1.2.7.5.1.5 Treatment Effect by Week

The sponsor compared the Changes from Baseline for the primary efficacy variable, DNSS averaged over 4 weeks. The following figure displays the treatment effect over time.

Figure 4. Study #246, Mean Change From Baseline (± Standard Error) in Daytime Nasal Symptoms Score (Modified Intention-to-Treat Approach)



Source: clinsat/studies/p246.pdf./p.100

These results demonstrate that separation of curves between montelukast and placebo was clearly shown by Week 1, although the difference was not statistically significant at any time point. Note that effect size is considerably greater with cetirizine compared to placebo, which was shown to be statistically significant.

10.1.2.7.5.2 Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoints included the following presented as change from baseline averaged over the first 4-week period and presented over the entire 6-week treatment period:

- End-of-Day Nasal Symptom Score
- Nighttime Symptoms score
- Composite Symptoms Score
- Individual Daytime Nasal Symptom scores
- Individual End-of-Day Symptom scores
- Individual Nighttime scores
- Daytime Eye Symptoms Score
- Daytime Throat Symptoms Score
- Rhinoconjunctivitis Quality-of-Life score
- Perennial Allergic Rhinitis score based on Perennial Allergic Rhinitis Questionnaire
- Eosinophil Count (change from Baseline to the end of the 6-week treatment period)

Additionally, the Global Evaluation of Allergic Rhinitis by Patient and Physician were performed. This was not performed at Baseline, but was an assessment of how the patient felt at the end of the first 4-weeks of treatment.

10.1.2.7.5.2.1 End-of-Day Nasal Symptoms Score

The End-of-Day Nasal Symptoms Score was based on the instantaneous recall of the average of congestion, rhinorrhea, and sneezing. Baseline scores were 1.84, 1.86, and 1.81 for the montelukast, cetirizine, and placebo groups, respectively. The LS Mean changes from Baseline were -0.33, -0.38, and -0.29 for three treatment groups, respectively. The LS Mean difference between montelukast and placebo was -0.05 and -0.09 between cetirizine and placebo. **[Vol. 4, p. 151]**

10.1.2.7.5.2.2 Nighttime Symptoms Score

Results for this endpoint were based on the average of nasal congestion upon awakening, difficulty going to sleep, and nighttime awakenings. For this endpoint averaged over first 4-week period, slight numerical trends favoring montelukast and cetirizine compared to placebo were noted. Baseline scores for the montelukast, cetirizine, and placebo groups were 1.63, 1.65, and 1.58, respectively. Respective LS Mean changes from Baseline were -0.28, -0.30, and -0.26. The LS Mean difference between montelukast and placebo was -0.03 and between cetirizine and placebo was -0.05. Similar, although slightly greater changes from Baseline were noted when symptom scores were averaged over the 6-week period. **[Vol. 4, p. 102-104]**

10.1.2.7.5.2.3 Composite Symptoms Score

The Composite Symptoms Score comprised the average of the Daytime Nasal Symptoms Score and the Nighttime Symptoms score. Baseline scores for montelukast, cetirizine, and placebo were 1.86, 1.89, and 1.82, respectively. The LS Mean changes from Baseline were -0.34, -0.38, and -0.30, respectively. The LS Mean difference between montelukast and placebo was 0.03, and between cetirizine and placebo was 0.08. Similar trends were noted when the symptoms were evaluated over a 6-week period. **[Vol. 4, p. 106-109]**

10.1.2.7.5.2.4 Daytime Eye Symptoms Score

For the Daytime Eye Symptoms averaged over the first 4-weeks, no treatment effect was noted between montelukast and placebo. Mean baseline scores were 1.49, 1.62, and 1.48 for the montelukast, cetirizine, and placebo groups, respectively. The LS Mean changes from Baseline, respectively, were -0.30, -0.37, and -0.30. The LS Mean difference between montelukast and placebo was zero, and between cetirizine and placebo was -0.07. Similar results were noted with the results averaged over the entire 6-week treatment period: treatment difference between montelukast and placebo was -0.01 and between cetirizine and placebo was -0.05.

10.1.2.7.5.2.5 Daytime Throat Symptoms Score

Montelukast was only slightly favored for this endpoint averaged over the first 4 weeks compared to placebo, whereas greater improvements were noted for cetirizine compared to placebo. Baseline scores were 2.10, 2.14, and 2.04 for montelukast, cetirizine, and placebo, respectively, The LS Mean difference between montelukast and placebo was -0.02 compared to a treatment difference of -0.11 between cetirizine and placebo. Respective LS Mean differences between montelukast and placebo, and cetirizine and placebo for the entire 6-week treatment period were -0.03 and -0.08.

10.1.2.7.5.2.6 Individual Symptoms Scores

As with the other endpoints, the sponsor evaluated the individual symptoms averaged over the first 4 weeks of therapy and also over the entire 6-week treatment period. In general with one exception, there were trends toward numerical improvements favoring montelukast over placebo, although the effect size was small. As seen with the other endpoints, cetirizine showed greater improvements in symptoms compared to placebo than did montelukast compared to placebo. Slightly greater changes from Baseline were noted in individual symptoms when the results were averaged over the first 4 weeks compared to average over the entire 6-week study period.

Results of the individual nasal symptoms of congestion, rhinorrhea, and sneezing averaged over the first 4 weeks of treatment, favored improvement in the montelukast group compared to placebo; this favorable effect was not noted with the individual symptom of nasal itching. The LS Mean changes from Baseline for these four symptoms ranged between -0.37 to -0.42, -0.40 to -0.50, and -0.33 to -0.39 in the montelukast, cetirizine, and placebo groups respectively. The LS Mean differences between montelukast and placebo ranged between -0.04 to -0.06 for the symptoms of congestion, rhinorrhea, and sneezing. For nasal itching, the LS Mean difference was only -0.01. This relative lack of efficacy in the treatment of the individual symptom of nasal pruritus was not noted when treatment effect of cetirizine was compared to placebo; LS Mean differences between cetirizine and placebo for all four of the nasal symptoms ranged from -0.06 to -0.14. Clearly, the lack of efficacy noted with montelukast in the individual symptom of nasal pruritus, skewed the primary efficacy endpoint unfavorably with respect to the primary comparison of montelukast to placebo. Similar results were observed when the data were averaged over the entire 6 weeks of therapy, although slightly greater improvements were noted from Baseline in all treatment groups. Since all treatment groups, including placebo showed greater improvements in from Baseline with average of data over 6 weeks, the LS Mean

differences the primary comparison of montelukast and placebo remained the same for the most part. The results of the individual symptoms are summarized in the following table.

Table 39. Study #246, Summary Results for Individual Nasal Symptom Scores, Averaged Over First 4 Weeks and Over the Entire 6-Week Study Period

	Montelukast n=626	Cetirizine n=120	Placebo n=609	Outcomes	
				Montelukast vs. Placebo	Cetirizine vs. Placebo
	LS Mean	LS Mean	LS Mean	Delta	Delta
Nasal Congestion					
Baseline	2.44	2.49	2.42	----------	----------
Change from Baseline *	-0.37	-0.40	-0.33	0.04	0.08
Change from Baseline†	-0.43	-0.44	-0.37	0.05	0.07
Rhinorrhea					
Baseline	2.12	2.18	2.15	----------	----------
Change from Baseline*	-0.41	-0.44	-0.35	0.06	0.09
Change from Baseline†	-0.047	-0.46	-0.41	0.07	0.06
Nasal Itching					
Baseline	1.93	1.97	1.94		
Change from Baseline*	-0.38	-0.46	-0.39	0.01	0.07
Change from Baseline†	-0.44	-0.47	-0.44	0.00	0.03
Sneezing					
Baseline†	1.84	1.89	1.78		
Change from Baseline*	-0.42	-0.50	-0.36	0.06	0.14
Change from Baseline†	-0.47	-0.53	-0.41	0.06	0.12

*pre-specified endpoint: Scores averaged over the first 4-week period

†Scores averaged over the entire 6-week period

Source: Vol. 4, p. 97, 99, 144, 163 /clinstat/studies/p246.pdf/appendix 4.10.4/1380-1398

10.1.2.7.5.2.7 Quality-of-Life Questionnaire

The questionnaire Rhinoconjunctivitis Quality-of-Life Questionnaire: patients completed a self-administered questionnaire at Baseline and at the end of both the first 4 weeks of therapy and 6 weeks of therapy; this questionnaire contained 28 questions relating to activity, sleep, non-nasal symptoms, non-ocular symptoms, nasal symptoms, ocular symptoms, practical problems, and

emotions. Each question was rated on a 7-point scale ranging from best response (0) to worst response (6). The results of the QOL questionnaire were summarized in 7 domains: activity domain, sleep domain, non-nose/non-eye domain, practical problems domain, nasal domain, eye domain, and emotions domain.

The Baseline values for the average of the domains were 3.16, 3.28, and 3.12 in the montelukast, cetirizine, and placebo groups, respectively. The LS Mean changes from Baseline for the average of the domains over the first 4-weeks, were -0.95, -0.93, and -0.84 for the montelukast, cetirizine, and placebo groups, respectively. The LS Mean difference between montelukast and placebo was -0.11 and between cetirizine and placebo was -0.09. Results were similar when the domains were averaged over the entire 6-week period.

10.1.2.7.5.2.8 Global Evaluation of Rhinitis by Patient

After the first 4 weeks of therapy (or at time of discontinuation from the study), patients completed a Global Evaluation of Rhinitis, when all patients evaluated their allergic rhinitis symptoms compared to when they started the study based on whether they were:

- Very much better
- Moderately better
- A little better
- Unchanged
- A little worse
- Moderately worse
- Very much worse

The LS Mean scores for montelukast, cetirizine, and placebo were 2.22, 2.15, and 2.41, respectively. The LS Mean difference between montelukast and placebo was -0.15, and between cetirizine and placebo was -0.26. For this endpoint, the effect size seems to be larger compared to the other secondary endpoints. **[Vol. 4, p. 111-112]**

10.1.2.7.5.2.9 Physician's Global Evaluation of Rhinitis

For this endpoint, at the end of four weeks, the LS Mean scores for montelukast, cetirizine, and placebo were, 2.26, 2.20, and 2.33. The LS Mean difference between montelukast and placebo was -0.07 and between cetirizine and placebo was -0.13. **[Vol. 4, p. 113-114]**

Reviewer's comments: For the endpoints of Quality of Life Questionnaire, Global Evaluation of Rhinitis by Patient, and Physician's Global Evaluation of Rhinitis, the treatments were not comparable at Baseline. It is therefore, difficult to draw any conclusions from these secondary endpoints, as the differences between treatment groups at Baseline, in many instances exceeded the difference between treatments in terms of effect. The sponsor also performed a Perennial Allergic Rhinitis Questionnaire, and the results were fairly similar to the Quality-of-Life Questionnaire, and will not be summarized.

10.1.2.7.5.2.10 Eosinophil Count

The sponsor also performed an analysis of the change from Baseline in the LS Mean eosinophil count at the end of the 6-weeks of treatment. At Baseline, the mean eosinophil count (10^3/mcL) was 0.21, 0.21, and 0.20 in the montelukast, cetirizine, and placebo groups, respectively. The LS

Mean change from Baseline was -0.03, 0, and -0.01 in the three treatment groups, respectively. **[Vol. 4, p. 149]**

10.1.2.7.5.3 Other Analyses

10.1.2.7.5.3.1 Subgroup Analysis

Subgroup analyses based on gender, age, race, history of SAR, history of allergic conjunctivitis, history of asthma, recent symptoms of asthma, and baseline congestion demonstrated that the treatment effect was variable dependent on the group evaluated. Although greater improvements were noted in females and in patients 65 years of age and older, no meaningful conclusions can be drawn since the number of patients in each subgroup was not equal. Additionally, no meaningful treatment-by-subgroup interactions were noted in this study. This was concurred with discussions with the Biostatistics Reviewer, Dr. Feng Zhou.

However, it should be noted that from the subgroup analysis with respect to Baseline DNSS, it appears that patients with more severe disease demonstrated greater improvements in the montelukast and placebo groups. In the montelukast group, if the Baseline DNSS was <1.86, the improvement was -0.25 compared to -0.41 and -0.54 in the 1.86-2.29 and >2.29 group, respectively. Since the number of patients in each of the subgroups for this parameter, were similar, this may suggest that patients with more severe disease, respond more favorably to montelukast, although similar trends were noted in the placebo group as well. The subgroup analyses results for the primary efficacy analysis are summarized in the following table.

Table 40 . Study #246: Subgroup Analyses Results with Respect to Mean Change from Baseline in the DNSS Averaged Over the First 4 Weeks of Active Treatment Comparing Montelukast to Placebo

	Montelukast		Placebo	
	n	Mean (SD)	n	Mean (SD)
Gender				
Female	416	-0.43 (0.52)	416	-0.38 (0.480
Male	210	-0.32 (0.48)	193	-0.30 (0.44)
Age (by age distribution)				
< 18	54	-0.21 (0.46)	46	-0.17 (0.30)
≥ 18 to < 65	565	-0.41 (0.52)	551	-0.37 (0.48)
≥ 65	7	-0.59 (0.37)	12	-0.34 (0.40)
Race				
White	495	-0.38 (0.50)	485	-0.34 (0.46)
Black	55	-0.45 (0.55)	60	-0.40 (0.49)
Hispanic	46	-0.44 (0.51)	37	-0.46 (0.55)
Other	30	-0.45 (0.67)	27	-0.37 (0.47)
History of Seasonal Allergic Rhinitis				
No	494	-0.38 (0.50)	487	-0.34 (0.46)
Yes	131	-0.45 (0.56)	119	-0.41 (0.50)
Baseline Daytime Nasal Congestion Score				
< 2	74	-0.35 (0.58)	87	-0.30 (0.48)

	Montelukast		Placebo	
	n	Mean (SD)	n	Mean (SD)
≥ 2	552	-0.40 (0.50)	522	-0.36 (0.47)
Baseline Daytime Nasal Symptom Score				
< 1st tertile (1.86)	213	-0.25 (0.47)	207	-0.22 (0.44)
Between first and second tertile (between 1.86 and 2.25, exclusive)	210	-0.41 (0.51)	216	-0.36 (0.44)
> second tertile (2.25)	203	-0.54 (0.52)	186	-0.49 (0.50)
Source: clinstat/studies/p246.pdf/Appendix 4.16.3/p. 1438-39				

10.1.2.7.5.4 Efficacy Conclusions

Although there were numerical trends supporting the efficacy of montelukast, compared to placebo, this study failed to demonstrate statistically significant improvements in the primary efficacy endpoint. However, results are supportive of a favorable trend for montelukast over placebo.

If a post-hoc analysis is performed using the same primary efficacy endpoint as was used in Study 265, the differences noted between montelukast and placebo were noted to reach statistical significance. Although these results were obtained using a post-hoc analysis and given the limitations of such analysis, these results are supportive of montelukast, nonetheless.

10.1.2.7.6 Safety Outcomes

10.1.2.7.6.1 Extent of Exposure

The extent of exposure was fairly comparable between treatment groups, especially between montelukast and placebo, the primary comparison. The extent of exposure was adequate to allow for a safety analysis. The mean number of days on drug in the montelukast, cetirizine, and placebo group was 39.1, 38.6, and 38.8 days, respectively. The number of days on treatment ranged from 1-54 for the treatment groups. The majority of patients (92.1%, 89.3%, and 90.7% in the montelukast, cetirizine, and placebo groups, respectively) were exposed to treatment for greater than 4 weeks. The recommended trial duration for PAR is a minimum of 4 weeks, and this level of exposure is adequate to assess for safety. The extent of exposure is summarized in the following table.

Table 41. Study #246, Extent of Exposure

Extent of Exposure (Days)	Montelukast (n=630) n (%)	Cetirizine (n=122) n (%)	Placebo (n=613) n (%)
1 to 14	26 (4.1)	7 (5.7)	30 (4.9)
15 to 21	11 (1.7)	4 (3.3)	16 (2.6)
22 to 28	13 (2.1)	2 (1.6)	11 (1.8)
29 to 35	14 (2.2)	3 (2.5)	18 (2.9)
36 to 42	184 (29.2)	29 (23.8)	177 (28.9)

> 42	382 (60.6)	77 (63.1)	361 (58.9)
Total > 28 days	580 (92.1)	109 (89.3)	556 (90.7)
Mean Number of Days on Drug	39.5	38.6	38.8
Range of Days on Drug	1 to 52	1 to 50	1 to 54
Source: Vol. 4, p. 170-71			

10.1.2.7.6.2 Adverse Events

Adverse events were reported in 516 patients (37.8%). The incidence of AEs was similar across treatment groups. A total of 242 patients (38.4%), 43 patients (35.2%), and 231 patients (37.7%) in the montelukast, cetirizine, and placebo groups, respectively, reported adverse events. There were no deaths in this study, although 5 SAEs were reported, 3 in the montelukast group, and 2 in the placebo group. A slightly greater percentage of patients discontinued from the study due to AEs in the montelukast group compared to the other two treatments. A total of 56 patients (4.1%) discontinued from the study due to adverse events: 28 (4.4%) from the montelukast group, 4 (4.0%) from the cetirizine group, and 24 (3.9%) from the placebo group.

Generally, the incidence of any particular adverse event was low and fairly comparable between treatment groups with a few exceptions. The most commonly reported AEs in the montelukast group were headache reported in 7.5% (cetirizine, 6.6%; placebo, 5.9%), upper respiratory tract infection reported in 6.5% (cetirizine, 6.6%; placebo, 5.5%), pharyngitis reported in 2.7% (cetirizine, 2.5%; placebo, 3.3%), and sinusitis reported in 2.4% of patients (cetirizine, 0; placebo (2.8%). The incidences of these AEs were comparable between treatment groups. Other AEs occurring at lower incidences, but with greater frequency in the montelukast group include bronchitis (montelukast, 1.3%; cetirizine, 0; placebo 0.3%), back pain (montelukast, 1.1%; cetirizine, 0; placebo 0.7%), and gastroenteritis (montelukast, 0.8%; cetirizine and placebo, none). Dry mouth was also reported in a greater percentage of montelukast patients (1.1%) compared to placebo (0%); however, the incidence was lower compared to the cetirizine group (2.5%). These results are summarized in the following table.

Table 42. Study #246, Adverse Events Reported in Greater than 0.5% in the Montelukast Treatment Group

Adverse Event	Montelukast (n=630) n (%)	Cetirizine (n=122) n (%)	Placebo (n=613) n (%)
Patients with Adverse Events	**242 (38.4)**	**43 (35.2)**	**231 (37.7)**
Digestive System Disorders			
Diarrhea	7 (1.1)	3 (2.5)	7 (1.1)
Dry Mouth	5 (0.8)	3 (2.5)	0
Gastroenteritis	6 (1.0)	0	0
Infectious Gastroenteritis	0	0	3 (0.5)
Nausea	9 (1.4)	0	11 (0.8)
General Disorders			
Abdominal Pain	4 (0.6)	0	9 (1.5)

Adverse Event	Montelukast (n=630) n (%)	Cetirizine (n=122) n (%)	Placebo (n=613) n (%)
Asthenia/Fatigue	7 (1.1)	3 (2.5)	7 (1.1)
Dizziness	6 (1.0)	2 (1.6)	3 (0.5)
Fever	4 (0.6)	2 (1.6)	9 (1.5)
Influenza-like Illness	7 (1.1)	0	10 (1.6)
Upper Respiratory Tract Infection	41 (6.5)	8 (6.6)	34 (5.5)
Viral Syndrome	4 (0.6)	0	3 (0.5)
Eyes, Ears, Nose, and Throat			
Dry Nose	4 (0.6)	2 (1.6)	0
Otic Pain	5 (0.8)	0	6 (1.0)
Pharyngitis	17 (2.7)	3 (2.5)	20 (3.3)
Sinusitis	15 (2.4)	0	17 (2.8)
Musculoskeletal and Connective Tissue Disorders			
Back Pain	7 (1.1)	0	4 (0.7)
Neck Injury	5 (0.8)	0	0
Nervous System Disorders			
Headache	47 (7.5)	8 (6.6)	36 (5.9)
Insomnia	5 (0.8)	0	5 (0.8)
Sinus Headache			
Respiratory Disorders			
Bronchitis	8 (1.3)	0	2 (0.3)
Cough	11 (1.7)	2 (1.6)	8 (1.3)
Miscellaneous			
Rash	11 (1.7)	1 (0.8)	9 (1.5)
Urinary Tract Infection	7 (1.1)	1 (0.8)	6 (1.0)
Source: Vol. 4, p. 175-181			

Reviewer's comments: Review of the adverse events in general, does not raise any new concerns. Overall, the incidences were low, and any AE that occurred in a greater frequency than placebo occurred at an incidence that was low, making it difficult to draw any definitive conclusions regarding causation.

Adverse events judged to be treatment related will not be summarized as these were only in the opinion of the investigator. However, it will be stated that the incidence of these adverse events was quite low, all in less than 1% of patients, and the only notable AE reported much more frequently in the montelukast group (as judged by the investigator) was dry mouth. This was reported in 0.6% of patients in the montelukast group and in 0 in the placebo treated group. It is interesting to note, that this finding was noted in the Study 265 as well.

10.1.2.7.6.3 Deaths

There were no deaths reported in this study. **[Vol. 4, p. 185]**

10.1.2.7.6.4 Serious Adverse Events

Five Serious Adverse Events were reported for this study, 2 in the montelukast group and 3 in the placebo group. These are briefly summarized below. **[Vol. 4, p.184-187]**

10.1.2.7.6.4.1 Montelukast

Two SAEs were reported in the montelukast group: laceration and pregnancy. Their narratives are briefly presented in the following bullets.

- Laceration: A 15-year old male, on Day 2, sustained a laceration injury to his right calf as a result of dropping his knife while fishing. On Day 4, the patient was admitted to the hospital for surgical repair of the peroneal nerve and study therapy was interrupted. Patient recovered and completed the study.
- Pregnancy: 27-year old female notified the investigator that she was pregnant on Day 27, which was confirmed by the investigator with serum and urine β-hCG tests. The patient was discontinued from the study, and later revealed that she was pregnant with triplets. Follow up information revealed that the patient delivered 3 healthy females by cesarean section.

Reviewer's comments: Review of the narratives demonstrates that it is unlikely that these SAEs were caused by montelukast.

10.1.2.7.6.4.2 Placebo

Three patients in the placebo arm experienced SAEs. The first was unstable angina in a 58-yr old male with hyperlipidemia and hypertension diagnosed on Day 31. The second was a pregnancy in a 21 year old female, noted on protocol-specified urine pregnancy testing one day following completion of the double-blind period. The woman later reported a spontaneous abortion. The third SAE was also a pregnancy. This 20-year old patient also completed the study, and was noted to be pregnant on the post-treatment urine HCG testing. She elected for a non-surgical abortion. These three SAEs will not be further discussed as they occurred in the placebo arm, and therefore not attributable to montelukast.

10.1.2.7.6.5 Discontinuations Secondary to Adverse Events [Vol. 4, p. 189-191]

A total of 56 patients (4.1%) discontinued from the study due to adverse events, 28 (4.4%) in the montelukast group, 4 (3.3%) in the cetirizine group, and 24 (3.9%) in the placebo group. The most common reasons for study discontinuation in the montelukast group were sinusitis (1.3%), upper respiratory tract infection (1.0%), bronchitis (0.3%), and influenza-like disease (0.3%). The incidences of these AEs were comparable between montelukast and placebo. No unexpected concerns were noted from review of events. The AEs resulting in discontinuation in 0.3% or more patients in the montelukast group are summarized in the following table.

Table 43. Study #246: Discontinuations due to Adverse Event in 0.3% or Greater in the Montelukast Treatment Group

Adverse Event	Montelukast (n=630) n (%)	Cetirizine (n=122) n (%)	Placebo (n=613) n (%)
Sinusitis	8 (1.3)	0	6 (1.0)
Upper Respiratory Tract	6 (1.0)	1 (0.8)	2 (0.3)

Adverse Event	Montelukast (n=630) n (%)	Cetirizine (n=122) n (%)	Placebo (n=613) n (%)
Infection			
Bronchitis	2 (0.3)	0	1 (0.2)
Influenza-like Disease	2 (0.3)	0	2 (0.3)
Source: Vol.4, p. 190-191			

10.1.2.7.6.6 Laboratory, Vital Signs, EKGs

10.1.2.7.6.6.1 Laboratory

Unlike Study P265, in this study, the sponsor did perform pre and post-treatment laboratory examinations. Of the 1365 randomized patients, 1343 (98.4%) had at least one post-treatment laboratory test result and 30 patients (2.2%) had laboratory adverse events. Sixteen patients (2.6%), 4 patients (3.4%), and 10 patients (1.7%) in the montelukast, cetirizine, and placebo groups had laboratory AEs. Five patients discontinued due to laboratory AEs, 3 from the montelukast group, and 2 from the placebo group.

The majority of laboratory AEs were reported in serum chemistry, whereas ≤1 (comment: is this a percentage?) of patients in the active treatment groups had laboratory AEs reported in hematology or urinalysis. . Of the laboratory tests routinely performed, elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were the most commonly reported, although the incidence was low (1.3% in the active treated group). These elevations are notable since none were reported in the placebo group. Eight patients (1.3%) in the montelukast group, 1 patient (0.8%) in the cetirizine group, and none in the placebo group had elevations in ALT. Three patients (0.5%) in the montelukast group, 1 patient (0.8%) in the cetirizine group, and none in the placebo group had elevations in AST. Note that these patients could have both had increases in ALT and AST and therefore the same patient could be listed as having elevations in ALT and AST. These elevations will be further explored in the following section. The incidences and types of other laboratory AEs were similar across treatment groups and occurred in one or less patients in the active treatment groups, the review of which did not raise any specific concerns. These results are presented in the following table.

Table 44. Study #246: Number (%) of Patients With Specific Laboratory Adverse Events

Adverse Event	Montelukast (n=630) n/m*	Cetirizine (n=122) n/m* (%)	Placebo (n=613) n/m* (%)
Total with Laboratory AEs	**16/620 (2.6)**	**4/119 (3.4)**	**10/604 (604)**
Serum Chemistry	**13/619 (2.1)**	**3/119 (2.5)**	**5/600 (0.8)**
Alanine aminotransferase increased	8/619 (1.3)	1/119 (0.8)	0
Aspartate aminotransferase increased	3/612 (0.5)	1/119 (0.8)	0
Creatine phosphokinase increased†	1/24 (4.2)	1/6 (16.7)	2/12 (16.7)
Gamma-glutamyl transpeptidase increased	1/10 (10)	0	0

Adverse Event	Montelukast (n=630) n/m*	Cetirizine (n=122) n/m* (%)	Placebo (n=613) n/m* (%)
Hyperbilirubinemia	1/619 (0.2)	1/119 (0.8)	0
Hypercalcemia	1/619 (0.2)	0	0
Hyperglycemia	1/619 (0.2)	0	1/599 (0.2)
Nonfasting blood glucose decreased	1/619 (0.2)	0	0
Nonfasting blood glucose increased	1/619 (0.2)	0	1/599 (0.2)
Hematology	**1/616 (0.2)**	**0**	**1/599 (0.2)**
Hemoglobin decreased	0	0	1/599 (0.2)
Leukocytes decreased	1/616 (0.2)	0	0
Lymphocytes decreased	1/616 (0.2)	0	0
Neutrophils decreased	1/616 (0.2)	0	0
Urinalysis	**3/615 (0.5)**	**1/119 (0.8)**	**4/602 (0.7)**
Glycosuria	1/615 (0.2)	0	0
Hematuria	1/615 (0.2)	0	4/602 (0.7)
Leukocyturia	1/615 (0.2)	0	0
Proteinuria	0	1/119 (0.8)	0

*Total in whom particular lab results were measured

†Creatine phosphokinase (CPK) was not routinely measured; however, in individuals with LFT elevations, CPK was evaluated as well

Source: Vol.4, p. 190-191

10.1.2.7.6.6.1.1 Increases in Liver Function Tests

Review of laboratory abnormalities did not reveal any concerns, with the exception of liver function tests. Although there did not appear to be any clinically important changes from Baseline in the mean ALT or AST, some patients did have increases in ALT and AST in the study, at a greater incidence compared to placebo. Treatment groups were comparable for mean ALT and AST values at Baseline. There did not appear to be any clinically important changes from Baseline in the mean ALT or AST. The mean ALT at Baseline was 21.7, 20.3, and 21.5 IU/L for the montelukast, cetirizine, and placebo groups, respectively. The mean AST at Baseline was 21.9, 21.1, and 22.3, for the montelukast, cetirizine, and placebo groups, respectively. The mean change from Baseline in ALT was 0.2 or less in all treatment groups. The mean change from Baseline in AST was 0 or less. **[clinstat/studies/p246.pdf/appendix 4.26.1/p. 1576]**

Although the incidences of increases in ALT and AST were quite low (1.3% or less), the fact that they were noted in the active treatment groups, and not in the placebo treatment group (see reviewer's comment below), is suggestive of a possibility that they are drug related. Note that only one patient in the cetirizine had elevations in LFTs, compared to the montelukast treatment group. Since the study population is much larger in the montelukast group compared to cetirizine, conclusions regarding inter-treatment differences between these groups are difficult to make. Nonetheless, these results are suggestive that montelukast may possibly cause increases in ALT/AST.

Reviewer's comments: As defined by the sponsor, Dr. Feng Zhou printed out data illustrating increases in ALT and AST. Her printout also demonstrated that 2 patients had increases in ALT and 1 had an increase in AST. This was not noted in the table above by the sponsor. However, reviewing the results of these placebo patients, it was noted that these two patients clearly had increases in ALT or AST prior to randomization. It is assumed that this is the reason the sponsor did not include these as laboratory adverse experiences.

As this reviewer was interested in the number of patients with increases in ALT or AST compared to Baseline, this reviewer requested Dr. Feng Zhou to summarize this data. These results were individually reviewed, with pre and post comparison data, obtained from Dr. Feng Zhou. Evaluation of these results reveals that the majority of patients had minor elevations in ALT and AST when pre and post-treatment comparisons were made. Of the nine patients with increases in ALT and/or AST in the montelukast group, three had increases noted from screening to the pre-randomized period. Since the increases in these parameters occurred prior to receiving montelukast, it is unlikely that this may represent a drug effect. Of the remaining six patients, four patients had decreases after discontinuation of therapy, suggestive of a potential drug effect, although two did have an increased value at the final post-treatment value. Given the small number of patients reported with these increases, it is difficult to draw any definitive conclusions as to the causality of these increases in ALT/AST. These results are summarized in the following table.

Table 45. Study #246, ALT and AST Increases in Patients Noted as Laboratory Adverse Experiences

	ALT			AST		
Patient Number	Pre (day)	Post (day)	Final (day)	Pre (day)	Post (day)	Final (day)
Montelukast						
AN 4742†	26 (1)	81 (42)	78 (94)	25 (1)	52 (42)	48 (94)
AN 4763†	48 (1)	127 (9)	28 (37)	34 (1)	52 (9)	27 (37)
AN 5272	33 (1)	28 (12)	26 (28)	27 (-12)*	45 (1)	39 (28)
AN 5274	38 (1)	66 (40)	47 (49)	25 (1)	36 (40)	None
AN 5447	17 (1)	40 (40)	78 (57)	21 (1)	31 (40)	50 (57)
AN 5452†	48 (1)	65 (12)	50 (41)	35 (1)	None	28 (41)
AN 5578†	21 (1)	60 (43)	63 (57)	14 (1)	31 (43)	37 (57)
AN 5844†	26 (-35)	70 (1)*	47 (42)	25 (-35)*	51 (1)	33 (42)
AN 5873	23 (-16)	106 (8)*	100 (40)	23 (-16)	76 (8)	60 (40)
Cetirizine						
AN5592	11 (1)	55 (43)	15 (67)	12 (1)	59 (43)	22 (67)

*Note that these patients had normal screening laboratories; however, increases in ALT and/or AST were noted prior to randomized treatment period. For these patients, only the highest post-treatment value is listed; however, initial increases were noted prior to taking study drug.

†Note that patients AN 4742, 4763, 5452, 5578, and 5844 were taking concomitant acetaminophen, although only patient 4763 was taking 1-4 grams/day of acetaminophen, doses that could potentially lead to elevations in LFTs. [Vol. 4, p. 200]

Source: SAFETY.sas created by Dr. Feng Zhou on 15 March 2005 where data was created for individuals with increases in ALT and AST as defined as laboratory AEs by the sponsor

The sponsor also provided results based on the percentage of patients with ALT or AST elevations separated based on interval of elevations above the upper limits of normal, regardless of pre-randomization values. This data was not helpful, as it did not identify whether these values were increased, decreased, or changed from Baseline. Nonetheless, this reviewer requested that Dr. Zhou print out all patients with post-randomization elevated values. These were perused, and a total of 112 (18%), 25 (21%), and 86 patients (14%) in the montelukast, cetirizine, and placebo groups, respectively had elevations in ALT and/or AST. The majority of elevated values were less than 75 IU/L in all treatment groups. Only 3 (0.5%), 2 (1.7%), and 3 (0.5%), patients respectively, had values of ≥75 and < 100 IU/L. Similarly, a very small percentage had values of 100 IU/L or greater in each of the treatment groups (montelukast, 5 patients (0.8%); cetirizine, 1 patient (0.8%); placebo, 4 patients (0.7%). These results show that, generally, the types and frequencies of elevations in ALT and/or AST were similar for the different patients. No new particular concerns were raised as the current package insert makes note of potential for elevated liver function tests. **[Vol. 4, p. 207]**

10.1.2.7.6.6.2 Vitals and Physical Examinations

There were no clinically meaningful changes from Baseline in these parameters.

10.1.2.8 Discussion/Summary

This was a randomized, double-blind, placebo-controlled, parallel group study in 1365 patients age 15 years and older. Following a 1 week placebo-run period, patients were randomized to receive either montelukast 10 mg once daily in the evening, cetirizine 10 mg once daily, or placebo for 6 weeks.

A total of 1365 patients were randomized, 630 to the montelukast group, 122 to the cetirizine group, and 613 to the placebo group. Greater than 86% of patients completed the study with 99% or greater compliance with treatment. Demographics and baseline characteristics were fairly comparable between treatment groups. The majority of patients were female, White and were in the 18 to 64 year age group.

The primary efficacy endpoint was the change from baseline in the Daytime Nasal Symptoms Score (average of four nasal symptoms of congestion, sneezing, nasal pruritus, and rhinorrhea) averaged over the first 4 weeks of therapy. In this study, the sponsor failed to demonstrate statistically significant differences between montelukast and placebo for the prespecified primary efficacy endpoint. The Baseline DNSS were 2.08, 2.13, and 2.07 in the montelukast, cetirizine, and placebo groups, respectively. The mean change from Baseline in the LS mean DNSS in the montelukast group was -0.39, -0.45 in the cetirizine group, and -0.36 in the placebo group. The LS Mean difference between montelukast and placebo was -0.04, which was not statistically significant (p=0.150). However, the LS Mean difference between cetirizine and placebo of -0.10 was statistically significant (p=0.038). Thus, montelukast failed to demonstrate a statistically significant difference compared to placebo for the pre-specified primary efficacy endpoint in this trial.

Although the sponsor failed to show statistically significant improvement in the pre-specified primary comparison on the primary efficacy endpoint, there was a trend favoring montelukast compared to placebo. To explore this trend toward improvement, a few post-hoc analyses were performed defining the primary efficacy endpoint using the same criteria as were done in Study P265. If the DNSS is defined as in Study P265 (the average of three nasal symptom scores, excluding nasal pruritus) and the results are averaged over the 6-week period, a "statistically significant" difference is seen between montelukast and placebo. Since this is a post-hoc analysis, the meaning of a p-value or the term "statistically significant" is not valid. These results do suggest an improved change from Baseline when comparing montelukast to placebo. The LS Mean changes from Baseline for montelukast, cetirizine, and placebo using 3 symptoms in the DNSS averaged over the first 4-week period were -0.40, -0.45, and -0.34, respectively. The LS Mean difference between montelukast and placebo was 0.05. If the DNSS defined with 3 symptoms is averaged over the entire 6-week study period, the corresponding LS Mean changes from Baseline for montelukast, cetirizine, and placebo are -0.46, -0.48, and -0.40, respectively. In this case, the LS Mean difference between montelukast and placebo is 0.06, similar to the statistically significant difference in LS Means between montelukast and placebo noted in Study P265.

Analysis of secondary endpoints favored montelukast as well for the most part, although the differences between montelukast and placebo were quite small. Evaluation of individual symptoms revealed that improvements were noted in only three of the four symptoms used in the DNSS: congestion, rhinorrhea, and sneezing. The lack of improvement in nasal pruritus clearly skewed the results unfavorably towards montelukast.

In terms of safety, montelukast appears to be generally well tolerated in this study. A total of 242 patients (38.4%), 43 patients (35.2%), and 231 patients (37.7%) in the montelukast, cetirizine, and placebo groups, respectively, reported adverse events. There were no deaths in this study, although 5 SAEs were reported, 3 in the montelukast group, and 2 in the placebo group. A slightly greater percentage of patients discontinued from the study due to AEs in the montelukast group compared to the other two treatments. A total of 56 patients (4.1%) discontinued from the study due to adverse events: 28 (4.4%) from the montelukast group, 4 (4.0%) from the cetirizine group, and 24 (3.9%) from the placebo group.

Generally, the incidence of any particular adverse event was low and fairly comparable between treatment groups with a few exceptions. The most commonly reported AEs in the montelukast group were headache reported in 7.5% (cetirizine, 6.6%; placebo, 5.9%), upper respiratory tract infection reported in 6.5% (cetirizine, 6.6%; placebo, 5.5%), pharyngitis reported in 2.7% (cetirizine, 2.5%; placebo, 3.3%), and sinusitis reported in 2.4% of patients (cetirizine, 0; placebo (2.8%). The incidences of these AEs were comparable between treatment groups. Review of laboratory AEs, demonstrates a possibility for montelukast-related increases in liver function tests, although given the small number of patients with said abnormality, it may be difficult to draw any definitive conclusions. Otherwise, no clinically meaningful differences were noted between montelukast and placebo in other laboratory tests, vital signs, or physical examinations when compared to Baseline.

In conclusion, this study fails to demonstrate a statistically significance difference between montelukast and placebo with respect to the primary efficacy endpoint. Although this study itself would not support the efficacy of montelukast in the treatment of PAR, the results are suggestive of trends favoring montelukast. In terms of safety, montelukast was generally well tolerated, and definitive evidence of any new safety signals is lacking, although there is a suggestion of increases in LFTs.

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/s/

Tejashri Purohit-Sheth
7/12/05 02:50:10 PM
MEDICAL OFFICER

Lydia McClain
7/12/05 03:16:53 PM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 20-829, 20-830, 21-409	**TRADE NAME:**	SINGULAIR™ Tablets, Chewable Tablets, and Granules
APPLICANT/SPONSOR:	Merck Research Laboratories	**USAN NAME:**	Montelukast sodium
MEDICAL OFFICER:	Tejashri Purohit-Sheth, MD		
TEAM LEADER:	Lydia Gilbert-McClain, MD	**CATEGORY:**	Leukotriene Antagonist
REVIEW DATE:	08 November 8, 2004	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
9/30/04	10/5/04	SE8-033	Supplemental application for the indication of Perennial Allergic Rhinitis

RELATED APPLICATIONS

Document Date	Application Type	Comments
2/21/1997	NDA 20-829, NDA 20-830	Original applications for Singulair tablets (10 mg) and chewable tablets (5 mg) for asthma
5/6/1999	NDA 20-830, S-008	Supplemental application for 4 mg chewable tablets for asthma
	NDA 21-409	Application for oral granules for asthma
	SE8 for all of above NDAs	Supplemental application for seasonal allergic rhinitis

REVIEW SUMMARY:

The sponsor submits two studies in adults and children 15 years and older to support the indication of perennial allergic rhinitis, with the intent to obtain an indication in adults and children 6 months and older. Although not a filing issue, the ability of the sponsor to support the indication in 6 months to 1 year may be difficult, as the use in children under the age of 12 months has not previously been approved. Given that the pathophysiology is the same in adults and children with allergic rhinitis, extrapolating efficacy down to 6 months may be supported. However, the sponsor needs to provide data to support the dose in the 6-12 month age group. Additionally, the sponsor also needs to provide data to support safety in this age group as well. Whether the sponsor will be allowed to claim an indication in the 6-12 month age group will be a review issue, dependent upon the documents the sponsor provides in support.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	____	**SAFE TO PROCEED**	____	**CLINICAL HOLD**			
NDA/SUPPLEMENTS:	X	**FILEABLE**	____	**NOT FILEABLE**			
	____	**APPROVAL**	____	**APPROVABLE**	____	**NOT APPROVABLE**	
OTHER ACTION:							

I. General Information

Merck Research Laboratories' (MRL) product SINGULAIR™, is currently indicated for the prophylaxis and treatment of asthma in adults and pediatric patients 12 months and older, and for the relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older.

It is currently available as 10-mg film-coated tablets, 4-mg and 5-mg chewable tablets, and 4-mg oral granules. The sponsor submits this supplemental application to all of the NDAs for all of these formulations, for the treatment of symptoms of perennial allergic rhinitis in adults and children 6 months and older.

II. Background/Rationale

Allergic rhinitis comprises nasal symptoms – nasal pruritis, sneezing, rhinorrea, and nasal congestion–and non-nasal symptoms –ocular pruritis, tearing, and injection and palatal pruritis. The symptoms are mediated by a large number of mediators, to include histamine, leukotrienes, kinins, prostaglandins, chemotactic factors, neuropeptides, interleukins, and tumor necrosis factor-alpha. Blocking the effects of these mediators may be useful in treating the disease. Singulair is an oral, Type 1 cysteinyl leukotriene ($CysLT_1$) antagonist, which inhibits to some degree the effects of the pro-inflammatory cysteinyl leukotrienes.

Currently the major pharmaceutical therapies available are anti-histamines and intranasal corticosteroids. Singulair is an additional option for patients with SAR. Since the underlying pathophysiology for SAR and PAR is similar, and patients with SAR have shown modest benefits with Singulair, it can be expected that blockade of the CysLT1 receptor in patients with PAR will have some clinical benefit as well.

Consistent with the common pathophysiology of SAR and PAR, the Draft Guidance for Allergic Rhinitis states that a sponsor can submit one SAR and one PAR Phase 3 study to support both indications. The sponsor therefore feels that a single positive study demonstrating efficacy and safety in PAR may be considered substantial evidence for product labeling. To this effect, the sponsor submits two studies in PAR, one considered pivotal.

Since allergic rhinitis (seasonal and perennial) is a similar disease in adults and children and, therefore, can be treated with similar medications, MRL believes that the demonstrated efficacy for PAR in adults can be extrapolated to pediatric patients. This is consistent with the approach accepted for approval for SAR. To this end, the pivotal study was done in adults and adolescents 15 years of age and older.

III. Regulatory and Foreign Marketing History

A. Regulatory History

The original marketing applications for Singulair 10-mg film coated tablets (NDA 20-829) and 5-mg chewable tablets (NDA 20-830) were approved on February 20, 1998. A supplemental application for 4-mg chewable tablets was approved on March 3, 2000 (NDA 20-830/S-008). An application for Singulair Oral Granules (NDA 21-409) was approved July

26, 2000. The above applications were submitted for the treatment of asthma. A supplemental application was filed to all of the above NDAs for the treatment of symptoms of seasonal allergic rhinitis and approved on December 31, 2002.

The sponsor now submits this efficacy supplement in support of the treatment of symptoms of perennial allergic rhinitis in pediatric patients 6 months and older and adults. Prior to the submission of this NDA, a teleconference was held at the sponsor's request on May 30, 2003 when concurrence on the registration with one pivotal PAR study and concurrence on the proposed study design for said pivotal study were requested.

B. Foreign Marketing History

Singulair 5-mg and 10-mg tablets have received marketing approval for the treatment of asthma in 83 countries. Singulair 4-mg chewable tablets have received marketing approval for the treatment of asthma in 72 countries. Singulair 5-mg and 10-mg tablets and 4-mg chewable tablets have received approval for the treatment of symptoms of seasonal allergic rhinitis in 45 countries. Singulair oral granules have received approval for the treatment of asthma in 43 countries.

The following table illustrates the marketing approval for all of the formulations of Singulair. All of the countries in this table have received approval for asthma for the 5-mg and 10-mg tablets. All of the countries with the exception of the yellow highlighted countries have received approval for Singulair 4-mg chewable tablets for the treatment of asthma. All of the countries in red have received approval for all of the tablet formulations (see above) for the treatment of the symptoms of allergic rhinitis. All asterisked countries represent where approval was given for Singulair Oral Granules.

Argentina*	Greece*	Pakistan*
Aruba	Guatemala*	Panama
Australia*	Guyana†	Peru*
Austria	Honduras*	Philippines*
Bahrain*	Hong Kong*	Poland
Belgium	Hungary	Portugal*
Bolivia	Iceland*	Qatar
Bosnia	Ireland*	Romania*
Brazil*	Israel*	Russia
Bulgaria*	Italy*	Saudi Arabia
Canada*	Jamaica*	Singapore*
Chile*	Japan	Slovak Republic
China	Jordan	Slovenia*
Colombia*	Korea*	South Africa
Costa Rica*	Kuwait*	Spain*
Croatia	Latvia*	Sweden*
Curacao	Lebanon	Switzerland*
Cyprus	Lithuania	Taiwan
Czech Republic	Luxembourg*	Thailand
Denmark	Macao†	Trinidad
Dominican Republic	Malaysia*	Turkey
Ecuador*	Mexico*	United Arab Emirates
Egypt	Morocco	United Kingdom*
El Salvador*	Netherlands	United States*
Estonia*	New Zealand	Uruguay
Finland*	Nicaragua*	Venezuela*
France	Norway	Yugoslavia
Germany*	Oman	

(b) (4)

(b) (4)

As of July 30, 2004, marketing approval of Singulair tablets, chewable tablets, or granules has not been rejected, withdrawn, suspended or revoked in any country.

IV. Items Required for Filing and Reviewer Comments

A. Reviewer Comments

This is primarily an electronic submission, with a few paper volumes, to include the cover letter and labeling. The electronic section contains the full supplemental NDA.

Merck Research Laboratories (MRL) certifies that none of the investigators were paid employees of their company. The sponsor states that 1194 investigators participated per protocol, and 41 (3%) had "significant payments of other sorts" or equity interests. The sponsor does not provide the information per each individual study. This will be requested from the sponsor. Nonetheless, it is doubtful that the study results would have been affected by any bias from the small percentage of investigators who had financial disclosures for both studies.

B. Necessary Elements (21 CFR 314.50)

The sponsor has provided all of the necessary requirements for filing as outlined in the table below. Items not submitted were deemed not/applicable by the sponsor and this reviewer concurs with this assessment.

Table 1. Necessary Elements

Item	Type	Status	Location (paper/*electronic*)
	Application Form (FDA 356h)	Present	Vol. 1, electronic
1	Index / Table of Contents	Present	Vol. 1/ Electronic Section 1
2	Samples(if applicable) and Labeling		
	Proposed Package Insert	Present	Vol. 1/Electronic Section 2
	Proposed Label Text in MS WORD	Absent	need
	Proposed Medication Guide (if applicable)	N/A	
3	Summary	Present	Electronic/Section 3
	Labeling	Present	Electronic/Section 3
	Statement of Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits	Present	Electronic/Section 3
	Marketing History	Present	Electronic/5.3.6.1
	Chemistry, Manufacturing, & Controls (CMC)	N/A	N/A

Item	Type	Status	Location (paper/*electronic*)
	Nonclinical Pharmacology and Toxicology	N/A	N/A
	Human Pharmacokinetics and Bioavailability	N/A	N/A
	Clinical	Present	Electronic/2.5
	Benefits vs. Risks	Present	Electronic 2.5.6
4	CMC	Present	Electronic/CMC
	Environmental Impact statement	Present: Categorical Exclusion under 21 CFR 25.31 (b)	Electronic
5	Nonclinical Pharmacology and Toxicology	N/A	N/A
6	Human Pharmacokinetics and Bioavailability	N/A	N/A
8	Clinical	Present	Electronic/clinstat
	Controlled studies	Present	Electronic/clinstat/studies/p. 246.pdg and p265.pdf
	Integrated Summary of Effectiveness (subsets for age, gender, and race)	Present	Electronic/2.7.3
	Integrated Summary of Safety	Present	Electronic/2.7.4
	Potential for Abuse	Absent	N/A
	Benefits vs. Risks	Present	Electronic/2.5
	Statements of Good Clinical Practice:	Present	Electronic/clinstat
	Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures	Present	Electronic/clinstat/studies
	Auditing information	Absent	N/A
9	Safety Updates	N/A	
10	Statistics	Present	Electronic/clinstats
11	Case Report Tabulations	Present	Electronic/crt
12	Case Report Forms (for patients who died or did not complete studies)	Present	Electronic/crf
13	Patent Information	Present	Vol. 1/Electronic
14	Patent Certification	Absent	N/A
16	Investigator Debarment Certification	Present	Vol. 1/Electronic
17	Field copy certification (if applicable)	Absent	N/A
18	User Fee Cover Sheet	Present	Vol.1, Electronic
19	Financial Disclosure	Present	Vol.1, Electronic
20	Other		
	Claimed Marketing Exclusivity	N/A	
	Pediatric Use	N/A	

C. Decision

This application is fileable.

V. Clinical Studies

This submission consists of results of two phase III studies evaluating Perennial Allergic Rhinitis. Study 246 is stated to be an initial study and Study 265 is stated to be the pivotal PAR study. Both studies were multicenter, randomized, double-blind, placebo-controlled phase III studies. In the first study, the sponsor was unable to show a statistically significant difference between Singulair and placebo for the primary efficacy endpoint, Daytime Nasal Symptom Score, which was a composite of nasal congestion, sneezing, rhinorrhea, and nasal pruritis. The sponsor attributed this lack of efficacy to the individual symptom of pruritis, for which Singulair did not show benefit. Thus, for the second study, the pivotal study, the sponsor changed the primary efficacy endpoint, Daytime Nasal Symptom Score, to include only nasal congestion, rhinorrhea, and sneezing–the Draft Guidance on Allergic Rhinitis states that the primary endpoint of total nasal symptom score should contain at least 3 of the four nasal symptoms. In this pivotal study, the sponsor was able to show that Singulair was statistically superior to placebo.

Table 2. Summary of Pivotal Studies

Study	Design	Treatment	Patients	Evaluations
246	Phase III, 6-week, multicenter, randomized, parallel group, double-blind, placebo and active- controlled trial in PAR patients ages 15-82 yrs	Montelukast 10 mg Cetirizine 10 mg Placebo	1356	Primary Efficacy Daytime Nasal Sx Score (nasal congestion, sneezing, rhinorrhea, nasal pruritis)
265	Phase III, 6-week, multicenter (16), randomized, double-blind, parallel, placebo controlled trial in PAR patients ages 15-81 yrs	Montelukast 10 mg Placebo	1992	Primary Efficacy Daytime Nasal Symptom Score (nasal congestion, rhinorrhea and sneezing)

Reviewer's comments: it is interesting to note that the sponsor has a secondary endpoint, nighttime symptom score, comprised of average of congestion upon awakening, difficulty going to sleep, and nighttime awakenings. This has not previously been used as a valid secondary endpoint by the Division. However, ODS may have validated this endpoint. This needs to be investigated further during the review of the NDA.

The sponsor submits two studies in adults and children 15 years and older to support the indication of perennial allergic rhinitis, with the intent to obtain an indication in adults and children 6 months and older. Although not a filing issue, the ability of the sponsor to support the indication in 6 months to 1 year may be difficult, as the use in children under the age of 12 months has not previously been approved. Given that the pathophysiology is the same in adults and children with allergic rhinitis, extrapolating efficacy down to 6 months may be supported. However, the sponsor needs to provide data to support the dose in the 6-12 month age group. Additionally, the sponsor also needs to provide data to support safety in this age group as well. Whether the sponsor will be allowed to claim an indication in the 6-12 month

age group will be a review issue, dependent upon the documents the sponsor provides in support.

VI. DSI Review / Audit

After cursory review of this application, a DSI audit is not needed. No discrepancies have been identified at this time. However, if any irregularity is suspected during the review of this NDA, a DSI audit may be requested.

VII. Timeline for Review

Table 3. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	October 5, 2004
Study 246	December 21, 2004
Study 265	January 20, 2005
ISS, ISE	February 15, 2005
Label Review	March 15, 2005
Draft Review	April 21, 2004
Wrap-up	May 15, 2004
Division Goal Date	July 17, 2004
PDUFA Date	July 31, 2004

VIII. Comments to Applicant

1) Submit PK data to support the proposed dose in 6 – 11 month old patients.

2) Submit safety information in 6 – 11 month old patients.

3) Provide the total number of investigators in each individual study, and the number of individuals in each study who had financial disclosures.

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/s/

Tejashri Purohit-Sheth
11/16/04 02:45:48 PM
MEDICAL OFFICER

Lydia McClain
11/18/04 11:40:36 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPADP	**20-829, 20-830, 21-409**

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Merck and Company Inc. P. O. Box 2000 Rahway NJ 07065		**20-829SE1/033** **20-830SE1/035** **21-409SE1/012**	**9/30/04** **9/30/04** **9/30/04**

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Singulair™ Tablets (10 mg) Singulair™ Chewable Tablets (4, 5 mg) Singulair™ Oral Granules (4 mg)	Montelukast Sodium

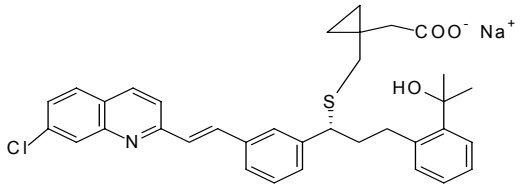
8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC. Number	Date
Perennial Allergic Rhinitis (SAR) as an alternate indication for Singulair Tablets, Singulair Chewable Tablets and Singulair Oral Granules and modified packaging/labeling to reflect addition of this new indication.	**20-829SE1/017***	**7/25/05**
	20-830SE1/020*	**7/25/05**
	21-409SE1/003*	**7/25/05**
	*** Subject of this Review**	

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Leukotriene Antagonist	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
Tablets, Chewable Tablets, and Oral Granules	4 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE

Sodium 1-[[[(R)-*m*-[(E)-2-(7-chloro-2-quinolyl)vinyl]-α-[*0*-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio]methyl]cyclopropaneacetate



16. RECORDS AND REPORTS

CURRENT YES NO

REVIEWED YES NO

17. COMMENTS: Since no manufacturing changes are reported, an EES for its sites have not been requested. The applicant has claimed a categorical exclusion for the preparation of an environment assessment under 21 CFR 25.15 and 25.31 (a).

cc:
HFD-570/div. File
HFD-570/PPeri
HFD-570/RLostritto
HFD-570/LGarcia
R/D Init. by:_____
doc # N20829SE1033CR2

Other Related NDAs

18. CONCLUSIONS AND RECOMMENDATIONS: **From chemistry, manufacturing and controls perspective the supplement may be approved.** Cartons for Oral Granules should be revisited during then EIB supplement for this drug product.

19. REVIEWER NAME	1. SIGNATURE	21. DATE COMPLETED
S. Prasad Peri, Ph.D.		7/26/2005

__2__ Page (s) Withheld

__✓__ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-829/S033; 20-30/S035; 21-409/S012

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/s/

Prasad Peri
7/26/05 04:09:47 PM
CHEMIST

Richard Lostritto
7/27/05 12:45:55 PM
CHEMIST

CHEMIST'S REVIEW

1. ORGANIZATION	2. NDA NUMBER
HFD-570 DPADP	**20-829, 20-830, 21-409**

3. NAME AND ADDRESS OF APPLICANT (City and State)	4. AF NUMBER	5. SUPPLEMENT(S) NUMBER	DATE
Merck and Company Inc. P. O. Box 2000 Rahway NJ 07065		**20-829SE1/033** **20-830SE1/035** **21-409SE1/012**	**9/30/04** **9/30/04** **9/30/04**

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Singulair™ Tablets (10 mg) Singulair™ Chewable Tablets (4, 5 mg) Singulair™ Oral Granules (4 mg)	Montelukast Sodium

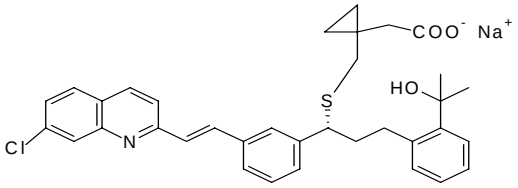
8. SUPPLEMENT PROVIDES FOR:	9. AMENDMENT(S), REPORT(S), ETC. Number	Date
Perennial Allergic Rhinitis (SAR) as an alternate indication for Singulair Tablets, Singulair Chewable Tablets and Singulair Oral Granules and modified packaging/labeling to reflect addition of this new indication.	**20-829SE1/017***	**1/02/03**
	20-830SE1/020*	**1/02/03**
	21-409SE1/003*	**1/02/03**
	*** Subject of this Review**	

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED	12. RELATED IND/NDA/DMF
Leukotriene Antagonist	RX X OTC _	

13. DOSAGE FORM(S)	14. POTENCY
Tablets, Chewable Tablets, and Oral Granules	4 mg, 5 mg, and 10 mg

15. CHEMICAL NAME AND STRUCTURE

Sodium 1-[[[(R)-*m*-[(E)-2-(7-chloro-2-quinolyl)vinyl]-α-[*0*-(1-hydroxy-1-methylethyl)phenethyl]benzyl]thio]methyl]cyclopropaneacetate



16. RECORDS AND REPORTS

CURRENT YES NO

REVIEWED YES NO

17. COMMENTS: Since no manufacturing changes are reported, an EES for its sites have not been requested. The applicant has claimed a categorical exclusion for the preparation of an environment assessment under 21 CFR 25.15 and 25.31 (a).

cc:
HFD-570/div. File
HFD-570/PPeri
HFD-570/RLostritto
HFD-570/LGarcia
R/D Init. by:_____
doc # N20829SE1033CR1

Other Related NDAs

18. CONCLUSIONS AND RECOMMENDATIONS: **From chemistry, manufacturing and controls perspective the supplement may be approved, pending an adequate response to the Agency's labeling comments.**

19. REVIEWER NAME	1. SIGNATURE	21. DATE COMPLETED
S. Prasad Peri, Ph.D.		7/7/2005

___6___ Page (s) Withheld

__✓___ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-829/S033; 20-830/S035; 21-409/S012

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/s/

Prasad Peri
7/8/05 02:09:55 PM
CHEMIST

Richard Lostritto
7/8/05 02:58:18 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033

20-830/S035

21-409/S012

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**20-829, 20-830 and 21-409**
SERIAL NUMBER:	**SE1-033 In NDA 20-829** **SE1-035 in NDA 20-830** **SE1-012 in NDA 21-409**
DATE RECEIVED BY CENTER:	**30-SEP-04**
PRODUCT:	**Singulair® tablets and oral granules**
INTENDED CLINICAL POPULATION:	**Patients 6 months & older with 1) symptoms of perennial allergic rhinitis or 2)** (b) (4)
SPONSOR:	**Merck Research Laboratory, Rahway**
DOCUMENTS REVIEWED:	**Proposed labeling**
REVIEW DIVISION:	**HFD-570**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Lori Garcia**

Date of review submission to Division File System (DFS): July 6, 2005

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
Approval of these supplements is recommended.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
None. The review recommends revisions to the Carcinogenesis, Mutagenesis, Impairment of Fertility and Overdosage sections of the labeling proposed by the sponsor on October 1, 2004. Detailed recommendations can be found on Page 12 of the review. The recommendations were faxed to the sponsor on June 21, 2004. The sponsor has accepted the recommendations and revised the labeling accordingly on June 24, 2004. Thus, no additional actions are necessary.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Not applicable because no data was submitted. See original NDA reviews.

B. Pharmacologic activity
Not applicable because no data was submitted. See original NDA reviews.

C. Nonclinical safety issues relevant to clinical use
None.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number:	20-829, 20-830 and 21-409
Review Number :	N/A
Sequence number/date/ submission type:	NDA 20-829: SE1-033/ 11-OCT-04/ BZ NDA 20-830: SE1-035/ 17-DEC-04/ BL NDA 21-409: SE1-12/ 17-DEC-04/ BL
Information to the Sponsor:	Yes (X), No ( )
Sponsor/or Agent:	Merck Research Laboratory, Rahway
Manufacturer of the Drug Substance:	Merck Research Laboratory, Rahway
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
HFD #:	HFD-570
Review Completion Date:	July 6, 2005
Drug:	
Trade Name:	Singulair™
Generic Name:	Montelukast sodium
Code Name:	L706,631
Chemical Name:	Sodium 1-(((1(R)-(3-(2-(7-chloro-2-quinolinyl)-(E)-ethyl)(3-(2-(1-hydroxy-1-methylethyl)propyl)thio)-methyl)cyclopropane)acetate
CAS Register Number:	N/A
Molecular Form and Weight:	$C_{35}H_{35}ClNNaO_3S$; 608.2
Relevant IND/NDAs/DMFs:	INDs (b) (4) 47,726 and 58,819; DMFs (b) (4)
Drug Class:	Leukotriene D_4/E_4 receptor antagonist
Intended clinical population:	Patients 6 months & older with perennial allergic rhinitis or (b) (4)
Clinical Formulation:	10-mg tablets, 5-mg and 4-mg chewable tablets and 4-mg oral granules
Route of Administration:	Oral

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies Submitted and Reviewed in the Review: None.

Studies Submitted but Not Reviewed in this Review: None.

Background:

Montelukast (Singulair™) is an approved leukotriene receptor antagonist currently marketed and indicated for the prophylaxis and chronic treatment of asthma in patients 12 months and older and relief of seasonal allergic rhinitis in patients 2 years of age and older. Dosage forms of Singulair™ include 10-mg tablets, 5-mg and 4-mg chewable tablets, and 4-mg oral granules. They are approved for adults and children aged 6 - 14 years, 2 – 5 years, and 12 - 23 months, respectively.

The current supplemental submissions seek to add the indication of perennial allergic rhinitis in children 6 months of age and older to the currently approved uses. The proposed dose of montelukast in the children 6 – 11 months of age will be 4-mg oral granule. The doses for the newly proposed indication of montelukast for patients 12 months of age and older remains the same as what has been approved.

The submissions do not contain any nonclinical information, but they do contain additional clinical AUC data of montelukast. These data affect dose ratios in the nonclinical sections of the montelukast labeling. This review addresses the labeling review only.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Not applicable because no data was submitted.

2.6.2.2 Primary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.3 Secondary pharmacodynamics

Not applicable because no data was submitted.

2.6.2.4 Safety pharmacology

Not applicable because no data was submitted.

2.6.2.5 Pharmacodynamic drug interactions

Not applicable because no data was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Not applicable because no data was submitted.

2.6.4.2 Methods of Analysis

Not applicable because no data was submitted.

2.6.4.3 Absorption

Not applicable because no data was submitted.

2.6.4.4 Distribution

Not applicable because no data was submitted.

2.6.4.5 Metabolism

Not applicable because no data was submitted.

2.6.4.6 Excretion

Not applicable because no data was submitted.

2.6.4.7 Pharmacokinetic drug interactions

Not applicable because no data was submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable because no data was submitted.

2.6.4.9 Discussion and Conclusions

Not applicable because no data was submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data was submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no data was submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Not applicable because no data was submitted.

2.6.6.2 Single-dose toxicity

Not applicable because no data was submitted.

2.6.6.3 Repeat-dose toxicity

Not applicable because no data was submitted.

2.6.6.4 Genetic toxicity

Not applicable because no data was submitted.

2.6.6.5 Carcinogenicity

Not applicable because no data was submitted.

2.6.6.6 Reproductive and Developmental Toxicology:

Not applicable because no data was submitted.

2.6.6.7 Local tolerance

Not applicable because no data was submitted.

2.6.6.8 Special toxicology studies

Not applicable because no data was submitted.

2.6.6.9 Discussion and Conclusions

Not applicable because no data was submitted.

2.6.6.10 Tables and Figures

Not applicable.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The approval of Supplements SE1-033 for NDA 20-829, SE1-035 for NDA 20-830 and SE1-12 for NDA 21-409 is recommended from the nonclinical perspective. The three supplements propose the same changes since there is a single label although the full supporting information was submitted only to NDA 20-829. They propose to add the indication of perennial allergic rhinitis (PAR) as another indication to the marketed products – Singulair™ (montelukast). The proposed population for this indication only is subjects 6 months of age and older. The supplements do not contain any nonclinical pharmacology and toxicology data. They do contain additional clinical exposure (AUC) data of montelukast that affect dose ratios in the nonclinical sections of the product labeling. This review conducts a labeling review based on the new clinical exposure data. It recommends revising the ratios and the text accordingly. An annotated version of the recommendations can be found on Page 12. The sponsor has accepted the recommendations. Thus, an approval is recommended.

The doses for the proposed indication of montelukast are the same as what have been approved for Singulair™ 10-mg tablets, 5-mg and 4-mg chewable tablets, and 4-mg gram oral granules in patients aged 12 months and older. For the patients aged 6 to 11 months, the supplements propose a dosage of 4-mg oral granule, once a day.

The Division previously completed its nonclinical safety evaluation of montelukast in patients 6 months and older. Merck had requested this patient population in NDA 21-409. The Division determined that Merck has satisfied the nonclinical requirement for pediatric patients of 6 month of age and older. This determination was documented in a nonclinical review by Dr. Luqi Pei dated July 19, 2002 in NDA 21-409 (Singulair™ granules). That review does not identify any outstanding nonclinical issues. When the review of NDA 21-409 was completed, the Division granted the approval for patients 12 months and older for the indication of asthma but (b) (4) The current submissions propose to use the same formulation and dosage as in NDA 21-409. There are no additional nonclinical data warranting any modification of the previous conclusion. Thus, Merck has established the nonclinical safety of the proposed use of montelukast.

The current submissions reported mean plasma montelukast AUC values that differ slightly from previous submissions. Changes in mean AUC values render it necessary to review the AUC ratios between animals and humans in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Overdosage sections of the currently approved labeling. The ratios in the approved labeling were derived from a mean plasma AUC of 3.57 mcg.hr/ml, a value for children 12 – 23 months of age. The current submissions reported a mean AUC of 4.3 mcg.hr/ml for children of 6 – 11 months of age, a value 20% higher than what was used for calculating the AUC ratios. The new AUC values would result in a 20% decrease in the dose ratios, rendering it necessary to revise the ratios in these sections.

Due to differences in exposures between and adult and pediatric populations, it is recommended that the labeling present the dose ratios for both adults and children; the currently approved label uses a single value for both sub-groups. The additional clinical kinetic data show that adults and pediatrics possess significant differences (up to 67%) in

mean plasma AUCs. For example, the mean AUC is 2.67 and 4.3 mcg.hr/ml for adults and children of 6 – 11 months of age, respectively. A presentation of AUC ratios for both adults and pediatrics reflects a more accurate and informative AUC ratio profile. Thus, the review recommends the labeling to describe AUC ratios for both adult and pediatric populations. The review also finds it necessary to revise the text of the labeling to make easier to comprehend. Overall, the approval of the supplements is recommended, pending acceptance of the recommended labeling revisions.

Unresolved toxicology issues: None

Recommendations:

This application is recommended for approval from a nonclinical perspective, pending acceptance of recommended changes to the labeling. The recommended changes in the labeling are the revisions of the dose ratios between animals and humans in the sections of Carcinogenesis, Mutagenesis and Fertility and Overdose. The Pregnancy section of the label is not affected since it does not include pediatric exposures. See the Labeling Review section (below) for detail.

LABELING REVIEW:

The current submissions contain new and different mean plasma AUC data of montelukast in children that warrant revising AUC ratios between animals and humans in the Carcinogenesis, Mutagenesis, Impairment of Fertility and Overdosage sections of the labeling. The AUC ratios help readers determine the safety profiles of the drug regarding its intended use. Changes in the ratios subsequently affect the reader's safety evaluation of the intended use of the drug. The relevant sections of the currently approved Carcinogenesis, Mutagenesis, Impairment of Fertility and Overdosage state:

> "No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague-Dawley rats at oral gavage doses up to 200 mg/kg/day (estimated exposure was approximately 90 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral gavage doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the AUC for adults and children at the maximum recommended daily oral dose).
>
> …
>
> No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 250 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 170 times the AUC for adults and children at the maximum recommended daily oral dose)."

The above text was based on a labeling review by Dr. Luqi Pei dated July 19, 2002 and an addendum to the review dated July 25, 2005 in NDA 21-409. These dose ratios are the smallest ratios between animals and humans for a particular animal study because they are the most conservative of estimates of the safety profile of the drug. The July 19, 2002 review recommends using one dose ratio to cover both adult and pediatric populations because the review finds no remarkable difference in AUCs (14%) between pediatrics of 12 – 23 months of age (3.04 mcg.hr/ml) and adults (2.67 mcg.hr/ml). Merck and the Division agreed with the approach. During a telephone conference held on July 25, 2002 (See memo to file by Dr. Pei dated 25-JUL-04), Merck and the Division also agreed to revise the AUC value in pediatrics to 3.57 mcg.hr/ml and calculate the ratios accordingly, despite the apparent enhancement of the difference in AUC ratios between adult and pediatric populations.

The current submissions reported a further 20% increase in the mean AUCs in children aged 6-11 months. The mean plasma AUC was 4.3 and 3.57 mcg.hr/ml for children 6 – 11 months of age and 12 – 23 months of age, respectively. The increase in pediatric plasma concentration results in a 20% reduction in AUC ratios between animals and humans. Of note, the sponsor did not propose to adjust the ratios in the current submissions. Table 1 (below) presents the dose ratios calculated from montelukast plasma AUCs in the different human populations. Using the mouse carcinogenesis data as an example, the difference between adults and pediatrics was 38% and 63% for children aged 12 – 23 months and 6 – 11 months, respectively. Such a difference is significant and, therefore, both ratios for adult and pediatrics should be presented on the product label to better reflect the data.

Table 1. Derived AUC Ratios for Preclinical Labeling of Montelukast

Labeling Section	Species	Dose (mg/kg/day)	AUC (μg.h/ml) [a]	AUC Ratio (animal/human)		
				Adult [b]	Pediatrics	
					12 – 23 mo [c]	6 – 11 mo [d]
Carcinogenesis	Mice	100	116.7	43	32	27
	Rat	200	326.9	122	91	76
Overdosage	Mice	5000	901.7	335	252	210
	Rat	5000	616.5	229	172	143

a. Source: Pharmacology and Toxicology review by Dr. Luqi Pei dated July 19, 2004 in NDA 21-409 (p 4, Table 4)
b. Based on the mean plasma AUC of 2.69 mcg.hr/ml in adults. Note the mean AUC for adults differs slightly from that in the original approved labeling (2.57 mcg.hr/ml).
c. Based on the mean AUC of 3.57 mcg.hr/ml in children 12 – 23 months of age.
d. Based on the mean plasma AUC of 4.3 mcg.hr/ml in children of 6 – 11 months of age.

Table 2 (next page) presents the calculated and recommended AUC ratios for different human populations. It is recommended that ratios for both adults and children 6 – 11 months of age be presented in the labeling. This approach reflects better the data. It also gives the reader a spectrum of the data.

Table 2. Recommended AUC Ratios for Preclinical Labeling of Montelukast

Labeling	Species	Dose	AUC Ratio (animal/human)

Section		(mg/kg/day)	Category	Adult [c]	12 - 23 mo	6 – 11 mo
Carcinogenesis	Mice	100	Derived [a]	43	32	27
			Recommended [b]	45	30 [d]	25 [e]
	Rat	200	Derived	122	91	76
			Recommended	120	90 [d]	75 [e]
Overdosage	Mice	5000	Derived	335	252	210
			Recommended	335	250 [d]	210 [e]
	Rat	5000	Derived	229	172	143
			Recommended	230	170 [d]	145 [e]

a. Source: Table 1, above.
b. Derived numbers are rounded to nearest 5 or 10.
c. Dose ratios calculated from the AUC data using the mean AUC of 2.69 mcg.hr/ml in adult population.
d. Dose ratios in current approved labeling.
e. Recommended for pediatric populations in future labeling.

Revisions to the text of the labeling are also recommended. The sentences in the approved labeling are quite long already (See Section A). The discussions above find it necessary to present additional information; that is, to present AUC ratios for adult and pediatric populations separately. Addition of such information to the current format would make these sentences even longer and more difficult to understand. The problem can be easily corrected by shortening the sentences.

The following sections present sequentially the text of the sponsor's newly proposed labeling, the newly suggested labeling, and the annotated copy suggested for the sections of montelukast labeling. The currently approved labeling is not presented because it is identical to the sponsor's newly proposed one.

A. Merck's proposed labeling for the Carcinogenesis and Overdosage sections of the montelukast label (note: this is also the currently approved labeling).

No evidence of tumorigenicity was seen in either a 2-year carcinogenicity study in Sprague-Dawley rats at oral gavage doses up to 200 mg/kg/day (estimated exposure was approximately 90 times the area under the plasma concentration versus time curve (AUC) for adults and children at the maximum recommended daily oral dose) or in a 92-week carcinogenicity study in mice at oral gavage doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the AUC for adults and children at the maximum recommended daily oral dose).

…

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 250 times the AUC for adults and children at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 170 times the AUC for adults and children at the maximum recommended daily oral dose).

B. The reviewer's suggested text for the labeling

No evidence of tumorigenicity was seen in carcinogenicity studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. The estimated exposure in rats was approximately 120 and 75 times the area under the plasma concentration versus time curve (AUC) for adults and children, respectively, at the maximum recommended daily oral dose. The estimated exposure in mice was approximately 45 and 25 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose.

…

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 335 and 210 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose) and rats (estimated exposure was approximately 230 and 145 times the AUC for adults and children, respectively, at the maximum recommended daily oral dose).

C. Annotated Review of the proposed labeling

Recommended deletions are indicated by strikeouts and inserts are indicated by underlines.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was seen in ~~either a 2 year~~ carcinogenicity ~~study~~ studies of either 2 years in Sprague-Dawley rats or 92 weeks in mice at oral gavage doses up to 200 mg/kg/day or 100 mg/kg/day, respectively. ~~(~~The estimated exposure in rats was approximately 120 and 75 ~~90~~ times the area under the plasma concentration versus time curve (AUC) for adults and children, respectively, at the maximum recommended daily oral dose.~~)~~ The estimated exposure ~~or in a 92 week carcinogenicity study~~ in mice ~~at oral gavage doses up to 100 mg/kg/day (estimated exposure~~ was approximately 45 and 25~~30~~ times the AUC for adults and children, respectively, at the maximum recommended daily oral dose~~)~~..

…

OVERDOSAGE

No mortality occurred following single oral doses of montelukast up to 5000 mg/kg in mice (estimated exposure was approximately 335 and 210~~250~~ times the AUC for adults and children, respectively, at the maximum recommended daily oral dose) and rats

(estimated exposure was approximately 230 and 145~~170~~ times the AUC for adults and children, respectively, at the maximum recommended daily oral dose).

The sponsor has accepted the above recommendations on labeling revision on June 24, 2005 (via email communication to Ms. Lori Garcia). No further nonclinical action is needed on the supplement.

Luqi Pei, Ph.D.
Pharmacologist/Toxicologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Luqi Pei
7/6/05 11:32:07 AM
PHARMACOLOGIST

Timothy McGovern
7/6/05 12:52:01 PM
PHARMACOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	N20-829/SE1-033
	N20-830/SE1-035
	N21-409/SE1-012
Drug Name:	Singulair™ Tablets, Granules, and Chewable Tablets
Indication(s):	Proposed Indication: PAR in adults and pediatric patients 6 months of age and older
Applicant:	Merck Research Laboratories
Date(s):	Received 9/31/04; User Fee 7/31/05
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Sue Jan Wang, Ph.D. (Acting Biometrics Team Leader)
Medical Division:	Division of Pulmonary and Allergy Drug Products (HFD-570)
Clinical Team:	Tejashri Purohit-Sheth, M.D. (Medical Reviewer)
	Badrul A Chowdhury, M.D. (Medical Division Director)
Project Manager:	Lori Garcia (HFD-570)

Keywords: Clinical Studies, NDA review, Dropouts

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1. EXECUTIVE SUMMARY

Montelukast [trade name: Singulair™], an orally active cysteinyl leukotriene type 1 ($CysLT_1$) receptor antagonist, was approved for the prophylaxis and chronic treatment of Asthma on 20 February 1998 [NDA 20-829 (2/20/1998), 10-mg film coated tablets; NDA 20-830 (2/20/1998), 5-mg chewable tablets; NDA 20-830/S-008 (3/3/2000),4-mg chewable tablets; NDA 21-409 (7/26/2000), 4-mg oral granules]. Montelukast was also approved for the treatment of Seasonal Allergic Rhinitis (SAR) on 31 December 2002 [Supplemental Application to all of above NDAs]. The sponsor (Merck) submitted this supplement on 31 September 2004 (NDA 20-829/S33) in support of a new indication of relief of symptoms of Perennial Allergic Rhinitis (PAR) in adults and pediatric patients 6 months or older.

1.1 Conclusions and Recommendations

Based on the efficacy evaluation of studies PAR246 and PAR265, each of which were a phase-III, randomized, multicenter, double-blind, parallel-group, and placebo-control trial, only one study (PAR265) demonstrated that subjects treated with Montelukast 10mg once daily in the evening over a 6-week treatment period, compared with the Placebo, improved the primary endpoint, Daytime Nasal Symptoms score (i.e. average of scores for Congestion, Rhinorrhea, and Sneezing). The change in the primary efficacy variable in the Montelukast 10mg treatment group was numerically (but not statistically significantly) superior to Placebo group and worse than the Cetirizine treatment group in Study PAR246. In an exploratory evaluation, out of 3357 patients 15 to 82 years of age with a history of PAR, and daytime nasal symptoms score ≥ 1.5 at study entry, 41% of the 1626 patients, who received Montelukast 10mg treatment, reduced daytime nasal symptoms by 0.5 on average over the 6-week treatment period. The patients who had severe symptom at baseline appeared to improve more over the 6-week treatment period, compared with the patients who had mild symptoms at baseline.

Montelukast 10 mg administered once daily over a 6-week treatment period is generally well tolerated, with a safety profile comparable with that of placebo. There were 9 patients in Montelukast group, 1 in Cetirizine group, and 3 in placebo group who had ALT and/or AST increases.

1.2 Brief Overview of Clinical Studies

The sponsor's submission included two 6-weeks studies to demonstrate the efficacy and safety of Montelukast treatment in adults 15 years of age and older with Perennial Allergic Rhinitis (PAR). Study 246 (hereafter referred to PAR246) and Study 265 (hereafter referred to PAR265) were multicenter, double-blind, randomized, placebo-controlled, parallel-group studies investigating the clinical effects of Montelukast 10mg in patients with PAR. (See Table 2 for details.)

1.3 Statistical Issues and Findings

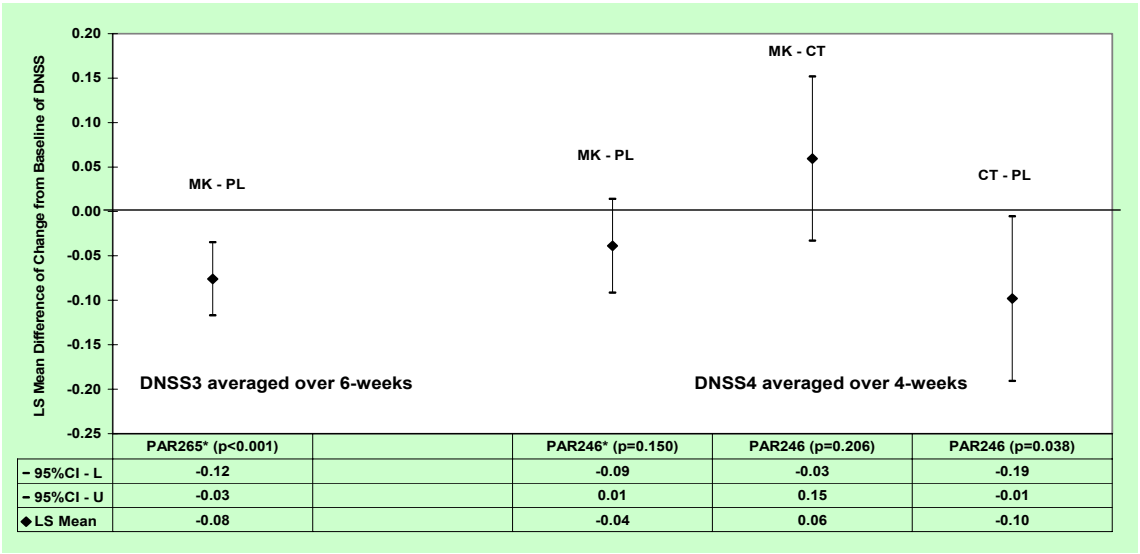
This reviewer explored, examined, and analyzed the sponsor's data for the two studies. In the re-analysis of the data, this reviewer focused on the efficacy of Montelukast, but also included some comments regarding the safety of the product. Table 1 summarizes the efficacy results for the two studies under review.

Table 1. Statistical Results of Two Studies

Study (# of centers)	*Study Population Age & Gender (N)*	*Design*	*Treatment groups (N)*	*Primary Efficacy Variable*	*LS Mean of Δ 95% CI p-value*
PAR246 74 centers in USA 6-weeks study	Age range: Male: 15 – 77 (443) Female: 15 – 82 (922)	Randomized Multicenter Double-blind Active-group parallel-group Placebo-controlled	Montelukast 10 mg (630) Cetirizine 10mg (122) Placebo (613)	Mean Change from Baseline of Daytime Nasal Symptoms Score DNSS4 (average of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing) over 4-weeks	MK- PL=-0.039 (-0.091, 0.014) 0.1501
PAR265 117 centers in 12 countries included USA 6-weeks study	Age range: Male: 15 – 79 (716) Female: 15 – 81 (1276)	Randomized Multicenter Double-blind parallel-group Placebo-controlled	Montelukast 10 mg (1002) Placebo (990)	Mean Change from Baseline of Daytime Nasal Symptoms Score3 (average of Nasal Congestion, Rhinorrhea, and Sneezing) over 6-weeks	MK- PL=-0.076 (-0.117, -0.035) 0.0003

The efficacy results of Montelukast are shown in Figure 1. For Study PAR265, the primary efficacy endpoint showed that Montelukast was statistically significantly better than Placebo. Study PAR246 only numerically showed the benefit of Montelukast. Cetirizine was statistically significantly better than Placebo in Study PAR246, even though, it was not an active comparator in the study design. The average effect size of Montelukast was small (0.06). Figure 2 shows that only 41% of patients improved the 0.5 point of Daytime Nasal Symptoms Score (measured in 0 – 3) after 6 weeks of treatment of Montelukast, 48% for Cetirizine, and 35% for Placebo.

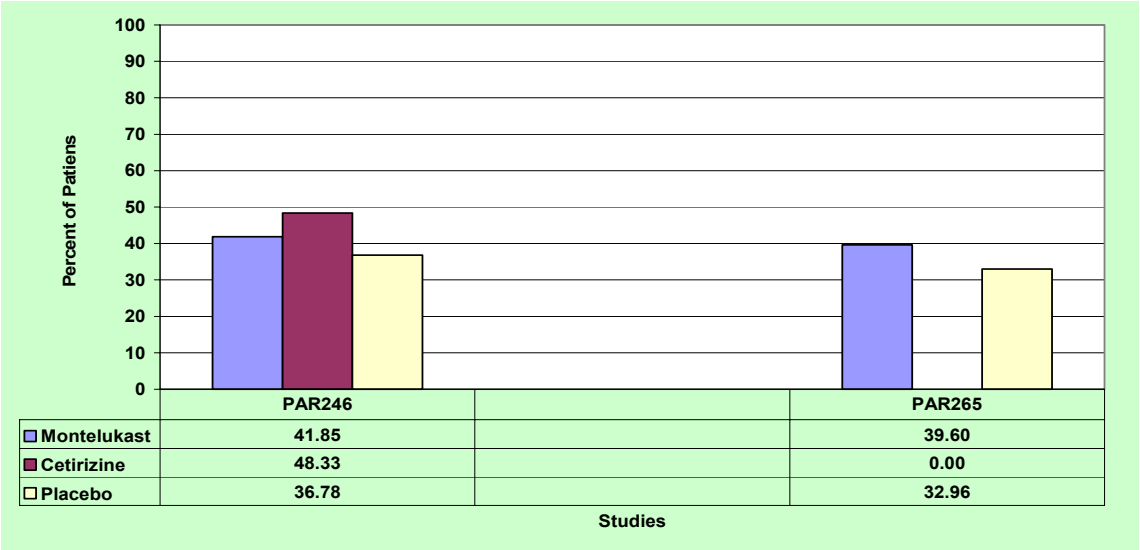
Figure 1. The Primary Efficacy Results



	PAR265* (p<0.001)		PAR246* (p=0.150)	PAR246 (p=0.206)	PAR246 (p=0.038)
– 95%CI - L	-0.12		-0.09	-0.03	-0.19
– 95%CI - U	-0.03		0.01	0.15	-0.01
◆ LS Mean	-0.08		-0.04	0.06	-0.10

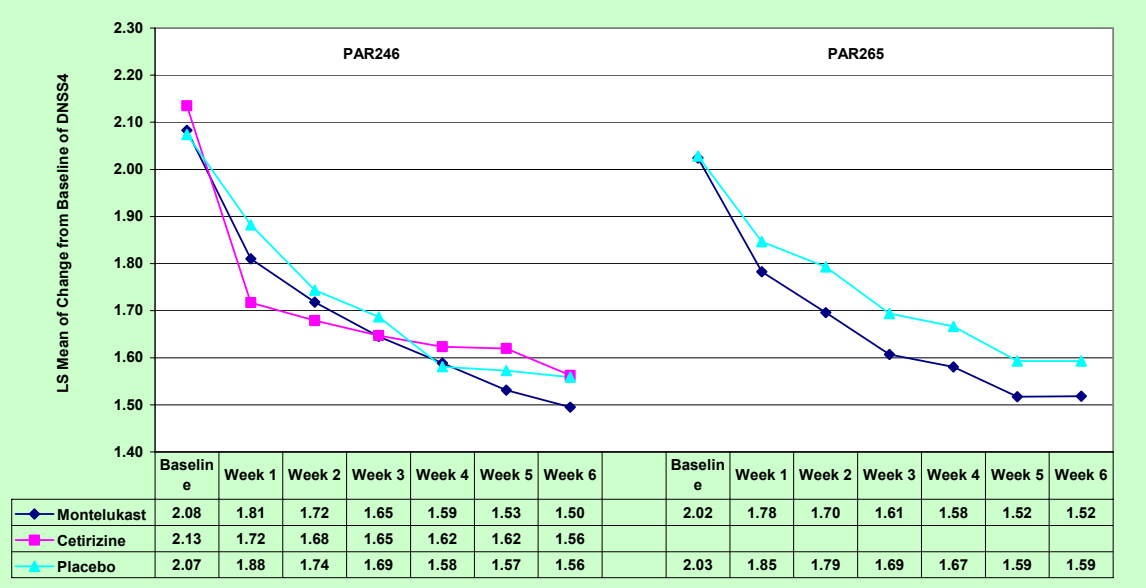
* indicate the primary endpoint for the study.

Figure 2. Percentage of Responders based on Mean Change from Baseline of DNSS4 ≤ -0.5 Averaged over of 6-Week Study – ITT Patients



The efficacy results of Montelukast over time are shown in Figure 3. The symptom improvement started at the first week. Figure 4 shows the patients who had the more severe symptoms at baseline had more improvement than the patients who had mild symptoms at baseline.

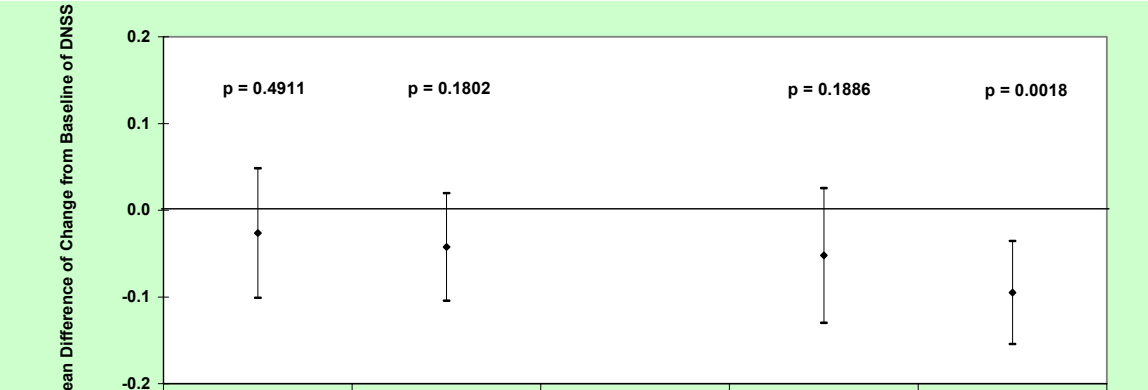
Figure 3. Change from Baseline of DNSS4 by Weeks



	PAR246								PAR265						
	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6		Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Montelukast	2.08	1.81	1.72	1.65	1.59	1.53	1.50		2.02	1.78	1.70	1.61	1.58	1.52	1.52
Cetirizine	2.13	1.72	1.68	1.65	1.62	1.62	1.56								
Placebo	2.07	1.88	1.74	1.69	1.58	1.57	1.56		2.03	1.85	1.79	1.69	1.67	1.59	1.59

Figure 4. Efficacy of Montelukast by Sub-group of Baseline Symptoms Severity

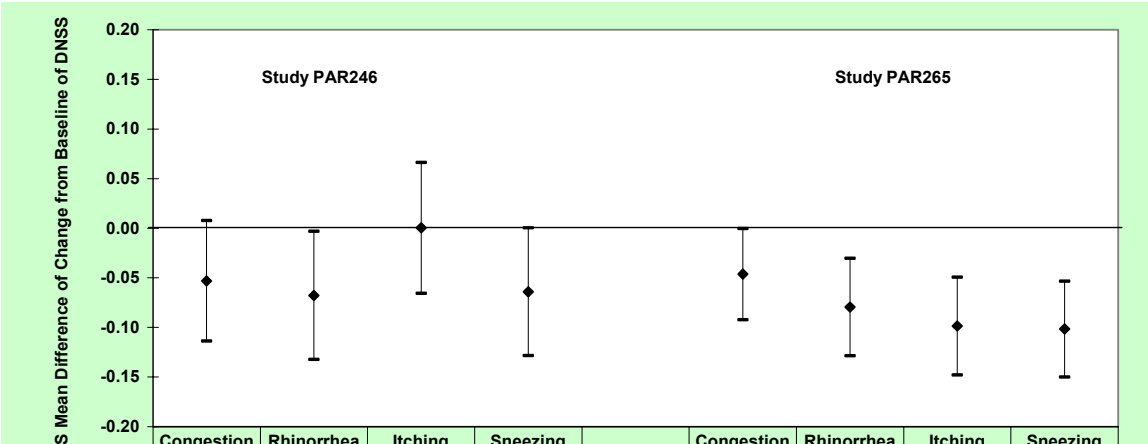
LS Mean and 95% CI (MK – PL)



	PAR246 (DNSS4 - averaged over 4-wks)	PAR265 (DNSS3 - averaged over 6-wks)		PAR246 (DNSS4- averaged over 4-wks)	PAR265 (DNSS3 - averaged over 6-wks)
– 95% CI - Lower	-0.10	-0.10		-0.13	-0.15
– 95% CI - Upper	0.05	0.02		0.03	-0.04
◆ LSMean	-0.03	-0.04		-0.05	-0.09
	Baseline DNSS <= 2			Baseline DNSS > 2	

The efficacy results of Montelukast in terms of improving the individual daytime nasal symptoms score are shown in Figure 5. In Study PAR246, Montelukast numerically improved the nasal congestion, sneezing, and rhinorrhea. No improvement in itching was observed. In the study design of PAR265, itching was not included in the primary endpoint and the study results showed that Montelukast numerically improved the four daytime nasal symptom scores and the congestion had the smallest improvement among the four daytime nasal symptoms.

Figure 5. Change from Baseline of Individual DNSS for Both Studies (MK – PL)



	Congestion (p=0.0864)	Rhinorrhea (p=0.03973)	Itching (p=0.9931)	Sneezing (p=0.0509)		Congestion (p=0.0485)	Rhinorrhea (p=0.0015)	Itching (p<0.0001)	Sneezing (p<0.0001)
– Low-95%CI	-0.11	-0.13	-0.07	-0.13		-0.09	-0.13	-0.15	-0.15
– Upper-95%CI	0.01	0.00	0.07	0.00		0.00	-0.03	-0.05	-0.05
◆ LS Mean	-0.05	-0.07	0.00	-0.06		-0.05	-0.08	-0.10	-0.10

2. INTRODUCTION

2.1 Overview

Montelukast [trade name: Singulair™], an orally active cysteinyl leukotriene type 1 ($CysLT_1$) receptor antagonist, was approved for the prophylaxis and chronic treatment of Asthma on 20 February 1998 [NDA 20-829 (2/20/1998), 10-mg film coated tablets; NDA 20-830 (2/20/1998), 5-mg chewable tablets; NDA 20-830/S-008 (3/3/2000), 4-mg chewable tablets; NDA 21-409 (7/26/2000), 4-mg oral granules]. Montelukast was also approved for the treatment of Seasonal Allergic Rhinitis (SAR) on 31 December 2002 [Supplemental Application to all of above NDAs]. The sponsor (Merck) submitted this supplement on 31 October 2004 (NDA 20-829/S33) in support of a new indication of relief of symptoms of Perennial Allergic Rhinitis (PAR) in adults and pediatric patients 6 months and older. The sponsor proposed to add the following statements to the Clinical Studies section of the Package Insert: (p9, Labeling)

(b) (4)

The sponsor's submission included two studies to demonstrate the efficacy and safety of Montelukast treatment in adults 15 years of age and older with Perennial Allergic Rhinitis (PAR). Study PAR246 and Study PAR265 were multicenter, double-blind, randomized, placebo-controlled, parallel-group studies investigating the clinical effects of Montelukast in patients with PAR. Cetirizine 10mg was included in Study PAR246 as an active group to verify the sensitivity of the study. (See Table 2 for details.)

Table 2. Clinical Trials

Study (# of centers)	***Study Population Age & Gender (N)***	***Design***	***Treatment groups (N)***	***Primary Efficacy Variable***
PAR246 74 centers in USA 6-weeks study	Age range: Male: 15 – 77 (443) Female: 15 – 82 (922)	Randomized Multicenter Double-blind Active-group parallel-group Placebo-controlled	Montelukast 10mg (630) Cetirizine 10mg (122) Placebo (613)	Mean Change from Baseline of Daytime Nasal Symptoms Score DNSS4 (average of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing) over 4-weeks
PAR265 117 centers in 12 countries included USA 6-weeks study	Age range: Male: 15 – 79 (716) Female: 15 – 81 (1276)	Randomized Multicenter Double-blind parallel-group Placebo-controlled	Montelukast 10mg (1002) Placebo (990)	Mean Change from Baseline of Daytime Nasal Symptoms Score3 (average of Nasal Congestion, Rhinorrhea, and Sneezing) over 6-weeks

Studies PAR246 and PAR265 differ in several important ways:

- PAR246 had an active-control (Cetirizine 10mg); PAR265 did not have an active control
- The primary efficacy variable for PAR246 was the average of four nasal symptoms scores - nasal congestion, rhinorrhea, nasal itching, and sneezing; The primary efficacy variable for PAR265 was the average of three nasal symptoms scores - nasal congestion, rhinorrhea, and sneezing, excluding the nasal itching which had motivated the least improvement in Study PAR246; and
- Entry criteria differed, as follows:

Table 3. Some Differences in Patients Entry Criteria in Two Primary Studies

Some Enter Criteria	***PAR246***	***PAR265***
Skin Test	1 positive skin test to 1 of the relevant perennial allergens	≥ 2 positive skin test to ≥ 2 of the relevant perennial allergens
Minimal Predefined Level of Daytime Nasal Symptoms Score (a 5-day score) in Period I	≥ 23	≥ 30
Cumulative smoking history	≤ 1 pack/day for 10 years	≤ 1 pack/day for 20 years
Weight for height and body build	40% over or under normal	50% over or under normal

2.2 Data Sources

Documents and datasets reviewed: \\N20829\S_033\clinstat\studies, \\N20829\S_033\clinstat\summary, \\N20829\S_033\labeling, and \\N20829\S_033\CRT\datasets

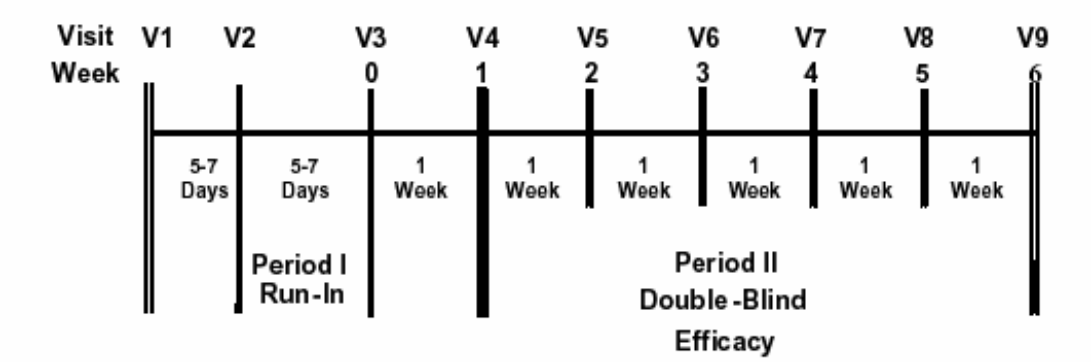
3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

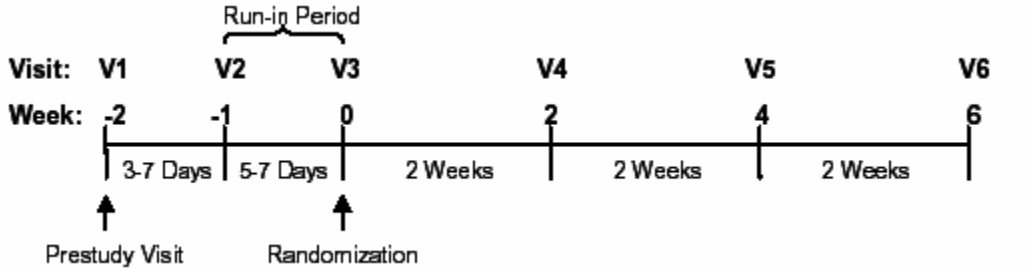
3.1.1 Design

Both PAR246 and PAR265 were phase-III, randomized, multicenter, double-blind (with in-house blinding procedures), 2-period, 6-week, placebo-controlled, parallel-group studies evaluating the ability of Montelukast to improve the symptoms of Perennial Allergic Rhinitis compared with placebo. Cetirizine 10mg was included in Study PAR246 as an active group to verify the sensitivity of the study. Period I was a 5- to 7-day, single-blind, placebo run-in period. Eligible patients were randomly allocated at the beginning of Period II (i.e. the 6-week, double-blind treatment period) to treatment groups according to a computer-generated, randomized allocation schedule. Subjects were seen every week (PAR246) or every 2 weeks (PAR265) for 6 weeks. (See the study flow charts below.)

Study PAR246 (conducted 11/27/2001 to 5/5/2002)



Study PAR265 (conducted 10/27/2003 to 5/3/2004)



The objectives of both studies were: 1. to assess the treatment effect of Montelukast 10mg versus placebo on the primary, secondary, and other exploratory endpoints, over the treatment period, which was the first 4 weeks of a 6-week in study PAR246 and a 6-week treatment period in study PAR265, in patients with perennial allergic rhinitis; and 2. to determine the tolerability profile of Montelukast 10 mg in patients with perennial allergic rhinitis.

3.1.2 Efficacy Variables

Efficacy Variables	*Study PAR246*	*Study PAR265*
Primary	Daytime Nasal Symptoms score (average of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing) (hereafter referred as **DNSS4**)	Daytime Nasal Symptoms score (average of Nasal Congestion, Rhinorrhea, and Sneezing) (hereafter referred as **DNSS3**)
Secondary	(a) Global Evaluation of Allergic Rhinitis by Patient; (b) Overall Rhino-conjunctivitis Quality-of-Life score (average of scores for Activity, Sleep, Non-Nose/Non-Eye Symptoms, Practical Problems, Nasal Symptoms, Eye Symptoms, and Emotions domains).	(a) Patient's and Physician's Global Evaluations of Allergic; (b) Rhinitis Composite Symptoms score (average of Daytime Nasal Symptoms and Nighttime Symptoms scores); (C) Nighttime Symptoms score (average of Nasal Congestion Upon Awakening, Difficulty Going to Sleep, and Nighttime Awakenings).
Others	(a) End-of-Day Nasal Symptoms score (average of scores for Congestion, Rhinorrhea, and Sneezing rated using instantaneous recall), (b) Nighttime Symptoms score (average of scores for Congestion Upon Awakening, Difficulty Going to Sleep, and Nighttime Awakenings), (c) Daily Rhinitis Symptoms score (average of Daytime Nasal Symptoms score and Nighttime Symptoms score), (d) Daytime Nasal Symptoms + Itching score (Average of scores for Congestion, Rhinorrhea, Sneezing, and Itching), (e) End-of-Day Nasal Symptoms + Itching score (Average of scores for Congestion, Rhinorrhea, Sneezing, and Itching rated using instantaneous recall), (f) Individual Daytime Nasal Symptoms scores (Congestion, Rhinorrhea, Sneezing, and Itching), (g) Individual domains of the Rhino-conjunctivitis Quality-of-Life score (Activity, Sleep, Nose/Non-Eye symptoms, Practical Problems, Nasal Symptoms, Eye Symptoms, Non- and Emotions), (h) Individual End-of-Day Nasal Symptoms scores (Congestion, Rhinorrhea, Sneezing, and Itching rated using instantaneous recall), (i) Individual Nighttime Nasal Symptoms scores (Congestion Upon Awakening, Difficulty Going to Sleep, and Nighttime Awakenings).	(a) Daytime Eye Symptoms score (average of Tearing and Itchy Eyes), (b) Individual Daytime Nasal Symptoms scores (Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing), (c) Overall and Individual Daytime Throat Symptoms scores (Mucus Dripping Down Throat/Postnasal Drip and Clearing of Throat), (d) Individual Nighttime Symptoms scores (Nasal Congestion Upon Awakening, Difficulty Going to Sleep, and Nighttime Awakenings), (e) Overall and Individual Domains of the Rhino-conjunctivitis Quality-of-Life score, (f) Perennial Allergic Rhinitis Questionnaire overall and individual scores, (g) Total Peripheral Blood Eosinophil Count; (f) End-of-Day Nasal Symptoms score (average of Nasal Congestion, Rhinorrhea, Nasal Itching, and Sneezing).

3.1.3 Patient Disposition

A total of 3357 subjects (ITT population) who met the criteria were randomly assigned to receive Montelukast 10mg or Cetirizine 10mg (Study PAR246 only), or Placebo. 22 subjects were excluded from the primary analysis because there were no baseline and no treatment period data available (this is a modified ITT approach, hereafter referred as MITT). The numbers (percents) of subjects excluded from the modified intention-to-treat efficacy analysis for the primary endpoint are presented in Table 4. The primary reason subjects discontinued treatment in both groups was due to "adverse events". Overall, the percentages of discontinuation were similar in all three treatment groups. The relative proportions of dropouts due to AEs were different in the two studies. The Montelukast treatment group had the higher rate (4.9%) in Study PAR 246 and the lower rate (3.2%) in Study PAR265 compared to Placebo (3.5%).

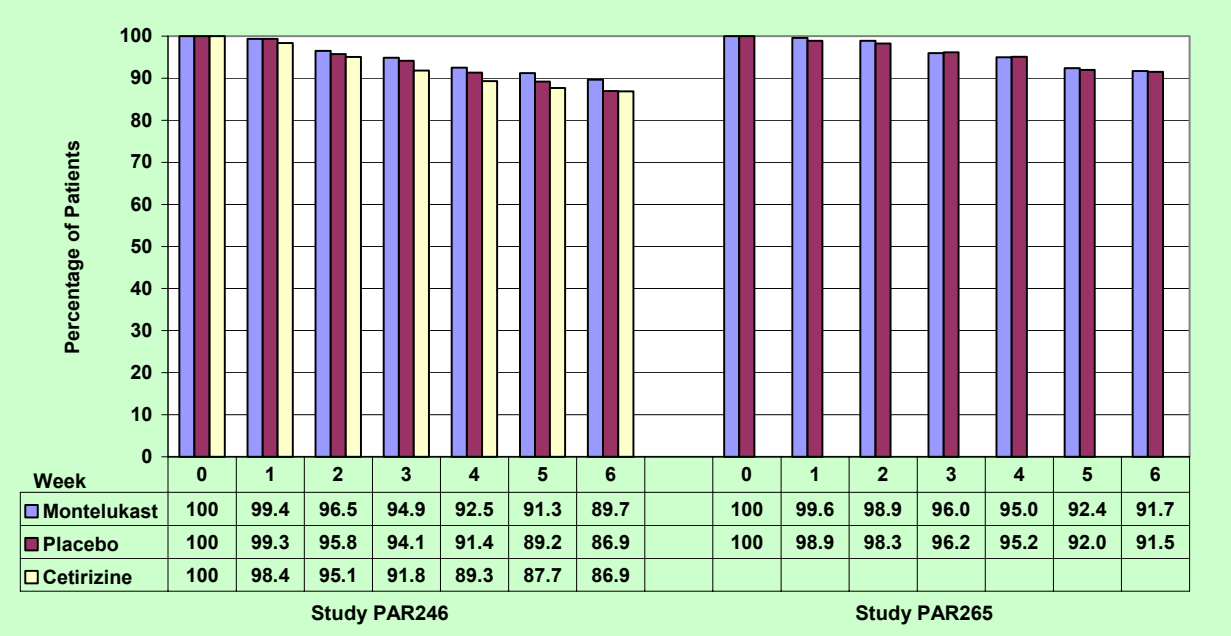
Table 4. ITT Patients' Accountability (N, %)

	PAR246 (n=1365)			***PAR265 (n=1992)***		***Total (n=3357)***
	Montelukast 10mg	***Placebo***	***Cetirizine 10mg***	***Montelukast 10mg***	***Placebo***	
Entered (**ITT**)	630 (46.2)	613 (44.9)	122 (8.9)	1002 (50.3)	990 (49.7)	3357
Completed (**PP**)	562 (89.2)	530 (86.5)	106 (86.9)	913 (91.1)	906 (91.5)	3017 (89.9)
Excluded from efficacy analysis	4	4	2	2	10	22
Modified ITT (**MITT**)	626 (99.4)	609 (99.3)	120 (98.4)	1000 (99.8)	980 (99.0)	3335 (99.3)
Discontinued	68 (10.8)	83 (13.5)	16 (13.1)	89 (8.9)	84 (8.5)	340 (10.1)
Reason of early discontinuation						
Adverse Event	31 (4.9)	27 (4.4)	4 (3.3)	32 (3.2)	35 (3.5)	129 (3.8)
Non-Compliance	13 (2.1)	18 (2.9)	4 (3.3)	25 (2.5)	23 (2.3)	83 (2.5)
Lack of Efficacy	3 (0.5)	9 (1.5)	2 (1.6)	14 (1.4)	12 (1.2)	40 (1.2)
Pt. Withdraw Consent	14 (2.2)	16 (2.6)	5 (4.1)	10 (1.0)	4 (0.4)	49 (1.5)
Pt. Withdraw for Other	5 (0.8)	11 (1.8)	0 (0)	5 (0.5)	6 (0.6)	27 (0.8)
Lost Follow-up	2 (0.3)	2 (0.3)	1 (0.8)	3 (0.3)	4 (0.4)	12 (0.4)

Data: Dispos.xpt; Code: Demog.sas

Figure 6 shows the patients disposition of treatment duration (weeks) by treatment groups for the two studies. There was no difference in treatment duration between the treatment groups.

Figure 6. Patients Disposition



Data: Diary.xpt; Code: Diary.sas; Dispos.xls

3.1.4 Demographic and Baseline Characteristics

The baseline characteristics for all randomized patients (ITT) for both studies are summarized in Table 5. The majority of the subjects were female (65.5%) and Caucasian (81.4%). There were no significant differences in baseline anthropomorphic variables between the treated group and untreated group. The average age at baseline was about 35 years (range 15 – 82) with average of 18 years AR history. The baseline DNSS3 and DNSS4 were higher in study PAR246 than in study PAR265.

Table 5. ITT Subjects' Demographics and Baseline Characteristics

	PAR246 (n=1365)			***PAR265 (n=1992)***		***Total***
	MK 10mg	***Placebo***	***Ceti. 10mg***	***MK 10mg***	***Placebo***	***(n=3357)***
Sex						
Female	419 (66.5)	418 (68.2)	85 (69.7)	644 (64.3)	632 (63.8)	2198 (65.5)
Male	211 (33.5)	195 (31.8)	37 (30.3)	358 (35.7)	358 (36.2)	1159 (34.4)
Race						
Black	55 (8.7)	60 (9.8)	11 (9.0)	84 (8.4)	78 (7.9)	288 (8.6)
Hispanic American	46 (7.3)	37 (6.0)	13 (10.7)	52 (5.2)	56 (5.7)	204 (6.1)
White	499 (79.2)	488 (79.6)	89 (73.0)	839 (83.7)	818 (82.6)	2733 (81.4)
Others[1]	30 (4.8)	28 (4.6)	9 (7.4)	27 (2.7)	38 (3.8)	132 (3.9)
Age						
15 – 17	54 (8.6)	47 (7.7)	4 (3.3)	60 (6.0)	46 (4.7)	211 (6.3)
18 – 64	569 (90.3)	553 (90.2)	113 (92.6)	912 (91.0)	921 (93.0)	3068 (91.4)
Over 64	7 (1.1)	13 (2.1)	5 (4.1)	30 (3.0)	23 (2.3)	78 (2.3)
Mean (SD)	35.3 (12.9)	36.3 (13.2)	35.3 (13.7)	36.3 (13.6)	36.6 (13.1)	
Median	34	34	34	34	36	
Range	15 – 76	15 – 82	15 – 75	15 – 81	15 – 79	
Duration of AR (yr)						
Mean (SD)	18.0 (12.3)	17.7 (12.6)	18.4 (12.9)	18.0 (12.1)	18.6 (12.3)	
Median	15	14	16	15	16	
Range	0 – 63	0 – 66	2 – 56	0 – 66	1 – 60	
History of AC						
	538 (85.5)	515 (84.2)	99 (81.1)	831 (82.9)	835 (84.3)	2818 (83.9)
Age at first treated for AR						
< 15	277 (44.0)	279 (45.5)	55 (45.1)	439 (43.8)	426 (43.0)	
15 – 29	244 (38.7)	207 (33.8)	44 (36.1)	369 (36.8)	375 (37.9)	
30 – 44	85 (13.5)	106 (17.3)	16 (13.1)	153 (15.3)	138 (13.9)	
> 44	22 (3.5)	20 (3.3)	6 (4.9)	39 (3.9)	44 (4.5)	
Missing	2 (0.3)	1 (0.1)	1 (0.8)	2 (0.2)	7 (0.7)	
History of Asthma						
	148 (23.5)	152 (24.7)	32 (26.2)	274 (27.3)	288 (29.1)	894 (26.6)
Daytime Nasal Symptoms Score DNSS4 (Scale 0 to 3)						
Mean (SD)	2.08 (0.40)	2.07 (0.40)	2.13 (0.37)	2.02 (0.44)	2.03 (0.46)	
Median	2.05	2.04	2.11	2.0	2.0	
Range	1.4 – 3.0	1.0 – 3.0	1.5 – 3.0	1.0 – 3.0	0.6 – 3.0	
Daytime Nasal Symptoms Score DNSS3 (Scale 0 to 3)						
Mean (SD)	2.13 (0.40)	2.12 (0.39)	2.19 (0.40)	2.09 (0.40)	2.10 (0.41)	
Median	2.11	2.08	2.17	2.07	2.07	
Range	1.2 – 3.0	0.9 – 3.0	1.3 – 3.0	1.1 – 3.0	0.6 – 3.0	
Nighttime Symptoms Score (Scale 0 to 3)						
Mean (SD)	1.63 (0.62)	1.58 (0.62)	1.65 (0.61)	1.56 (0.60)	1.59 (0.62)	
Median	1.62	1.53	1.59	1.57	1.61	
Range	0.0 – 3.0	0.2 – 3.0	0.5 – 3.0	0.0 – 3.0	0.2 – 3.0	

1: Other includes African, Asian, Asiatic, European, Indian, Multiracial, Native American, and Polynesian.
Data: Demog.xpt; Code: Demog.sas

3.1.5 Statistical Methodologies

Primary Endpoint:
In PAR246, the primary endpoint was the mean change from baseline of Daytime Nasal Symptoms score (i.e. the average of scores for Congestion, Rhinorrhea, Nasal itching, and Sneezing), derived from the patient's diaries, over the 4-weeks treatment period.

In PAR265, the primary endpoint was the mean change from baseline of Daytime Nasal Symptoms score (i.e. the average of scores for Congestion, Rhinorrhea, and Sneezing), derived from the patient's diaries, over the 6-weeks treatment period.

Baseline Comparability among the Treatment Groups
Baseline comparability among the treatment groups was evaluated by summarizing the following parameters. No formal statistical tests were performed.

Demographics:	Age, gender, race, disease history (allergic rhinitis [seasonal and perennial], allergic conjunctivitis), weight, and height.
Endpoints:	Primary and secondary endpoints.

Multiplicity With Respect to Efficacy Variables:
The primary variable was the average change from baseline in Daytime Nasal Symptoms score. Secondary efficacy variables (Global Evaluation of Allergic Rhinitis by Patient and Overall Rhino-conjunctivitis Quality-of-Life score) were used primarily to describe the efficacy profile of Montelukast and to assess the secondary hypotheses.

The secondary hypotheses were assessed in a sequential manner:

- The Global Evaluation of Allergic Rhinitis by Patient was tested first;
- If a significant difference is observed, the Overall Rhino-conjunctivitis Quality-of-Life score was assessed.

The sponsor claimed that with this sequential procedure, no adjustment of the α-level of the individual tests was needed. Each test was run at 5% α -level. Other exploratory efficacy variables were also used to describe the efficacy profile of Montelukast and no multiplicity adjustment was made for these analyses.

Sample Size and Power
In PAR246, for the primary comparison of Daytime Nasal Symptoms score (DNSS4) over 4 weeks, a sample size of 500 patients each in the Montelukast and Placebo groups had 88% power to detect a treatment difference of 0.10 between the 2 treatment groups (SD=0.51). A sample size of 100 patients in the Cetirizine group and 500 in the placebo group had 89% power to detect a treatment difference of 0.18 between the 2 groups after 4 weeks of treatment (SD=0.51).
In PAR265, for the primary comparison of Daytime Nasal Symptoms score (DNSS3) over 6 weeks, a sample size of 800 patients each in the Montelukast and Placebo groups had 90% power to detect a treatment difference of 0.075 between the 2 treatment groups (SD=0.46).

Interim Analyses
No interim analysis was performed.

3.1.6 Sponsor's Results and Conclusions

The sponsor concluded as (p19, summary.pdf)

"*In the pivotal PAR study, montelukast 10 mg administered once daily over a 6-week treatment period, compared with placebo, demonstrates: 1. Improvement in the primary endpoint, Daytime Nasal Symptoms score (average of scores for Congestion, Rhinorrhea, and Sneezing). 2. Patient-perceived improvement of allergic rhinitis as assessed by the secondary endpoints of Global Evaluation of Allergic Rhinitis by Patient and Rhino-conjunctivitis Quality-of-Life Questionnaire overall score. 3. Persistence of treatment effect through the entire 6-week treatment period.*"

Table 6. Sponsor's Primary Efficacy Analyses Results over a 6-week Treatment Period

Study	***N***		***Mean Baseline (Score)***		***Change from Baseline (Score) (Mean ± SD)***		***Difference in LS Means (95% CI)***
	MK	***PL***	***MK***	***PL***	***MK***	***PL***	***MK - PL***
Daytime Nasal Symptoms Score DNSS3 (Scale 0 to 3)							
PAR246	626	609	2.13	2.12	-0.46 (0.54)	-0.39 (0.49)	-0.06 (-0.12, -0.01) *p=0.024*
PAR265	1000	980	2.09	2.10	-0.42 (0.51)	-0.35 (0.48)	-0.08 (-0.12, -0.04) *p ≤ 0.001*
Daytime Nasal Symptoms Score DNSS4 (Scale 0 to 3)							
PAR246	626	609	2.08	2.07	-0.45 (0.53)	-0.40 (0.48)	-0.05 (-0.10, 0.01) *p = 0.086*
PAR265	1000	980	2.02	2.03	-0.41 (0.50)	-0.33 (0.47)	-0.08 (-0.12, -0.04) *p ≤ 0.001*
Nighttime Nasal Symptoms Score (Scale 0 to 3)							
PAR246	626	609	1.63	1.58	-0.33 (0.47)	-0.29 (0.44)	-0.03 (-0.07, 0.02) *p = 0.247*
PAR265	1000	983	1.56	1.59	-0.30 (0.48)	-0.25 (0.47)	-0.06 (-0.10, -0.02) *p ≤ 0.001*
End-of-Day Nasal Symptoms Score EDNSS3 (Scale 0 to 3)							
PAR246	626	609	1.87	1.84	-0.39 (0.56)	-0.31 (0.51)	-0.07 (-0.12, -0.01) *p = 0.015*
PAR265	1000	980	1.83	1.85	-0.35 (0.53)	-0.30 (0.50)	-0.06 (-0.10, -0.02) *p = 0.007*
End-of-Day nasal Symptoms Score EDNSS4 (Scale 0 to 3)							
PAR246	626	609	1.84	1.81	-0.39 (0.55)	-0.32 (0.50)	-0.06 (-0.11, -0.00) *p = 0.041*
PAR265	1000	980	1.78	1.80	-0.35 (0.52)	-0.30 (0.49)	-0.06 (-0.10, -0.02) *p = 0.004*
Patient's Global Evaluation of Allergic Rhinitis							
PAR246	626	609	.	.	.	.	-0.07 (-0.21, 0.06) *p = 0.289*
PAR265	977	969	.	.	.	.	-0.15 (-0.27, -0.04) *p = 0.007*
Rhino-conjunctivitis Quality-of-Life Questionnaire Overall Score							
PAR246	617	6060	3.16	3.12	-1.02 (1.16)	-0.88 (1.15)	-0.13 (-0.25, -0.01) *p = 0.031*
PAR265	977	969	2.94	2.97	-0.81 (1.14)	-0.68 (1.14)	-0.15 (-0.24, -0.06) *p ≤ 0.001*

3.1.7 Reviewer's Efficacy Analysis

Primary Efficacy Endpoints –
Table 7 shows the statistical results of primary efficacy variables at the end of study. In Study PAR246, Montelukast 10mg was numerically superior to Placebo, but the difference did not reach the statistical significance; Cetirizine 10mg was statistically significantly better than Placebo. The difference between Montelukast and Placebo was smaller than the difference between Cetirizine and Montelukast in DNSS4 averaged over 4-weeks. In Study PAR265, Montelukast 10mg had better effect than placebo and this result was statistically significant.

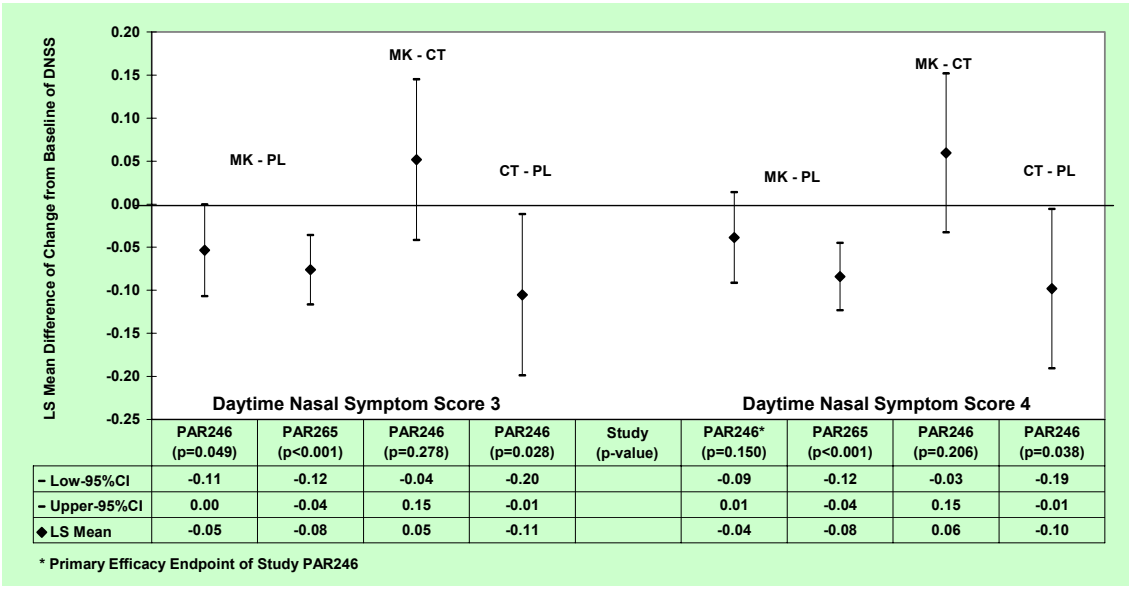
Table 7. The Comparison between the Treatment Groups for Primary Efficacy Endpoint

Weeks	Treatment/ Treatment Contrast	N	LS Mean[1] (SE)	95% CI	p-Value	LS Mean (SE)	95% CI	p-Value
STUDY PAR246			**DNSS3[2]**			**DNSS4[3]**		
Baseline	Montelukast	630	2.139 (0.02)	-	-	2.086 (0.02)	-	-
	Cetirizine	122	2.187 (0.04)	-	-	2.132 (0.03)	-	-
	Placebo	613	2.125 (0.02)	-	-	2.080 (0.02)	-	-
	MK – PL	-	0.014 (0.02)	(-0.029, 0.057)	0.5333	0.006 (0.02)	(-0.036, 0.049)	0.7742
	MK – CT	-	-0.048 (0.04)	(-0.123, 0.027)	0.2126	-0.046 (0.04)	(-0.120, 0.028)	0.2246
	CT – PL	-	0.061 (0.04)	(-0.014, 0.137)	0.1102	0.052 (0.04)	(-0.022, 0.127)	0.1694
			Change from Baseline					
4-Weeks	Montelukast	626	-0.398 (0.02)	-	-	-0.394 (0.02)	-	-
	Cetririzine	120	-0.450 (0.04)	-	-	-0.453 (0.04)	-	-
	Placebo	609	-0.344 (0.02)	-	-	-0.356 (0.02)	-	-
	MK – PL	-	-0.054 (0.03)	(-0.107, -0.000)	0.0486	**-0.039 (0.03)**	**(-0.091, 0.014)**	**0.1501**
	MK – CT	-	0.052 (0.05)	(-0.042, 0.145)	0.2776	0.059 (0.05)	(-0.033, 0.152)	0.2064
	CT – PL	-	-0.105 (0.05)	(-0.199, -0.012)	0.0276	-0.098 (0.05)	(-0.191, 0.005)	0.0378
6-Weeks	Montelukast	626	-0.460 (0.02)	-	-	-0.456 (0.02)	-	-
	Cetririzine	120	-0.482 (0.04)	-	-	-0.481 (0.04)	-	-
	Placebo	609	-0.397 (0.02)	-	-	-0.409 (0.02)	-	-
	MK – PL	-	-0.063 (0.03)	(-0.116, -0.008)	0.0239	-0.047 (0.03)	(-0.101, 0.006)	0.0860
	MK – CT	-	0.022 (0.05)	(-0.074, 0.118)	0.6496	0.025 (0.05)	(-0.069, 0.120)	0.5983
	CT – PL	-	-0.085 (0.05)	(-0.181, 0.011)	0.0823	-0.073 (0.05)	(-0.168, 0.022)	0.1332
STUDY PAR265			**DNSS3**			**DNSS4**		
Baseline	Montelukast	1002	2.062 (0.014)	-	-	1.986 (0.015)	-	-
	Placebo	990	2.070 (0.014)	-	-	1.986 (0.015)	-	-
	MK – PL	-	-0.008 (0.017)	(-0.042, 0.026)	0.6418	-0.000 (0.019)	(-0.037, 0.037)	0.9949
			Change from Baseline					
4-Weeks	Montelukast	1000	-0.400 (0.02)	-	-	-0.390 (0.02)	-	-
	Placebo	980	-0.323 (0.02)	-	-	-0.306 (0.02)	-	-
	MK – PL	-	-0.076 (0.02)	(-0.116, -0.036)	0.0002	-0.084 (0.02)	(-0.123, -0.049)	<.0001
6-Weeks	Montelukast	1000	-0.448 (0.02)	-	-	-0.438 (0.02)	-	-
	Placebo	980	-0.373 (0.02)	-	-	-0.357 (0.02)	-	-
	MK – PL	-	**-0.076 (0.02)**	**(-0.117, -0.035)**	**0.0003**	-0.082 (0.02)	(-0.122, -0.041)	<.0001

[1] Analysis of Covariance Model with Center, Baseline, and Treatment as fix-effect
[2] Primary Efficacy Endpoint for Study PAR265 Average over 6-Weeks of Treatment Periods
[3] Primary Efficacy Endpoint for Study PAR246 Average over 4-Weeks of Treatment Periods

Figure 7 and Figure 8 display the LS mean and 95% confidence intervals of pairwise comparisons of three treatment groups in Study PAR246 and two treatment groups in Study PAR265. For the primary efficacy endpoint, only Study PAR265 showed that Montelukast was statistically significantly better than Placebo. Study PAR246 only numerically showed the benefit of Montelukast. Out of 8 efficacy measurements, Montelukast was statistically significantly better than Placebo in 6 measurements.

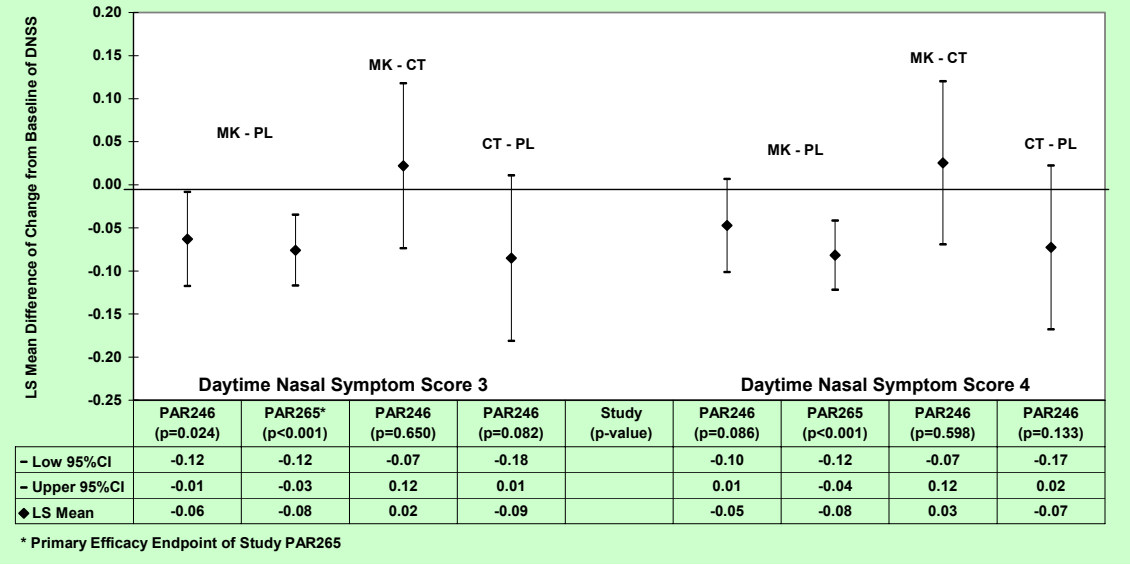
Figure 7. LS Mean and 95% CI Comparison for Mean Change from Baseline of DNSS Averaged over 4-week



	PAR246 (p=0.049)	PAR265 (p<0.001)	PAR246 (p=0.278)	PAR246 (p=0.028)	Study (p-value)	PAR246* (p=0.150)	PAR265 (p<0.001)	PAR246 (p=0.206)	PAR246 (p=0.038)
– Low-95%CI	-0.11	-0.12	-0.04	-0.20		-0.09	-0.12	-0.03	-0.19
– Upper-95%CI	0.00	-0.04	0.15	-0.01		0.01	-0.04	0.15	-0.01
◆LS Mean	-0.05	-0.08	0.05	-0.11		-0.04	-0.08	0.06	-0.10

* Primary Efficacy Endpoint of Study PAR246

Figure 8. LS Mean and 95% CI Comparison for Mean Change from Baseline of DNSS Averaged over 6-week



	PAR246 (p=0.024)	PAR265* (p<0.001)	PAR246 (p=0.650)	PAR246 (p=0.082)	Study (p-value)	PAR246 (p=0.086)	PAR265 (p<0.001)	PAR246 (p=0.598)	PAR246 (p=0.133)
– Low 95%CI	-0.12	-0.12	-0.07	-0.18		-0.10	-0.12	-0.07	-0.17
– Upper 95%CI	-0.01	-0.03	0.12	0.01		0.01	-0.04	0.12	0.02
◆LS Mean	-0.06	-0.08	0.02	-0.09		-0.05	-0.08	0.03	-0.07

* Primary Efficacy Endpoint of Study PAR265

Individual Daytime Nasal Symptoms Scores –

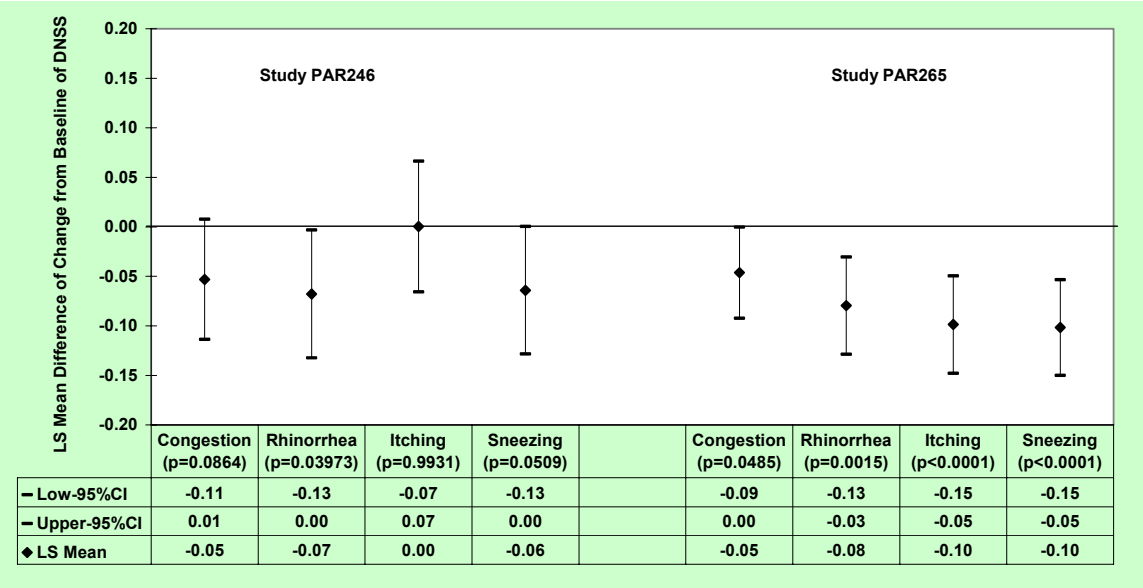
Table 8 and Figure 9 display the pairwise comparisons of individual daytime nasal symptoms scores between the treatment groups. Montelukast numerically improved the nasal congestion, sneezing, and rhinorrhea compared to Placebo in Study PAR246; the nasal itching had no improvement and was excluded in the primary efficacy endpoint for Study PAR265. In Study PAR265, the nasal congestion had the smallest improvement among the four daytime nasal symptoms.

Table 8. Individual DNSS Analyses Results over a 6-week Treatment Period

Study	***Montelukast 10mg vs. Placebo***		***Cetirizine 10mg Vs. Placebo***		***Montelukast 10mg Vs. Cetirizine 10mg***	
	LS Mean Diff.	**95% CI**	**LS Mean Diff.**	**95% CI**	**LS Mean Diff.**	**95% CI**
Nasal Congestion						
PAR246	-0.0531	(-0.1137, 0.0076)	-0.0666	(-0.1733, 0.0401)	0.0135	(-0.0928, 0.1199)
PAR265	-0.0463*	(-0.0923, -0.0003)				
Rhinorrhea						
PAR246	-0.0677*	(-0.1323, -0.0032)	-0.0580	(-0.1714, 0.0054)	-0.0098	(-0.1229, 0.1034)
PAR265	-0.0795**	(-0.1286, -0.0305)				
Sneezing						
PAR246	-0.0641	(-0.1284, 0.0002)	-0.1211*	(-0.2342, -0.0080)	0.0570	(-0.0057, 0.1697)
PAR265	-0.1016**	(-0.1499, -0.0534)				
Nasal Itching						
PAR246	0.0003	(-0.0657, 0.0663)	-0.0274	(-0.1431, 0.0888)	0.0274	(-0.882, 0.1431)
PAR265	-0.0986**	(-0.1478, -0.0494)				

* indicates the significant at α=0.05
** indicates the significant at α=0.0125.

Figure 9. LS Mean Difference (MK – PL) of Individual of Daytime Nasal Symptoms Score

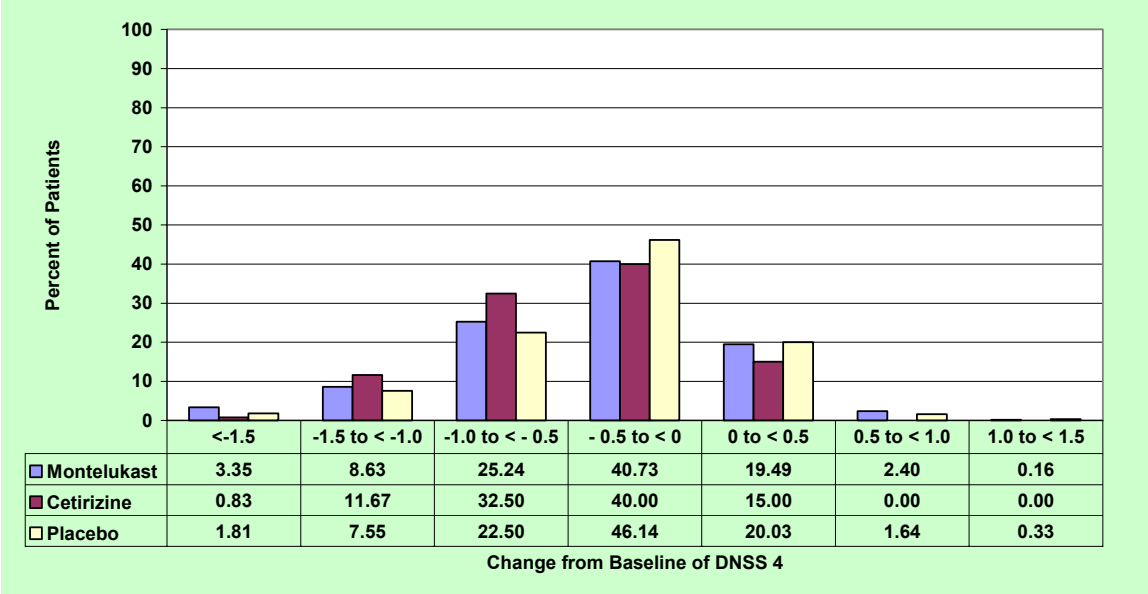


	Congestion (p=0.0864)	Rhinorrhea (p=0.03973)	Itching (p=0.9931)	Sneezing (p=0.0509)		Congestion (p=0.0485)	Rhinorrhea (p=0.0015)	Itching (p<0.0001)	Sneezing (p<0.0001)
– Low-95%CI	-0.11	-0.13	-0.07	-0.13		-0.09	-0.13	-0.15	-0.15
– Upper-95%CI	0.01	0.00	0.07	0.00		0.00	-0.03	-0.05	-0.05
◆ LS Mean	-0.05	-0.07	0.00	-0.06		-0.05	-0.08	-0.10	-0.10

Responder Analysis –

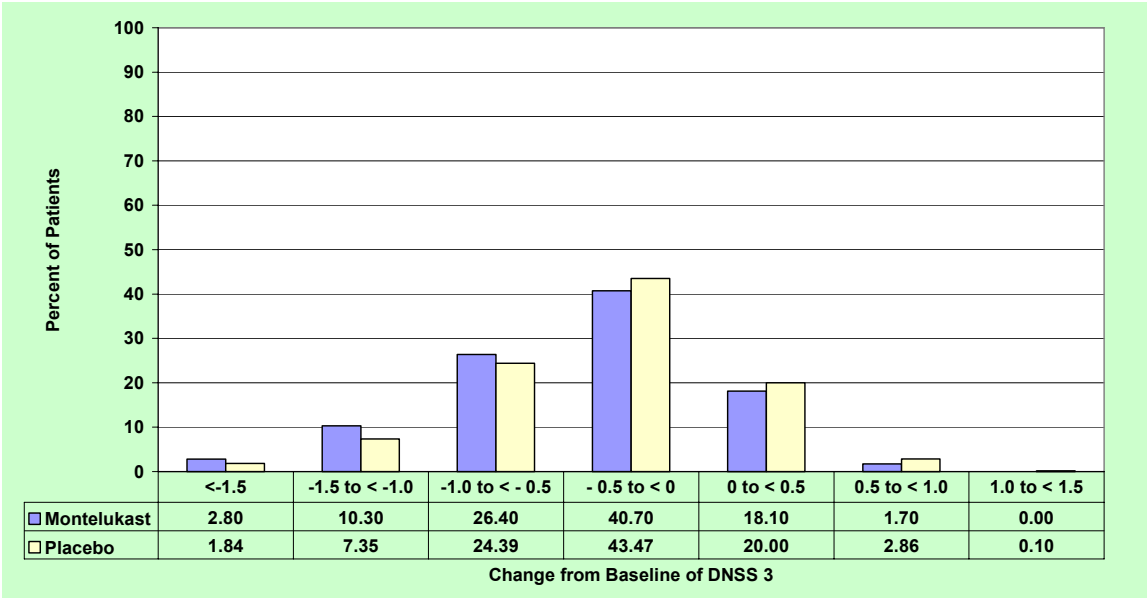
Figure 10 and Figure 11 show that less than 40% of patients improved the 0.5 or more point of Daytime Nasal Symptoms Score (measured in 0 – 3) after 4 or 6 weeks of treatment with Montelukast.

Figure 10. Percentage of Patients in Change from Baseline of DNSS 4 over 4-week, PAR246



	<-1.5	-1.5 to < -1.0	-1.0 to < - 0.5	- 0.5 to < 0	0 to < 0.5	0.5 to < 1.0	1.0 to < 1.5
Montelukast	3.35	8.63	25.24	40.73	19.49	2.40	0.16
Cetirizine	0.83	11.67	32.50	40.00	15.00	0.00	0.00
Placebo	1.81	7.55	22.50	46.14	20.03	1.64	0.33

Figure 11. Percentage of Patients in Change from Baseline of DNSS3 over 6-week, PAR265

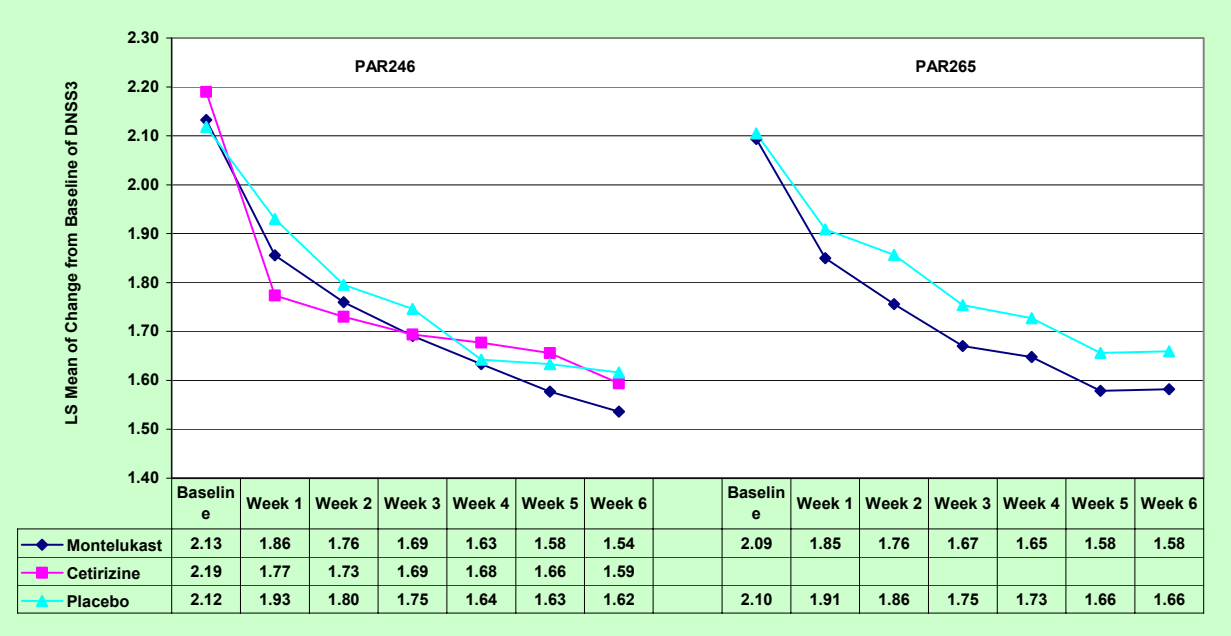


	<-1.5	-1.5 to < -1.0	-1.0 to < - 0.5	- 0.5 to < 0	0 to < 0.5	0.5 to < 1.0	1.0 to < 1.5
Montelukast	2.80	10.30	26.40	40.70	18.10	1.70	0.00
Placebo	1.84	7.35	24.39	43.47	20.00	2.86	0.10

Assessment of Treatment Effect over Time –

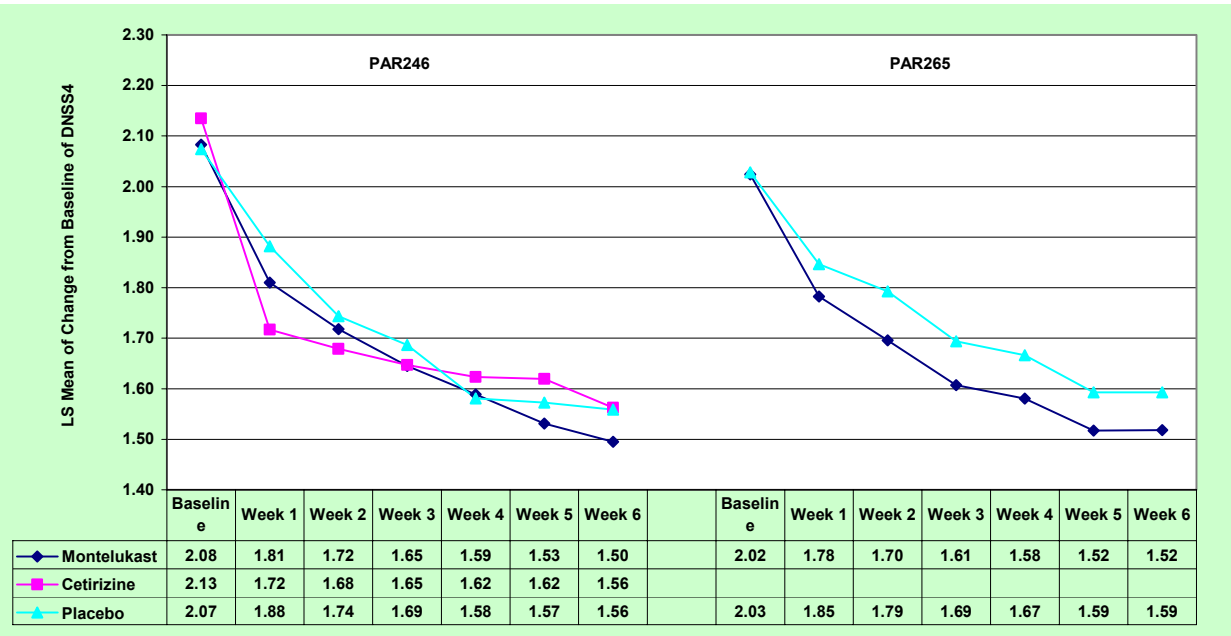
Figure 12 and Figure 13 show that the improvement started at the first week and through the entire 6-week treatment period, with effect size as small as 0.05.

Figure 12. Change from Baseline of DNSS3 by Weeks



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6		Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Montelukast	2.13	1.86	1.76	1.69	1.63	1.58	1.54		2.09	1.85	1.76	1.67	1.65	1.58	1.58
Cetirizine	2.19	1.77	1.73	1.69	1.68	1.66	1.59								
Placebo	2.12	1.93	1.80	1.75	1.64	1.63	1.62		2.10	1.91	1.86	1.75	1.73	1.66	1.66

Figure 13. Change from Baseline of DNSS4 by Weeks



	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6		Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Montelukast	2.08	1.81	1.72	1.65	1.59	1.53	1.50		2.02	1.78	1.70	1.61	1.58	1.52	1.52
Cetirizine	2.13	1.72	1.68	1.65	1.62	1.62	1.56								
Placebo	2.07	1.88	1.74	1.69	1.58	1.57	1.56		2.03	1.85	1.79	1.69	1.67	1.59	1.59

Assessment of Baseline Effect –

Figure 14 and Figure 15 display the scatter plot of each patient's primary endpoint, which correlated with baseline severity of the daytime nasal symptoms.

Figure 14. Analysis of Baseline Effect of DNSS4 at 4-week for Study PAR246

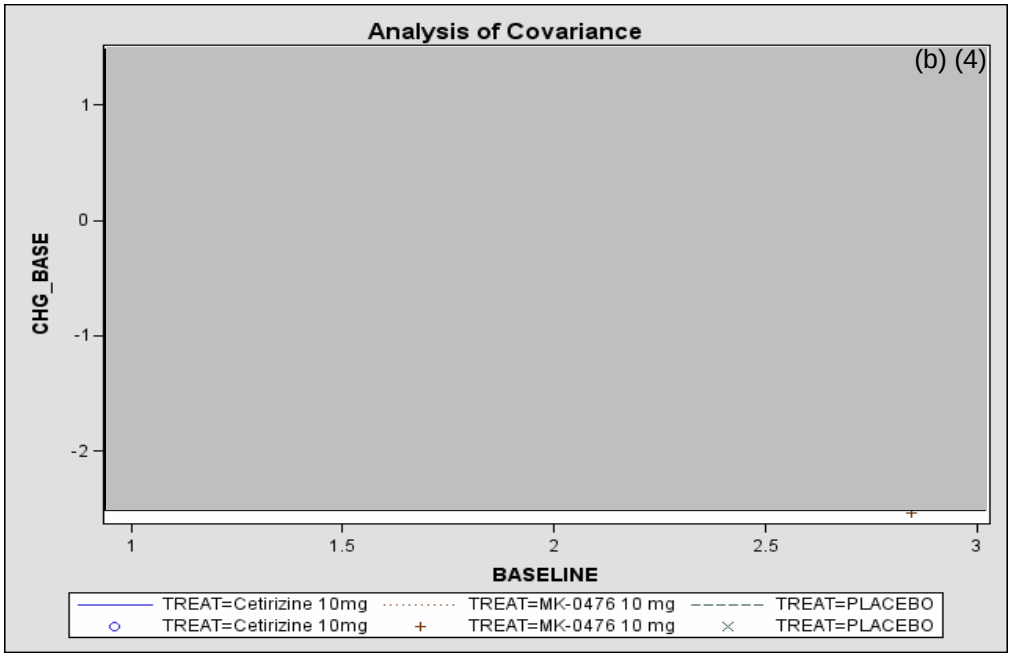


Figure 15. Analysis of Baseline Effect of DNSS3 at 6-week for Study PAR265

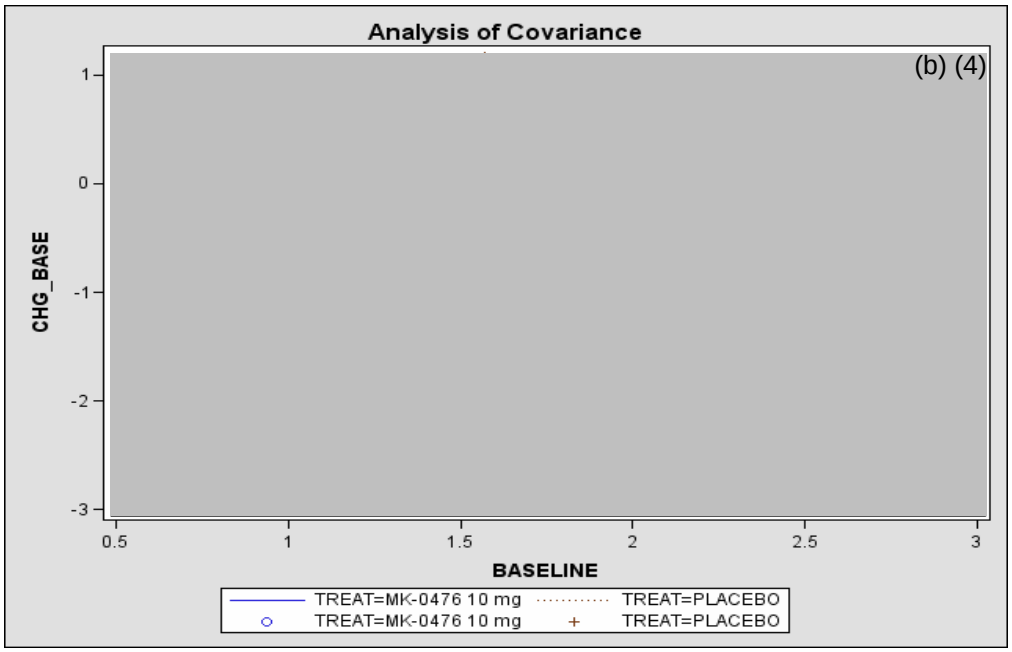
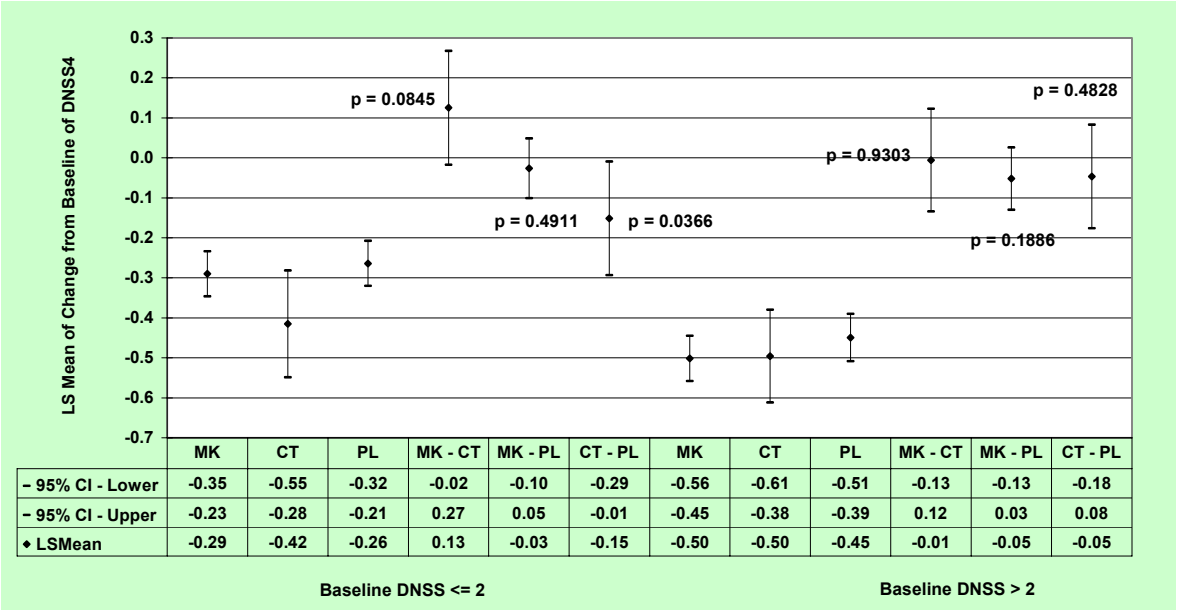


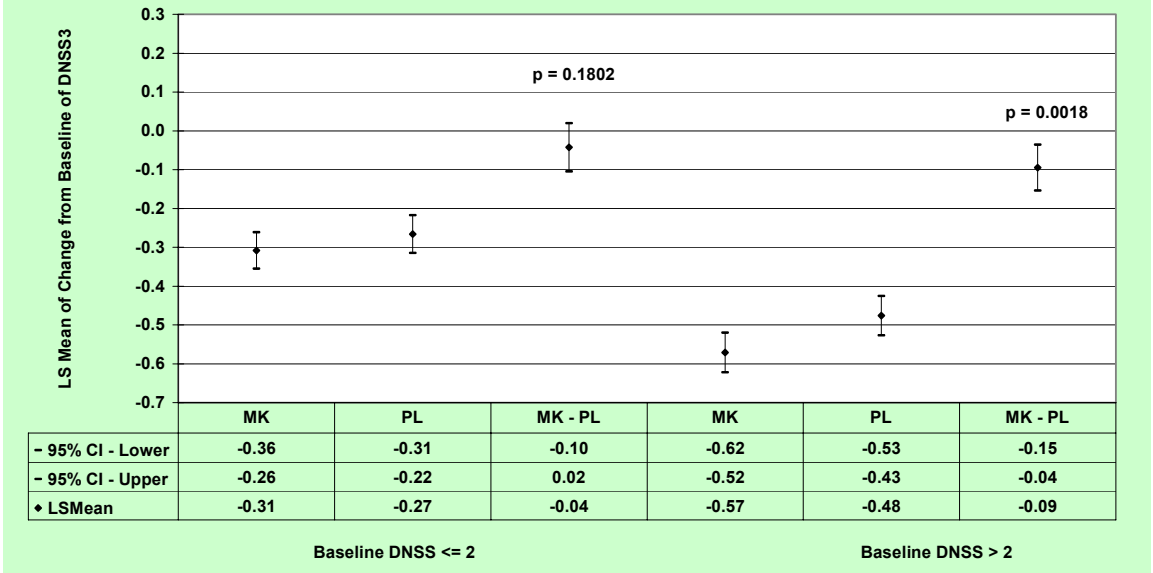
Figure 16 and Figure 17 demonstrate that the patients who had the more severe symptoms at baseline had more improvement than the patients who had mild symptoms at baseline.

Figure 16. Change from Baseline of DNSS4 over 4-week Study Period by Baseline Symptoms Severity for Study PAR246



	MK	CT	PL	MK - CT	MK - PL	CT - PL	MK	CT	PL	MK - CT	MK - PL	CT - PL
– 95% CI - Lower	-0.35	-0.55	-0.32	-0.02	-0.10	-0.29	-0.56	-0.61	-0.51	-0.13	-0.13	-0.18
– 95% CI - Upper	-0.23	-0.28	-0.21	0.27	0.05	-0.01	-0.45	-0.38	-0.39	0.12	0.03	0.08
◆ LSMean	-0.29	-0.42	-0.26	0.13	-0.03	-0.15	-0.50	-0.50	-0.45	-0.01	-0.05	-0.05
	Baseline DNSS <= 2						Baseline DNSS > 2					

Figure 17. Change from Baseline of DNSS3 over 6-week Study Period by Baseline Symptoms Severity for Study PAR265



	MK	PL	MK - PL	MK	PL	MK - PL
– 95% CI - Lower	-0.36	-0.31	-0.10	-0.62	-0.53	-0.15
– 95% CI - Upper	-0.26	-0.22	0.02	-0.52	-0.43	-0.04
◆ LSMean	-0.31	-0.27	-0.04	-0.57	-0.48	-0.09
	Baseline DNSS <= 2			Baseline DNSS > 2		

Reviewer's Conclusion

Based on the efficacy evaluation of studies PAR246 and PAR265, each of which were a phase-III, randomized, multicenter, double-blind, parallel-group, and placebo-control trial, only one study (PAR265) demonstrated that subjects treated with Montelukast 10mg once daily in the evening over a 6-week treatment period, compared with the Placebo, improved the primary endpoint, Daytime Nasal Symptoms score (i.e. average of scores for Congestion, Rhinorrhea, and Sneezing). The change in the primary efficacy variable in the Montelukast 10mg treatment group was numerically (but not statistically significantly) superior to Placebo group and worse than the Cetirizine treatment group in Study PAR246. In an exploratory evaluation, out of 3357 patients 15 to 82 years of age with a history of PAR, and daytime nasal symptoms score ≥ 1.5 at study entry, 41% of the 1626 patients, who received Montelukast 10mg treatment, reduced daytime nasal symptoms by 0.5 on average over the 6-week treatment period. The patients who had severe symptom at baseline appeared to improve more over the 6-week treatment period, compared with the patients who had mild symptoms at baseline.

3.2 Evaluation of Safety

Details of the safety review can be found in the medical review and evaluation. This review includes selected safety data for comparison with the proposed label. In the proposed label, the sponsor stated as following:

> *'Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis*
> *SINGULAIR has been evaluated for safety in (b) adult and adolescent patients 15 years of age and older with perennial allergic rhinitis in two, 6-week, clinical studies. SINGULAIR administered once daily was generally well tolerated, with a safety profile consistent with that observed in patients with seasonal allergic rhinitis and similar to that of placebo. In these two studies, the following events were reported with SINGULAIR with a frequency ≥1% and at an incidence greater than placebo, regardless of causality assessment: sinusitis, upper respiratory infection, sinus headache, cough, epistaxis, and increased ALT. The incidence of somnolence was similar to that of placebo.'*

Table 9 displays those adverse events with an incidence rate greater than 1% and the following figures show the Kaplan-Meier curve of those events.

Table 9. Number (%) of Patients with Adverse Experiences (Incidence Rate ≥ 1 % in Treatment Groups or Some Other Adverse Events)

Adverse Event	Montelukast 10mg N=1632 (%)	Placebo N=1603 (%)	Hazard Ratio	95% Confidence Interval	p-value
Nasopharyngitis	47/1632 (2.88)	51/1603 (3.18)	0.90	(0.603,1.333)	0.5897
Pharyngolaryngeal Pain	31/1632 (1.90)	30/1603 (1.87)	1.00	(0.608,1.660)	0.9847
Sinusitis	26/1632 (1.59)	21/1603 (1.31)	1.21	(0.679,2.146)	0.5206
Upper Respiratory Tract Infection	63/1632 (3.86)	45/1603 (2.81)	1.36	(0.930,1.999)	0.1119
Headache	62/1632 (3.80)	74/1603 (4.62)	0.81	(0.581,1.140)	0.2311
Sinus headache	18/1632 (1.10)	13/1603 (0.81)	1.35	(0.663,2.763)	0.4050
Nausea	19/1632 (1.16)	22/1603 (1.37)	0.84	(0.456,1.558)	0.5856
Cough	20/1632 (1.23)	12/1603 (0.75)	1.63	(0.795,3.328)	0.1827
Epistaxis	19/1632 (1.16)	17/1603 (1.06)	1.09	(0.566,2.093)	0.8004
Somnolence	5/1632 (0.31)	6/1603 (0.37)	0.82	(0.249,2.678)	0.7392
Dry Mouth	14/1632 (0.86)	2/1603 (0.12)	6.86	(1.559,30.18)	0.0109
Back Pain	15/1632 (0.92)	9/1603 (0.56)	1.63	(0.712,3.718)	0.2483
Pharyngitis	10/1632 (0.61)	6/1603 (0.37)	1.62	(0.589,4.461)	0.3494
ALT increased*	8/630 (1.27)	2/613 (0.33)	3.79	(0.805,17.86)	0.0918
AST increased*	5/630 (0.79)	2/613 (0.33)	2.41	(0.467,12.40)	0.2940

*: Study PAR246 only. Study PAR265 did not collected LFT data for all patients.

Figure 18. Kaplan-Meier Curve of Time to Adverse Event - Headache

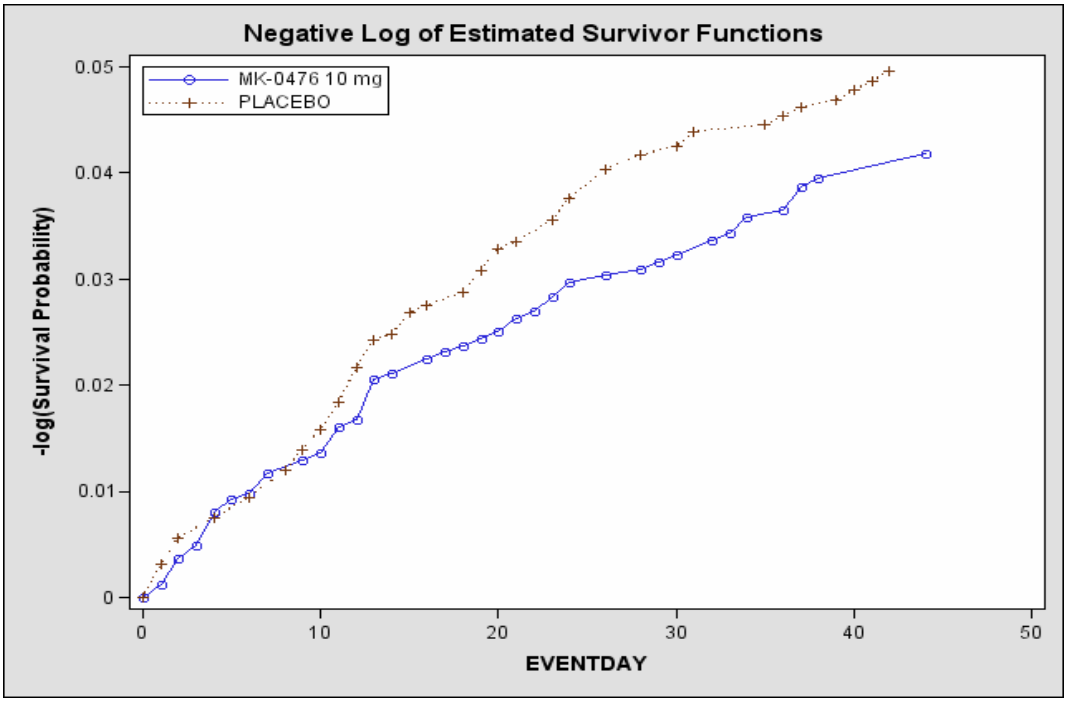


Figure 19. Kaplan-Meier Curve of Time to Adverse Event – Upper Respiratory Tract Infection

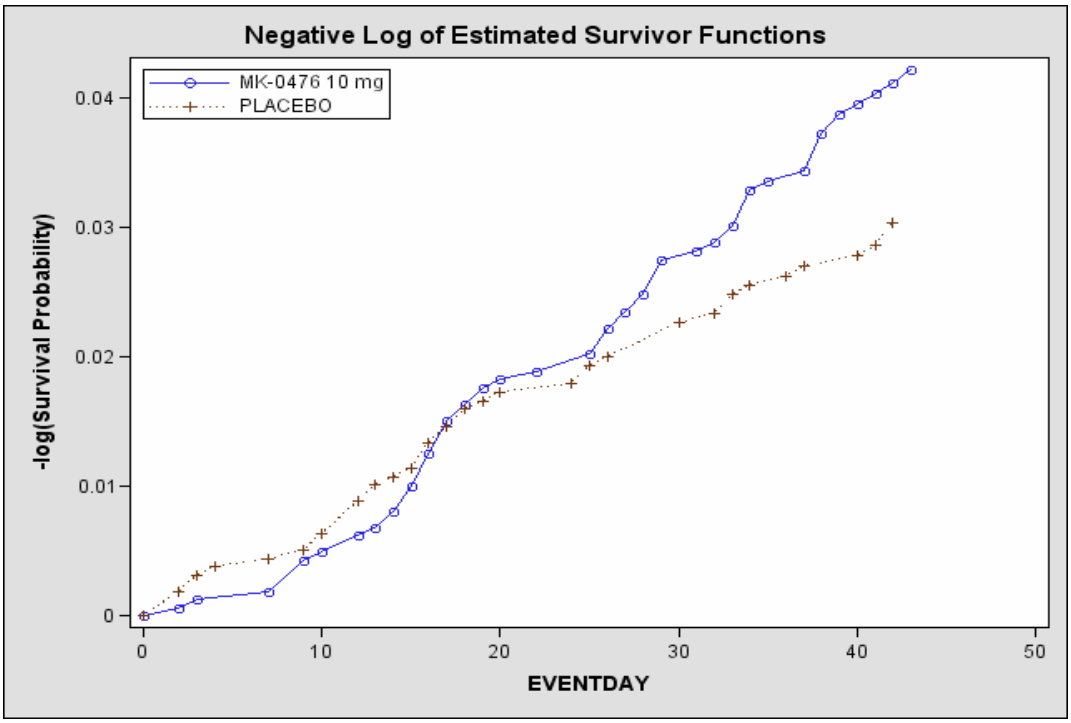


Figure 20. Kaplan-Meier Curve of Time to Adverse Event - Pharyngitis

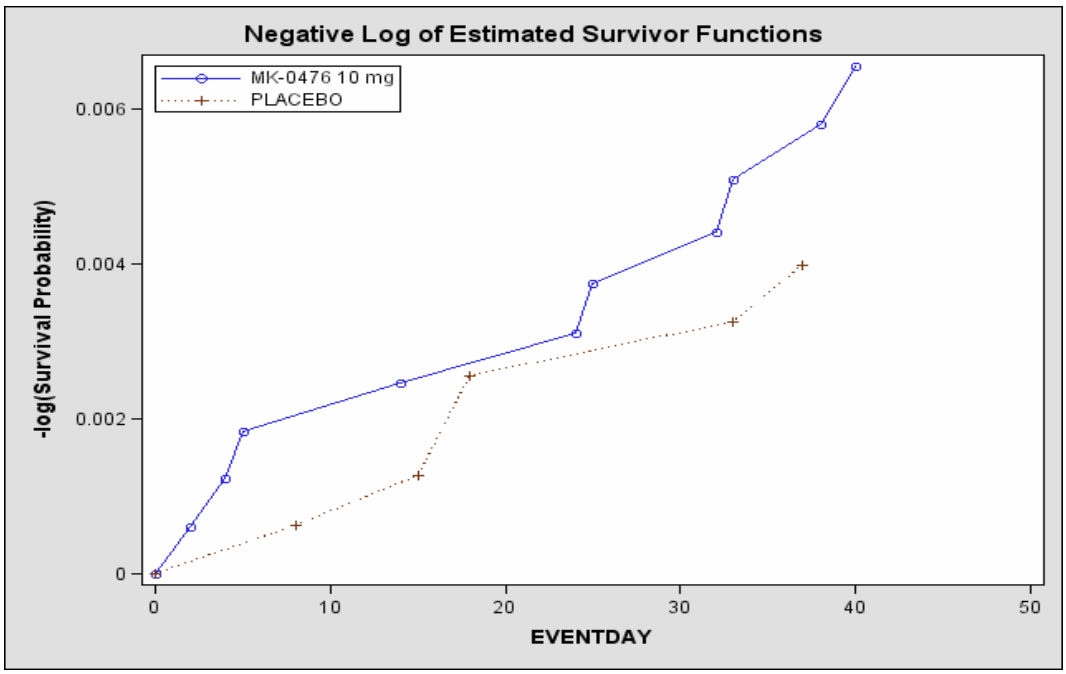


Figure 21. Kaplan-Meier Curve of Time to Adverse Event - Nasopharyngitis

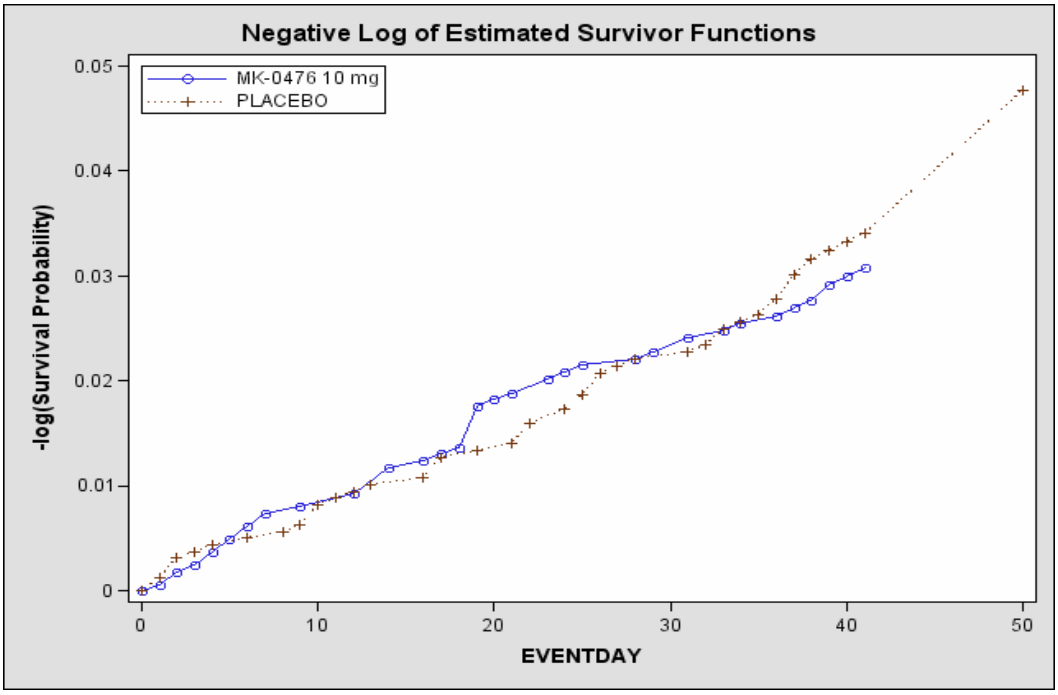


Figure 22. Kaplan-Meier Curve of Time to Adverse Event - Nausea

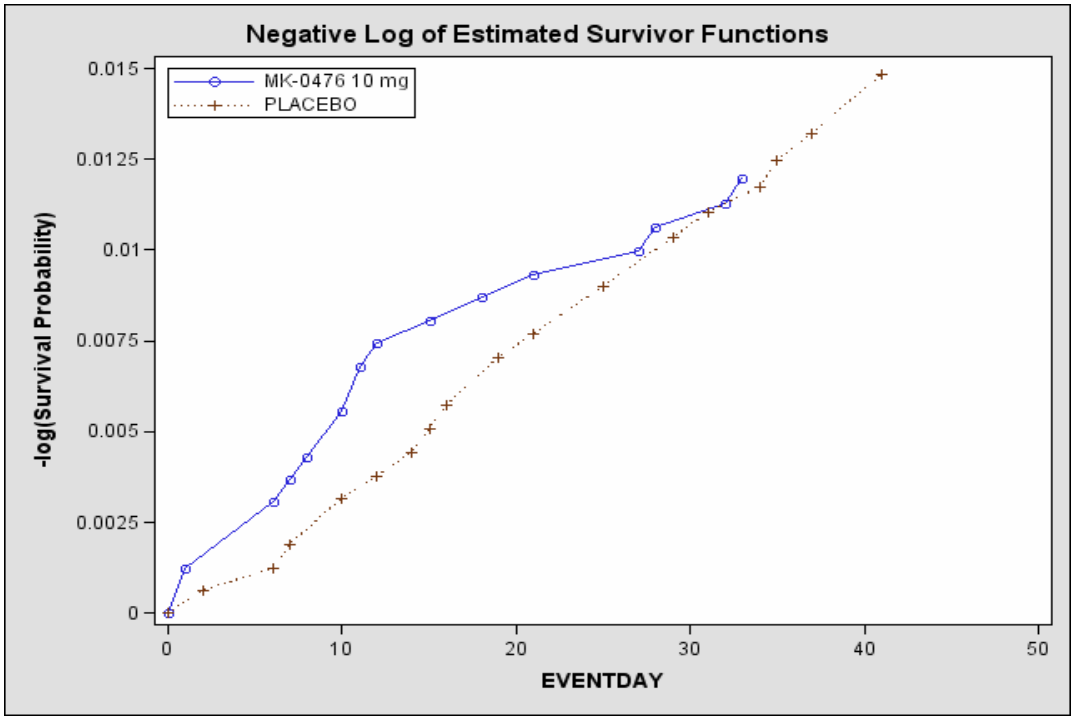


Figure 23. Kaplan-Meier Curve of Time to Adverse Event - Sinusitis

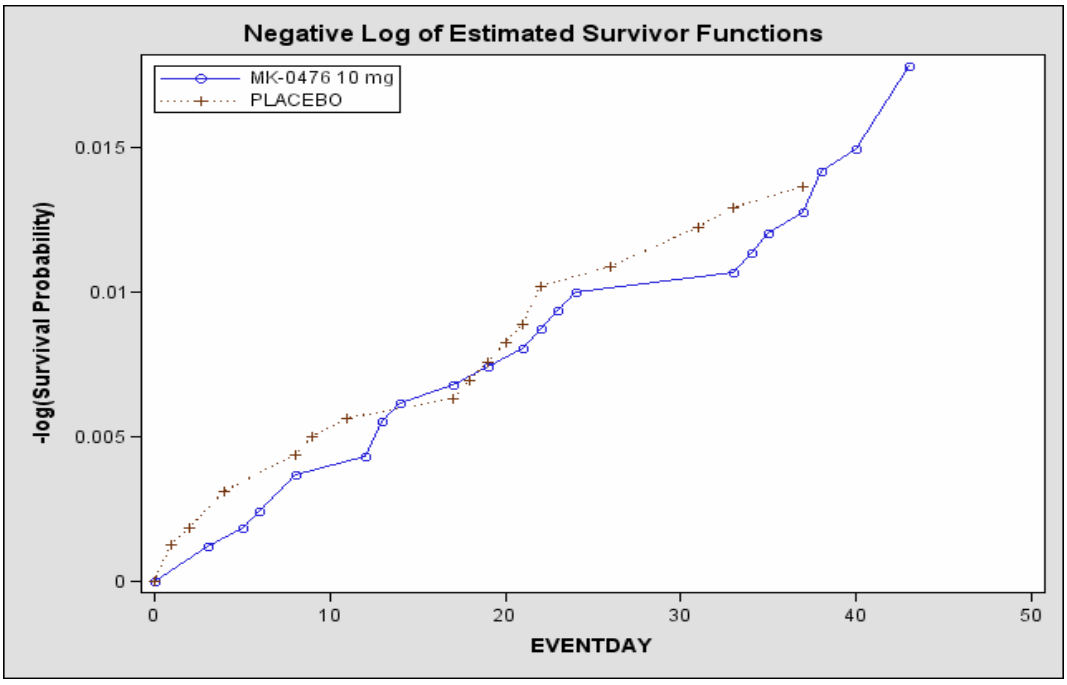


Figure 24. Kaplan-Meier Curve of Time to Adverse Event - Epistaxis

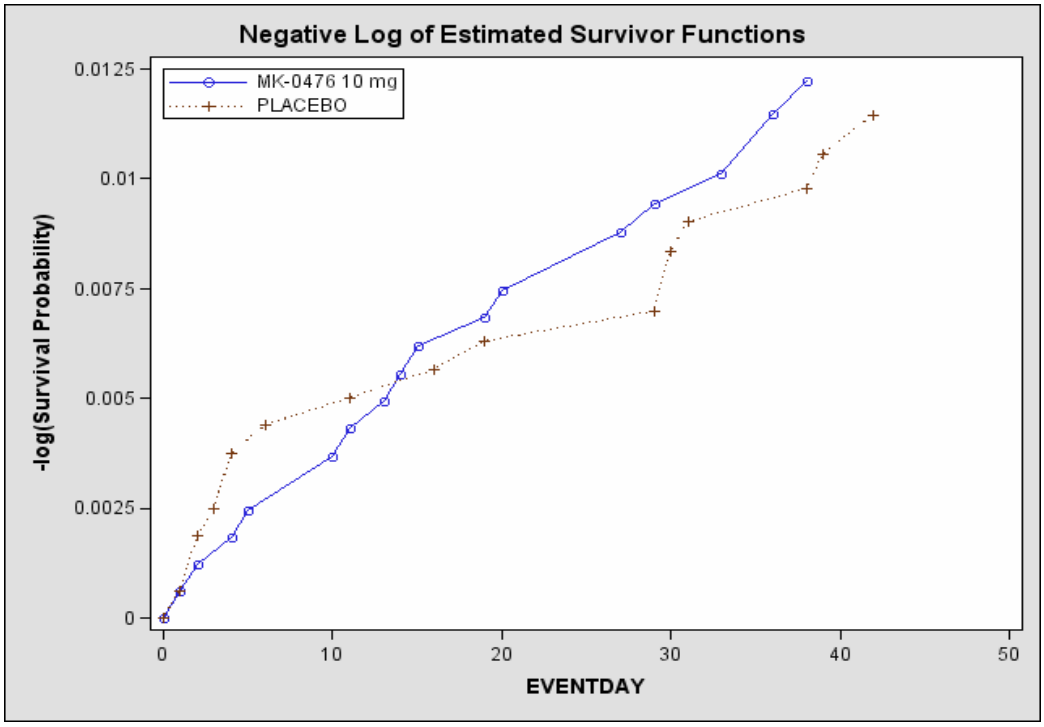


Figure 25. Kaplan-Meier Curve of Time to Adverse Event - Cough

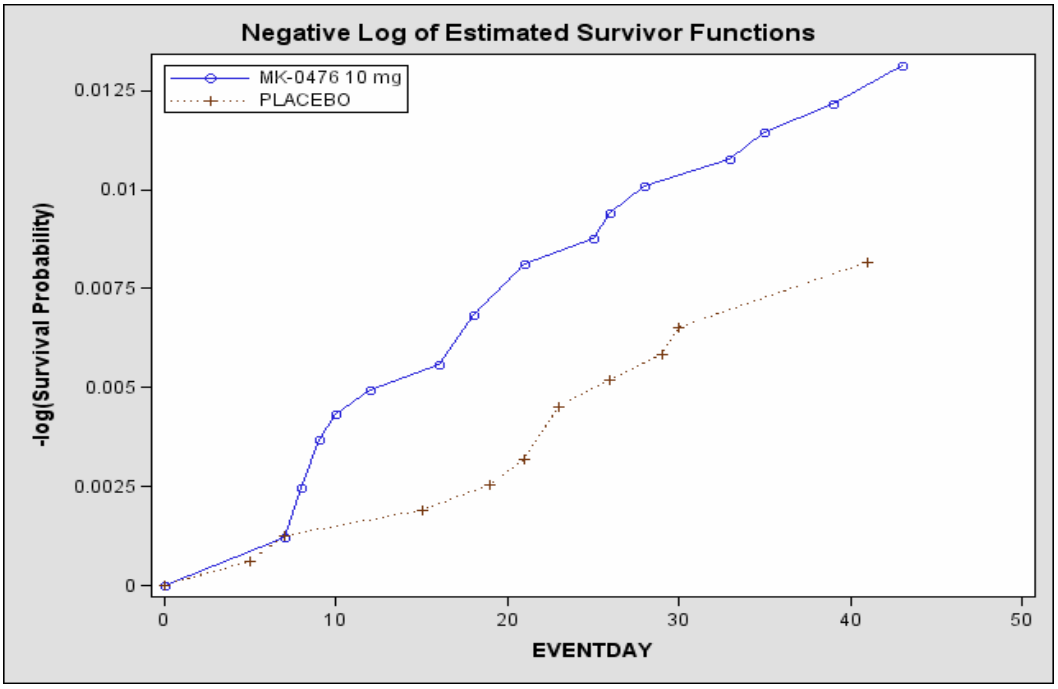


Figure 26. Kaplan-Meier Curve of Time to Adverse Event - Somnolence

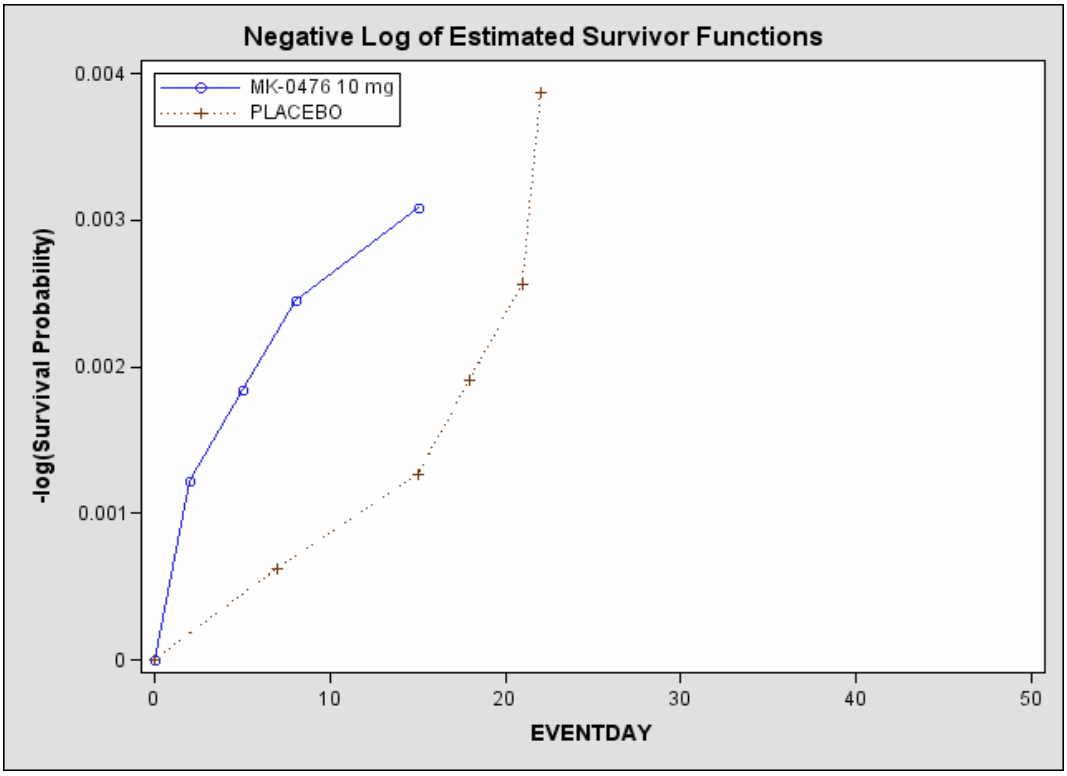


Figure 27. Kaplan-Meier Curve of Time to Adverse Event – Sinus headache

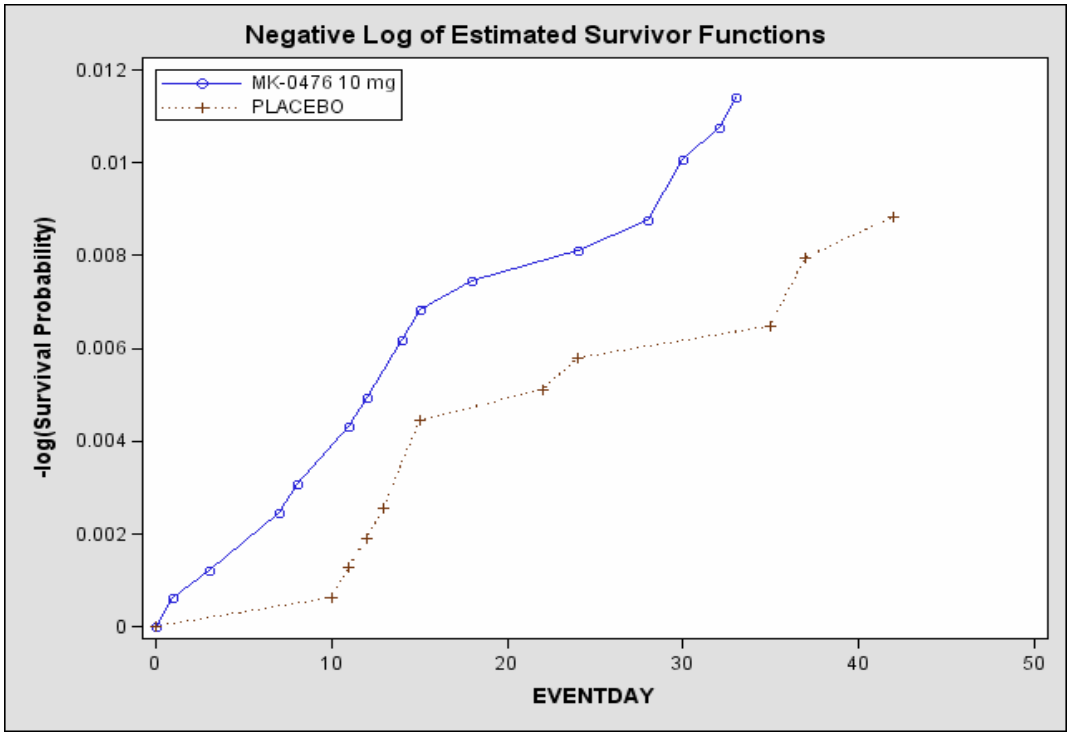


Figure 28. Kaplan-Meier Curve of Time to Adverse Event – Dry mouth

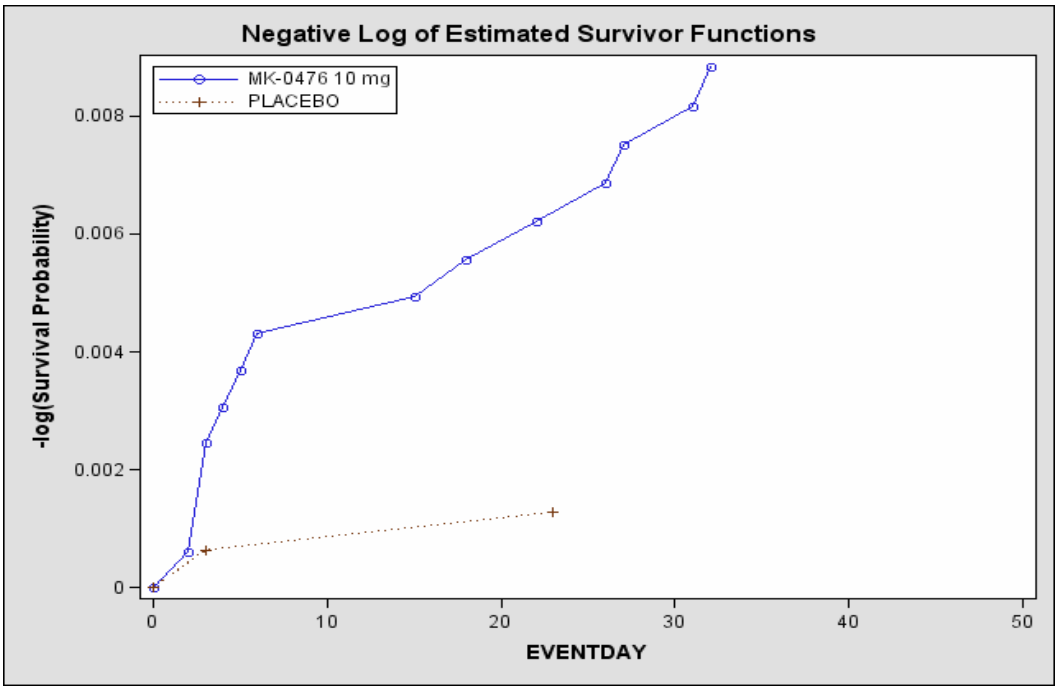


Figure 29. Kaplan-Meier Curve of Time to Adverse Event – Back pain

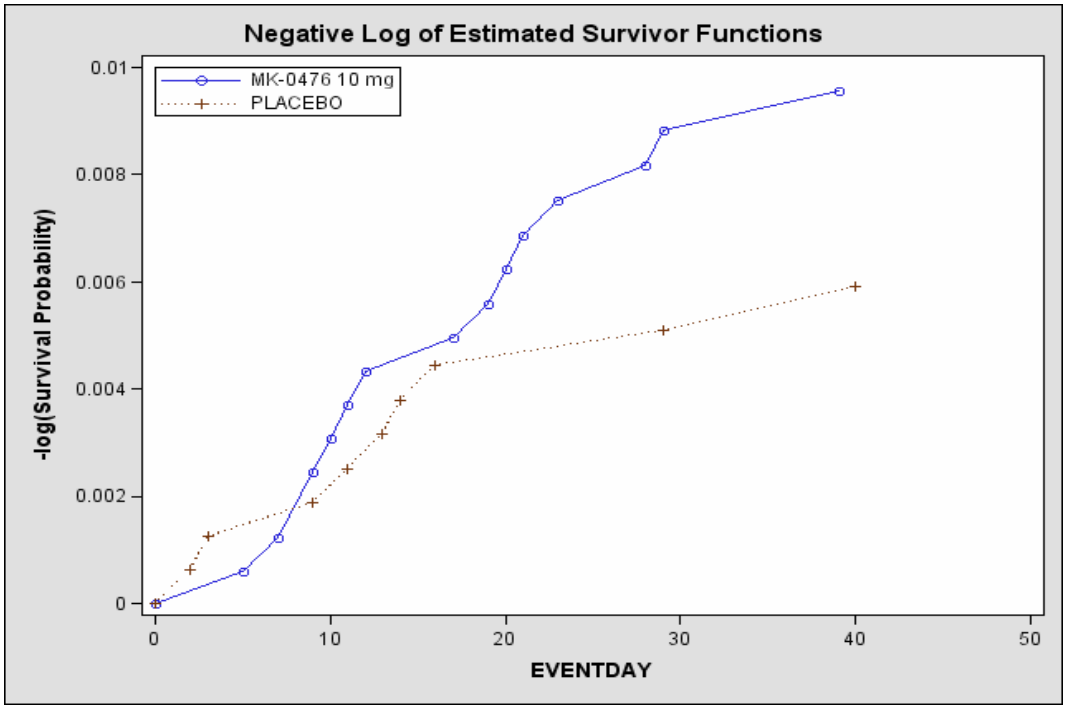


Figure 30. Kaplan-Meier Curve of Time to Adverse Event – ALT increased

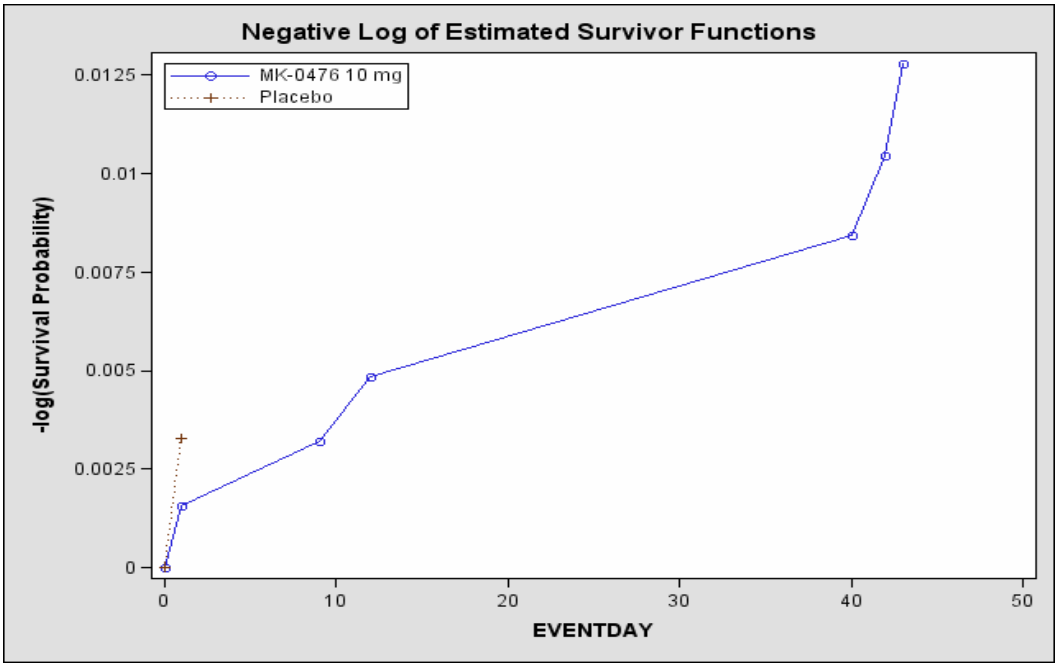
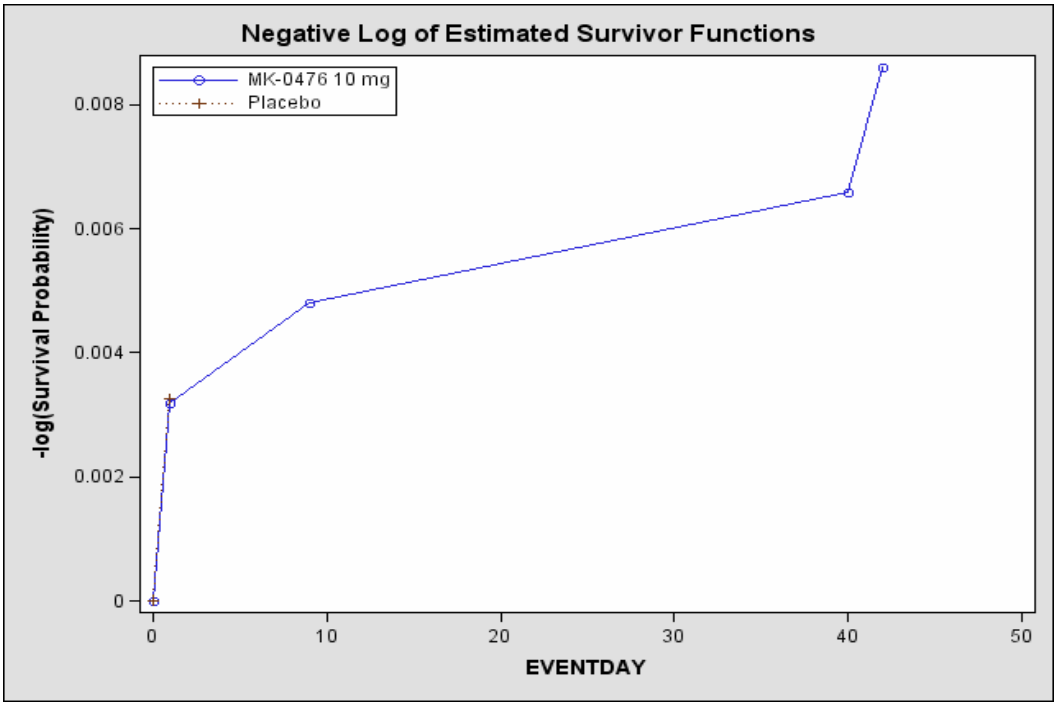


Figure 31. Kaplan-Meier Curve of Time to Adverse Event – AST increased



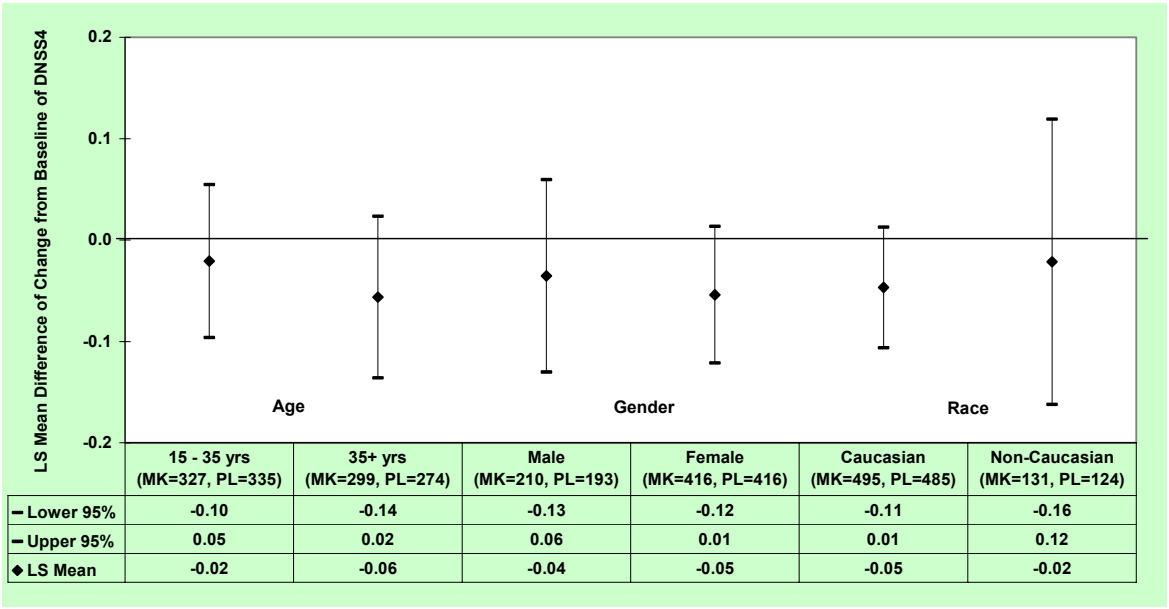
Source: SAFETYsas

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

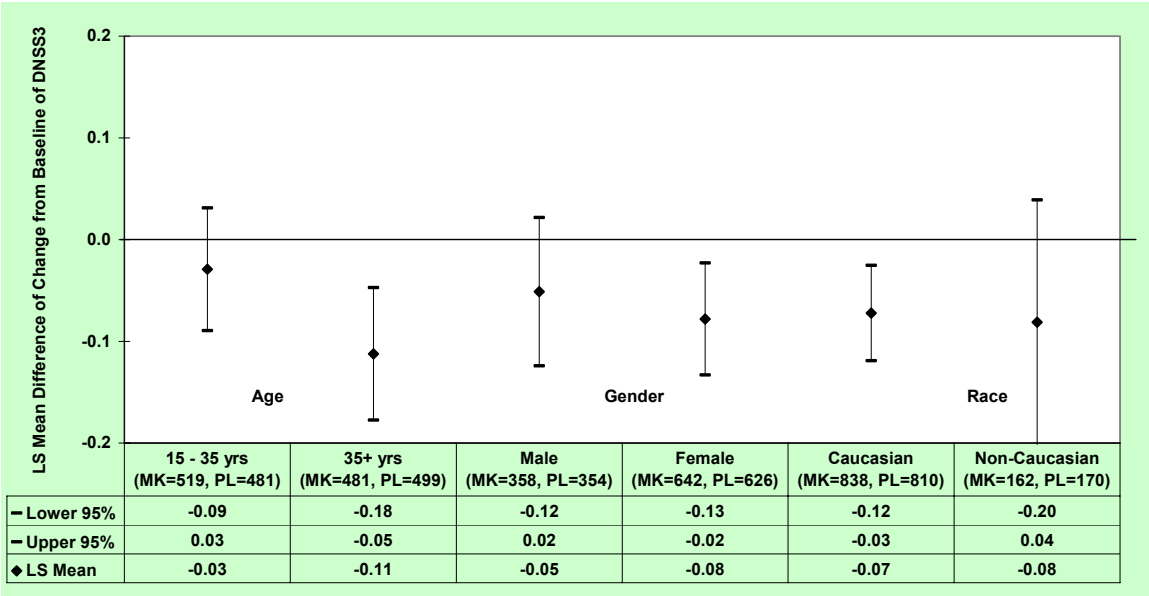
Figure 32 and Figure 33 display the primary efficacy endpoints by subgroups for both studies. There was not much difference between the sub-groups and no special concern for any subgroup.

Figure 32. Change from Baseline of DNSS4 over 4-week Study Period by Subgroup for PAR246



	15 - 35 yrs (MK=327, PL=335)	35+ yrs (MK=299, PL=274)	Male (MK=210, PL=193)	Female (MK=416, PL=416)	Caucasian (MK=495, PL=485)	Non-Caucasian (MK=131, PL=124)
– Lower 95%	-0.10	-0.14	-0.13	-0.12	-0.11	-0.16
– Upper 95%	0.05	0.02	0.06	0.01	0.01	0.12
◆ LS Mean	-0.02	-0.06	-0.04	-0.05	-0.05	-0.02

Figure 33. Change from Baseline of DNSS3 over 6-week Study Period by Subgroup for PAR265

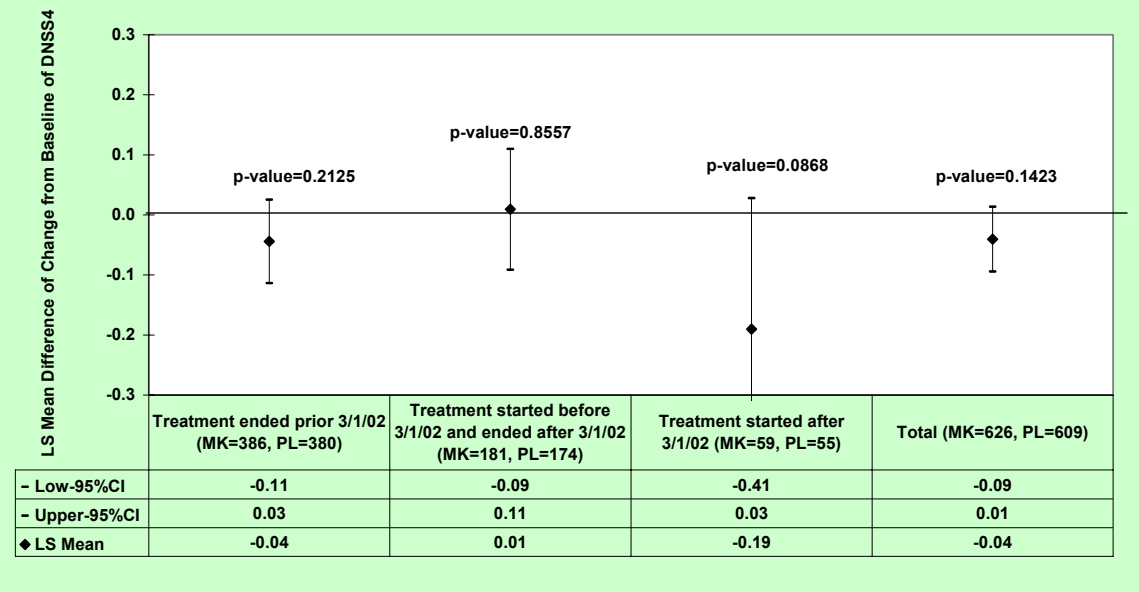


	15 - 35 yrs (MK=519, PL=481)	35+ yrs (MK=481, PL=499)	Male (MK=358, PL=354)	Female (MK=642, PL=626)	Caucasian (MK=838, PL=810)	Non-Caucasian (MK=162, PL=170)
– Lower 95%	-0.09	-0.18	-0.12	-0.13	-0.12	-0.20
– Upper 95%	0.03	-0.05	0.02	-0.02	-0.03	0.04
◆ LS Mean	-0.03	-0.11	-0.05	-0.08	-0.07	-0.08

4.2 Other Special/Subgroup Populations

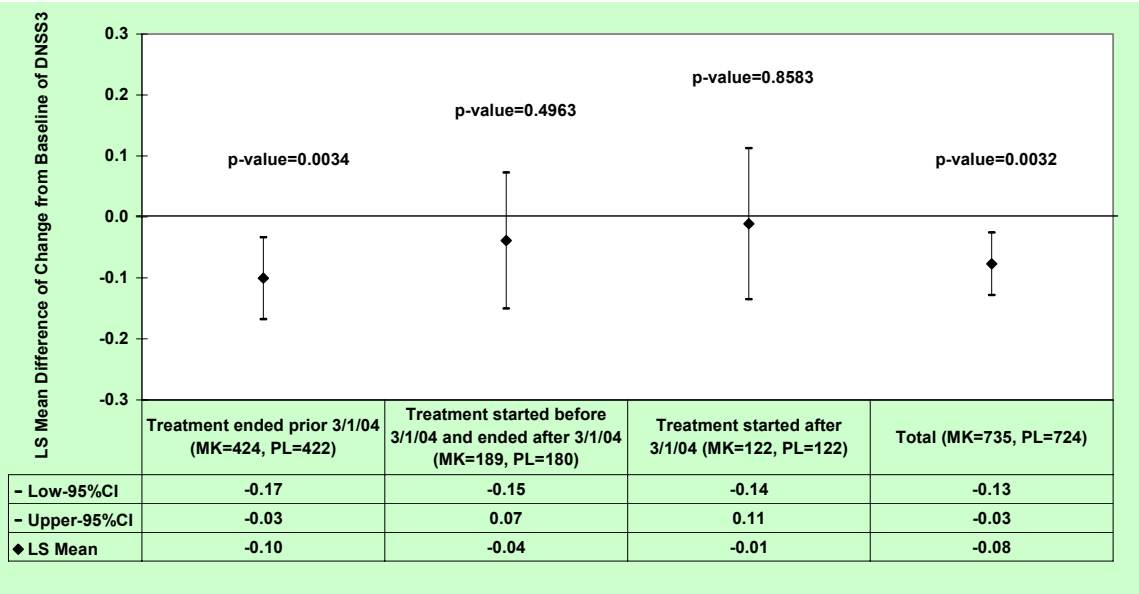
Subgroup Analyses in US Population –
Both studies finished in the month of May, the medical reviewer was concerned as to whether efficacy of Montelukast 10mg for PAR was affected by the SAR season. This reviewer grouped US patients into three sub-groups: patients finishing the treatment prior to March 1; patients starting the treatment after March 1; and the remainder. More than 50% of patients ended the treatment prior March 1 and the efficacy results were similar with ITT US population in both studies.

Figure 34. Change from Baseline of DNSS4 over 4-week, PAR246 (US only)



	Treatment ended prior 3/1/02 (MK=386, PL=380)	Treatment started before 3/1/02 and ended after 3/1/02 (MK=181, PL=174)	Treatment started after 3/1/02 (MK=59, PL=55)	Total (MK=626, PL=609)
- Low-95%CI	-0.11	-0.09	-0.41	-0.09
- Upper-95%CI	0.03	0.11	0.03	0.01
◆ LS Mean	-0.04	0.01	-0.19	-0.04

Figure 35. Change from Baseline of DNSS3 over 6-week for US subjects only, PAR265



	Treatment ended prior 3/1/04 (MK=424, PL=422)	Treatment started before 3/1/04 and ended after 3/1/04 (MK=189, PL=180)	Treatment started after 3/1/04 (MK=122, PL=122)	Total (MK=735, PL=724)
- Low-95%CI	-0.17	-0.15	-0.14	-0.13
- Upper-95%CI	-0.03	0.07	0.11	-0.03
◆ LS Mean	-0.10	-0.04	-0.01	-0.08

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Statistical Issues

- Sponsor's application included adequate statistical design and analyses plan. The results of one of the primary studies support the sponsor's claim.

Sponsor's Label Claim

This reviewer reviewed the sponsor's labeling claims, statistical figures and tables; there is one recommendation for changes in the labeling - p9, Labeling)

Clinical Studies – Perennial Allergic Rhinitis
The efficacy of SINGULAIR tablets for the treatment of perennial allergic rhinitis was investigated in 3357 (b) (4) *patients 15 to 82 years of age with a history of perennial allergic rhinitis, positive skin test results to relevant perennial allergens (including dust mites, animal dander, and mold spores), and active symptoms of perennial allergic rhinitis at study entry….*

5.2 Conclusions and Recommendations

Based on the efficacy evaluation of studies PAR246 and PAR265, each of which were a phase-III, randomized, multicenter, double-blind, parallel-group, and placebo-control trial, only one study (PAR265) demonstrated that subjects treated with Montelukast 10mg once daily in the evening over a 6-week treatment period, compared with the Placebo, improved the primary endpoint, Daytime Nasal Symptoms score (i.e. average of scores for Congestion, Rhinorrhea, and Sneezing). The change in the primary efficacy variable in the Montelukast 10mg treatment group was numerically (but not statistically significantly) superior to Placebo group and worse than the Cetirizine treatment group in Study PAR246. In an exploratory evaluation, out of 3357 patients 15 to 82 years of age with a history of PAR, and daytime nasal symptoms score ≥ 1.5 at study entry, 41% of the 1626 patients, who received Montelukast 10mg treatment, reduced daytime nasal symptoms by 0.5 on average over the 6-week treatment period. The patients who had severe symptom at baseline appeared to improve more over the 6-week treatment period, compared with the patients who had mild symptoms at baseline.

Montelukast 10 mg administered once daily over a 6-week treatment period is generally well tolerated, with a safety profile comparable with that of placebo. There were 9 patients in Montelukast group, 1 in Cetirizine group, and 3 in placebo group who had ALT or/and AST increased.

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/s/

Feng Zhou
7/27/05 11:17:27 AM
BIOMETRICS

Sue Jane Wang
7/27/05 11:35:08 AM
BIOMETRICS
concur with review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033

20-830/S035

21-409/S012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	20-830, 20-829 and 21-409
Proprietary Drug Name:	Singulair
Generic Name:	Montelukast Sodium
Indication:	Treatment of PAR
Dosage Form:	Tablets, chewable tablets and oral granules
Strength:	10 mg tablets, 5 mg chewable tablets, 4mg oral granules
Route of Administration:	Oral
Applicant:	Merck Research Laboratories
Clinical Division:	DPADP (HFD-570)
Submission Dates:	September 30, 2004; December 3, 2004
Reviewer:	Sandra Suarez-Sharp, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceuticals / Division of Pharmaceutical Evaluation-II (OCPB / DPE-II) has reviewed this application submitted to NDAs 20-830, 21-829 and 21-409 on September 30, 2004 to support the use of Singulair for the treatment of Perennial Allergic Rhinitis (PAR). The present report provides information on the systemic exposure of montelukast in asthmatic children 6 months to 1 year of age following administration of Singulair oral granules. This information was submitted and reviewed under NDA 21-409 received on September 28, 2001. This reviewer will rely on these data since the PK in asthmatics and PAR patients is assumed to be similar. The NDA's Human Pharmacokinetics and Bioavailability Section is acceptable to OCPB.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Singulair™ (montelukast) is an antagonist of the Type I cysteinyl leukotriene (CysLT1) receptor that inhibits the effects of the pro-inflammatory cysteinyl leukotrienes. Singulair is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 1 year of age and older. The original applications for Singulair 10 mg film-coated tablets (NDA 20-829), 5-mg chewable tablets (NDA 20-830), a supplemental application for 4-mg chewable tablets (NDA 20-830/S-008), and 4-mg oral granules (NDA 21-409) have been approved by the Agency. A supplemental application for seasonal allergic rhinitis (NDA 20-829, 20-830, 21-409) was approved on December 31, 2002.

In the present submission the sponsor, Merck Research Laboratories is seeking approval of SINGULAIR Tablets, Chewable Tablets, and Oral Granules for the relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older. In support of this NDA the sponsor submitted the results of one pivotal clinical study involving the montelukast tablets formulation in PAR patients 15 years and older. No efficacy or safety study was conducted in younger PAR patients including children. According to the sponsor, the extensive safety data for montelukast using approved age-appropriate formulations in asthmatic pediatric patients receiving same approved doses as proposed in this submission, could support the approval of montelukast for the treatment of PAR in patients down to 6 months of age. The sponsor is seeking approval of Singulair in these younger patients based on the fact that PAR disease process is similar in both adult and children populations and the outcome of therapy is likely to be comparable. This approach was the basis by which adult SAR (Seasonal Allergic Rhinitis) efficacy data have supported the use of montelukast for SAR in pediatric patients.

In September 28, 2001, the sponsor submitted under NDA 21-409 the results of a study that evaluated the systemic exposure of Singulair oral granules 4 mg in children 6 months to 2 years of age using a population pharmacokinetic approach (Study P136c/138). (b) (4)

(b) (4). This population PK study showed that in children 6 months to < 1 year of age, the mean AUC (4298 ng•hr/mL; range 1200 to 7153) was 62% higher and the mean C_{max} (667 ng/mL; range 201.1 to 1057.8]) was 89% higher than those observed in adults (mean AUC 2644.8 ng•hr/mL; range 1521 to 4595]) and mean C_{max} (353 ng/mL; range 180 to 548).

The systemic exposure in the ≥ 1 year to <2 year olds was less variable, but still higher compared to that in adults. The mean AUC was 34% higher and the mean Cmax was 58% higher that those observed in adults (Table 1). No correlation was found between the pharmacokinetic parameters clearance and volume of distribution and weight or age.

Table 1. Mean montelukast population PK parameters following single administration of Singulair sprinkles 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets 4-mg to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM.

	Montelukast formulations: sprinkles, chewable tablets, film-coated tablets				
PK Parameter	**Children ≥6m to <1y**	**Children ≥1yto <2y**	**Children ≥6m to <2y**	**Children ≥2y to <6y**	**Adults**
AUC_{pop} (ng*hr/mL)[a]	4298.2±542.1	4060.4±401.9	3907 ±286.4	2761.1±200.7*	2644.8±154.1
$Cmax_{pop}$ (ng/mL) [a]	666.6±77.9	561.9±47.4	610.2 ±44.4	504.4±46.1*	352.6±25.53**
CL_{pop} (ml/min) [a]	20.47±4.1	19.59±1.33	19.96±1.86	25.7±1.58*	66.7±18.75
Tmax (hr) [b]	1.5±0.2	1.52±0.16	1.51±0.18	1.81±0.78	3.87±1.36**
T1/2[b]	3.39±1.5	3.37±0.97	3.38±1.22	2.36±0.9	1.94±0.33[c]

[a] mean ± SE; [b]mean±SD; *Data estimated using NONMEM from protocol no. 066; **calculated using non-compartmental methods; [c]based on 2CBM parameters

1.4 COMMENTS TO THE MEDICAL OFFICER

1. There is no correlation between clearance (and therefore AUC), volume of distribution and weight or age in the group of children ≥6 months to < 2 years of age. This suggests that the dosage regimen in this group of children should not be based on weight.
2. High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair oral granules for this population would give a similar systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for loss of efficacy considering a target AUC of 1200 ng*hr/mL to 4500 ng*hr/mL.
3. According to the sponsor, overdoses of up to at least 150 mg have been generally well tolerated with no major adverse events. Therefore, safety data from older populations from doses higher than those indicated can be used to support the safety of the 4 mg dose of montelukast in children 6 months to 1 year of age. However, the medical officer should evaluate the risk (safety) involved in having a > 60 % exposure in children ≥6 months to < 1 year of age receiving 4-mg of Singulair oral compared to that in adults receiving 10-mg oral tablets.

Reviewer
Sandra Suarez-Sharp, Ph.D.
Office of Clinical Pharmacology and Biopharmaceuticals

Division of Pharmaceutical Evaluation II

Final version signed by Emmanuel Fadiran, Ph.D., Team leader _____
cc :
NDAs: 20-829, 20-830, and 21-409
HFD-870: Malinowski, Hunt
HFD-570: Fadiran, Purohit-sheth, Chowdhury, Lori, Suarez-Sharp

2. QUESTION BASED REVIEW

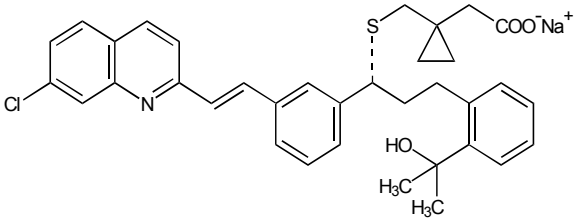
2.1. What are the general attributes of Singulair?

Chemical name:

Montelukast sodium, the active ingredient in SINGULAIR™, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene $CysLT_1$ receptor.

Montelukast sodium is described chemically as [R-(E)]-1-[[[1-[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)phenyl]propyl]thio]methyl] cyclopropaneacetic acid, monosodium salt.

Structural formula:



Molecular formula: $C_{35}H_{35}ClNNaO_3S$
Molecular weight: 608.18
Solubility: Montelukast sodium is a hygroscopic, optically active, white to off-white powder. Montelukast sodium is freely soluble in ethanol, methanol, and water and practically insoluble in acetonitrile.

FORMULATION USED IN THE POPULATION PK STUDY

Each packet of SINGULAIR 4-mg oral granules for oral administration contains 4.2 mg montelukast sodium, which is the molar equivalent to 4.0 mg of (b) (4). The sprinkle formulation contains the following inactive ingredients: mannitol, hydroxypropyl cellulose, and magnesium stearate (Table 1.1).

(

Table 2.1.1. Market Composition, Montelukast Sodium oral Granules, 4-mg and 4mg chewable tablets

	4-mg	4-mg
Ingredient (mg)	**Chewable Tablet**	**Sprinkle**
		(b) (4)
Montelukast sodium		
(b) (4)		
Mannitol, USP		
Microcrystalline cellulose, NF		
Hydroxypropyl cellulose, NF		
Red Ferric Oxide, NF		
Croscarmellose sodium, NF		
Cherry flavor		
Aspartame, NF		
Magnesium stearate, NF		
Total Weight	240.0 mg	500.0 mg

(

INDICATION (as per proposed label)

SINGULAIR is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older.

SINGULAIR is indicated for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older).

DOSAGE AND ADMINISTRATION (as per proposed label)

SINGULAIR should be taken once daily. For asthma, the dose should be taken in the evening. For allergic rhinitis, the time of administration may be individualized to suit patient needs. Patients with both asthma and allergic rhinitis should take only one tablet daily in the evening.

Adults and Adolescents 15 Years of Age and Older with Asthma or Allergic Rhinitis

The dosage for adults and adolescents 15 years of age and older is one 10-mg tablet daily.

Pediatric Patients 6 to 14 Years of Age with Asthma or Allergic Rhinitis

The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily. No dosage adjustment within this age group is necessary.

Pediatric Patients 2 to 5 Years of Age with Asthma or Allergic Rhinitis

The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet or one packet of 4-mg oral granules daily.

Pediatric Patients 12 to 23 Months of Age with Asthma

The dosage for pediatric patients 12 to 23 months of age is one packet of 4-mg oral granules daily to be taken in the evening.

Pediatric Patients 6 to 23 Months of Age with Perennial Allergic Rhinitis

The dosage for pediatric patients 6 to 23 months of age is one packet of 4-mg oral granules daily (b) (4)

2.2. What is known about the pharmacokinetics of Montelukast?

The following pharmacokinetics of montelukast were presented in previous NDA (20-829).

Absorption

Montelukast is rapidly absorbed following oral administration. After administration of the 10-mg film-coated tablet to fasted adults, the mean peak montelukast plasma concentration (C_{max}) is achieved in 3 to 4 hours (T_{max}). The mean oral bioavailability is 64%. The oral bioavailability and C_{max} are not influenced by a standard meal in the morning.

For the 5-mg chewable tablet, the mean C_{max} is achieved in 2 to 2.5 hours after administration to adults in the fasted state. The mean oral bioavailability is 73% in the fasted state versus 63% when administered with a standard meal in the morning.

For the 4-mg chewable tablet, the mean C_{max} is achieved 2 hours after administration in pediatric patients 2 to 5 years of age in the fasted state.

Distribution

Montelukast is more than 99% bound to plasma proteins. The steady-state volume of distribution of montelukast averages 8 to 11liters.

Metabolism

Montelukast is extensively metabolized. In studies with therapeutic doses, plasma concentrations of metabolites of montelukast are undetectable at steady state in adults and pediatric patients.

In vitro studies using human liver microsomes indicate that cytochromes P450 3A4 and 2C9 are involved in the metabolism of montelukast. Clinical studies investigating the effect of known inhibitors of cytochromes P450 3A4 (e.g., ketoconazole, erythromycin) or 2C9 (e.g., fluconazole) on montelukast pharmacokinetics have not been conducted. Based on further *in vitro* results in human liver microsomes, therapeutic plasma concentrations of montelukast do not inhibit cytochromes P450 3A4, 2C9, 1A2, 2A6, 2C19, or 2D6.

Elimination

The plasma clearance of montelukast averages 45 mL/min in healthy adults. Following an oral dose of radiolabeled montelukast, 86% of the radioactivity was recovered in 5-day fecal collections and <0.2% was recovered in urine. Coupled with estimates of montelukast oral bioavailability, this indicates that montelukast and its metabolites are excreted almost exclusively via the bile. In several studies, the mean plasma half-life of montelukast ranged from 2.7 to 5.5 hours in healthy young adults. The pharmacokinetics of montelukast are nearly linear for oral doses up to 50 mg. During

once-daily dosing with 10-mg montelukast, there is little accumulation of the parent drug in plasma (14%).

Special Populations
Gender: The pharmacokinetics of montelukast are similar in males and females.
Elderly*:* The pharmacokinetic profile and the oral bioavailability of a single 10-mg oral dose of montelukast are similar in elderly and younger adults. The plasma half-life of montelukast is slightly longer in the elderly. No dosage adjustment in the elderly is required.

Race*:* Pharmacokinetic differences due to race have not been studied.

Hepatic Insufficiency*:* Patients with mild-to-moderate hepatic insufficiency and clinical evidence of cirrhosis had evidence of decreased metabolism of montelukast resulting in 41% (90% CI=7%, 85%) higher mean montelukast AUC following a single 10-mg dose. No dosage adjustment is required in patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of SINGULAIR in patients with more severe hepatic impairment or with hepatitis have not been evaluated.

Renal Insufficiency: Since montelukast and its metabolites are not excreted in the urine, the pharmacokinetics of montelukast were not evaluated in patients with renal insufficiency. No dosage adjustment is recommended in these patients.

Adolescents and Pediatric Patients*:* The plasma concentration profile of montelukast following administration of the 10-mg film-coated tablet is similar in adolescents 15 years of age and young adults. The 10-mg film-coated tablet is recommended for use in patients 15 years of age.

Drug Interactions
Montelukast at a dose of 10 mg once daily dosed to pharmacokinetic steady state did not cause clinically significant changes in the kinetics of theophylline, warfarin, digoxin, terfenadine oral contraceptive containing norethindrone 1 mg/ethinyl estradiol 35 mcg, prednisone or prednisolone.

Phenobarbital, which induces hepatic metabolism, decreased the AUC of montelukast approximately 40% following a single 10-mg dose of montelukast. No dosage adjustment for SINGULAIR is recommended. It is reasonable to employ appropriate clinical monitoring when potent cytochrome P450 enzyme inducers, such as phenobarbital or rifampin, are co-administered with SINGULAIR.

2.3. Was the systemic exposure in children 6 months to 1 year of age following administration of Singulair oral granules similar to the one in adults receiving Singulair 10mg film-coated tablets?

Study P136c/138 was a population pharmacokinetic study conducted to assess the systemic exposure of a single dose of 4-mg Singulair oral granules in children. This study was an open label, single dose, multicenter study to evaluate the safety, tolerability, and

plasma concentration profiles of Montelukast oral granules in ≥ 6 months to 24-month old children. This study compared montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax) obtained from the ≥6- to <24-month-old children after administration of a 4-mg dose of the sprinkle formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the FCT of montelukast using a population PK approach. To have a more complete picture, this reviewer also analyzed the data generated in the 2 to 5 years olds receiving 4 mg chewable tablet using a population PK approach.

Subjects (32) received the following treatment:

- One pouch of 4-mg oral granules delivered in 1 teaspooful of applesauce.

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. Different models were fitted to the adult and children data separately and together.

When all the data were pooled together, a 2-compartment model with first order absorption and elimination was used. The effect of covariates, such as weight and age were introduced into the basic adult and children model, and was evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data were handled separately, a 1-compartment model with first-order absorption and elimination best described the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the values of the average population PK parameters.

A 2-compartment model with first order absorption and elimination better described the adult data from protocol 034. The adult Cmax was calculated using non-compartmental methods and the children Cmax was calculated based on the estimates of ke, ka and Vd. T1/2 has calculated using the estimated rate of elimination.

The effect of covariates, such as weight and age were introduced into the basic adult and children models. The analysis showed no correlation between clearance (and therefore, AUC) and volume of distribution and weight or age in the group of children ≥6 months to < 2 years of age receiving Singulair oral granules 4mg. This suggests that the dosage regimen in this group of children should not be based on weight.

This reviewer used WinNonlin in an attempt to estimate, be the most appropriate dose for children population in terms of achieving similar exposure as that obtained in adults. Simulations were done using the estimated average PK parameters (post-hoc estimates) generated in the population PK analysis (data not shown).

High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age (Table 6.1 and Figures 6.1 and 6.2, respectively). Based on simulation studies, a lower dose of Singulair oral granules for this population would give similar systemic exposure observed to that in adults. However, due to the high variability in exposure some children may be at risk for loss of efficacy considering a target AUC of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

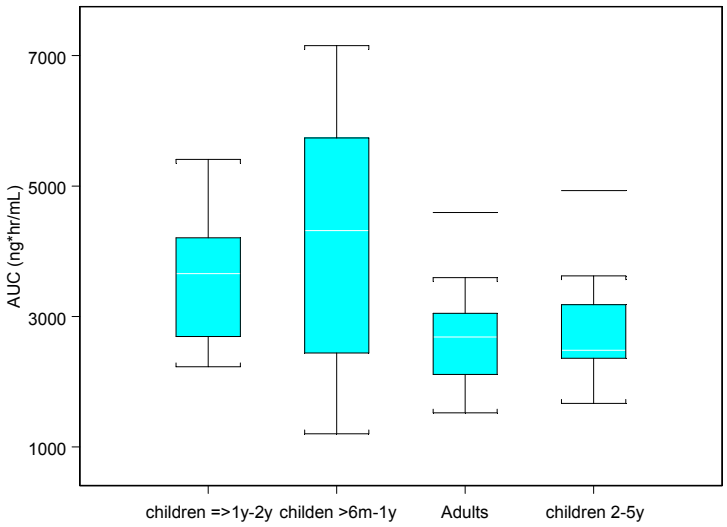


Figure 2.3.1. Box plot for population AUC (AUCpop) following single administration of Singulair oral granlues 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old group.

Table 2.3.1. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast

Comparison	**PK parameter**	**Point estimates**		**90% confidence intervals**	
		Sponsor's findings*	This reviewer' findings	Sponsor's findings**	This reviewer' findings
≥6m to <1 y/adult	AUC Cmax	135	148.1 178.9	102-154	119.3-183.9 141.4-226.4
≥1y to <2y/adult	AUC Cmax	118	133.7 157.8	97-144	108.7-164.5 125.9-197.3
≥2y to <6 y/adult	AUC Cmax	105	103.2 141.8	90-122	84.2-126.5 113.6-176.9

* CI back calculated from log-transformed scale; **sponsor reported 95% confidence intervals

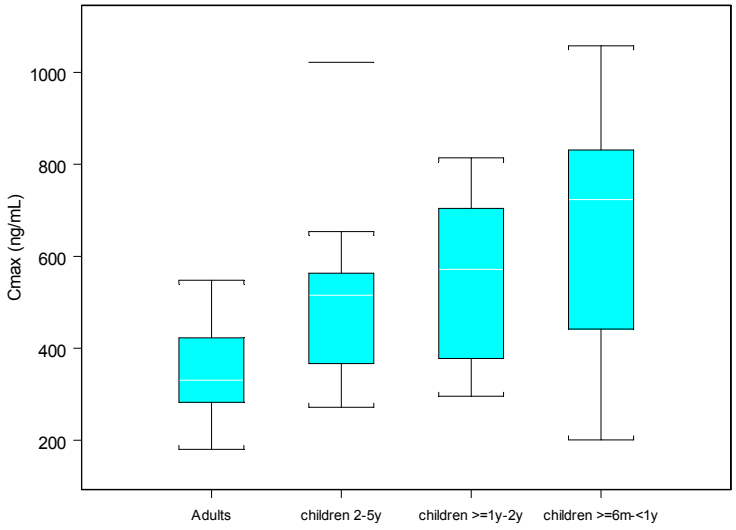


Figure 2.3.2 Box plot for population Cmax (Cmaxpop) following single administration of Singulair oral granules 4 mg to children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years and single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. The Cmax adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6m-2y old group.

CONCLUSIONS

- There is no correlation between Cmax or AUC and weight in the group of children ≥6 months to < 2 years of age.
- High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair oral granules to this population would give a similar systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

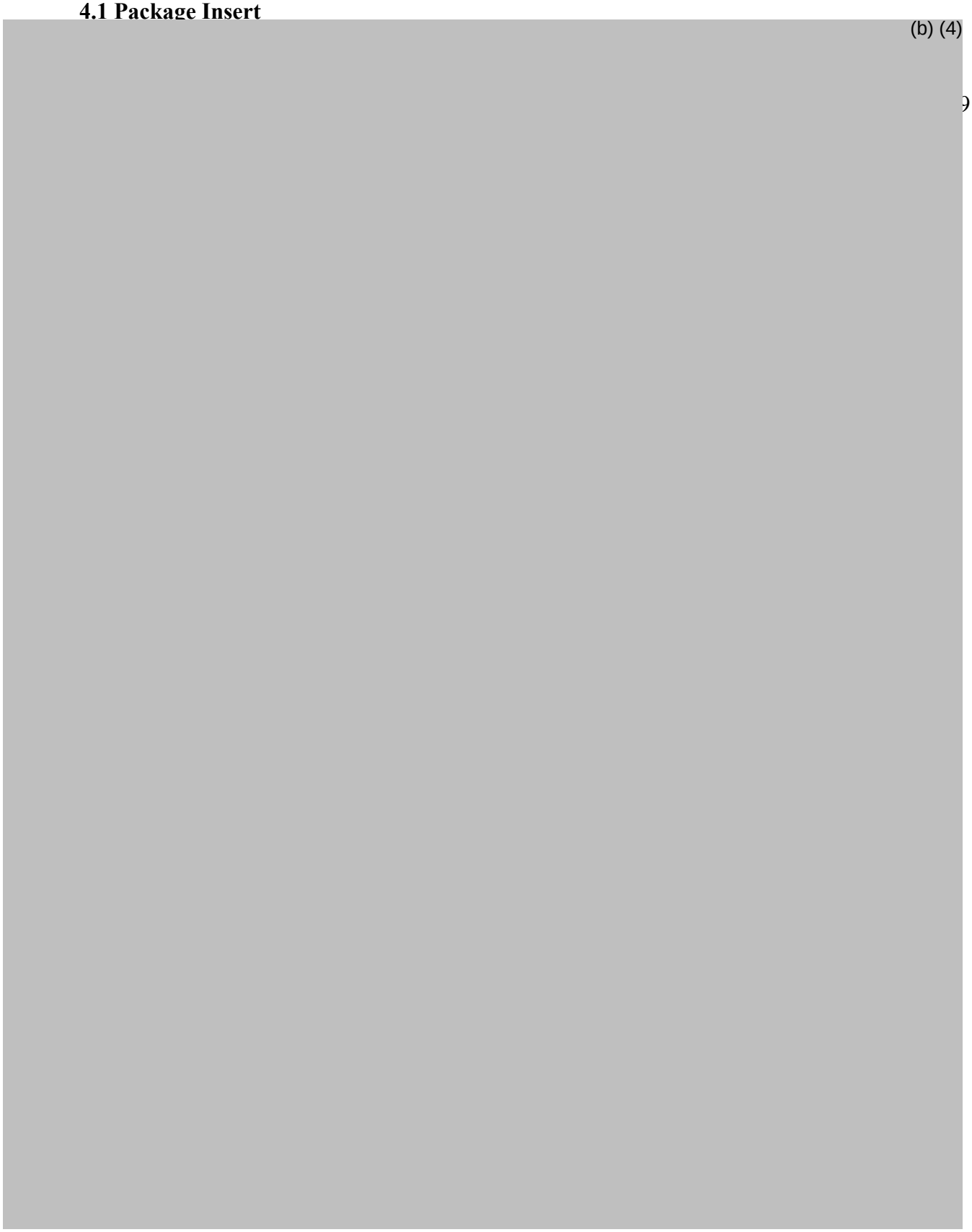
3. LABELING COMMENTS

There are not CPB labeling comments at this time. The PK information generated from the population PK study in children 6 months to 1 year of age was incorporated in the label under NDA 21-409 at the time of this NDA approval.

4. INDIVIDUAL REPORTS

4.1 Package Insert

(b) (4)



___14___ Page (s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

__✓___ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

Withheld Track Number: Clinical Pharm/Bio-20-829/S033; 20-30/S035; 21-409/S012

4.2 Individual Reports

"AN OPEN, SINGLE-DOSE, MULTICENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND PLASMA CONCENTRATION PROFILES OF MONTELUKAST ORAL GRANULES IN 6- TO 24-MONTH-OLD CHILDREN"

Study Protocol 136/138

Study Initiation Date (FPI):	Jan 17, 2000
Study Completion Date (LPO):	May 25, 2001
Investigator Name/Affiliation:	Multicenter study
Clinical Study Report Date	Aug 17, 2001

OBJECTIVES

- To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax, estimated C24hrr, and apparent elimination t½) obtained from ≥6- to <12-month-, ≥12- to <24-month-, and ≥6- to <24-month-old children after administration of a 4-mg dose of the sprinkle formulation of montelukast with historical data in adult subjects after administration of a 10-mg dose of the FCT of montelukast.
- To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUCpop, Cmax, Tmax, estimated C24hr, and apparent elimination t½) between ≥6- to <12-month-, ≥12- to <24-month-, and ≥6- to <24-month-old children after administration of a 4-mg dose of the sprinkle formulation of montelukast.
- To evaluate the safety and tolerability of a 4-mg (and/or either a 2-mg or 6-mg) dose of the sprinkle formulation of montelukast in =6- to <24-month-old children.

SUBJECTS

The demographic characteristics and patient accounting for this study is described in the tables below. A total of 26 patients were evaluable for pharmacokinetic analysis. Out of the 32 who received the test product, 1 did not completely consume the dose, 1 vomited shortly after test product administration, 2 did not have their 12-hour blood samples obtained and 2 were excluded due to modeling limitations.

	Age-Specific Group	
	≥6 Months to <1 Year	≥1 to <2 Years
PATIENTS:		
ENTERED: Total	14	18
Male (age range, months)	9 (6 to 11)	5 (17 to 23)
Female (age range, months)	5 (8 to 11)	13 (12 to 22)
COMPLETED:	13	17
DISCONTINUED: Total	1	1
Clinical adverse experience	1	0
Laboratory adverse experience	0	0
Other	0	1[†]

[†] The patient was lost to follow-up but completed the pharmacokinetic sampling and was included in the pharmacokinetic and safety analyses, except for the poststudy safety evaluation.

AN	Protocol	Site	Age (months)	Gender	Race	Weight (kg)	Height (cm)
≥6 Months to <1 Year							
102	136	1	8	F	Multiracial	9.3	72.5
103	136	1	10	M	White	10.2	69.9
104	136	1	11	F	Black	8.4	73.0
105	136	1	11	M	Multiracial	10.8	78.5
201	138	1	11	M	Hispanic	10.5	75.2
202	138	3	8	F	Hispanic	8.2	69.0
205	138	5	11	F	White	9.0	71.0
206	138	5	7	M	White	7.9	67.0
225	138	3	6	M	Hispanic	8.9	70.0
226	138	5	8	M	White	10.8	71.0
227	138	3	11	F	Hispanic	9.7	77.0
228	138	2	9	M	Multiracial	7.9	68.0
229	138	3	9	M	Hispanic	8.5	73.5
230	138	3	8	M	Hispanic	7.9	73.0
≥1 Year to <2 Years							
101	136	1	12	F	Black	10.9	75.2
107	136	1	21	F	Black	12.6	85.0
108	136	1	20	M	White	12.4	86.6
109	136	1	23	M	Black	13.4	84.0
110	136	1	14	F	White	9.8	75.5
112	136	1	21	F	Multiracial	10.2	79.0
131	136	1	22	F	Black	12.1	83.8
132	136	1	20	F	White	10.8	80.0
133	136	1	19	M	White	10.9	80.0
203	138	2	12	F	Multiracial	10.9	73.0
204	138	2	12	F	Multiracial	8.9	77.5
207	138	1	19	F	Multiracial	12.6	83.0
208	138	1	21	F	White	11.8	84.5
209	138	5	20	F	White	10.4	83.0
210	138	2	19	F	Multiracial	10.5	78.0
231	138	1	20	F	Hispanic	12.7	82.0
234	138	1	19	M	Hispanic	12.2	83.5
235	138	3	17	M	Hispanic	10.3	82.0
Mean							
Male			13			10.2	75.9
Female			16			10.5	77.9
Range							
Male			6 to 23			7.9 to 13.4	67.0 to 86.6
Female			8 to 22			8.2 to 12.7	69.0 to 85.0
Mean Combined			14			10.4	77.0
Range Combined			6 to 23			7.9 to 13.4	67.0 to 86.6

STUDY DESIGN AND TREATMENT ADMINISTRATION

This was a multicenter, open-label, single-dose study in ≥6-month- to <2-year-old patients. A single 4-mg dose of the sprinkle formulation of montelukast was administered to each patient with 1 tablespoon of applesauce.

Patients were allowed to consume clear apple juice approximately 1 hour prior to administration of test product. Water was consumed ad libitum. There were no food restrictions other than ensuring that meals did not interfere with clinical procedures.

FORMULATION

The following formulations and batch numbers where used in this study.

Table 1. Montelukast formulation used in this study

Test product	Potency	Formulation	Control number	Formulation Number
Montelukast	4 mg	Sprinkles/pouch	CA-A678, CA-A704B, CA-A704, CA-A704D	MR-3808

PHARMACOKINETIC MEASUREMENTS

Blood sampling

Blood samples for pharmacokinetic analysis were obtained up to 24 hours after drug administration according to 1 of 2 possible fixed, 4-time point sampling schedules (Schedule A or B, Table below). The sampling schedule used in this study was selected based on a more extensive (13-time point) sampling schedule employed after administration of a single 4-mg dose of the sprinkle formulation of montelukast in adult subjects (Protocol 090; N=24).

Treatment	Test Product/Dose	Number of Doses	Blood Sampling Times
A	Sprinkle formulation of montelukast, 4 mg	1	0 (predose) and 2.5, 5, and 12 hours postdose
B	Sprinkle formulation of montelukast, 4 mg	1	0 (predose) and 3, 8, and 24 hours postdose

Analytical Method

Plasma concentrations of montelukast were determined by HPLC assay procedure with fluorescence detection.

DATA ANALYSIS

Pharmacokinetic Analysis

The primary pharmacokinetic parameters of montelukast evaluated in this study were determined by population analysis and included the estimates: area under the concentration-time curve (AUCpop), Cmax, Tmax and t½. The sponsor estimated all PK parameters using a nonlinear mixed-effects model except for t½, where a linear mixed-effects model was used. A 1-compartment model with first-order absorption and elimination was used to fit the concentration-time data, with the log clearance parameter and log elimination rate constant constraints assumed to be randomly distributed around a population mean.

REVIEWER'S REMARKS

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. This reviewer fitted the adult and children data separately and together.

When all the data were pooled together, a 2-compartment model with first order absorption and elimination was used. The effect of covariates, such as weight and age were introduced into the basic adult and children model, and was evaluated based on the change in value of the objective function. Body weight was the only covariant that affected drug clearance (data not shown).

When data were handled separately, a 1-compartment model with first-order absorption and elimination was used to fit the concentration-time data generated in children 6 month to 2 years of age. The analysis was done with the inclusion and exclusion of subjects 101 and 132 who appear to be outliers. The exclusion of these subjects did not affect the outcome of the average population PK parameters.

The sponsor used the SAS software to estimate the population PK of the drug. This reviewer used NONMEM software to reproduce the results submitted in this NDA. Different model were fitted to the adult and children data separately and together.

A 2-compartment model with first order absorption and elimination better described the adult data from protocol 034. The adult Cmax was calculated using non-compartmental methods and the children Cmax was calculated based on the estimates of ke, ka and Vd. T1/2 has calculated using the estimated rate of elimination.

The effect of covariates, such as weight and age were introduced into the basic adult and children models. The analysis showed no correlation between Cmax or AUC and weight in the group of children ≥6 months to < 2 years of age receiving Singulair oral granules 4mg (Figure 6.1). This suggests that the dosage regimen in this group of children should not be based on weight.

This reviewer used WinNonlin in an attempt to estimate, which would be the most appropriate dose for this children population in terms of achieving similar exposure as that obtained in adults. Simulations were done using the estimated average PK parameters generated in the population PK analysis (data not shown).

STATISTICAL ANALYSIS

The AUCpop was computed based on the population means of the above parameters and was compared with adult historical data analyzed similarly (Protocol 034, 10-mg FCT in adults). Since an interim analysis was provided, all confidence intervals (CIs) for the AUCpop ratios were calculated at a conservative 95% level of confidence, instead of at a 90% level. The 95% CI for the AUCpop ratio (pediatric/adult) was evaluated against the prespecified comparability bounds of (0.50, 2.00). Summary statistics were provided for all other parameters. Analyses for the age-specific subgroups were also performed.

SAFETY MEASUREMENTS

Safety was evaluated in this study by monitoring of adverse events, laboratory safety data, physical examinations, 12-lead ECGs, and vital sign evaluations.

RESULTS

Analytical Method Pre-Study Validation

Recovery: Not included in this submission

Limit of Quantitation: Not included in this submission

Stability: Not included in this submission

Table 2. Assay performance (in-study validation) for Montelukast

	Montelukast
Linearity	Satisfactory: Standard curve range from 3-1000ng/mL; $r^2 \geq 0.99$
Accuracy	Satisfactory: 92.6 at 4.82 ng/mL; 99.4% at 48.2 ng/mL; 100.7% at 482 ng/mL.
Presicion	Satisfactory: (%RSD) 8.3% at 4.82 ng/mL; 6% at 48.2 ng/mL; 5% at 482 ng/mL.
Specificity	Satisfactory: Chromatograms submitted

Pharmacokinetic Results

The individual observed and predicted plasma concentration-time profiles for montelukast in children ≥ 6month to < 2 years of age receiving a single 4-mg oral dose of the MTL sprinkle formulation are shown in Figure 1. Figures 2 and 3 show the relationship between AUCpop and weight and between WRES and Predicted concentration, respectively for this children population. For the adult population this relationships are shown if Figures 4 and 5.

Table 3 summarizes the finding for the model building procedure in the children and adult populations. This table shows that neither the adult clearance nor the children clearance is affected by covariates such as age and weight factors.

Table 4 summarizes the mean population pharmacokinetic parameters calculated based on individual estimations of ka, ke, CL and Vd values using NONMEM. Likewise Table 5 shows the population PK parameters calculated by the sponsor. Table 6 shows the 90% confidence intervals applied to the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast.

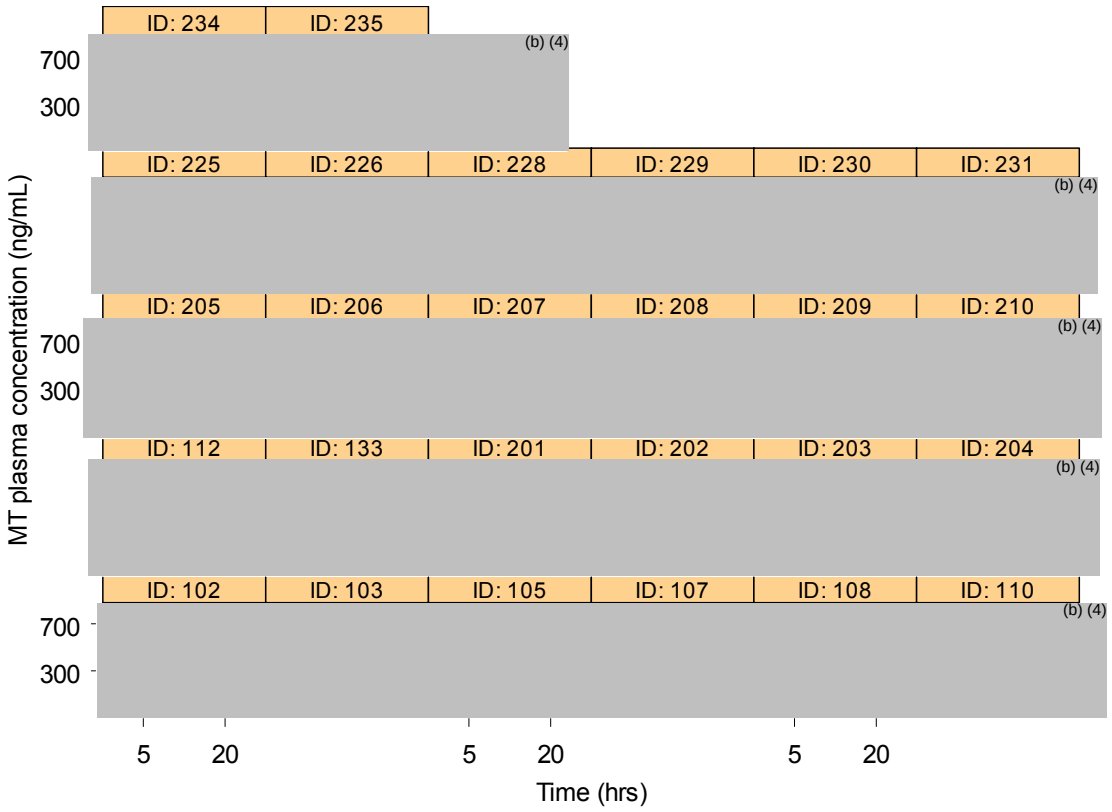


Figure 1. Individual Montelukast plasma concentration-time profiles following single administration of MTL oral granlues 4 mg to asthmatic children ≥6 months to 2 years of age.

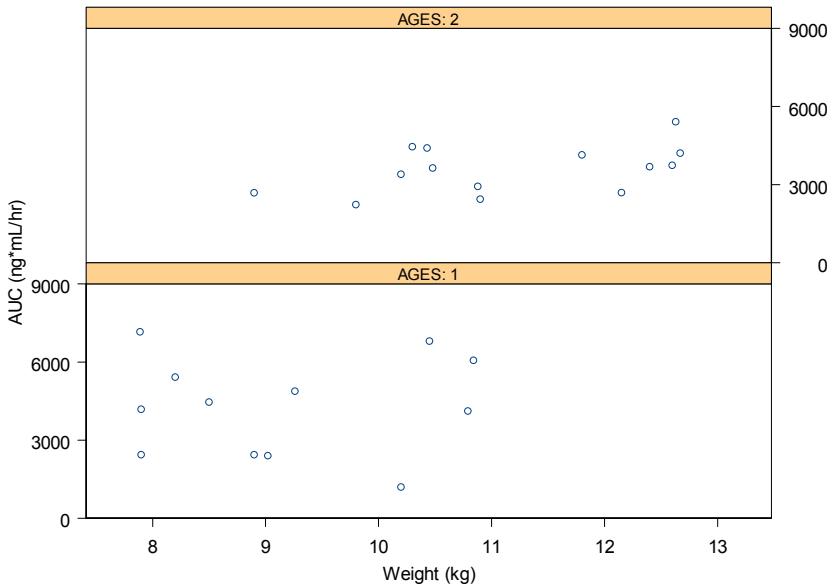


Figure 2. Individual AUC vs. WT in children receiving single dose of Montelukast sprinkles 4 mg. Ages 1 correspond to children ≥6 months < 1 year and ages 2 correspond to children ≥ 1 years to <2 years of age.

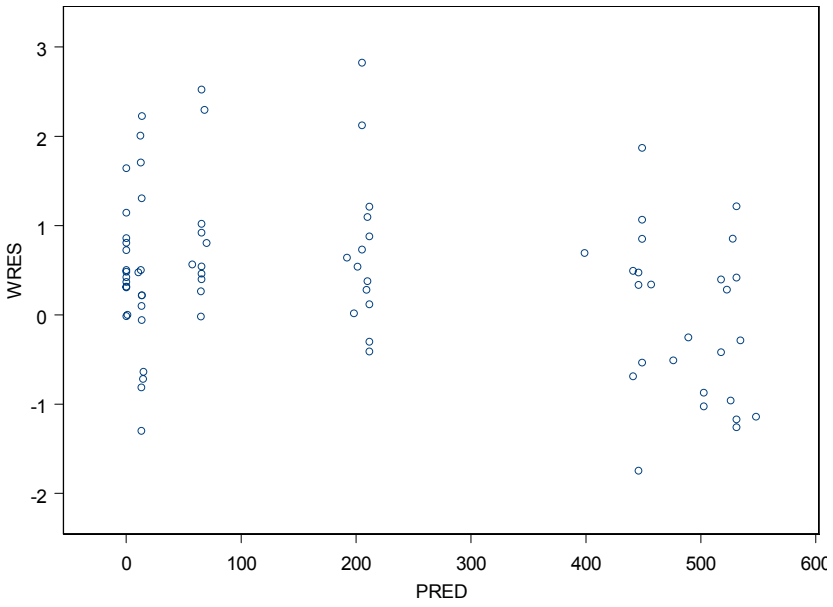


Figure 3. WRES vs. predicted values (PRED) in children receiving single dose of Montelukast oral granlues 4 mg.

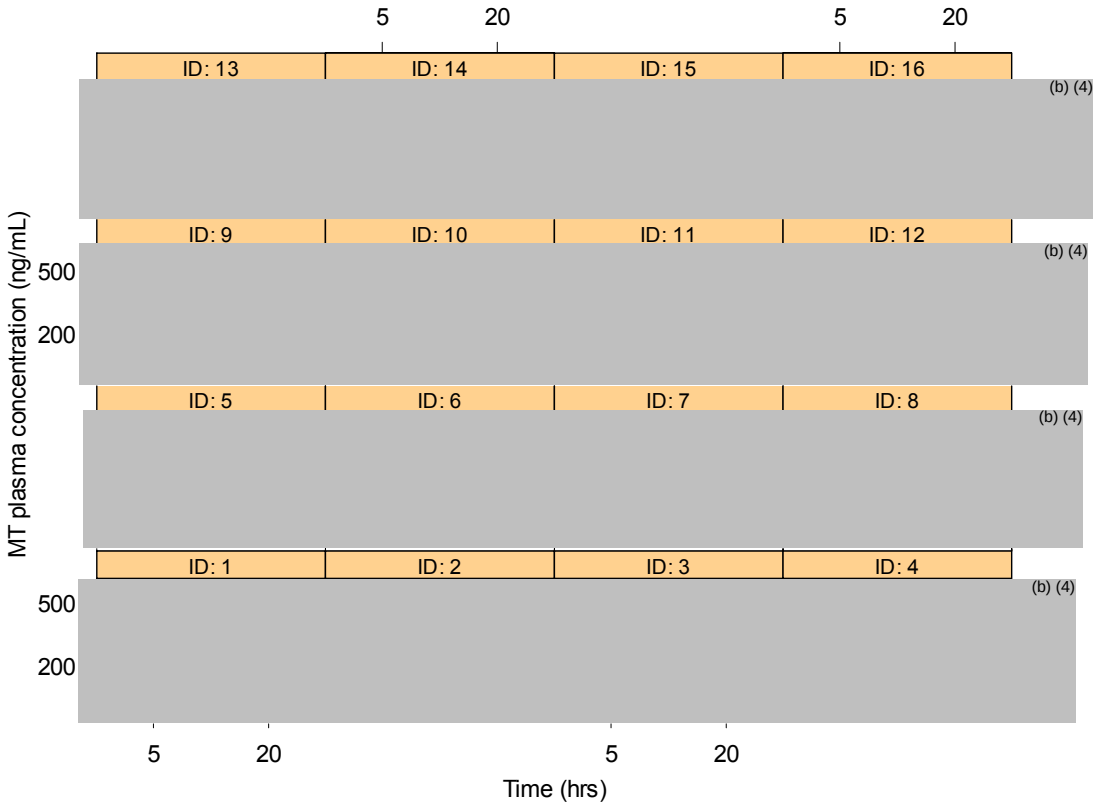


Figure 4. Individual Montelukast plasma concentration-time profiles following single administration of MTL film-coated tablets 10 mg to healthy adult volunteers. Data was fitted to a 2-compartment model with first order absorption and elimination. Data from protocol 034.

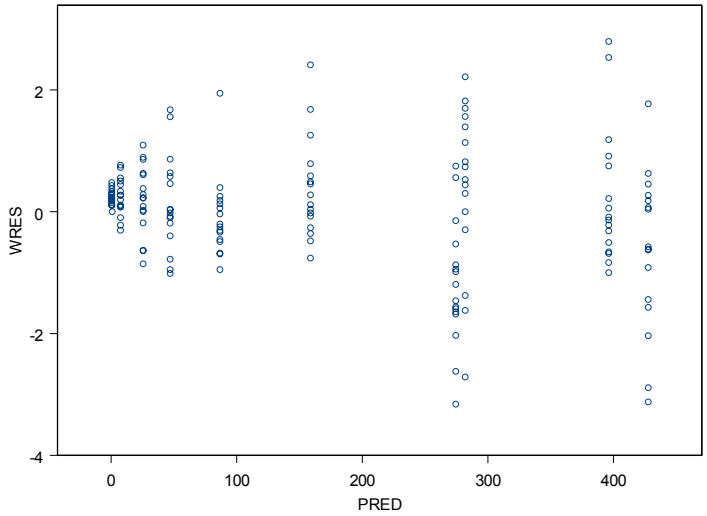


Figure 5. Weight of residuals versus predicted concentration plasma concentration-time profiles following single administration of MTL film-coated tablets 10 mg to healthy adult volunteers. Data was fitted to a 2-compartment model with first order absorption and elimination. Data from protocol 034.

Table 3. Model building results

	Children data		
Model	**OBF**	**Δ OBF**	**KEEP**
Basic 1CBM	734.185		Yes
Basic :CL+ WT	734.19	0	NO
Basic:CL+AGE	734.084	0.101	NO
	Adult data		
Basic 2CBM	1201.45		YES
Basic:CL+WT	1201.3	0.15	NO
Basic:CL+AGE	1201.35	0.1	NO

Table 4. Mean montelukast population pharmacokinetic parameters following single administration of Singulair sprinkles 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM.

Montelukast formulations: sprinkles, chewable tablets, film-coated tablets					
PK Parameter	**Children ≥6m to <1y**	**Children ≥1yto <2y**	**Children ≥6m to <2y**	**Children ≥2y to <6y**	**Adults**
AUC_{pop} (ng*hr/mL)[a]	4298.2±542.1	4060.4±401.9	3907 ±286.4	2761.1±200.7*	2644.8±154.1
$Cmax_{pop}$ (ng/mL) [a]	666.6±77.9	561.9±47.4	610.2 ±44.4	504.4±46.1*	352.6±25.53**
CL_{pop} (ml/min) [a]	20.47±4.1	19.59±1.33	19.96±1.86	25.7±1.58*	66.7±18.75
Tmax (hr) [b]	1.5±0.2	1.52±0.16	1.51±0.18	1.81±0.78	3.87±1.36**
T1/2[b]	3.39±1.5	3.37±0.97	3.38±1.22	2.36±0.9	1.94±0.33[c]

[a] mean ± SE; [b]mean±SD; *Data estimated using NONMEM from protocol no. 066; **calculated using non-compartmental methods; [c]based on 2CBM parameters

Table 5. Mean montelukast population pharmacokinetic parameters following single administration of Singulair sprinkles 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by sponsor

Montelukast formulations: sprinkles, chewable tablets, film-coated tablets					
PK Parameter	**Children ≥6m to <1y**	**Children ≥1yto <2y**	**Children ≥6m to <2y**	**Children ≥2y to <6y**	**Adults**
AUC_{pop} (ng*hr/mL)[a]	3470.9±499.3	3039.3±212.5	3226.6±250	2721±164.4	2595±164.5
Cmax (ng/mL) [a]	583.5±84.8	470.1±40.7	514.4±43.1	471.01±65.3	283.7±54.3
CL_{pop} (ml/min) [a]	19.2±2.8	21.9±1.5	20.7±1.6	-	64.9±4.2
Tmax (hr) [b]	2.07±0.28	2.34±0.14	2.24±0.14	2.07±0.3	3.39±0.2
T1/2[b]	3.24±0.36	3.48±0.2	3.39±0.2	3.17±0.2	4.09±0.17

[a] mean ± SE; [b]mean±SD

Table 6. Point estimates and 90% confidence intervals for the log-transformed Cmax and AUC comparing different children populations to adults receiving montelukast

Comparison	**PK parameter**	**Point estimates**		**90% confidence intervals**	
		Sponsor's findings*	This reviewer' findings	Sponsor's findings*	This reviewer' findings
≥6m to <1 y/adult	AUC	135	148.1	102-154	119.3-183.9
	Cmax		178.9		141.4-226.4
≥1y to <2y/adult	AUC	118	133.7	97-144	108.7-164.5
	Cmax		157.8		125.9-197.3
≥2y to <6 y/adult	AUC	105	103.2	90-122	84.2-126.5
	Cmax		141.8		113.6-176.9

*sponsor reported 95% confidence intervals

Figures 6, 7 and 8 are box plots for the population CL, AUC and Cmax, respective for children 6 months to <5 years of age and adult volunteers. These parameters were calculated based on individual estimation of PK parameters calculated using a population PK approach. The adult Cmax individual values for calculated using non-compartmental methods.

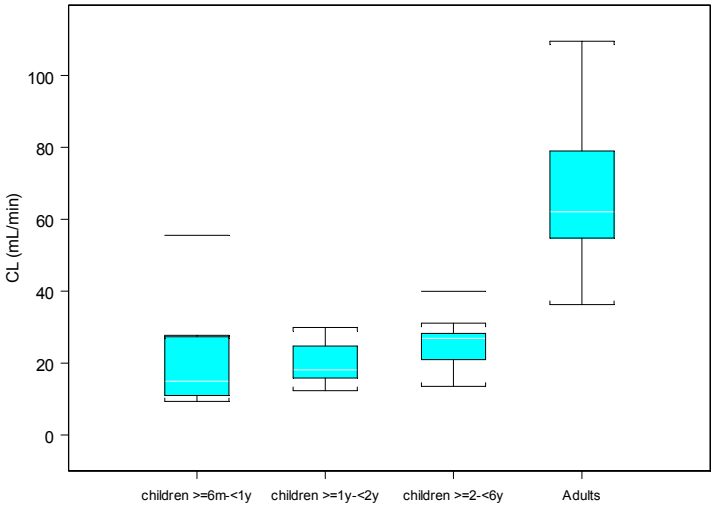


Figure 6. Box plot for population clearances (CL) following single administration of Singulair sprinkles 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old Group.

children >=6m-<1y

(b) (4)

```
1st Qu.: 11.655000
Mean: 20.470000
Median: 14.960000
3rd Qu.: 27.315000
```

(b) (4)

```
Std Dev.: 13.660793
SE Mean:  4.118884
LCL Mean: 11.292555
UCL Mean: 29.647445
```

children >=1y-<2y

(b) (4)

```
1st Qu.: 15.895000
Mean: 19.590000
Median: 18.100000
3rd Qu.: 23.760000
```

(b) (4)

```
Std Dev.:  5.142417
SE Mean:  1.327766
LCL Mean: 16.742224
UCL Mean: 22.437776
```

children >=2-<6y

(b) (4)

```
1st Qu.: 22.550000
Mean: 25.650000
Median: 26.860000
3rd Qu.: 28.105000
```

(b) (4)

```
Std Dev.:6.132151
SE Mean:  1.583314
LCL Mean: 22.254128
UCL Mean: 29.045872
```

Adults

(b) (4)

```
1st Qu.:  55.952500
Mean:  66.675000
Median:  62.070000
3rd Qu.:  78.007500
```

(b) (4)

```
Std Dev.:  18.751380
SE Mean:   4.687845
LCL Mean:  56.683095
UCL Mean:  76.666905
```

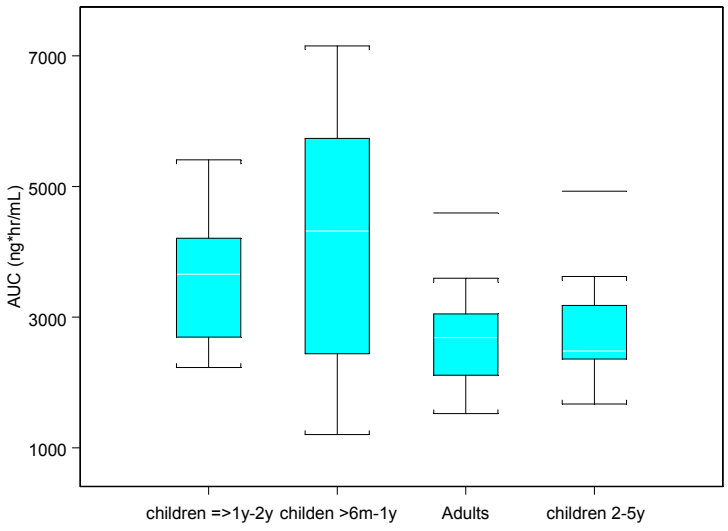


Figure 7. Box plot for AUC following single administration of Singulair sprinkles 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. Subjects 101 and 132 excluded from the 6m-2y old Group.

Children =>1y-2y

(b) (4)
1st Qu.: 2752.5750
Mean: 3573.9214
Median: 3657.3500
3rd Qu.: 4190.0750
(b) (4)
Std Dev.:
907.0569
SE Mean:
242.4212
LCL Mean: 3050.2024
UCL Mean: 4097.6405

Children >6m-1y

(b)
1st Qu.: 2441.325
Mean: 4295.592
Median: 4318.400
3rd Qu.: 5576.600
(b) (4)
Std Dev.: 1889.144
SE Mean: 545.349
LCL Mean: 3095.287
UCL Mean: 5495.897

Adults

(b) (4)
1st Qu.: 2137.6000
Mean: 2689.4188
Median: 2685.2500
3rd Qu.: 2982.8500
(b) (4)
Std Dev.: 765.7512
SE Mean: 191.4378
LCL Mean: 2281.3787
UCL Mean: 3097.4588

Children 2-5y

(b) (4)
1st Qu.: 2371.8000
Mean: 2761.0933
Median: 2482.4000
3rd Qu.: 2971.3000
(b) (4)
Std Dev.: 777.3142
SE Mean: 200.7017
LCL Mean: 2330.6311
UCL Mean: 3191.5556

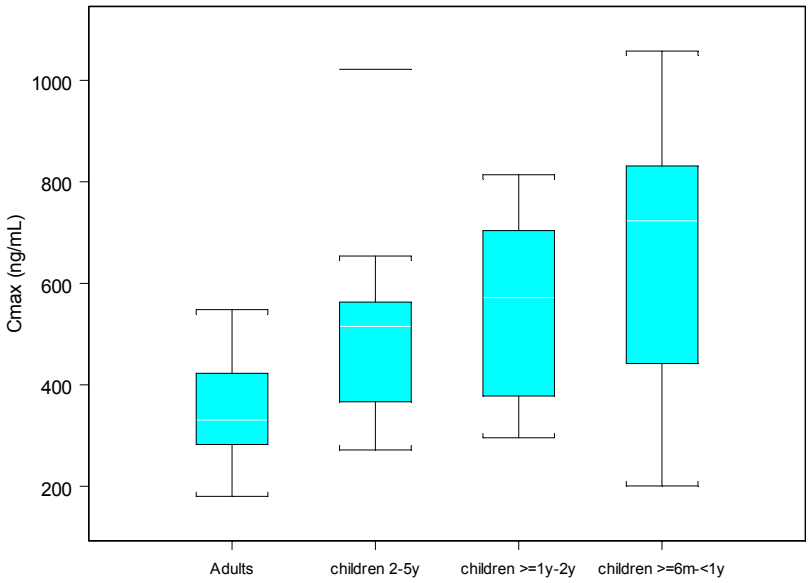


Figure 6. Box plot for population Cmax (CLpop) following single administration of Singulair sprinkles 4 mg in children 6 months to <2 years of age, single dose of Singulair chewable tablets to children ≥2y to <6 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Data calculated by this reviewer using NONMEM. The Cmax adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6m-2y old Group.

Adults

(b) (4)
1st Qu.: 295.25000
Mean: 352.56250
Median: 330.50000
3rd Qu.: 419.00000
(b) (4)
Std Dev.: 102.15476
SE Mean: 25.53869
LCL Mean: 298.12807
UCL Mean: 406.99693

children 2-5y

(b) (4)
1st Qu.: 392.46000
Mean: 504.44267
Median: 515.19000
3rd Qu.: 547.72500
(b) (4)
Std Dev.: 178.70098
SE Mean: 46.14039
LCL Mean: 405.48136
UCL Mean: 603.40397

children >=1y-2y

(b) (4)
1st Qu.: 400.87500
Mean: 561.98571
Median: 571.64000
3rd Qu.: 699.55250
(b) (4)
Std Dev.: 177.52427
SE Mean: 47.44536
LCL Mean: 459.48625
UCL Mean: 664.48518

children >=6m-<1y

(b) (4)
1st Qu.: 465.14250
Mean: 666.55750
Median: 723.40500
3rd Qu.: 824.71000
(b) (4)
Std Dev.: 269.83232
SE Mean: 77.89388
LCL Mean: 495.11422
UCL Mean: 838.00078

DISCUSSION

As observed in Tables 3 and 4 the estimated average population PK parameters calculated by this reviewer for the adults and 2- to 5 years olds are in agreement with the values reported by the sponsor. However, the calculated values by this reviewer for Cmax and AUC for children 6 months to <2 years of age are much higher than the ones reported by the sponsor. This discrepancy might be due to a difference in the procedure for calculating these parameters. This reviewer calculated the average population PK parameters based on the estimation of individual values. The sponsor's approach was to calculate the average population clearances and AUC based on average estimated population parameters. This speculation is supported by simulation done using the average estimated population PK parameters calculated by this reviewers, which showed similar values than those reported by the sponsor (data not shown).

As shown in Table 5 and Figures 7 and 8, the variability in the data for the 2 years to <6 year olds and adults is similar, indicating similar safety and efficacy. However, AUC and Cmax values for the 6 month to <2 year olds, especially the 6month to <1 year of age are highly variable. AUC values range from 1200 ng*hr/mL to 7153 ng*hr/mL and the mean value was 48% higher than the observed in adults. Cmax ranges from 465.1 to 1057.8 ng/ml and the mean value increase by 79% compared to adults. Higher variability in Cmax values compared to variability in AUC values has been observed in the already approved formulation for children 2 to <6 years of age whose Cmax was 42% higher compare to that observed in adults. There might be several reasons for this variability in the younger children population. One can speculate that it might be due to differences in metabolic clearance, extend of absorption, compliance, etc.

The systemic exposure in the ≥ 1 year to <2 year olds is less variable, but still higher compared to the one in adults. The mean AUC was 34% higher and mean Cmax was 58% higher that those observed in adults.

Simulations were done by this reviewer considering the estimated average PK parameters generated in the population PK analysis using WinNonlin in an attempt to estimate which would be the most appropriate dose for this children population in terms of achieving similar exposure (AUC) as that obtained in adults. It was found that 3.5-mg better compares with the AUC obtained for the adult population. However, one should keep in mind that this simulations were done considering average PK parameters which means that those patients who had a exposure of 1200 ng*hr/ml receiving 4 mg may be at risk of efficacy assuming a target exposure of efficacy between 1200 to 4500 ng*hr/mL as reported by the sponsor.

It is clear from Table 5 that the exposure in the 1-2 year olds, especially the one in the 6 months to <2 years, is significantly different that the one observed in adults. How clinical relevant are these differences in exposure needs to be evaluated by the medical reviewer.

CONCLUSION

- It seems that clearance and therefore AUC are not correlated with weight in the group of children ≥6 months to < 2 years of age.
- High variability in exposure (AUC and Cmax) was observed in the children ≥6 months to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair sprinkles to this population would give more comparable average

systemic exposure to that in adults. However, due to the high variability in exposure some children may be at risk for efficacy considering a target of 1200 ng*hr/mL to 4500 ng*hr/mL. Therefore, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age.

4.3 Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	**20-829, 20-830, 21-409**	**Brand Name**	**Singulair granules**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Montelukast Sodium**
Medical Division	**DPADP**	**Drug Class**	**Leukotriene antagonist**
OCPB Reviewer	**Sandra Suarez-Sharp**	**Indication(s)**	Supplemental application for the indication of Perennial Allergic Rhinitis (PAR)
OCPB Team Leader	**Emmanuel Fadiran**	**Dosage Form**	It is currently available as 10-mg film-coated tablets, 4-mg and 5-mg chewable tablets, and 4-mg oral granules. The sponsor submits this supplemental application to all of the NDAs for all of these formulations.
Date of Submission	**Sep 30, 2004**	**Dosing Regimen**	
Estimated Due Date of OCPB Review	**April 2005**	**Route of Administration**	**oral**
PDUFA Due Date	**July 2005**	**Sponsor**	**Merck Research Lab.**
Division Due Date	**June 2005**	**Priority Classification**	**Standard**

3 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	**Comments**
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**X**	Comments have been sent to firm (or attachment included). FDA letter date if applicable. 1) Submit PK data to support the proposed dose in 6 – 11 month old patients.

QBR questions (key issues to be considered)	**1. Does the PK data support the dosage regimen in children 6 months to 1 year of age?**

Other comments or information not included above	This supplemental NDA contains two studies in adults and children 15 years and older to support the indication of PAR. The sponsor is seeking approval of this indication in children 6 months and older. According to the medical team it is reasonable to assume similar disease progression and similar response to intervention and therefore, it is possible to extrapolate efficacy down to 6 moth old kids. Singulair has been approved down to 1 year of age for the treatment of asthma based on similar systemic exposure in older kids and adults. Since singulair is not approved down to age 6 months, Merck needs to provide justification for the proposed dose for the 6 month -olds in this application. Hence, the sponsor has been requested for PK data to be submitted to the sNDA for review. It should be noted that the sponsor has already submitted PK information in asthmatic children 6 months and above and the data has been reviewed and entered in DFS. For the current submission, this reviewer will rely on the data already reviewed since the PK in asthmatics and PAR patients is assumed to be similar.
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CC: NDA 21-409, HFD-870 (Electronic Entry or Lee), HFD-570 (Garcia), HFD-870 (Fadiran, Hunt, Malinowski))

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/s/

Sandra Suarez
6/7/05 10:59:16 AM
BIOPHARMACEUTICS

Emmanuel Fadiran
6/7/05 11:28:36 AM
BIOPHARMACEUTICS
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033

20-830/S035

21-409/S012

OTHER REVIEW(S)

NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

Regulatory Project Management Labeling Review

Background

Merck submitted efficacy supplements for the 3 Singulair NDAs on September 30, 2004, to support the use of Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules for the relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older, and to provide for changes to the US package insert (PI), patient product information (PPI), and the container/carton labels.

Review

The labeling was reviewed by the CMC, Clinical, Clinical Pharmacology/Biopharmaceutics, Statisics, Pharmacology/Toxicology and Project Management teams. The Statistics, Clinical Pharmacology/Biopharmaceutics and CMC teams found the draft labeling (PI) text to be acceptable from the standpoint of their individual disciplines, and did not recommend any revisions.

The Clinical and Pharmacolgy/Toxicology teams recommended revisions to the original draft labeling (PI) which were sent via facsimile to Merck on June 21, 2005. Merck responded via e-mail on June 24, 2005, and requested a teleconference to discuss some of the proposed revisions. A teleconference was held on June 27, 2005, to discuss the recommended revisions to the Clinical Studies and ADVERSE REACTIONS sections (see Memorandum of Telecon).

Based upon the discussion at the teleconference, Merck submitted revised draft labeling on July 1, 2005. The Division reviewed the labeling and sent revisions to Merck on July 6, 2005. Merck agreed to accept the changes as proposed in the facsimile dated July 6, 2005, and submitted revised draft labeling on July 19, 2005. This submission was sent to the Clinical and CMC teams for verification that all proposed revisions had been made by Merck, as requested by the Division. The labeling was found to be acceptable.

I compared the draft labeling submitted July 19, 2005, to the agreed-upon labeling from the facsimile dated July 6, 2005. All of the changes requested by the FDA to the labeling were made by Merck. No other changes other than those which were approved were noted.

Recommended revisions to the carton/container labels and the Patient Product Information (PPI) were sent on July 6, 2005, and July 19, 2005, respectively. Merck requested a teleconference (held on July 20, 2005) to clarify some questions regarding the carton/container labels. Merck agreed to the changes proposed by the Division to the cartons/containers and PPI. Revised draft labeling (PPI and cartons/containers) was

submitted on July 22, 2005, and circulated to the review teams (CMC and Clinical). The labeling was found to be acceptable.

Conclusion

The revised draft labeling text (PI dated July 19, 2005; Patient Product Information (PPI) and carton/container labels submitted July 22, 2005) are acceptable.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products

Drafted: LGarcia/July 22, 2005

Initialed: SBarnes/July 26, 2005

Finalized: LGarcia/July 27, 2005

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/s/

Lori Garcia
7/27/05 12:13:53 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 29, 2005

TO: Badrul Chowdhury, M.D., Director
Division of Pulmonary and Allergy Drug Products
HFD-570

VIA: Lori Garcia, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products
HFD-570

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Singulair® (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules, NDAs 20-829/S-033, 20-830/S-035, and 21-409/S-012

Background and Summary

The Sponsor submitted Efficacy Supplements, September 30, 2004, for Singulair® (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules, NDAs 20-829/S-033, 20-830/S-035, and 21-409/S-012 for the addition of the indication of perennial allergic rhinitis. The PPI was revised to reflect the new indication.

Comments and Recommendations

We have only reviewed proposed changes to the PPI and recommend the following revisions for ease of patient comprehension.

1. Under the heading,**" What is SINGULAIR?"** (b) (4) "See the end of this leaflet for more information about asthma" at the end of the asthma indication statement.

2. Under the heading,**" What is SINGULAIR?",** revise the allergic rhinitis section as follows:

Allergic Rhinitis

SINGULAIR is used to help control the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose). SINGULAIR is used to treat:

- **seasonal allergic rhinitis** (outdoor allergies that happen part of the year) in adults and children ages 2 years and older
- **perennial allergic rhinitis** (indoor allergies that happen all year) in adults and children ages 6 months and older

(b) (4)

All other proposed revisions are acceptable from a patient comprehension standpoint.

Please call us if you have any questions.

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/s/

Jeanine Best
6/29/05 10:10:24 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/30/05 01:51:00 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER(s):

20-829/S033
20-830/S035
21-409/S012

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 20-829/S-033; 20-830/S-035; 21-409/S-012 SUPPL #

HFD # 570

Trade Name Singulair

Generic Name montelukast sodium

Applicant Name Merck

Approval Date, If Known July 27, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-829 Singulair (montelukast sodium) 10mg Tablets

NDA# 20-830 Singulair (montelukast sodium) 4mg and 5mg Chewable Tablets

NDA# 21-409 Singulair (montelukast sodium) 4mg Oral Granules

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 265
Study 246

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar

investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 265
Study 246

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
(b) (4) YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
(b) (4) YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Lori A. Garcia
Title: Regulatory Project Manager
Date: July 21, 2005

Name of Office/Division Director signing form: Badrul A. Chowdhury, M.D., Ph.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Badrul Chowdhury
7/27/05 12:40:05 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 20-829, 20-839, 21409 Supplement Type (e.g. SE5): SE1 Supplement Number: 033, 035, 012

Stamp Date: September 30, 2004 Action Date: July 27, 2005

HFD 570 Trade and generic names/dosage form: Singulair (montelukast sodium) Tablets, Chewable Tablets, Oral Granules

Applicant: Merck Therapeutic Class: Leukotriene receptor antagonist

Indication(s) previously approved:
Prophylaxis and Chronic Treatment of Asthma in Adults and Pediatric Patients 12 months of Age and Older.
Relief of Symptoms of Seasonal Allergic Rhinitis in Adults and Pediatric Patients 2 Years of Age and Older.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **xxNo: Please check all that apply: x Partial Waiver ___ Deferred x Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other: _____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ___ kg ___ mo. 0 yr. ___ Tanner Stage ___
Max ___ kg ___ mo. <6 yr. ___ Tanner Stage ___

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**

- ❑ **X Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.** =6 **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc:

NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:** _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-###
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Lori Garcia

7/27/05 11:58:56 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 20-829 NDA 20-830 NDA 21-409	Efficacy Supplement Type SE-1	Supplement Number S-033 S-035 S-012	
Drug: Singulair Tablets, Chewable Tablets and Oral Granules		Applicant: Merck	
RPM: Lori Garcia		HFD-570	Phone # 301-827-5580

Application Type: **(x)** 505(b)(1) **( )** 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** **( )** Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

❖ Application Classifications:	
• Review priority	**(x)** Standard **( )** Priority
• Chem class (NDAs only)	
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	July 31, 2005
❖ Special programs (indicate all that apply)	**(x)** None Subpart H **( )** 21 CFR 314.510 (accelerated approval) **( )** 21 CFR 314.520 (restricted distribution) **( )** Fast Track **( )** Rolling Review **( )** CMA Pilot 1 **( )** CMA Pilot 2
❖ User Fee Information	
• User Fee	**(x)** Paid UF ID number ___4832_____
• User Fee waiver	**( )** Small business **( )** Public health **( )** Barrier-to-Innovation **( )** Other (specify) _____
• User Fee exception	**( )** Orphan designation **( )** No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **( )** Other (specify) _____
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	**( )** Yes **(x)** No
• This application is on the AIP	**( )** Yes **(x)** No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(x)** Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(x)** Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **( )** Verified 21 CFR 314.50(i)(1) **( )** (ii) **( )** (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	**( )** N/A (no paragraph IV certification) **( )** Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	**( )** Yes **( )** No **( )** Yes **( )** No **( )** Yes **( )** No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	**( )** Yes **( )** No **( )** Yes **( )** No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	July 27 , 2005
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	**( )** Yes, Application #_____ **(x)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	**(x)** AP **( )** TA **( )** AE **( )** NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	**(x)** Materials requested in AP letter **( )** Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**( )** Yes **(x)** Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**( )** None **( )** Press Release **( )** Talk Paper **( )** Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	July 6, 2005 (PI) July 19, 2005 (PPI)
• Most recent applicant-proposed labeling	July 19, 2005 (PI) July 22, 2005 (PPI)
• Original applicant-proposed labeling	September 30, 2004
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC: May 27, 2005 DSCRS: June 30, 2005 TCON June 27, 2005 TCON July 20, 2005 PM review: July 27, 2005
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	July 1, 2005 (comments)
• Applicant proposed	September 30, 2004 (original) July 22, 2005 (revised)
• Reviews	July 8, 2005 (CMC) May 27, 2005 (DDMAC)
❖ Post-marketing commitments	N/A
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	December 8, 2005 (74-day letter) January 10 ,2005 (e-mail) March 3, 2005 (peds waiver) July 1, 2005 (carton/container comments) July 6, 2005 (revised PI) July 19, 2005 (revised PPI)
❖ Memoranda and Telecons	July 26, 2005 July 26, 2005
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	July 25, 2005(Medical TL) July 26, 2005 (revised Medical TL) July 27, 2005 (Division Director)
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	July 12, 2005
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	July 12, 2005, page 49
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	July 21, 2005
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	July 27, 2005
❖ Biopharmaceutical review(s) *(indicate date for each review)*	June 7, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	N/A
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	July 8, 2005
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	July 8, 2005
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Not requested **( )** Acceptable **( )** Withhold recommendation
❖ Methods validation	**( )** Completed (X) N/A **( )** Requested **( )** Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	July 6, 2005
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Lori Garcia

7/27/05 12:22:42 PM

MEMORANDUM OF TELECON

DATE: July 20, 2005

APPLICATION NUMBER: NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

BETWEEN:

Martin Himmel, M.D., Regulatory Affairs
Frank Seebach, M.D., Regulatory Affairs

AND

Gilbert McClain, Lydia I, M.D., Clinical Team Leader
Peri, Prasad, Ph.D., CMC reviewer
Badrul A. Chowdhury, M.D., Ph.D., Division Director
Purohit-Sheth, Tejashri, M.D., Clinical reviewer
Lori Garcia, R.Ph., Project Manager

SUBJECT: FDA recommended revisions to the draft labeling submitted by Merck on September 30, 2004.

The Division recommended revisions to the Singulair carton/container labels in a facsimile sent to Merck on July 6, 2005. An additional carton/container label comment was included in the fax dated July 19, 2005. Merck requested a teleconference to clarify the Division's comments with respect to the carton and container labels. The Division's comments (as provided in the fax dated July 6, 2005, and July 19, 2005) are in regular font and pertinent discussion is in *italics.*

Comment 1(July 6, 2005):
Singulair 4mg Oral Granules Trade Carton and packet
"DIRECTIONS FOR USE: See accompanying circular. Once opened, use the contents of this packet within 15 minutes (with or without mixing with food). Discard any unused portion."

Merck agrees to revise the label as recommended in this comment.

Comment 2 (July 6, 2005):

We note that only the 4 mg oral granules packet label lists the excipients, where as the 4 mg, 5 mg and 10 mg sample cartons and blister labels do not list the excipients.

A separate statement, however, is included on the sample cartons (only) that states "Singulair is contraindicated in patients who are hypersensitive to the components of this product".

List all excipients on the cartons or revise to "Singulair is contraindicated in patients who are hypersensitive to the components of this product. For a list of excipients see accompanying circular".

Merck asked the Division to clarify if the statements "Singulair is contraindicated in patients who are hypersensitive to the components of this product. For a list of excipients see accompanying circular" should be included on all cartons. The Division confirmed that unless all the excipients are listed, the cartons should be revised to contain these statements. Merck agreed to this recommended revision.

Comment 3 (July 6, 2005):

The color contrast of the text on the Singulair 5 mg carton is not distinct.
The white font should be changed to black for better legibility. This is also consistent with the 5 mg blister label.

Merck noted that they could not print black on the blister labels for technical reasons, and would prefer to use the white print. Additionally, Merck stated that there has been no post-marketing complaints related to the legibility of the Singulair packaging. The Division stated that the black is more legible (in our opinion), but Merck may choose to use white print.

Additional comment (July 19, 2005, fax):

Replace the phrase "For Allergic Rhinitis" with "For the Symptoms of Allergic Rhinitis" on all Cartons, Blisters, and Trays.

Merck agreed to this revision, however, they requested the Division's agreement that it would be acceptable to exhaust and replace approximately 5 months' worth of pre-printed blister foil with the previously submitted language "For Allergic Rhinitis."

(b) (4)

[redacted]

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia
7/26/05 03:13:15 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 19, 2005

To: Frank Seebach	**From:** LT Lori Garcia Regulatory Project Manager
Company: Merck	Division of Pulmonary and Allergy Drug Products
Fax number: 732-594-1030	**Fax number:** 301-827-1271
Phone number: 732-594-0222	**Phone number:** 301-827-5580

Subject: N20-829/S-033 PAR/proposed labeling revisions/PPI/Cartons/containers

Total no. of pages including cover: 9

Comments:

Document to be mailed: **YES** xx **NO**

N20-829/S-033
N20-830/S-035
N21-409/S-012

Dear Dr. Seebach:

We have reviewed the draft labeling for the Patient Information sheet submitted on September 30, 2004, and we are proposing the following revisions. Recommended insertions are indicated by underlines.

We are also providing another comment regarding the draft labeling for the cartons/containers (in addition to the comments regarding the cartons/containers sent via facsimile on July 6, 2005).

Submit revised draft labeling by Friday, July 22, 2005, if the recommended revisions provided in this facsimile are acceptable to you, or you may request a teleconference if you feel that further discussion regarding the recommended revisions is necessary.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301)-827-5580.

__5____ Page (s) Withheld

____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Withheld Track Number: Administrative-20-829/S033

Additional comment related to Cartons, Blisters, and Trays.

1. Replace the phrase "For Allergic Rhinitis" with "For the Symptoms of Allergic Rhinitis" on all Cartons, Blisters, and Trays.

Drafted: LGarcia/July 19, 2005

Initialed: SBarnes/July 19, 2005
TPurohit-Sheth/ July 19, 2005
LGilbert-McClain/ July 19, 2005

Finalized: LGarcia/ July 19, 2005

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/s/

Lori Garcia
7/19/05 04:12:05 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 6, 2005

To: Frank Seebach	**From:** LT Lori Garcia Regulatory Project Manager
Company: Merck	Division of Pulmonary and Allergy Drug Products
Fax number: 732-594-1030	**Fax number:** 301-827-1271
Phone number: 732-594-0222	**Phone number:** 301-827-5580

Subject: N20-829/S-033 PAR/proposed labeling revisions

Total no. of pages including cover: 20

Comments:

Document to be mailed: **YES** xx **NO**

N20-829/S-033
N20-830/S-035
N21-409/S-012

Dear Dr. Seebach:

We have reviewed the revised draft labeling for the package insert (PI) submitted on July 1, 2005, and we are proposing the following revisions. Recommended deletions are indicated by ~~strikeouts~~ and inserts are indicated by underlines.

Submit revised draft labeling within 1 week from the date of this facsimile if the recommended revisions provided in this facsimile are acceptable to you, or you may request a teleconference if you feel that further discussion regarding the recommended revisions to the PI is necessary.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301)-827-5580.

__17___ Page (s) Withheld

____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Withheld Track Number: Administrative-20-829/S033

Drafted: LGarcia/July 6, 2005

Initialed: SBarnes/July 6, 2005
Purohit-Sheth/July 6, 2005
LGilbert-McClain/ July 6, 2005
BChowdhury/July 6, 2005

Finalized: LGarcia/July 6, 2005

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/s/

Lori Garcia
7/6/05 12:59:15 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: July 1 , 2005

To: Frank Seebach	LT Lori Garcia **From:** Regulatory Project Manager
Company: Merck	Division of Pulmonary and Allergy Drug Products
Fax number: (732) 594-1030	**Fax number:** 301-827-1271
Phone number: (732) 594-0222	**Phone number:** 301-827-5580
Subject: Singulair PAR supplements/carton comments	
Total no. of pages including cover: 3	
Comments:	

Document to be mailed: YES NO

N20-829/S-033
N20-830/S-035
N21-409/S-012

Dear Dr. Seebach:

We have reviewed the labeling for the cartons and containers submitted September 30, 2004. Our comments and recommendations are listed below.

We request your response to our proposed revisions and comments within 1 week from the date of this facsimile.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301)-827-5580.

1. **Singulair 4mg Oral Granules Trade Carton and packet**
"DIRECTIONS FOR USE: See accompanying circular. Once opened, use the contents of this packet within 15 minutes (with or without mixing with food). Discard any unused portion."

2. We note that only the 4 mg oral granules packet label lists the excipients, where as the 4 mg, 5 mg and 10 mg sample cartons and blister labels do not list the excipients.

   A separate statement, however, is included on the sample cartons (only) that states "Singulair is contraindicated in patients who are hypersensitive to the components of this product".

   List all excipients on the cartons or revise to "Singulair is contraindicated in patients who are hypersensitive to the components of this product. For a list of excipients see accompanying circular".

3. The color contrast of the text on the Singulair 5 mg carton is not distinct. The white font should be changed to black for better legibility. This is also consistent with the 5 mg blister label.

Drafted: LGarcia/June 27, 2005

Initialed: SBarnes/June 28, 2005
PPeri/June 28, 2005
RLostritto/June 28, 2005
BChowdhury/June 29, 2005

Finalized: LGarcia/July 1, 2005

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/s/

Lori Garcia
7/1/05 01:44:34 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: Director, Division of Surveillance, Research, and Communication Support (DSRCS), HFD-410 PKLN Rm. 6-22

FROM:
Lori Garcia, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products
HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
June 27, 2005		20-829/S-033 20-830/S-035 21-409/S-012	SE1	October 11, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Singulair Tablets, Chewable Tablets and Oral granules	Standard	LT receptor antagonist	July 11, 2005 (if possible, please) (PDUFA goal = July 31, 2004)

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- **xx☐ OTHER *(SPECIFY BELOW)*:**

PPI

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
These efficacy supplements provide for the use of Singulair for PAR. Please review the PPI.
This submission is available in the EDR (N20-829/S-033/October 11, 2004):
\\Cdsesub1\n20829\S 033\2004-10-11\summary (for annotated PI, PPI and cartons)
\\Cdsesub1\n20829\S 033\2004-10-11\labeling (for Word version of PPI)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Garcia
6/27/05 11:15:13 AM

MEMORANDUM OF TELECON

DATE: June 27, 2005

APPLICATION NUMBER: NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

BETWEEN:

Martin Himmel, M.D., Regulatory Affairs
Frank Seebach, M.D., Regulatory Affairs
Diane Benezra-Kurshan, M.D., Worldwide Product
Theodore F. Reiss, M.D. Respiratory and Allergies
Barbara Knorr, M.D., Respiratory and Allergies
George Philip, M.D., Respiratory and Allergies
Naomi Nomura, Worldwide Product Labeling
Robert G. Sharrar, M.D., Clinical Risk Management
Ann Strauss, M.D., Clinical Risk Management
Ganesh Bala, B.V.Sc., Ph.D., Safety Assessment
Tom M. Casola, Office of Medical Legal
Debra V. Ewanciw, Worldwide Product Labeling
John Wagner, M.D., Clinical Pharmacology

AND

Gilbert McClain, Lydia I, M.D., Clinical Team Leader
Peri, Prasad, Ph.D., CMC reviewer
Badrul A. Chowdhury, M.D., Ph.D., Division Director
Pei, Luqi, Ph.D., Pharm/Tox Reviewer
Suarez, Sandra, Ph.D., Clin.Pharm/Biopharm reviewer
Fadiran, Emmanuel, Ph.D., Clin.Pharm/Biopharm Team Leader
Wilson, Stephen E, Deputy Director, Division of Biometrics II
Davi, Ruthanna C, Statistics Team Leader
Purohit-Sheth, Tejashri, M.D., Clinical reviewer
Lori Garcia, R.Ph., Project Manager

SUBJECT: FDA recommended revisions to the draft labeling submitted by Merck on September 30, 2004.

The Division recommended revisions to the Singulair label for the efficacy supplements identified above, which were provided to Merck in a facsimile dated June 21, 2005. Based upon their review of the Division's proposed changes, Merck submitted revised draft labeling on June

24, 2005 (via e-mail). The official submission was dated June 30, 2005, and was received on July 1, 2005.

Merck requested a teleconference, which was held on June 27, 2005, to discuss the proposed revisions to the CLINICAL PHARMACOLOGY and ADVERSE REACTIONS sections.

- CLINICAL PHARMACOLOGY
  Pharmacodynamics

  FDA agreed that Merck may retain the abbreviation "mg" to be consistent with their standard format.

- CLINICAL PHARMACOLOGY
  Clinical Studies-Perennial Allergic Rhinitis

  The Division acknowledged Merck's proposed changes to this section. The Division stated that the inclusion of Table 4 was negotiable. (b) (4) in order to place the efficacy of montelukast for PAR in the right context. Merck stated that they would address this issue and submit revised text for the Division's review. The Division noted that the label should include information regarding the effect size, confidence interval, and # of subjects enrolled in the study. (b) (4)

- ADVERSE REACTIONS
  Pediatric Patients 12 to 23 Months of Age with Asthma

  In the first sentence of the first paragraph, the Division noted that the number of pediatric patients was changed to 175 in error in our fax dated June 21, 2005. The correct number should be 124, as it is in the current label. Additionally, the correct age of pediatric patients in this sentence should be "12-23 months of age," not "6 to 23 months." Merck agreed to maintain this paragraph in this section as in the current label, but would like to re-evaluate the wording of this section. Any additional revisions will be proposed in the next draft.

- ADVERSE REACTIONS
  Adults and Adolescents 15 Years of Age and Older with Perennial Allergic Rhinitis

  The Division accepted Merck's proposal to delete the last sentence of this section, which the FDA had proposed in the facsimile dated June 21, 2005, regarding AEs occurring at an incidence (b) (4)

- ADVERSE REACTIONS
  Pediatric Patients 6 Months to 14 Years of Age with Perennial Allergic Rhinitis

  The Division accepted Merck's revisions (as proposed in the fax from Merck dated June 24, 2005) to this section.

All other FDA recommended revisions (dated June 21, 2005) were accepted by Merck.

Merck was reminded to include the recently approved labeling changes (changes approved May 26, 2005, and June 27, 2005) in their revised draft labeling.

Merck was reminded to officially submit the revised draft labeling (that was e-mailed to the Division on June 24, 2005) to the sNDAs.

_____

Lori Garcia, R.Ph.
Regulatory Project Manager

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/s/

Lori Garcia
7/26/05 03:01:46 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: June 21, 2005

To: Frank Seebach	**From:** LT Lori Garcia Regulatory Project Manager
Company: Merck	Division of Pulmonary and Allergy Drug Products
Fax number: 732-594-1030	**Fax number:** 301-827-1271
Phone number: 732-594-0222	**Phone number:** 301-827-5580

Subject: N20-829/S-033 PAR/proposed labeling revisions

Total no. of pages including cover: 22

Comments:

Document to be mailed: **YES** xx **NO**

N20-829/S-033
N20-830/S-035
N21-409/S-012

Dear Dr. Seebach:

We have reviewed the labeling submitted September 30, 2004. Our proposed revisions to the Package Insert are enclosed. Recommended deletions are indicated by ~~strikeouts~~ and inserts are indicated by underlines. FDA comments regarding recommended revisions are provided in **bold** font**.**

We have a teleconference scheduled for June 22, 2005, from 11:00am-12:00pm, to discuss the labeling for these supplements. You have the option of canceling this teleconference and submitting revised draft labeling if the recommended revisions provided in this facsimile are acceptable to you.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301)-827-5580.

__19___ Page (s) Withheld

____ Trade Secret / Confidential (b4)

__✓__ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

Withheld Track Number: Administrative-20-829/S033

Drafted: **LGarcia/June 17, 2005**

Initialed: **Sandy Barnes/June 20, 2005**
TMcGovern/June 21, 2005
TPurohit-Sheth/ June 21, 2005
BChowdhury/ June 21, 2005

Finalized: **LGarcia/**

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/s/

Lori Garcia
6/21/05 02:33:32 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

Merck and Co., Inc
P.O. Box 2000, RY32-605
Rahway, NJ 07065-0900

Attention: Frank Seebach, MD, RAC
Director, Regulatory Affairs

Dear Dr. Seebach:

Please refer to your September 30, 2004, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 29, 2004, in accordance with 21 CFR 314.101(a).

We request that you submit the following information:

1. You are proposing approval of montelukast sodium for PAR down to 6 months of age, which is below the age that montelukast sodium is currently approved for other indications. Submit the appropriate rationale and support for the new age group of 6-11 months. This should include adequate PK data to support the proposed dose in 6-11 month old patients, and adequate data to support safety for 6-11 month old patients.

2. Provide the total number of investigators in each individual study, and the number of investigators in each study who had financial disclosures.

3. Submit the analysis data sets and programs for Protocol 246, the same as was submitted for Protocol 265. The package should include data [.XPT files] and programs [.SAS files] used in the analysis of the efficacy section of the body of the CSR for the protocol 246 [A multicenter, double-blind, randomized, placebo-controlled, parallel group study, Investigating the Clinical Effects of Montelukast in Patients with Perennial Allergic Rhinitis].

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Badrul Chowdhury
12/8/04 01:01:55 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Drug Marketing, Advertising and Communications
HFD-244 PKLN Rm. 17B-17

FROM:
Lori Garcia, Regulatory Project Manager
Division of Pulmonary and Allergy Drug Products
HFD-570

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 10, 2004		N20-829/S-033; N20-830/S-035; N21-409/S-012	Efficacy Supplement	September 30 ,2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Singulair (montelukast sodium)	Standard	LT receptor antagonist	**February 28, 2005**

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- xx☐ **LABELING REVISION**
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review labeling for these new supplemental NDAs. Labeling is available in the EDR (http://edr/) under the N20-829 11-Oct-2004 BZ submission.

Please note that our **internal goal date is March 31, 2005**, due to the move to White Oak in April/May. The PDUFA goal is July 31, 2005, but we would like to wrap this one up early, if possible.

Thanks ☺

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Lori Garcia

11/10/04 02:30:42 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-829/S-033
NDA 20-830/S-035
NDA 21-409/S-012

Merck and Co., Inc
P.O. Box 2000, RY32-605
Rahway, NJ 07065-0900

Attention: Frank Seebach, MD, RAC
Director, Regulatory Affairs

Dear Dr. Seebach:

We have received your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules
NDA Numbers:	20-829 20-830 21-409
Supplement numbers:	S-033 S-035 S-012
Review Priority Classification:	Standard (S)
Date of Application:	September 30, 2004
Date of Receipt:	September 30, 2004

These supplements contain clinical data to support the use of Singulair (montelukast sodium) Tablets, Chewable Tablets, and Oral Granules for the relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 months of age and older and provides for changes to the US package circular and patient product information.

Unless we notify you within 60 days of the receipt date that the applications are not sufficiently complete to permit a substantive review, we will file the applications on November 29, 2004, in

accordance with 21 CFR 314.101(a). If the applications are filed, the user fee goal date will be July 30, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies in patients less than 6 months old for these applications. Once the applications have been filed we will notify you whether we have waived the pediatric study requirement in this population for these applications.

We note that you have submitted pediatric studies in patients 6 months of age and older with these applications. Once the review of these applications is complete we will notify you whether you have fulfilled the pediatric study requirement in this population for these applications.

All communications concerning these supplements should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Lori Garcia, Regulatory Project Manager, at (301) 827-5580.

Sincerely,

{See appended electronic signature page}
Sandy Barnes
Supervisory CSO
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Lori Garcia
10/6/04 04:06:29 PM
signed for Sandy Barnes