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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-409

Medical Review(s)

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CLINICAL REVIEW

NDA:	21-409	Reviewer:	Peter Starke, MD
Applicant:	Merck Research Laboratories PO Box 2000, RY33-720 Rahway, NJ 07065	Review Date:	10 June 2002
		PDUFA Date	28 July 2002
Proprietary Name:	Singulair® 4 mg oral granules		
Generic Name:	Montelukast sodium oral granules		
Drug Class:	Cysteinyl leukotriene receptor antagonist		
Formulation:	4 mg oral granules		
Route:	Oral		

Submissions Reviewed

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Document ID</u>	<u>Comments</u>
28 September 2001	28 September 2001	N-000	Electronic NDA for Singulair® 4 mg oral granules
25 January 2002		N-000 BM	Missing CRF
28 January 2002		N-000 SU	Safety Update Report
4 June 2002	5 June 2002	N-000 BM	Response to clinical questions

Summary Comments

This NDA is an efficacy supplement for Singulair™ (montelukast sodium oral granules). Five clinical studies are submitted. Three studies provide adult pharmacokinetic and bioequivalence data to support the use of the 4 mg oral granule formulation as an alternative to the currently approved 4 mg chewable tablet in patients ages 2 to 5 years. Of these three adult studies, two are combination bioequivalence and food-effect bioavailability studies, and one is a dose-proportionality study. Two studies provide population PK, safety, and limited efficacy data using of the 4 mg oral granule formulation in 'asthma' patients ages [] to 23 months ([] to <2 years). On the basis of these studies, Merck requests an indication for Singulair 4 mg oral granules as a primary formulation for this age group. Efficacy for this age group is to be extrapolated from older age groups.

On March 4, 1999, the Agency issued a Written Request (WR) for four clinical studies with montelukast in pediatric patients ages 6 month to <2 years, and ≥2 to <6 (i.e. through age 5) years. The two studies for pediatric patients with asthma ages ≥2 to <6 years were submitted to NDA 20-830 as supplement S-008 on May 6, 1999. The other two studies are submitted with this NDA application. Pediatric Exclusivity was granted on December 10, 2001.

Action

Recommended Regulatory Action: X **APPROVAL FOR AGE 2 TO 5 YEARS**

1

Clinical Review of NDA 21-409

EXECUTIVE SUMMARY

1. RECOMMENDATIONS

1.1. Recommendation on Approvability

1.1.1. Recommendations for age 2 to 5 years

Approval, for the same indications as already approved, as an alternative formulation to the 4 mg chewable tablet in the 2 to 5 year old age range.

[

]

1.1.3. Labeling Recommendations

1.1.3.1. Summary of Proposed Labeling Changes

Merck proposes to add information to the following sections of the label:

- DESCRIPTION: Description of Singulair 4 mg oral granules.
- CLINICAL PHARMACOLOGY: Bioequivalence of the 4 mg chewable tablet and the 4 mg oral granules. [
- INDICATIONS AND USAGE: Adds information under the *Adolescents and Pediatric Patients* section discussing the AUCs of the oral granules and the age ranges for use of the oral granules.
- PRECAUTIONS: Added sentence under *Pediatric Use* section stating that "[
- ADVERSE REACTIONS: Extensively reworked to combine the 2 to 5 year old information with the 6 to 14 year old information into one section,
- DOSAGE AND ADMINISTRATION: As an alternative formulation for pediatric patients 2 to 5 years of age, as a primary formulation []" information regarding mixing with food and need to administer the dose immediately.
- HOW SUPPLIED: Description of Singulair 4 mg oral granules.

1.1.3.2. Summary of Suggested Labeling Changes

Add label statements concerning the following points:

- DESCRIPTION: Description of Singulair 4 mg oral granules as Merck suggests.
- CLINICAL PHARMACOLOGY: Bioequivalence of the 4 mg chewable tablet and the 4 mg oral granules. Remove the sentence regarding the demonstration safety of the 4 mg oral granule formulation by a clinical trial. Add information that
 - ◆ For the 12 to 23 month old population, the variability of exposure (AUC) is high, with no correlation between exposure and either weight or age. The C_{max} is significantly higher than in older populations.
 - ◆ Below the age of 12 months, the variability of exposure (AUC) is very high. There is no correlation between exposure and either weight or age. The C_{max} is significantly higher than in older populations.
- INDICATIONS AND USAGE: Add information under the *Adolescents and Pediatric Patients* section discussing the AUCs of the oral granules, but change the age range for use of the oral granules to 2 to 5 years of age.
- PRECAUTIONS: No changes needed to this section.
- ADVERSE REACTIONS: No changes needed to this section, although some of the suggested changes for incorporation of the 2-5 year olds information could be accepted.
- DOSAGE AND ADMINISTRATION:
 - ◆ Add information that the oral granules may be used as an alternative formulation for pediatric patients 2 to 5 years of age.
 - ◆ Even though developed as a pediatric formulation, the Montelukast 4 mg oral granules are not approved below age 2 years due to insufficient information to support efficacy.
 - ◆ Add information regarding mixing with food and need to administer the dose immediately.
- HOW SUPPLIED: Description of Singulair 4 mg oral granules as Merck suggests.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

To obtain approval for the prophylaxis and chronic treatment of asthma and other wheezing phenotypes in the age range 6 to 23 months, efficacy in these age ranges must be established by one or more efficacy and safety studies. The entire population of patients who qualify for controller therapy should be used, but an effort should be made to identify those patients who might fall into different wheezing phenotypes by demographic and family history, IgE levels, appropriate skin testing, and other diagnostic evaluations. Subgroups of 6 to 11 months and 12 to 23 months should be adequately represented to show efficacy for each group.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Background and Administrative Issues

This NDA is an efficacy supplement for Singulair™ 4 mg (montelukast sodium oral granules). Merck is submitting five clinical studies to support the use of Singulair 4 mg oral granules for two different age groups. Merck proposes Singulair 4 mg oral granules as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years and as a primary formulation for patients ages 6 to 23 months.

Please note that Merck submitted the NDA using the term "oral granules" but it was determined late in the review process that the preferred terminology is 'oral granules.' The reasoning is that the term "granules" does not refer to the dosage form, it describes an action which may or may not occur, and it is similar to the term used for some candy.

This determination was made at the labeling stage, after the bulk of this review was written. Prior to finalization of the review, an effort was made to find and change references from "granules" to oral granules, but some may have been missed, and some are left intentionally either when source material is quoted or when the reference is to what was stated by the sponsor (e.g. the title or objectives of a study). Therefore, the reader may find an occasional use of the term Singulair 4 mg granules but should bear in mind that what is meant is Singulair 4 mg oral granules.

Montelukast is an orally administered antagonist of the Type 1 cysteinyl leukotriene (CysLT₁) receptor. Cysteinyl leukotrienes are potent mediators in the pathogenesis of bronchoconstriction in asthma.

Singulair 10 mg film coated tablets (NDA 020-829) and 4 mg & 5 mg chewable tablets (NDA 020-830) are currently approved for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 2 years of age and older. The dosage for adults and adolescents 15 years of age and older is one 10 mg tablet daily to be taken in the evening. For pediatric patients 6 to 14 years of age the dosage is one 5 mg chewable tablet daily (in the evening), with no dosing adjustment within the age group. The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily (in the evening).

With this application Merck has requested a determination of Pediatric Exclusivity under Section 505A of the Food, Drug, and Cosmetic Act. At that time the Exclusivity Board made the determination that Merck had satisfied all the requirements of the Written Request and applicable amendments, and granted Pediatric Exclusivity.

2.2. Brief Overview of Clinical Program

On March 4, 1999, the Agency issued a pediatric Written Request (WR) for four clinical studies with montelukast in pediatric patients, two in patients 2 to 5 years of age, and two in patients 6 to 23 months of age. There were three amendments to the Written Request, dated April 18, 2000, September 28, 2000, and September 7, 2001. The two studies for pediatric patients with asthma ages 2 to 5 years were submitted to NDA 020-830 as supplement SE1-008 on May 6, 1999. On the basis of these studies, the application for Singulair 4 mg chewable tablets was approved for use in children 2 to 5 years of age in March of 2000. The other two studies in patients 6 to 23 months of age are submitted with this NDA application.

First, Merck proposes Singulair 4 mg oral granules as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years (2 years to <6 years). For the Singulair 4 mg chewable tablets, efficacy for ages 2 to 5 years was extrapolated from the demonstrated efficacy in adult, adolescent, and pediatric patients 6 years of age and above 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 one safety trail in which efficacy was a exploratory assessment.

Three studies (Table 1) provide adult pharmacokinetic and bioequivalence data in support of the application as an alternative formulation for ages 2 to 5 years. Of these three adult studies, one is a dose-proportionality study and two are combination bioequivalence and food-effect bioavailability studies.

Table 1. Studies for ages 2 to 5 years

Study	Design	Dosage	Subjects n / Sex	Evaluations
P127	Single-center, open-label, randomized, 3-period crossover fasted single-dose, dose-proportionality PK study in 16 healthy, non-smoking men and women between 18-45 years 3 single doses with water, 96 hours between treatments	2 mg oral granules 4 mg oral granules 6 mg oral granules	10 M 6 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety
P090	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study in 24 healthy, non-smoking men and women between 18-45 years 3 single doses, 96 hours between treatments	4 mg oral granules 4 mg oral granules + applesauce 4 mg chewable tab	9 M 15 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety
P183	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study in 31 healthy, non-smoking men and women between 18-45 years 3 single doses, 96 hours between treatments To-be-marketed formulation used	4 mg oral granules 4 mg oral granules + high-fat meal 4 mg chewable tab	20 M 11 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety

Second, Merck proposes Singulair 4 mg oral granules as a primary formulation for the prophylaxis and chronic treatment of pediatric "asthma" patients ages 2 to <23 months (2 to <2 years). This is a new indication / age group. Rationale for this indication is discussed below and in the body of this review. Efficacy for this population is again to be extrapolated from older age groups (i.e. asthmatic patients age 6 and above) 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 one safety trail in which efficacy was a exploratory assessment.

Two studies (Table 2) provide pharmacokinetic, safety, and limited efficacy data using the 4 mg oral granules in support of the application as a primary formulation in patients ages 2 to <23 months. The design for these studies followed the design suggested in the pediatric Written Request.

Table 2. Studies for ages 6 to 23 months (6 months to <2 years)

Study	Design	Dosage	Subjects n / Sex	Evaluations
P136C1	Multi-center, open-label, randomized, single-dose population PK study in 26 boys and girls, ages ≥6 months to <2 years, between 6kg and 15 kg, with a history of asthma or "asthma-like" symptoms who might benefit from controller therapy	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} C _{I/F} Safety
P176	6 week multi-center, randomized, double-blind, placebo-controlled, parallel group safety and tolerability study in 256 boys and girls, ages ≥6 months to <2 years, with a history of 3 episodes of asthma or "asthma-like" symptoms after 8 weeks of age and within 6 months of the study	4 mg oral granules Placebo mixed in applesauce QD hs	E / C: 175/169 * M: 116 F: 59 81/74 (Total 256)	Safety: AEs Lab AEs Exploratory efficacy: Days s β-ag β-ag Rx/d Unsch visits Oral CS Asthma attacks D/Cdt asthma Total Eos

2.3. Efficacy

2.3.4. Efficacy for 2 to 5 years of age

Three single-dose studies performed in adults are submitted to support the bioequivalence of the 4 mg oral granule formulation to the 4 mg chewable formulation, and to evaluate the effect of food on the pharmacokinetics of the oral granule formulation. Merck intends that the two formulations would be interchangeable for the 2 to 5 year age group, stating that they developed this formulation as an age appropriate alternative formulation.

Dose selection for the 2 to 5 year age group was previously carried out to gain the indication for the 4 mg chewable tablets, and was therefore not carried out as part of this NDA submission. However, the dose selection of 4 mg for this age range was based on a population pharmacokinetic study, which was part of the Written Request for the study of age-appropriate formulations in children. Dose-ranging studies in children have not been performed. The pediatric dose was selected based on the pharmacokinetic profile of single doses of montelukast, matching AUCs from adults to those in children 2 to 5 years of age via a population pharmacokinetic study. Likewise, efficacy for this population was extrapolated from efficacy data in patients 6 years of age and older, accepting that the AUCs in adults that are associated with efficacy will be similarly efficacious in the 2 to 5 year old age range. No efficacy data were submitted with this application.

Study P127 evaluated the dose proportionality of 2, 4 and 6 mg dosages of the oral granules in adults. Dose-adjusted geometric mean ratios confirmed dose proportionality.

P090 was a pilot bioequivalence study in adults, providing a preliminary comparison between the 4 mg oral granules, administered either fasting or with 2 tablespoons of

applesauce, and the 4 mg chewable tablet formulation. Study P183 was a final market image study in adults, conducted to confirm the bioequivalence of the final market image of the 4 mg oral granule and the 4 mg chewable tablet formulations, and to evaluate the effect of a high-fat breakfast on the pharmacokinetics of the 4 mg oral granules. In both studies, $AUC_{0-\infty}$ were quite similar regardless of whether subjects were fasting or being fed applesauce or a high fat meal, with geometric mean ratios were well within the 90% confidence intervals. These studies clearly showed that food affects the rate of absorption of the montelukast oral granules, affecting the T_{max} and C_{max} , but not the $AUC_{0-\infty}$. Since the therapeutic effect of montelukast is based on the AUC and not the T_{max} or C_{max} , this is not a clinical issue.

Merck intends that the chewable and oral granule formulations would be interchangeable for the 2 to 5 year age group, stating that they developed this formulation as an age appropriate alternative formulation. However, the two formulations are different in one specific characteristic. Whereas a chewable formulation is intended to be chewed and swallowed, a oral granule formulation inherently requires administration in a carrier, usually a food. Merck intends that the label state that applesauce be used for this purpose, but clearly other foods might be used. Merck is acknowledging this in Study P183 by evaluating the pharmacokinetics of the oral granules with a high-fat meal, as well as in the CMC section where stability was tested in several foods. However, use of the oral granule formulation was not evaluated in children age 2 to 5 years. Since a palatability study was not done, it is not clear what will happen if patients chew the oral granules. While this would be helpful to evaluate, it is not essential for approval.

On the basis of the three adult pharmacokinetic studies submitted, the montelukast 4 mg oral granule and 4 mg chewable tablet formulations are bioequivalent. It is reasonable to accept Merck's proposal that Singulair 4 mg oral granules may be used as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years, and approval is recommended for this age range.

2.3.5. Efficacy for-6 to 23 months of age

No primary efficacy data was provided in this application to support the use of montelukast in this age range. Study P176 was a safety study with exploratory efficacy endpoints (i.e. the study was not powered for efficacy, and all efficacy endpoints were declared as exploratory endpoints). Of significance, and in contradistinction to the trends found in the 2 to 5 year old safety study (a study with almost identical enrollment criteria), the exploratory efficacy data from study P176 taken as a whole appeared to trend in different directions depending upon the endpoint. A randomization imbalance resulted from enrolling fewer patients with a history of oral corticosteroid rescues in the placebo than in the montelukast group within the subgroup of 6 to 11 months of age. The randomization imbalance skewed the baseline as well as the results for patients 6 to 11 months of age, making all efficacy inferences (even exploratory ones) for this age group invalid, and making clinical safety measures for this age group difficult to assess (see Table 3 below).

However, for the subgroup of patients 12 to 23 months of age who did not experience a randomization imbalance efficacy trends favor montelukast with fewer asthma attacks, fewer unscheduled visits for asthma, and less albuterol use in the montelukast treatment arm

(see Table 3 below). There was no trend toward less use of oral corticosteroids, as was seen in study P072, a similar safety study in 2 to 5 year olds. This subgroup had sufficient numbers enrolled to evaluate as a group both from a safety and a potential efficacy perspective, allowing the potential to explore approval for this age subgroup, and the information is somewhat supportive of extrapolation to this age group.

Table 3. Study P176, Summary of exploratory efficacy outcomes by age group

Exploratory Efficacy Outcomes	6-11 months		12-23 months	
	Montelukast	Placebo	Montelukast	Placebo
Oral corticosteroid rescue (%)	22.0	0.0	12.1	12.5
Asthma attacks (%)	24.0	12.1	13.7	22.9
Unscheduled visit for asthma (%)	12.0	12.1	8.9	16.7
Beta-agonist treatments per day	0.79	0.90	0.73	0.86
Days without beta-agonist use (%)	63.13	57.29	67.88	61.07

For the specific phenotype of atopic asthma, it is reasonable to accept efficacy of montelukast in all age groups (as was done in the 2 to 5 year old age group). Even though Merck enrolled in study P176 many patients who (by the criteria of Castro-Rodriguez¹) might later be diagnosed with asthma, the separation of this phenotype from other asthma phenotypes may be impossible below 2 years of age making acceptance of such a limited indication impractical. Even if one accepts the efficacy of montelukast in the treatment of the atopic asthma phenotype in children of all ages, the question of the correct dose still arises. Merck has presumed that AUCs that are efficacious in older children and adults may be extrapolated to younger children because of the wide efficacy and safety margins for the drug. That extrapolation was accepted for the age range of 2 to 5 years of age as part of the approval of Singulair 4 mg chewable tablets. Based on the population pharmacokinetic study presented and previous evidence for montelukast, this is reasonable.

Accepting the possibility of an extrapolation of the dose in the atopic asthma phenotype below age 2 years down to age 12 months, and acknowledging that difficulties with separation of phenotypes and showing efficacy in younger age ranges that were in the sections discussed above, this reviewer believes that there must be more evidence to allow extrapolation below age 2 years. While trends for the 12 to 23 month group were suggestive, this reviewer believes that the trends for this age group not sufficient to make any statements regarding efficacy of montelukast for this age group, and that there must be more evidence to allow extrapolation to the 12 to 23 month age group. No such statement can be made for the 6 to 11 month age group, where no evidence for efficacy is available due to the randomization imbalance, and where the diagnosis is far more uncertain and the variability of exposure is higher.

Finally, there is limited information regarding whether leukotrienes play the same role in the airway obstruction of all three wheezing phenotypes found in infants and younger children.

¹ Castro-Rodriguez, J. A., C. J. Holberg, et al. (2000). "A clinical index to define risk of asthma in young children with recurrent wheezing." *Am J Respir Crit Care Med* 162(4 Pt 1): 1403-6.

If one were to accept the use of montelukast in the treatment of these conditions, this would broaden the diagnosis from the traditional asthma to any form of reversible obstructive airway disease in this age group. On this basis, the use of montelukast in children without a clear diagnosis of asthma (other wheezing phenotypes) would need to be supported by efficacy studies in this population and cannot be supported by extrapolation from use in asthmatics above six years of age.

2.4. Safety

The safety review included in-depth review of the five studies provided in this NDA. In addition, adverse event tables presented in several additional individual Study Reports, the Worldwide Clinical Summary, and the Safety Update Report were reviewed for incidence of adverse events, broken down by age group, gender, ethnic origin, and relationship to study drug use.

Although several minor laboratory trends were noted, no significant safety signals were found in the safety review of the five submitted studies or the other safety information that was reviewed. There were no deaths. In particular, the three adult single-dose pharmacokinetic studies yielded no new safety information. In the six-week safety and tolerability study, rates for AEs and withdrawals were similar for montelukast and placebo. While there were more serious AEs and laboratory AEs in these studies, no safety signals were noted.

While neither study in the 6 to 23 month old population showed significant clinical adverse event trends, there was a hint that montelukast might affect liver functions as well as blood and platelet counts. In study P176 (6 to 23 month old safety study) there was a trend apparent clinically as well as in the shift tables for mild, transient elevations in AST levels, which were often manifested at the time of a concurrent illness. This trend was previously noted clinically in the 2 to 5 year old safety study (P072). Further instances of elevations in AST were not reported in the limited data presented in the open-label extension of study P176 (P232). Laboratory shift tables trends toward a decrease or dampening in elevations in WBCs, Hematocrit, and Platelet counts, as well as an increase in ALT were mild and not manifested clinically. Information provided from the open-label extension of the safety study did not provide sufficient detail to add much to the safety evaluation of study P176 itself. The evidence is insufficient to conclude that there is a safety concern from these findings.

Variability of exposure is large, and was not adequately explained in the population of 6 to 11 month old infants studied, corresponding to a standard error of 499. There was no correlation between $AUC_{0-\infty}$ values and weight or age, although there was a trend to higher AUCs in the 6 to 11 month old than in the 12 to 23 month old population, implying that there is no way to predict which infants will have very high or very low exposures and that dosing should not be based on weight or age. Steady state pharmacokinetic information from study P176, might have provided more data, but would not completely resolve these issues.

Assuming that single-dose data may be extrapolated to what might occur with multiple dosing, some patients might have levels significantly lower than expected, while others

might have levels significantly higher than expected. Since there is a wide safety margin for montelukast in older individuals, differences in C_{max} , and T_{max} , and AUC are not likely to be significant either with regard to safety. In adults the 10mg tablets provided efficacy that did not dose-order with higher doses, allowing that variations in exposure might more readily translate into efficacy. This allows consideration of extrapolation down to 12 months of age based on the studies presented.

However, in the 6 to 11 month age range one cannot assume that this same margin exists either for efficacy or safety. It remains to be demonstrated that the disease and dose range for efficacy and safety are the same as in older populations. Therefore, at this time this magnitude of variance is unacceptable without further demonstration of both safety and efficacy by efficacy studies that incorporate safety evaluations.

2.5. Dosing and Administration

This application is for Singulair 4 mg oral granules to be used as an alternative to the 4mg chewable tablets for ages 2 to 5 years as well as a primary formulation for ages 23 months. Since the review recommends approval for the 2 to 5 year old application, there is no new dosing information in this review. However, the application presents evidence that the 4 mg oral granule formulation may be an appropriate formulation if efficacy and safety are established.

There are administration issues for montelukast in a oral granule formulation. Whereas a chewable formulation is intended to be chewed and swallowed, a oral granule formulation inherently requires administration in a carrier, usually a food. Merck intends that the label state that applesauce be used for this purpose, but clearly other foods might be used.

Stability data was submitted for four foods (ice cream, carrots, rice, and apple sauce) for up to 30 minutes. Merck did not submit stability data from any formulas or stability data in various foods extending to beyond two hours. In addition, Merck refused the Division's request to submit stability data for various other foods, and to extend the timing of the data to the dosing interval. Merck states that "after opening the packet, the full dose...must be administered immediately (within 15 minutes). If mixed with food, Singulair must not be stored for future use. Singulair are not intended to be dissolved in liquid for administration." Because further stability data is not available, it is recommended that this information be incorporated into the labeling.

2.6. Special Populations

The application was submitted as part of Merck's pediatric program for montelukast. There is insufficient information in this application to fully evaluate the effects of gender, race, or ethnicity on safety or efficacy.

CLINICAL REVIEW

1. CLINICAL BACKGROUND

1.1. Introduction and Rationale

1.1.6. Introduction

This NDA is an efficacy supplement for Singulair™ 4 mg (montelukast sodium oral granules: *please refer to the next section for an explanation of terminology*). Merck is submitting five clinical studies to support the use of Singulair 4 mg oral granules for two different age groups. Merck proposes Singulair 4 mg oral granules as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years. With this application Merck has requested a determination of Pediatric Exclusivity under Section 505A of the Food, Drug, and Cosmetic Act.

Montelukast is an orally administered antagonist of the Type 1 cysteinyl leukotriene (CysLT₁) receptor. Cysteinyl leukotrienes are potent mediators in the pathogenesis of bronchoconstriction in asthma.

1.1.7. Terminology of versus Oral Granules

Please note that Merck submitted the NDA using the term but it was determined late in the review process that the preferred terminology is 'oral granules.' The reasoning for this is threefold. The term does not refer to the dosage form, it describes an action which may or may not occur, and it is similar to the term used for some candy. This determination was made at the labeling stage, after the bulk of this review was written. Prior to finalization of the review, an effort was made to find and change references from to oral granules, but some may have been missed, and some are left intentionally either when source material is quoted or when the reference is to what was stated by the sponsor (e.g. the title or objectives of a study). Therefore, the reader may find an occasional use of the term Singulair 4 mg, but should bear in mind that what is meant is Singulair 4 mg oral granules.

1.1.8. Approved labeling and dosage

Singulair 10 mg film coated tablets and 4 mg & 5 mg chewable tablets are currently approved for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 2 years of age and older. The dosage for adults and adolescents 15 years of age and older is one 10 mg tablet daily to be taken in the evening. For pediatric patients 6 to 14 years of age the dosage is one 5 mg chewable tablet daily (in the evening), with no dosing adjustment within the age group. The dosage for pediatric patients 2 to 5 years of age is one 4 mg chewable tablet daily (in the evening).

1.1.9. Proposed labeling and dosage

First, Merck proposes Singulair 4 mg oral granules as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years (2 years to <6 years). For the Singulair 4 mg chewable tablets, efficacy for ages 2 to 5 years was extrapolated from the demonstrated efficacy in adult and adolescent patients 15 years of age and older and pediatric patients 6 to 14 years of age 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 one safety trial in which efficacy was a exploratory assessment.

Second, Merck proposes Singulair 4 mg oral granules as a primary formulation for the prophylaxis and chronic treatment of pediatric "asthma" patients ages — 23 months, — to <2 years). This is a new indication / age group. Rationale for this indication is discussed below and in the body of this review. Efficacy for this population is again to be extrapolated from older age groups (i.e. asthmatic patients age 6 and above) 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 one safety trial in which efficacy was a exploratory assessment.

1.1.10. Submitted clinical trials

On March 4, 1999, the Agency issued a pediatric Written Request (WR) for four clinical studies with montelukast in pediatric patients, two in patients 2 to 5 years of age, and two in patients 6 to 23 months of age. There were three amendments to the Written Request, dated April 18, 2000, September 28, 2000, and September 7, 2001. The two studies for pediatric patients with asthma ages 2 to 5 years were submitted to NDA 20-830 as supplement SE1-008 on May 6, 1999. On the basis of these studies, the application for Singulair 4 mg chewable tablets was approved for use in children 2 to 5 years of age in March of 2000. The other two studies in patients 6 to 23 months of age are submitted with this NDA application.

Three studies (Table 4) provide adult pharmacokinetic and bioequivalence data in support of the application as an alternative formulation for ages 2 to 5 years. Of these three adult studies, one is a dose-proportionality study and two are combination bioequivalence and food-effect bioavailability studies.

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Table 4. Studies for ages 2 to 5 years

Study	Design	Dosage
P127	Single-center, open-label, randomized, 3-period crossover fasted single-dose, dose-proportionality PK study in 16 healthy, non-smoking men and women between 18-45 years 3 single doses with water, 96 hours between treatments	2 mg oral granules 4 mg oral granules 6 mg oral granules
P090	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study in 24 healthy, non-smoking men and women between 18-45 years 3 single doses, 96 hours between treatments	4 mg oral granules 4 mg oral granules + applesauce 4 mg chewable tab
P183	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study in 31 healthy, non-smoking men and women between 18-45 years 3 single doses, 96 hours between treatments Study used to-be marketed formulation	4 mg oral granules 4 mg oral granules + high-fat meal 4 mg chewable tab

Two studies (Table 5) provide pharmacokinetic, safety, and limited efficacy data using the 4 mg oral granules in support of the application as a primary formulation in patients ages 6 to 23 months. The design for these studies followed the design suggested in the pediatric Written Request.

Table 5. Studies for ages 6 to 23 months (6 months to <2 years)

Study	Design	Dosage
P136C 1	Multi-center, open-label, randomized, single-dose population PK study in 26 boys and girls, ages ≥6 months to <2 years, between 6kg and 15 kg, with a history of asthma or "asthma-like" symptoms who might benefit from controller therapy	4 mg oral granules in applesauce
P176	6 week multi-center, randomized, double-blind, placebo-controlled, parallel group safety and tolerability study in 256 boys and girls, ages ≥6 months to <2 years, with a history of 3 episodes of asthma or "asthma-like" symptoms after 8 weeks of age and within 6 months of the study	4 mg oral granules Placebo mixed in applesauce QD hs

1.1.11. Terminology for Age Ranges (E11 standards)

A comment about the terminology regarding age ranges used in this review.

Current Singulair labeling (and labeling practice) uses the word 'to' in an inclusive manner, implying that the older age group referred to in the 'to' statement includes the stated year of age. For example, children '2 to 5 years' implies children ages ≥2 years to <6 years (through age 5 years or until the 6th birthday).

However, the Merck application (without mentioning the change in terminology) used 'to 2 years' in an exclusive manner, implying that 'to 2 years' actually means 'to <2 years (until the 2nd birthday)'. The older age referred to in this 'to' statement is exclusive of the year of age that is referred to. If one were to misread and use the current inclusive 'to' statement terminology, this could be interpreted to have meant ages through age 2 years. This switch is not only confusing, but it is in contradistinction to current labeling practice and to the recommendations of the E11

document "Clinical Investigation of Medicinal Products in the Pediatric Population.." The E11 document defines age ranges inclusively by use of "completed days, months, or years," and uses 'months' through 23 months, and 'years' thereafter. In this review, the E11 standard was adopted. However, for clarity to the reader, the qualifier '<' is also used in some locations, and in the description of the populations enrolled, further qualifiers are used. Therefore, children [

children ≥12 months to <24 months (through the 23rd month of life or until the birthday at 24 months of age).

1.1.12. Rationale

This section briefly paraphrases rationale sections found in the Worldwide Clinical Summary. No attempt is made in this section to synthesize the material presented. Citations are similar to those found in the Worldwide Clinical Summary, and all citations listed will be found in Section 11 of this review. [Worldwide Clinical Summary, pages 56-9; summary.pdf]

As rationale for a oral granule formulation of montelukast with an indication —
 Merck argues that asthma is a significant public health concern, including down to the — They state that asthma may begin at any age, but usually begins in childhood. The prevalence of asthma is highest in patients younger than 5 years of age, with the highest hospitalization rate for children between 0-4 years of age [CDC, 1997 #41]. Airway inflammation, the hallmark of asthma, is found in both children and in adults, and most experts agree that asthma is a similar disease in children and adults [Busse, 1995 #22] [Larsen, 1992 #33].

Because the diagnosis of asthma depends on recurrent episodes of symptoms and variable airflow obstruction, asthma is difficult to diagnose definitively in the youngest children, especially as it is difficult to perform pulmonary function studies on preschool children. However, there is no question that wheezing is very common in this age range. Merck cites the longitudinal study from Tuscon Arizona, in which 34% of those followed had an episode of wheezing within the first 2 years of life [Martinez, 1995 #4]. Of this subgroup, 41% had persistent wheezing and decreased lung function consistent with asthma at age 6 years. Of children hospitalized for wheezing in the first 2 years of life, approximately 50% are ultimately diagnosed with asthma, and anti-inflammatory therapy did not significantly diminish the risk of asthma [Wilson, 1997 #32] [Reijonen, 1998 #20][Reijonen, 2000 #21]. While it is known that the prevalence of asthma decreases as children get into the pre-adolescent age range, Merck states that three large longitudinal studies found that children who had early childhood wheezing had recurrence of symptoms in the second decade of life after a period of remission [Jenkins, 1994 #34] [Strachan, 1996 #37] [Oswald, 1994 #40]. [Worldwide Clinical Summary, pages 56-7; summary.pdf]

Merck argues that there is a need for controller therapy in infant and younger children as young as — . Merck argues that since the pathogenesis of asthma is similar in different age ranges, the medications for asthma in other age ranges should be used to treat asthma in all age ranges. Therefore, since no direct evidence of efficacy is provided in this application, they indirectly are stating that that efficacy from older ages (six and above) should be extrapolated to this age range. Since the controller medications currently

available for the treatment of asthma in the youngest children are limited to inhaled agents and oral corticosteroids, they argue that there is a place for an oral agent in the treatment armamentarium.

Whether asthma may be diagnosed in this age group, and whether there is in fact a need for non-steroidal controller therapy below age two will be one of the points discussed in this review.

1.2. State of Armamentarium for Indication(s)

Limited numbers of controller medications and age-appropriate formulations are available for use in children 5 years of age and below. For this age range, the most appropriate formulation is either a formulation for nebulization or an age-appropriate oral formulation. While metered dose inhalers (MDI) may be used in this age group, a spacer device is often required, creating difficulties with dosing and delivery. Use of a spacer with an MDI facilitates delivery to a child incapable of timing a breath with the puff from an MDI, but may create multiple problems associated with the use of a device not evaluated in clinical trials (e.g. adherence of particles to the spacer walls). Dry powder inhalers (DPI) require patients to be capable of taking a deep breath to inhale the powder into the lungs. Most children under age 4 are unable to do this (Serevent Diskus and Flovent Diskus are both approved for use in children 4 years of age and above). Oral formulations appropriate for children age 2 to 5 may differ from those age \leq 23 months. For age 2 to 5 years, syrup, chewable or oral granules are appropriate; whereas for age \leq 23 months, only syrup and oral granules are appropriate. Most children under age 5 are unable to swallow tablets or capsules.

For children below age 2 years, only one controller drug for asthma is currently available in an age-appropriate formulation and approved for use in the US. Pulmicort Respules™ (budesonide inhalation suspension) is indicated for maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. Approval for Pulmicort Respules was based on three efficacy studies in over 1000 children with asthma. No controller therapies are currently approved for use below age 12 months. Therefore, if approved, Singulair oral granules might fill a gap where no medications are approved for this indication in the \leq 23 months age range.

Cromolyn is an inhaled anti-inflammatory agent that been available since the mid 1980s. Sodium cromoglycate inhibits degranulation of sensitized mast cells after exposure to specific antigens. The mechanism of inhibition of the release of mediators from mast cells is said to occur by blocking calcium ions from entering the mast cell, thereby preventing mediator release (PI for Intal MDI). Cromolyn MDI is indicated as a prophylactic agent for the management of asthma in adults and pediatric patients 5 years of age and older (PI for Intal MDI). It is also available in an oral formulation for nebulization for patients 2 years of age and older (PI for Intal for Nebulization). There is limited systemic bioavailability of oral formulations, they are not appropriate for treatment of pulmonary conditions. Although nedocromil was evaluated in the Childhood Asthma Management Program (CAMP) study, nedocromil is not approved for use in the United States except in the form of an eye drop [The Childhood Asthma Management Program Research Group, 2000 #46].

No long-acting beta agonist is approved for use below 5 years of age. Serevent® Diskus and Serevent® Inhalation Aerosol (Salmeterol) are inhalers (DPI and MDI) indicated in the maintenance treatment of asthma and in the prevention of bronchospasm. Serevent® Diskus (DPI) is approved for patients 4 years of age and older. Foradil Aerolizer™ (Formoterol) is a dry powder inhaler indicated in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 5 years of age and older.

1.3. Important Issues with Pharmacologically Related Agents

No relevant issues.

1.4. Important Milestones in Product Development

1.4.1. Regulatory History

Table 6. List of related NDAs

Product	Age Range	NDA	Approval Date
Singulair 10 mg Film-coated Tablets	≥ 15 years	20-829	February 20, 1998
Singulair 5 mg Chewable Tablets	6 – 14 years	20-830	February 20, 1998
Singulair 4 mg Chewable Tablets	2 – 5 years	20-830, S-008	March 3, 2000

Source: Cover letter

1.4.2. Foreign Marketing History

Merck states that as of August 1, 2001, there are no pending applications, marketing approval, rejections, withdrawal, suspension, or revocation of approval for montelukast sodium oral granules in any country. [Item 3, Summary, Section D, Commercial Marketing History, page 179; summary.pdf]

Merck states that as of August 1, 2001, there are no pending applications, marketing approval, rejections, withdrawal, suspension, or revocation of approval for montelukast sodium (4, 5, and 10 mg tablets) in any country. [Item 3, Summary, Section D, Commercial Marketing History, page 181-2; summary.pdf]

Merck states that [Item 3, Summary, Section D, Commercial Marketing History, page 179-181; summary.pdf]:

“As of 01-Aug-2001, montelukast sodium (5-mg and 10-mg tablets) has received marketing approval for the treatment of asthma in the following countries:

- Argentina, Aruba, Australia, Austria, Bahrain, Belgium, Brazil, Bosnia, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Germany, Greece, Guatemala, Guyana, Honduras, Hong Kong, Hungary, Iceland, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Korea, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Macao, Malaysia, Mexico, Netherlands, New Zealand, Nicaragua, Norway, Pakistan, Panama, Peru, Philippines, Poland, Portugal, Qatar, Romania, Russia, Saudi Arabia, Singapore, Slovak Republic, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Trinidad,

Turkey, Ukraine, United Arab United Kingdom, United States, Uruguay, Venezuela, Yugoslavia.

As of 01-Aug-2001, montelukast sodium (4-mg tablets) has received marketing approval for the treatment of asthma in the following countries:

Argentina, Aruba, Australia, Austria, Bahrain, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Costa Rica, Curacao, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, El Salvador, Estonia, Finland, Germany, Greece, Guatemala, Honduras, Hong Kong, Ireland, Israel, Jamaica, Korea, Kuwait, Lithuania, Mexico, Netherlands, Nicaragua, Norway, Panama, Peru, Poland, Portugal, Spain, Sweden, Switzerland, Trinidad, United Kingdom, United States, Venezuela.

As of 01-Aug-2001, 6 applications are pending marketing approval for montelukast sodium (5-mg and 10-mg tablets) in the following countries:

⌈

⌋

As of 01-Aug-2001, 19 applications are pending marketing approval for montelukast sodium (4-mg tablets) in the following countries:

⌈

⌋

1.5. Other Relevant Information

1.5.1. Pediatric Exclusivity Determination

The information that follows in this section was provided to the Pediatric Exclusivity Board, which met on December 10, 2001. At that time the Exclusivity Board made the determination that Merck had satisfied all the requirements of the Written Request and applicable amendments, and granted Pediatric Exclusivity.

1.5.1.1. Relevant regulatory history and time-lines:

1.5.1.1.1. NDA

On February, 20, 1998, Singulair (montelukast sodium) 10mg film-coated tablets and 5mg chewable tablets were approved for use in the prophylaxis and chronic treatment of asthma in adults and patients age 6 years of age and older (NDA 20-829 for 10mg film-coated tablets, and NDA 20-830 for 5mg chewable tablets, submitted February 21, 1997). An efficacy supplement for 4 mg chewable tablets for use children in aged 2 to 5 years was approved on March 3, 2000 (NDA 20-830, SE1-008, submitted May 6, 1999). NDA 21-409 for Singulair 4 mg oral granules was submitted September 28, 2001.

1.5.1.1.2. Written Request

Original Request (March 4, 1999):

A Written Request (WR) was issued on March 4, 1999, and amended three times, on April 18, 2000, September 28, 2000, and September 7, 2001.

Note: The original WR was issued two months prior to the submission of the NDA efficacy supplement for the 4 mg chewable tablets, which contained the Study Reports for Studies 3 and 4. All WR Amendments were issued after the Study Reports for Studies 3 and 4 were submitted.

In the WR, the Division asked for two studies to assess the pharmacokinetics and safety of Singulair in children between the ages of ≥ 2 and < 6 years, and two studies to assess the pharmacokinetics and safety of Singulair in infants and toddlers between ≥ 6 months and < 2 years.

Study 1: Population pharmacokinetic (PK) study in pediatric asthma patients aged 6 months to < 2 years old.

Study 2: Six-week safety study in pediatric asthma patients aged 6 months to < 2 years.

Study 3: Population PK study in pediatric asthma patients aged ≥ 2 years to < 6 years.

Study 4: Six-week safety study in pediatric asthma patients aged ≥ 2 years to < 6 years.

Amendment #1 (April 18, 2000):

Changed the objective/rationale, study design, and entry criteria for Studies 1 and 3. In addition, the numbers of patients for all four studies were more clearly specified. Drug Information requested for Study 1 was amended. Finally, the timeframe for study reports was amended from January 2, 2001 to December 31, 2001. *Note: In retrospect, since Study 3 had already been submitted, no amendments should have been issued for this study.*

Amendment #2 (September 7, 2000):

Changed the entry criteria for Study 1.

Amendment #3 (September 7, 2001):

Changed study evaluations for Study 1, and Clinical Endpoints for Study 2. This Amendment also denied a request for post-hoc changes to Studies 3 and 4 since the studies had already been submitted to an approved NDA.

1.5.1.1.3. Study Reports

The final report for Study 3 (Study P066) was submitted to IND ~~20-830~~ on November 18, 1998. The results of the first two studies were submitted to NDA 20-830 on May 6, 1999 as supplement SE1-008 for Singulair 4 mg chewable tablets, which was approved on March 3, 2000. The study report for Study 4 (P072) submitted to the NDA supplement was an interim analysis report, with the final study report submitted May 25, 2000 as NDA 20-830, SE8-011.

Studies 1 and 2 were submitted on September 28, 2001 to NDA 21-409, N-000.

Table 7. Pediatric Exclusivity Timelines

	Date	Comments
NDA 20-829 and NDA 20-830 submitted	2/21/1997	10 mg Film-Coated Tablets and 5 mg Chewable Tablets for ages 6 through adult
NDA 20-829 and NDA 20-830 approved	2/20/1998	10 mg Film-Coated Tablets and 5 mg Chewable Tablets for ages 6 through adult
Written Request	3/4/1999	4 studies outlined
NDA 20-830, SE1-008 submitted	5/6/1999	4 mg Chewable Tablets for ages 2 to 5 years Final Study Report for Study 3 (PK ages 2-5 years) Interim Study Report for Study 4 (Safety ages 2-5 years)
WR Amendment #1	4/18/2000	Changed the objective/rationale, study design, and entry criteria for Studies 1 and 3, and numbers of patients for all four studies were more clearly specified. Drug Information requested for Study 1. Timeframe for study reports was amended from January 2, 2001 to December 31, 2001
NDA 20-830, SE1-008 approved	3/3/ 2000	4 mg Chewable Tablets for ages 2 to 5 years
NDA 20-830, SE8-011 submitted	5/25/2000	Final Report for Study 4 (Safety ages 2-5 years)
Original WR Due Date	1/2/2001	Applies to Studies 3 and 4
WR Amendment #2	9/28/2000	Changed Entry Criteria for Study 1
WR Amendment #3	9/7/2001	Changed Study Evaluations for Study 1, and Clinical Endpoints for Study 2
NDA 21-409 submitted	9/28/2001	4 mg oral granules Final Study Report for Study 1 (PK ages 6 to 23 months) Final Study Report for Study 2 (Safety 6 to 23 months)
Amended WR Due Date	12/31/2001	Applies to Studies 1 and 2

2. DESCRIPTION OF CLINICAL DATA AND SOURCES

2.1. Overall Data

This application includes five studies in support of the proposed label changes. Datasets for the studies were submitted and available to the reviewers. The entire submission was in an all-electronic format.

2.2. Clinical Trials

This submission includes five clinical studies that are considered pivotal in support of the proposed label changes. Three studies provide adult pharmacokinetic bioequivalence data to support the use of the 4 mg oral granule formulation as an alternate to the 4 mg chewable tablet in patients ages 2 to 5 years. Two of these adult studies also provide food-effect bioavailability data for the 4 mg oral granule formulation. Two studies provide pharmacokinetic, safety, and limited efficacy data using the 4 mg oral granule formulation in patients ages 6 months to <2 years.

CLINICAL REVIEW

NDA 21-409, Singulair® 4mg Oral Granules

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Table 8. NDA 21-409, Singulair® 4mg Oral Granules, Studies for ages 2 to 5 years

Study	Design	Treatment Groups	Duration	Dosage	Subjects n / Sex	Evaluations / Materials Submitted
P127	Single-center, open-label, randomized, 3-period crossover fasted single-dose, dose-proportionality PK study	Healthy, non-smoking men and women between 18-45 years 96 hours between treatments	3 single doses with water	2 mg oral granules 4 mg oral granules 6 mg oral granules	10 M 6 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety
P090	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study	Healthy, non-smoking men and women between 18-45 years 96 hours between treatments	3 single doses	4 mg oral granules 4 mg oral granules + applesauce 4 mg chewable tab	9 M 15 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety
P183	Single-center, open-label, randomized, 3-period crossover fasted single-dose BE and food-effect BA study	Healthy, non-smoking men and women between 18-45 years 96 hours between treatments Study used to-be marketed formulation	3 single doses	4 mg oral granules 4 mg oral granules + high-fat meal 4 mg chewable tab	20 M 11 F	PK: AUC _{0-∞} C _{max} T _{max} t _{1/2} Safety

Table 9. NDA 21-409, Singulair® 4mg Oral Granules, Studies for ages 6 to 23 months

Study	Design	Treatment Groups	Duration	Dosage	Subjects n / Sex	Evaluations / Materials Submitted
P136C1	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} C _{I/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 hs	Total 256 175/169 * M: 116 F: 59 81/74 *	Safety: AEs Lab AEs Exploratory efficacy: Days s β-ag β-ag Rx/d Unsch visits Oral CS Asthma attacks D/Cdt asthma Total Eos

* Enrolled/Completed number of patients

2.3. Postmarketing Experience

The Worldwide Clinical Summary within the Summary of Safety included worldwide post-marketing patient exposure data for montelukast through the cutoff date of May 31, 2001 [Summary, page 67; clinsum.pdf]. A Safety Update Report (SUR), submitted January 28, 2002, covered the period from May 31, 2001, to September 28, 2001 [SUR 02/01/28, page 1; cover.pdf]. In addition to reports of serious adverse events from the Worldwide Adverse Experience Reporting System, the SUR included patients enrolled in studies P072-10, P219, and P232 described below.

2.4. Literature Review

Merck included a number of references with the submission. In addition, a literature review was conducted via PubMed. Areas searched included all literature regarding the natural history and diagnosis of wheezing disorders and asthma in infants and young children, as well as the use of controller medications for asthma in children. References are cited in the body text and included in the Reference section at the end of this review.

3. CLINICAL REVIEW METHODS

3.1. Conduct of the Review

The review included both of the five submitted studies. Several questions were raised during the review process, and further data were requested and submitted by the applicant. This information will be discussed within the body of the review.

3.2. Materials Consulted and Documentation

This is an electronic NDA submission, with certain paper elements that are either required or provided for review purposes. All documents requiring signatures for certification are included as paper for archival purposes. In addition, Merck has provided, and called "review copies" in the cover letter, paper versions of the sections that would be necessary for international drug application. The formatting is that of an ICH paper submission. This paper material includes a Worldwide Clinical Summary, Study Reports minus data sets, and labeling information. The Worldwide Clinical Summary includes pharmacokinetic and bioequivalence of the oral granule formulation of montelukast, dose selection/pharmacokinetic in patients ages 6 months to <2 years, safety, postmarketing experience, published clinical literature, drug abuse and overdose information, efficacy, and benefits versus risk sections. Indeed, the same Worldwide Clinical Summary supplants separate Integrated Summaries of Efficacy and Safety in the electronic version as well.

The submission is organized around the electronic Table of Contents (TOC) [ndatoc.pdf]. The electronic TOC has a hierarchical structure, which provides hypertext links and bookmarks to the rest of the NDA. The electronic pointers or bookmarks open sections and sub-sections within the submission that may or may not be within the same document. The TOC provides links to Form 356h [356h.pdf] and to the cover letter [cover.pdf]. Adobe Acrobat was used to open these documents and electronically 'mark it up' during the review process.

Patients discontinued from four of the five studies. Of those discontinuations, only two of the studies had patients who discontinued due to AEs. Patients who discontinued for other reasons are not included in the Case Report Forms (CRFs). The CRFs submitted with the original application included six patients, all from study P176, who were discontinued due to AEs. However, in the original submission, one CRF was missing for one patient who discontinued due to an AE in Study P136C1. The missing CRF was submitted on January 25, 2002 [2002-01-25; cover.pdf].

A safety update report was submitted on January 28, 2002, including safety information from the cutoff date of the application, from May 31, 2001, to September 30, 2001. This submission includes adverse events from sources other than the case report forms for two of the submitted studies: P219 and P232. Study P219 included patients ages 2-5 years treated with montelukast chewable tablets. Study P232, the Extended Safety Study, included patients ages 6 months to <3 years treated with the oral granule formulation. Study P232 only included patients who were eligible to participate on the basis of having participated in study P176. The safety update also include post-marketing safety data for the 6-month to 5-year age group from post-marketing use of all marketed forms of montelukast. [2002-01-28; cover.pdf]

3.3. Data Quality and Integrity

No DSI audits were requested or conducted for this NDA. Singulair is not a new molecular entity. No irregularities that would raise the question of data integrity were raised during the review process. Therefore, a DSI audit was not needed for this NDA submission.

3.4. Ethical Standards

No ethical issues are raised.

3.5. Financial Disclosure

No financial disclosure issues are raised.

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4. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

4.1. Chemistry/Manufacturing and Controls

Merck states that the Montelukast oral granule formulation was developed as an alternative to the chewable tablet formulation. In addition, Merck states that the program was initiated in July of 1997, and predates the sNDA filing for the 4 mg chewable tablets in May of 1999. The formulation contains 4 mg of active drug, labeled as the free acid equivalent of montelukast sodium. Excipients are the same as for both the 4 mg and 5 mg chewable tablets, except that USP grade mannitol used for the oral granules [

] [CMC, Introduction, page 4; introduc.pdf]

It should be noted that there is about — of mannitol in each packet of montelukast. In the submission, Merck does not address the potential clinical effects of this dose of mannitol administered orally. Mannitol is a sugar that is not metabolized by the body and is excreted by the kidneys intact, acting as an osmotic diuretic. About 17 % of an oral dose is absorbed and excreted by the kidneys. The rest stays in the intestinal tract, acting as a hydroscopic agent. Therefore, there is concern that this dose might cause diarrhea, or accentuate diarrhea in a susceptible infant. This topic is explored further in the Integrated Review of Efficacy.

Table 10. Composition of to-be-marketed formulation of Singulair 4 mg oral granules

Ingredient	Composition (mg/packet)	Function
Montelukast Sodium (free acid equivalent)	4.160	Active drug
Mannitol, USP		
Hydroxypropyl Cellulose NF		
Magnesium Stearate, NF		
Total Packet Weight	500.0	

Sources: CMC, Drug Product, page 9; product.pdf and Introduction, page 7; introduc.pdf

The market image product

acceptable [CMC, Introduction, page 13; introduc.pdf].

Of significance is the stability data for montelukast oral granules when mixed with various foods. Merck reports stability data when exposed to light for up to 30 minutes in ice cream, carrot, rice, and applesauce (Table 11). This data shows that the presence of _____ increases to _____ when the oral granules are mixed with applesauce and exposed to light for 30 minutes. In rice, a very common baby food (rice cereal is often the first baby food recommended to a parent), the percent of _____ increases to _____ after 30 minutes, with the limit for _____ . Merck states that the _____ was previously qualified in preclinical studies at a level of _____ with a safety factor of ~10 to ~20. [CMC, Drug Product, page 86; product.pdf]

Absent is stability data from any formulas, as well as data _____ . Since it is not uncommon for some 6 to 12 month old infants to not have been exposed to applesauce and other foods, this is of some concern. Some infants and toddlers may be allergic to applesauce (and/or other foods) and require that the oral granules be administered in an alternate food. In addition, it is common current practice for parents to mix medications in formula, which may be the only food in infant is ingesting. Therefore, in addition to the foods already tested, it would have been preferable if stability testing were to include soy, and milk-based formulas as well as hydrolyzed protein formulas (since the population with asthma is a population more likely to be allergic to milk and soy protein). Other foods would include rice cereal instead of rice (since rice is an unlikely food for 6 to 12 or 15 months of age), milk, chocolate syrup and water. In addition, it is not uncommon for an infant to refuse a feed, or for some other reason a dose might be postponed after mixture in food. It is certainly possible for a feeding to be postponed for several hours if an infant is sleeping. Since dosing is once daily, it would have been preferable for Merck to provide stability data out to the next dose: _____ .

However, when stability testing in multiple foods was requested by the Division, Merck specifically refused to do so [Response of June 7, 2002]. They state that "after opening the packet, the full dose...must be administered immediately (within 15 minutes). If mixed with food, Singulair _____ must not be stored for future use. Singulair _____ are not intended to be dissolved in liquid for administration." For the reasons outlined above, it is recommended that this information be incorporated into the labeling, and Merck has placed this information into the suggested labeling.

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Table 11. Stability of montelukast oral granules in various baby foods

Food	Time (minutes)	
Montelukast sodium oral granules Lot 1005-42, (Initial Release Data)	N/A	
Lot 1005-42 on a spoon*	5	
Ice cream	5	
	10	
	15	
	30	
Carrot	5	
	10	
	15	
	30	
Rice	5	
	10	
	15	
	30	
Applesauce	5	
	10	
	15	
	30	

* Montelukast sodium oral granules on spoon with no food.

Source: CMC, Drug Product, Table C-50, page 86; product.pdf

4.2. Animal Pharmacology/Toxicology

No new preclinical pharmacology or toxicology studies were conducted in support of this application [Nonclinical Pharmacology and Toxicology, page 1; pharmtox.pdf].

It has been determined that the preclinical data support the use of montelukast down to 6 months of age.

4.3. Statistics

Since there were no efficacy studies submitted, no statistical analyses were performed relating to the clinical sections of this review.

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5. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

5.1. Pharmacokinetics

Information with regard to pharmacokinetics is critical to this review, since four of the five studies submitted are human pharmacokinetic studies. This review will discuss all the major biopharmaceutic issues and concerns within the Integrated Review of Efficacy. For further details, please refer to the Biopharmaceutics review of Dr. Sandra Suarez. Comments from Dr. Suarez' Executive Summary are included below.

5.2. 1.1 Biopharmaceutics Comments to the Medical Reviewer

1. "The submitted pharmacokinetic data support the use of the 4-mg oral granule formulation of montelukast as an alternate to the 4-mg chewable tablet in patients aged 2 to 5 years.
2. Food did not affect the AUC of montelukast delivered from the — formulation, however food did decrease C_{max} by 35% and change T_{max} from 2.3 hrs to 6.4 hrs. The effect of food on the BA of Montelukast delivered from the film-coated tablet and chewable formulations has been studied in the past. While food did not affect C_{max} and AUC for the film coated formulation, it did have similar effect as the one observed in the present case for the — formulation. Food decreased C_{max} by 52% and decreased F_{abs} from 73% (fasting) to 63% (fed) (data from NDA 20-830 submitted on 02/24/97). Although the effect of food on the C_{max} of the chewable formulation was statistically significant, it was decided that this effect was not clinically relevant (clinical trial conducted without regards to meals or timing of food ingestion did not show any safety of efficacy concerns) and therefore, the findings were not reflected in the label.
3. 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.
4. High variability in exposure (AUC and C_{max}) was observed in the children — to < 2 years of age, especially in the ≥6 months to < 1 years of age. A lower dose of Singulair — 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, the medical officer should evaluate the risk (safety) involved in having a 48% higher exposure in children ≥6 months to < 1 year of age receiving 4-mg of Singulair —

5.3. Pharmacodynamics

No pharmacodynamic studies were conducted in support of this application.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

Merck states that after opening the packet, the full dose must be administered immediately (within 15 minutes). If mixed with food, Singulair oral granules must not be stored for future use. Singulair oral granules are intended for either administration directly in the mouth or mixed with a spoonful of soft food, and are not intended to be dissolved in liquid for administration. This information should be clearly stated in the labeling.

On the basis of the three adult pharmacokinetic studies submitted, the montelukast 4 mg oral granule and 4 mg chewable tablet formulations are bioequivalent. It is reasonable to accept Merck's proposal that Singulair 4 mg oral granules may be used as an alternate formulation to the currently approved Singulair 4 mg chewable tablets for ages 2 to 5 years, and approval is recommended for this age range.

As a primary formulation for the prophylaxis and chronic treatment of pediatric "asthma" patients ages 2 to 23 months, the diagnosis has not been sufficiently established, the benefits (efficacy) have not been sufficiently established, and the risks have not been fully evaluated. Variability of exposure (AUC) increases in successively younger age groups of 12 to 23 months and 6 to 11 months. In particular, the variability of exposure in the 6 to 11 month old infants is excessively high, posing both safety and efficacy concerns. There is no relationship between exposure and either weight or height. Therefore, a clearly positive risk/benefit ratio has not been established.

6.2. General Approach to the Efficacy Review

In the following sections, a complete review of each trial will be presented. Only one multi-dose trial was submitted to this NDA. Therefore, rather than separating safety data for incorporation into the Integrated Review of Safety, the safety data is included in each review to facilitate readability. While each trial has a brief conclusions statement, conclusions for each of the two age indications are presented after the reviews, and repeated in the Conclusions and Recommendations section. Each trial was thoroughly evaluated, including the original protocol and the description of the protocol in the Study Report as well as all appendices. Any discrepancies are noted in the review. Data from SAS transport tables was not evaluated by this reviewer.

6.3. Detailed Review of Trials by Indication

6.3.1. Studies for Indication of Age 2 to 5 Years

Three single-dose studies performed in adults are submitted to support the bioequivalence of the 4 mg oral granule formulation to the 4 mg chewable formulation, and to evaluate the effect of food on the pharmacokinetics of the oral granule formulation (Table 8). Merck states that the two formulations would be interchangeable for the 2 to 5 year age group. Dose selection for the 2 to 5 year age group was previously carried out to gain the indication for the 4 mg chewable tablets, and was therefore not carried out as part of this NDA submission. However, the dose selection of 4 mg for this age range was based on a

population pharmacokinetic study, the results of which are summarized in Table 12 below. This study was part of the Written Request for the study of age-appropriate formulations in children outlined earlier in this review.

Study P127 evaluated the dose proportionality of 2, 4 and 6 mg dosages of the oral granules. P090 was a pilot bioequivalence study, providing a preliminary comparison between the 4 mg oral granules, administered either fasting or with 2 tablespoons of applesauce, and the 4 mg chewable tablet formulation. Study P183 was a final market image study conducted to confirm the bioequivalence of the final market image of the 4 mg oral granule and the 4 mg chewable tablet formulations, and to evaluate the effect of a high-fat breakfast on the pharmacokinetics of the 4 mg oral granules.

Table 12. Single-dose population pharmacokinetic studies for 4mg chewable tablets

Patients/Subjects Protocol	N	Dose Formulation	AUC _{pop} mean (SE) ng*hr/mL	C _{max} ng/mL	T _{max} hours	T _{1/2} hours
2 to 5 y Protocol 066	15	4mg CT	2721 (164)	471 (65)	2.1 (0.3)	3.2 (0.2)
Adults Protocol 034	16	10mg FCT	2595 (165)	284 (54)	3.4 (0.6)	4.1 (0.1)

Source: page 61; summary.pdf

6.3.1.1. Study P127

Protocol #: P127
 Title: An open, randomized, 3-period, crossover study to determine the dose proportionality of the montelukast — formulation in healthy adults
 Study Dates: 7 October 1999 to 30 October 1999
 Sites: Single-site
 Investigator: 
 IRB: 

Source: Clinical, Reference p127, pages 8 and 11; p127.pdf

6.3.1.1.1. Summary

This was an open-label, randomized, 3-period crossover, dose-proportionality study comparing the single-dose plasma concentration profiles of the 4 mg oral granule formulation of montelukast in healthy adults. Fasting subjects received 3 single 2 mg; 4 mg, and 6 mg doses of montelukast administered with a washout period of at least 96 hours between doses. Plasma drug concentrations showed no statistically significant pairwise-comparison differences between dosages for dose-adjusted AUC_{0-∞} or C_{max}, establishing dose-proportionality between the three dosages. There was one adverse experience of mild dizziness, possibly related to the test product.

6.3.1.1.2. Study Design

6.3.1.1.2.1. Description

This was an open-label, randomized, 3-period crossover, dose-proportionality study comparing the single-dose plasma concentration profiles of the 4 mg oral granule formulation of montelukast in healthy adults. Fasting subjects received 3 single 2 mg, 4 mg, and 6 mg doses of montelukast administered with a washout period of at least 96 hours between doses. Plasma drug concentrations were obtained at frequent time points over the 24 hours post-dosing in each period. [Clinical, Reference p127, pages 13, 159; p127.pdf]

6.3.1.1.2.2. Objectives

1. To evaluate the plasma concentration profile of 2, 4, and 6 mg single oral doses of the — formulation of montelukast.
2. To assess dose proportionality after administration of 2, 4, and 6 mg single oral doses of the — formulation of montelukast.
3. To evaluate the safety and tolerability of single oral 2, 4, and 6 mg doses of the — formulation of montelukast. [Clinical, Reference p127, pages 12, 157; p127.pdf]

6.3.1.1.2.3. Inclusion / Exclusion Criteria

Healthy, nonsmoking men and women between the ages of 18 and 45 years who were judged to be in good health on the basis of medical history, physical examination, and laboratory screening evaluations. [Clinical, Reference p127, pages 16-7, 157-9; p127.pdf]

No prescription or over-the counter medications were allowed for a period of 14 days prior to and during the study, except to treat an adverse experience. [Clinical, Reference p127, page 21; p127.pdf]

6.3.1.1.2.4. Safety Variables

Safety was assessed by history and physical examinations, blood and urine laboratory tests, electrocardiograms, and measurements of vital signs. Laboratory tests included CBC, urinalysis, urine pregnancy test, and serum chemistries, as well as Hepatitis B, C and HIV tests at the discretion of the investigator. [Clinical, Reference p127, pages 13, 15, 157; p127.pdf]

6.3.1.1.2.5. Conduct

Subjects were randomized according to a sample allocation schedule. Subjects were fasted from all food and drink except water beginning at midnight the night before dosing. Fasting was continued for two hours post-dosing, with administration of 250mL of clear apple juice 2 hours, and meals at 4 and 10 hours post-dose. Patients were discharged 24 hours after dosing after all procedures were completed. [Clinical, Reference p127, pages 13, 20, 160-1, 165; p127.pdf]

Pre-dose tests included laboratory safety tests, urine beta-HCG for women, and vital signs. Vital signs were also done at 2 hours and pre-discharge. [Clinical, Reference p127, page 14; p127.pdf]

6.3.1.1.2.6. Parameters

Blood (7 mL per sample) was drawn pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing for plasma montelukast assay [Clinical, Reference p127, pages 13, 165; p127.pdf]. Montelukast plasma concentrations were determined using a ζ [Clinical, Reference p127, page 22; p127.pdf].

6.3.1.1.3. Results of Study P127

6.3.1.1.3.1. Patient disposition

Sixteen (16) subjects were enrolled, and 15 subjects completed the study. One subject was discontinued due to a family emergency. Subjects had a mean age of 34 years (range 20-45 years), divided between 9 males and 6 females. Fourteen subjects were Hispanic, and one was Black. There were no compliance issues. [Clinical, Reference p127, pages 28-30; p127.pdf]

6.3.1.1.3.2. Pharmacokinetic parameters

Pairwise comparisons were used to evaluate dose proportionality. The primary pharmacokinetic parameters were the dose-adjusted (adjusted to 4 mg) $AUC_{0-\infty}$ and C_{max} . Other pharmacokinetic parameters included the time of the maximum observed plasma concentration (T_{max}) and the apparent elimination half-life ($t_{1/2}$). Individual plasma montelukast concentration-time data plots were based on actual plasma collection times listed in the finalized case report forms. The C_{max} and T_{max} were obtained by visual inspection of individual plasma concentration-time profiles. The area under the concentration-time curve to the last quantifiable time point (AUC_{last}) was calculated using the trapezoidal rule. [Clinical, Reference p127, page 22; p127.pdf]

Comment: It is unclear why the applicant felt the need to use dose-adjusted mean values, other than to satisfy the states study hypothesis. The point of the study was to show dose-proportionality, and this could have been accomplished by other comparisons of AUCs and C_{max} .

Dose-adjusted geometric mean values for $AUC_{0-\infty}$ and C_{max} are shown in Table 13. Median T_{max} and harmonic mean $t_{1/2}$ are also shown. A plot of the mean montelukast plasma concentrations is shown in Figure 1. There were no statistically significant pairwise differences between treatments for $AUC_{0-\infty}$ or C_{max} [Clinical, Reference p127, pages 31-3; p127.pdf].

Treatment comparisons for T_{max} between 2mg / 4 mg and 4 mg / 6 mg were statistically significant (2mg / 4 mg $p = 0.004$, 4 mg / 6 mg $p = 0.002$), but not between 2 mg / 6 mg. Merck argues that small differences in T_{max} are not meaningful to dose proportionality relative to the concentration-related parameters of $AUC_{0-\infty}$ and C_{max} . Treatment comparison for T_{max} between 2mg / 4 mg and 2 mg / 6 mg were statistically significant (2mg / 4 mg $p = 0.019$, 2 mg / 6 mg $p = 0.003$), but not between 4mg / 6 mg. [Clinical, Reference p127, pages 31-4; p127.pdf]

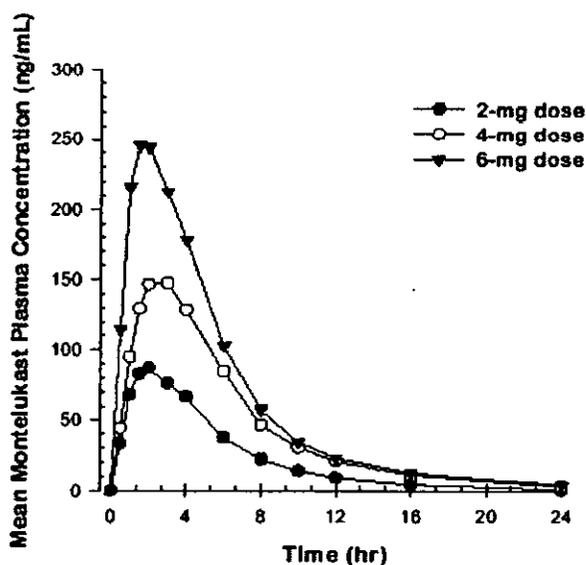
Table 13. Study P127, Summary of dose-adjusted † pharmacokinetic parameters

Dose	AUC _{0-∞} ng*hr/mL (GM ±SD)	AUC _{0-∞} GMR * (90% CI)	C _{max} ng/mL (GM ±SD)	C _{max} GMR * (90% CI)	T _{max} Median (min, max)	T _{1/2} Harmonic mean (hr ±SD)
2 mg	944.4 ± 419.2	0.90 (0.80, 1.02)	164.4 ± 87.7	1.03 (0.88, 1.21)	2.0	3.3 ± 0.5
4 mg	1047.3 ± 232.5		159.4 ± 43.1		3.0	3.7 ± 0.5
6 mg	1000.7 ± 202.4	0.96 (0.84, 1.08)	169.7 ± 54.8	1.07 (0.91, 1.24)	1.5	3.9 ± 0.7

† Back-transformed from log scale; SD = Standard deviation.
‡ Dose-adjusted to 4 mg.

Source: Clinical, Reference p127, Tables 6-11, page 31-5; p127.pdf

Figure 1. Study P127, Mean plasma montelukast plasma concentration



Source: Clinical, Reference p127, page 30; p127.pdf

6.3.1.1.3.3. Safety

All sixteen subjects were included in safety evaluations. There were no deaths, serious adverse events or pregnancies. While there were some laboratory results outside the normal range, there were no laboratory results considered to be clinically important, and no laboratory adverse events. There were no clinically important abnormalities in physical examinations, vital signs, or ECGs. [Clinical, Reference p127, page 37; p127.pdf]

There was one adverse experience of mild dizziness, determined to be possibly related to study drug. This is mentioned in the summary/discussion section of the report, but no further information was given (i.e. no line listings), except within the datasets. [Clinical, Reference p127, pages 38; p127.pdf]

6.3.1.1.4. Conclusions of Study P127

The primary purpose of this study was to evaluate the dose proportionality of montelukast after administration of single 2, 4, and 6 mg doses of the oral granule formulation of montelukast. A determination was made of pairwise GMRs for the dose-adjusted $AUC_{0-\infty}$ (primary hypothesis) and C_{max} (secondary hypothesis), and the GMRs and 90% CIs were compared to the predefined interval of (0.70, 1.43). The $AUC_{0-\infty}$ and C_{max} GMRs and 90% CIs for all comparisons for were within the specified range, supporting the hypothesis of dose-proportionality. [Clinical, Reference p127, page 37; p127.pdf]

The oral granule formulation was generally well tolerated in this study. There was one adverse experience of mild dizziness, possibly related to the test product.

6.3.1.2. Study P090

Protocol #:	P090	
Title:	An open, randomized, 3-period, crossover study to determine the bioequivalence of the chewable and — formulations of montelukast (MK-0476) in healthy adult volunteers	
Study Dates:	26 March 1999 to 22 April 1999	
Sites:	Single-site	
Investigator:	[]
IRB:	[]

Source: Clinical, Reference p090, pages 10 and 13; p090.pdf

6.3.1.2.1. Summary

This was an open, randomized, single-dose, 3-period crossover study to determine the plasma concentrations of the 4 mg chewable and 4 mg oral granule (fasted and with apple sauce) formulations of montelukast in 24 healthy adults. The plasma concentration profiles for the fasted 4 mg oral granules and 4 mg chewable tablets were similar. Co-administration of applesauce with the oral granules prolonged T_{max} slightly, lowered C_{max} slightly, but did not affect $AUC_{0-\infty}$. There were no tolerability issues. One subject experienced mild transient elevation in 2 liver enzymes at the third period of treatment.

6.3.1.2.2. Study Design

6.3.1.2.2.1. Description

This was an open-label, randomized, 3-period crossover study comparing the single-dose plasma concentration profiles of the 4 mg oral granule and chewable tablet formulations of montelukast in 24 healthy adults. Additionally, the effect of food on the pharmacokinetics of montelukast administered as a oral granule formulation was evaluated. Fasting subjects received each of 3 single doses of montelukast (4 mg oral granules fasted; 4 mg oral granules plus 2 tablespoons of applesauce; and a 4-mg chewable tablet fasted) administered

with a washout period of at least 96 hours between doses. Plasma drug concentrations were obtained at frequent time points over the 24 hours post-dosing in each period. [Clinical, Reference p090, page 15; p090.pdf]

6.3.1.2.2.2. Objectives

1. To demonstrate bioequivalence between the _____ and chewable formulations of montelukast in the fasted state.
2. To compare the plasma concentration profiles of the montelukast _____ formulation when given with and without applesauce in the fasted state.
3. To evaluate the tolerability of single oral doses of montelukast given as a _____ formulation. [Clinical, Reference p090, pages 14, 172; p090.pdf]

6.3.1.2.2.3. Inclusion / Exclusion Criteria

Healthy, nonsmoking men and women between the ages of 18 and 45 years who were judged to be in good health on the basis of medical history, physical examination, and laboratory screening evaluations. [Clinical, Reference p090, pages 18-9, 173-4; p090.pdf]

6.3.1.2.2.4. Safety Variables

Safety was assessed by history and physical examinations, blood and urine laboratory tests, electrocardiograms, and measurements of vital signs. Laboratory tests included CBC, urinalysis, serum and urine pregnancy tests, and serum chemistries. [Clinical, Reference p090, pages 15-17; p090.pdf]

6.3.1.2.2.5. Conduct

Subjects were randomized according to a sample allocation schedule. Subjects were fasted from all food and drink except water beginning at midnight the night before dosing. Fasting was continued for two hours post-dosing, with administration of 250mL of clear apple juice 2 hours, and meals at 4 and 10 hours post-dose. Patients were discharged 24 hours after dosing after all procedures were completed. [Clinical, Reference p090, pages 20-2, 176; p090.pdf]

Pre-dose tests included laboratory safety tests, urine beta-HCG for women, and vital signs. Vital signs were also done at 1, 2, and 8 hours, and pre-discharge. [Clinical, Reference p090, page 16; p090.pdf]

Subjects received treatment between 8-9 AM on each dosing day. For Treatment A, subjects ingested the 4-mg oral granules followed by 250 mL of water. For Treatment B, the 4-mg oral granules were mixed with 2 teaspoons of applesauce using a toothpick, and subjects ingested all of the applesauce mixture and licked the spoon and toothpick, followed by 250 mL of water. For Treatment C, subjects chewed the chewable tablet for approximately 30 seconds followed by 250 mL of water. [Clinical, Reference p090, page 15; p090.pdf]

6.3.1.2.2.6. Parameters

Blood (5 mL per sample) was drawn pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing for plasma montelukast assay [Clinical, Reference p090, page 15; p090.pdf]. Montelukast plasma concentrations were determined [Clinical, Reference p090, page 15; p090.pdf].

6.3.1.2.3. Results of Study P090

6.3.1.2.3.1. Patient disposition

Twenty-four (24) subjects were entered, and 24 completed the study, with no discontinuations. Nine subjects were male, ages 24-43, and 15 were female, ages 27-44. One subject was Black, one was White, and 22 were Hispanic. [Clinical, Reference p090, page 30-1; p090.pdf]

6.3.1.2.3.2. Pharmacokinetic parameters

The pharmacokinetic parameters included the area under the plasma concentration-time curve from Hour 0 to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and terminal half-life ($t_{1/2}$), except for the oral granules with applesauce, since food delayed T_{max} [Clinical, Reference p090, pages 24-5; p090.pdf]. An ANOVA model containing factors for subject, period, and treatment was used. Carryover effect was also assessed, and when insignificant, was dropped from the final model [Clinical, Reference p090, page 29-30; p090.pdf].

Table 14 shows the single-dose pharmacokinetics of both 4 mg formulations. Geometric mean ratios between formulations and fasted/fed conditions are also presented. Figure 2 graphically represents an overlay of the plasma concentrations over time for the three doses of montelukast. Figure 3 depicts differences between formulations graphically by showing the within-subject difference over time between the chewable tablet and oral granules, and between the oral granules fasted and with applesauce.

Under fasting conditions, the plasma concentration profiles for the 4 mg oral granules and the 4 mg chewable tablets were similar, with median T_{max} at 2 hours and median $t_{1/2}$ of 4.1 hours in both treatment groups. $T_{1/2}$ was within the range of seen in previous adult studies (2.7 to 5.5 hours). The geometric mean ratio of fasted oral granules to fasted chewable tablets for $AUC_{0-\infty}$ and C_{max} were 1.01 with a 90% CI of (0.92, 1.11) and 0.99 with a 90% CI of (0.86, 1.13), respectively. The geometric mean ratio was within the prespecified bioequivalence interval of 80-125%. [Clinical, Reference p090, pages 50-1; p090.pdf]

For 4 mg oral granules plus applesauce compared with fasted 4 mg oral granules, the $AUC_{0-\infty}$ was similar, but C_{max} was smaller and T_{max} was delayed by 1 hour to 3 hours. The geometric mean ratio of oral granules plus applesauce to fasted oral granules for $AUC_{0-\infty}$ and C_{max} were 1.00 with a 90% CI of (0.92, 1.10) and 0.92 with a 90% CI of (0.80, 1.06), respectively. [Clinical, Reference p090, pages 50-1; p090.pdf]

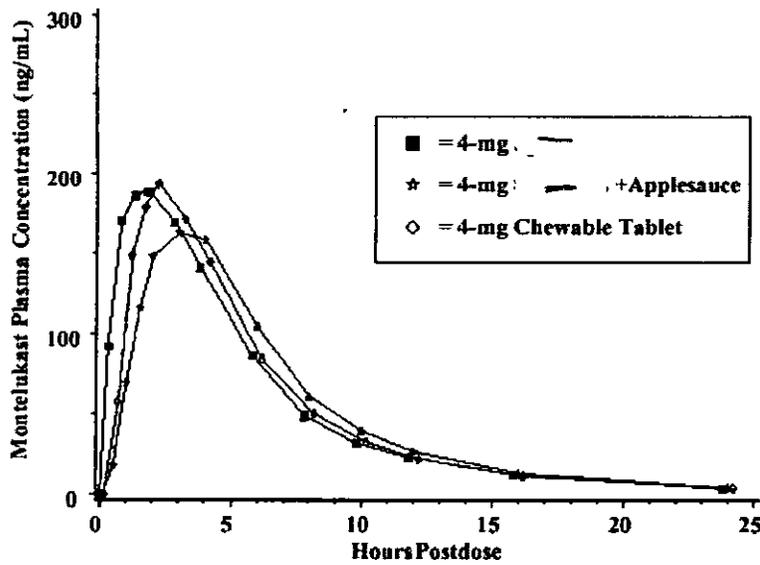
Table 14. Study P090, Single-dose pharmacokinetics

Dose Formulation	AUC _{0-∞} ng*hr/mL (GM ±SD)	AUC _{0-∞} GMR * (90% CI)	C _{max} ng/mL (GM ±SD)	C _{max} GMR * (90% CI)	T _{max} Median (min, max)	T _{1/2} Median (hr ±SD)
Fasted 4 mg chewable tab	1208.3 ± 467.4	1.01 (0.92, 1.11)	201.7 ± 91.6	0.99 (0.86, 1.13)	2.0	4.1 ± 0.8
Fasted 4 mg oral granules	1223.1 ± 342.3		198.8 ± 53.8		2.0	4.1 ± 0.8
Applesauce + 4 mg oral granules	1225.7 ± 528.9	1.00 (0.92, 1.10)	182.8 ± 78.2	0.92 (0.80, 1.06)	3.0	

* GMR = geometric mean ratio

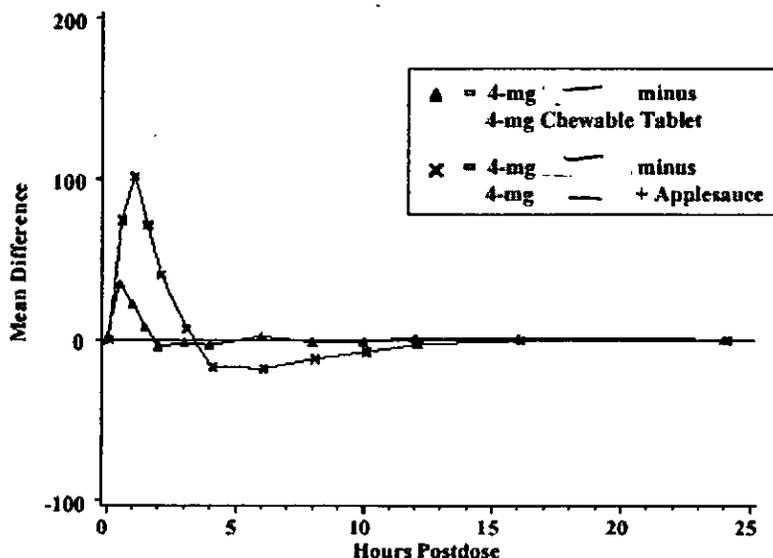
Source: Clinical, Reference p090, Tables 6-13 pages 36-46; p090.pdf

Figure 2. Study P090, Mean montelukast plasma concentrations



Source: Clinical, Reference p090, page 33; p090.pdf

Figure 3. Study P090, Mean montelukast plasma concentrations within-subject difference



Source: Clinical, Reference p090, page 34; p090.pdf

6.3.1.2.3.3. Safety

All subjects were included in safety evaluations. There were no deaths, serious adverse events or pregnancies. There were no clinically important abnormalities in physical examinations, vital signs, or ECGs. [Clinical, Reference p090, page 50; p090.pdf]

There were 5 clinical adverse experiences in 4 subjects, and none were serious. The most frequent clinical adverse experience was back pain (2 subjects). One subject reported somnolence (5 minutes after receiving study drug) that lasted approximately 4 hours and then resolved. The investigator considered the somnolence possibly related to study drug. [Clinical, Reference p090, pages 47-8; p090.pdf]

There were laboratory adverse experiences in one subject during Period III. Subject AN315 (Hispanic female, age 35 years) experienced transient elevations in ALT (140 IU/L) and AST (87 IU/L), both determined by the investigator to be possibly related to study drug. Follow-up laboratory tests were normal (26 and 23 IU/L). [Clinical, Reference p090, pages 49-51; p090.pdf]

6.3.1.2.4. Conclusions of Study P090

The plasma concentration profiles ($AUC_{0-\infty}$ and C_{max} GMRs and 90% CIs) for the fasted 4 mg oral granules and 4 mg chewable tablets were within the specified range over the 24-hour observation period, supporting the hypothesis that the oral granule and chewable tablet formulations of montelukast, when given in the fasted state, are bioequivalent. Co-administration of applesauce with the oral granule formulation delayed absorption and slightly blunted C_{max} , but did not affect the $AUC_{0-\infty}$. Since montelukast is intended to be

administered as chronic therapy for the treatment of asthma and the $AUC_{0-\infty}$ were similar, the observed differences in T_{max} between the 4 mg oral granules plus applesauce and 4 mg oral granules groups are not clinically important. There were no tolerability issues with single doses of the oral granule formulation. [Clinical, Reference p090, pages 50-1; p090.pdf]

6.3.1.3. Study P183

Protocol #: P183
Title: A 3-period, single-dose, crossover study in healthy adult subjects to establish the bioequivalence of the 4 mg tablet and _____ formulations of montelukast, and to evaluate the effect of food on the pharmacokinetics of the _____ formulation
Study Dates: 3 June 2000 to 7 July 2000
Sites: Single-site
Investigator: _____
IRB: _____
Source: Clinical, Reference p183, pages 10 and 14-5; p183.pdf

6.3.1.3.1. Summary

This was an open, randomized, single-dose, 3-period crossover study to determine the plasma concentrations of the final market images of 4 mg chewable and 4 mg oral granule (fasted and with a high-fat breakfast) formulations of montelukast in 30 healthy adults. The plasma concentration profiles for the fasted 4 mg oral granules and 4 mg chewable tablets were similar. Co-administration of a high-fat breakfast with the oral granules delayed T_{max} by ~4 hours, lowered C_{max} by ~36%, but did not affect $AUC_{0-\infty}$. The only tolerability issue was headaches in 5 subjects. The to-be-marketed formulation was used in this study (but not in studies P127 or P090). Since study P090 also compared pharmacokinetic parameters between the 4 mg oral granules and the 4 mg chewable tablets, and since the results were the same, the different oral granule formulations used in the pharmacokinetic studies are considered bioequivalent.

6.3.1.3.2. Study Design

6.3.1.3.2.1. Description

This was an open-label, randomized, 3-period crossover study comparing the single-dose plasma concentration profiles of the 4 mg oral granule and chewable tablet formulations of montelukast in 30 healthy adults. Additionally, the effect of a meal on the pharmacokinetics of montelukast administered as a oral granule formulation was evaluated. Fasting subjects received each of 3 single doses of montelukast (final market images of 4 mg oral granules fasted; 4 mg oral granules plus a high-fat breakfast; and a 4 mg chewable tablet fasted) administered with a washout period of at least 96 hours between doses. Plasma drug

concentrations were obtained at frequent time points over the 24 hours post-dosing in each period. [Clinical, Reference p183, pages 16, 182, 185; p183.pdf]

6.3.1.3.2.2. Objectives

1. To demonstrate the bioequivalence of the chewable tablet and — formulations of fasted montelukast as determined by the fasted $AUC_{0-\infty}$.
2. To compare the C_{max} of the chewable tablet and — formulations of fasted montelukast.
3. To evaluate montelukast $AUC_{0-\infty}$, C_{max} , T_{max} , and $t_{1/2}$ obtained after administration of the chewable tablet and — formulations fasted of montelukast.
4. To evaluate the plasma concentration profiles of the — formulation when administered with and without food.
5. To assess the general safety and tolerability of montelukast chewable tablet and — formulations. [Clinical, Reference p183, pages 15-6, 182; p183.pdf]

6.3.1.3.2.3. Inclusion / Exclusion Criteria

Healthy, nonsmoking men and women between the ages of 18 and 45 years who were judged to be in good health on the basis of medical history, physical examination, and laboratory screening evaluations. [Clinical, Reference p183, pages 19-20, 183-5; p183.pdf]

6.3.1.3.2.4. Safety Variables

Safety was assessed by history and physical examinations, blood and urine laboratory tests, electrocardiograms, and measurements of vital signs. Laboratory tests included CBC, urinalysis, urine pregnancy test, and serum chemistries, as well as Hepatitis B, C and HIV tests at the discretion of the investigator. [Clinical, Reference p183, pages 16-8, 26-7; p183.pdf]

6.3.1.3.2.5. Conduct

Subjects were randomized according to a sample allocation schedule. Subjects were fasted from all food and drink except water beginning at midnight the night before dosing. For subjects receiving fasted drug, fasting was continued for four hours post-dosing, with meals at 4 and 10 hours post-dose. Patients were discharged 24 hours after dosing after all procedures were completed. [Clinical, Reference p183, pages 21-4, 186-192; p183.pdf]

Pre-dose tests included laboratory safety tests, urine beta-HCG for women, and vital signs. Vital signs were also done post-dose and at 2, and 24 hours, and post-study. [Clinical, Reference p183, page 17; p183.pdf]

Subjects received treatment between 8-9 AM on each dosing day. For Treatment A, subjects chewed the chewable tablet for approximately 30 seconds followed by 250 mL of water. For Treatment B, the subjects swallowed all the contents of one 4-mg oral granules pouch followed by 250 mL of water. For Treatment C, the 4-mg oral granules were administered 5 minutes after consuming a high-fat breakfast. [Clinical, Reference p183, page 21; p183.pdf] The high-fat breakfast included 2 large eggs, 1 slice of toasted white bread

with 2 pats of butter, 2 strips of bacon, 240 cc of whole milk, and 4 oz of hash brown potatoes [Clinical, Reference p183, pages 21-4, 186-192; p183.pdf].

6.3.1.3.2.6. Parameters

Blood (7 mL per sample) was drawn pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing for plasma montelukast assay [Clinical, Reference p183, pages 16-7, 186-192; p183.pdf]. Montelukast plasma concentrations were determined using a λ

Reference p183, page 25; p183.pdf].

6.3.1.3.3. Results of Study P183

6.3.1.3.3.1. Patient disposition

Thirty-one (31) subjects were entered, and 30 completed the study, with one discontinuation. Subject AN 1029 (a 35 year old White female) discontinued the study due to difficulty with blood draws. Twenty subjects were male, ages 19-43, and 11 were female, ages 21-44. Six subjects were Black, 3 were Hispanic, and 22 were White. [Clinical, Reference p183, page 30-1; p183.pdf]

6.3.1.3.3.2. Pharmacokinetic parameters

The pharmacokinetic parameters included the area under the plasma concentration-time curve from Hour 0 to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and terminal half-life ($t_{1/2}$) [Clinical, Reference p183, page 25; p183.pdf]. An ANOVA model containing factors for subject, period, and treatment was used. Carryover effect was also assessed, and when insignificant, was dropped from the final model [Clinical, Reference p183, page 29-30; p183.pdf].

Table 15 shows the single-dose pharmacokinetics of both 4 mg formulations and the effect of food on the oral granule formulation. Geometric mean ratios between formulations and fasted/fed conditions are also presented. Figure 4 graphically represents an overlay of the plasma concentrations over time for montelukast oral granules and tablets without food. Figure 5 graphically depicts differences for the oral granule formulation when administered with and without a high-fat breakfast.

Under fasting conditions, the plasma concentration profiles for the 4 mg oral granules and the 4 mg chewable tablets were similar, with median T_{max} at 2 hours and median $t_{1/2}$ of 4:0 hours in both treatment groups. $T_{1/2}$ was within the range of seen in previous adult studies (2.7 to 5.5 hours). The geometric mean ratio of fasted oral granules to fasted chewable tablets for $AUC_{0-\infty}$ and C_{max} were 0.95 with a 90% CI of (0.91, 0.99) and 0.92 with a 90% CI of (0.84, 1.01), respectively. The geometric mean ratio was within the prespecified bioequivalence interval of 80-125%. [Clinical, Reference p183, pages 34-6; p183.pdf]

For 4 mg oral granules plus a high-fat breakfast compared with fasted 4 mg oral granules, the $AUC_{0-\infty}$ were similar, but C_{max} was 36% lower and T_{max} was delayed by 4 hours. The geometric mean ratio of oral granules plus applesauce to fasted oral granules for $AUC_{0-\infty}$ and

C_{max} were 1.04 with a 90% CI of (0.99, 1.09) and 0.64 with a 90% CI of (0.59, 0.71), respectively. [Clinical, Reference p183, pages 37-40; p183.pdf]

The to-be-marketed formulation was used in this study (but not in studies P127 or P090). Since study P090 also compared pharmacokinetic parameters between the 4 mg oral granules and the 4 mg chewable tablets, and since the results were the same, the different oral granule formulations used in the pharmacokinetic studies are considered bioequivalent.

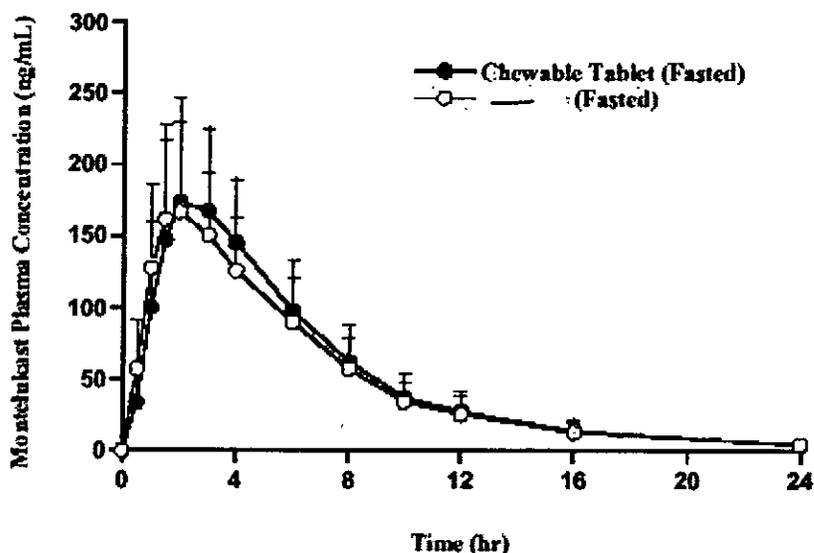
Table 15. Study P183, Single-dose pharmacokinetics

Dose Formulation	AUC _{0-∞} ng*hr/mL (GM ±SD)	AUC _{0-∞} GMR * (90% CI)	C _{max} ng/mL (GM ±SD)	C _{max} GMR * (90% CI)	T _{max} Median (min, max)	T _{1/2} Harmonic mean (hr ±SD)
Fasted 4 mg chewable tab	1210.3 ± 412.3	0.95 (0.91, 0.99)	190.0 ± 64.3	0.92 (0.84, 1.01)	2.0 —	3.9 ± 0.7
Fasted 4 mg oral granules	1148.5 ± 392.4		175.4 ± 59.2		2.0 —	4.0 ± 0.8
High-fat meal + 4 mg oral granules	1191.8 ± 380.3	1.04 (0.99, 1.09)	112.8 ± 26.2	0.64 (0.59, 0.71)	6.0 —	4.1 ± 1.2

* GMR = geometric mean ratio

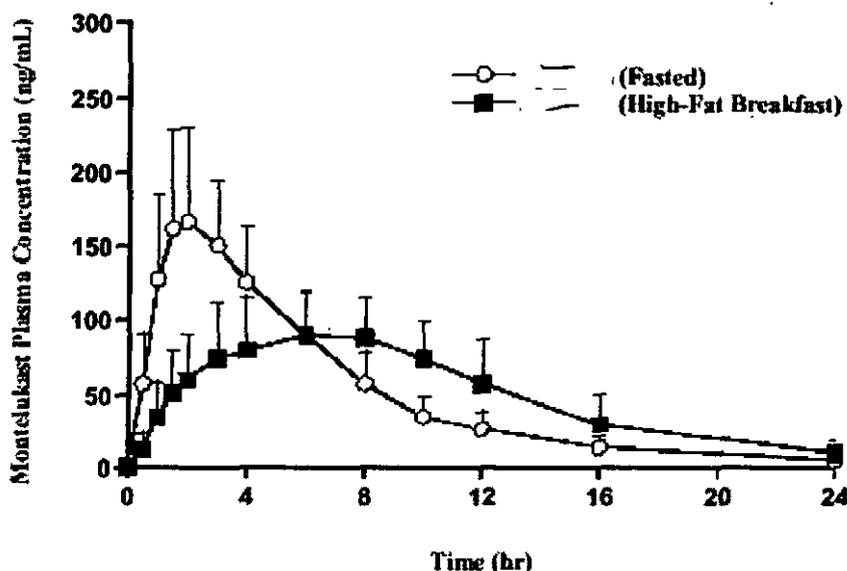
Source: Clinical, Reference p183, Tables 7-13 pages 34-40; p183.pdf

Figure 4. Study P183, Mean montelukast plasma concentrations



Source: Clinical, Reference p183, page 33; p183.pdf

Figure 5. Study P183, Food effect on mean montelukast plasma concentrations



Source: Clinical, Reference p183, page 37; p183.pdf

6.3.1.3.3.3. Safety

All subjects were included in safety evaluations. There were no deaths, serious adverse events or pregnancies. While there were some laboratory results outside the normal range, there were no laboratory results considered to be clinically important, and no laboratory adverse events. There were no clinically important abnormalities in physical examinations, vital signs, or ECGs. [Clinical, Reference p183, page 46; p183.pdf]

There were 33 clinical adverse experiences in 15 subjects. Six were moderate in intensity, but none were serious. Twenty-four adverse events were judged to be unrelated to study drug. Of these, the most frequent AE was venipuncture pain (8 of 33 AEs). Nine adverse events were judged to be possibly related to study drug of which two were moderate (headaches). Of the nine, six AEs (in five subjects) were headaches. [Clinical, Reference p183, pages 42-5; p183.pdf]

6.3.1.3.4. Conclusions of Study P183

The plasma concentration profiles ($AUC_{0-\infty}$ and C_{max} GMRs and 90% CIs) for the final market image fasted 4 mg oral granules and 4 mg chewable tablets were within the specified range over the 24-hour observation period, supporting the hypothesis that the oral granule and chewable tablet formulations of montelukast, when given in the fasted state, are bioequivalent. Co-administration of a high-fat meal with the oral granule formulation delayed absorption and blunted C_{max} , but did not affect the $AUC_{0-\infty}$. Since montelukast is

intended to be administered as chronic therapy for the treatment of asthma and the $AUC_{0-\infty}$ was similar, the observed differences in T_{max} between the 4 mg oral granules with and without a high-fat meal are not clinically important. These results are consistent with food-effect results obtained previously with the 5 mg chewable tablets in Study P060. Clinical trial data for the chewable and film-coated tablets also support that the observed food effect is not clinically relevant. The most common AE considered to be related to study drug was headache. [Clinical, Reference p183, pages 50-1; p183.pdf]

6.3.1.4. Summary Results of Adult Pharmacokinetic Studies for Age 2-5 Years

As shown in Table 13, Table 16 and in Figure 1, study P127 evaluated dose proportionality of the oral granule formulation of montelukast. Dose-adjusted geometric mean ratios confirmed dose proportionality.

Table 16. Study P127, Pairwise GMRs and 90% CIs for dose-adjusted $AUC_{0-\infty}$

Dose	N	Geometric mean $AUC_{0-\infty}$ (ng*hr/mL)	$AUC_{0-\infty}$ GMR * (90% CI)	
			2 or 6 mg / 4 mg	2 mg / 6 mg
2 mg	14	944	0.90 (0.80, 1.02)	0.94 (0.83, 1.07)
4 mg	14	1047		
6 mg	14	1000.7	0.96 (0.84, 1.08)	

† Back-transformed from log scale; SD = Standard deviation.
‡ Dose-adjusted to 4 mg.

Source: Summary, page 66; summary.pdf

The two bioequivalence studies, P090 and P183, evaluated bioequivalence for the 4 mg chewable tablet and the 4 mg oral granule formulations. These studies also characterized the effect of applesauce and high fat food on the pharmacokinetics of the oral granules. As shown in Table 17, $AUC_{0-\infty}$ were quite similar regardless of whether subjects were fasting or being fed applesauce or a high fat meal, and the geometric mean ratios were well within the 90% confidence intervals. These studies clearly showed that food affects the rate of absorption of the montelukast oral granules, affecting the T_{max} and C_{max} , but not the $AUC_{0-\infty}$.

Table 17. Single-dose pharmacokinetic studies supporting bioequivalence of 4 mg oral granules and 4 mg chewable tablets

Protocol	N	Dose Formulation	$AUC_{0-\infty}$ GM (SD) ng*hr/mL	$AUC_{0-\infty}$ GMR (90% CI)	C_{max} ng/mL GM (SD)	C_{max} GMR (90% CI)
Pilot Bioequivalence Study P090	24	4 mg oral granules	1223.1 (342.3)	1.01 (0.92, 1.11)	198.8 (53.8)	0.99 (0.86, 1.13)
	24	4 mg CT	1208.3 (467.4)		201.7 (91.6)	
Pilot Bioequivalence Study P090	24	Fasted 4 mg oral granules	1223.1 (342.3)	1.00 (0.92, 1.10)	198.8 (53.8)	0.92 (0.80, 1.06)
	24	Fed 4 mg oral granules	1225.7 (528.9)		182.8 (78.2)	

Protocol	N	Dose Formulation	AUC _{0-∞} GM (SD) ng*hr/mL	AUC _{0-∞} GMR (90% CI)	C _{max} ng/mL GM (SD)	C _{max} GMR (90% CI)
Final Market Image Study P183	30	4 mg oral granules	1148.5 (392.4)		175.4 (59.2)	
Fasting	30	4 mg CT	1210.3 (421.3)	0.95 (0.91, 0.99)	190.0 (64.3)	0.92 (0.84, 1.01)
Final Market Image Study P183	30	Fasted 4 mg oral granules	1148.5 (392.4)		175.4 (59.2)	
Fast vs high-fat meal	30	Fed 4 mg oral granules	1191.8 (380.3)	1.04 (0.99, 1.09)	112.8 (26.2)	0.64 (0.59, 0.71)

Source: Summary, pages 69, 71, 73; summary.pdf

6.3.2. Studies for Indication of Age 6 to 23 Months (6 Months to <2 Years)

Two studies were submitted supporting the use of montelukast 4mg oral granules .

Both studies followed the Division's suggestions for studies, as outlined in the pediatric Written Request. The first was a single-dose population pharmacokinetic study, and the second was a six-week safety and tolerability study. Both were done in infants and toddlers ages 6 to 23 months who had a history of recurrent episodes of wheezing. While the six-week study did have exploratory efficacy endpoints, no specific efficacy studies were requested as part of the Written Request, and none were done.

6.3.2.1. Study P136C1

Protocol #: P136 in US / P138 ex-US (two numbers used but identical protocols)
 Title: An open, single-dose, multicenter study to evaluate the safety, tolerability, and plasma concentration profiles of montelukast in 6- to 24-month-old children
 Study Dates: Jan 17, 2000 to May 25 2001
 Sites: 5 sites, one each in US, Chile, Peru, Colombia, and Brazil
 Investigators and IRBs: 5 site-specific investigators and IRBs

Source: Clinical, Reference p136c1, pages 10, 15, and Appendix 3.6, pages 516-7; p136c1.pdf

6.3.2.1.1. Summary

This was a multicenter, open-label, single-dose study to determine the population pharmacokinetics of the of 4 mg oral granule formulation of montelukast administered in applesauce in 32 patients ages 6 to 23 months. Study design was based on a Written Request issued by the Division of Pulmonary and Allergy Drug Products at the US FDA.

The study compared 4 sparse samples from 6 to 23 month olds with historical population pharmacokinetic data from adults to determine AUC_{pop}. In general, a single dose of montelukast oral granules was well tolerated. C_{max} in the 6 to 23 month olds is about double that in adults, but roughly similar to that found in 2 to 5 year olds (Study P066), but higher in the 6 to 11 month old than in the 12 to 23 month old patients. T_{max} was earlier in this population (2.2 hours) than in adults (3.4 hours). Mean exposure from a 4 mg oral granule

dose in the entire age range is ~ 25% greater than that for adults (10 mg FCT) or for 2 to 5 year olds (4 mg chewable), but similar to the exposure seen with the 5 mg chewable tablets in the 6 to 8 year old population. The breakdown by age group is about 18% (34% per Dr Suarez) higher in 12 to 23 month and 35% (48%, per Dr Suarez) higher in the 6 to 11 month olds.

The individual exposure varied significantly, from less than half the mean adult AUC_{pop} to about 2.5 times the adult AUC_{pop} . Although there was a trend to higher AUCs in the younger population, there was no clear relationship of AUC with age or weight.

Variance for this age group is largely unexplained. Steady-state pharmacokinetic evaluations that might have addressed this issue were not included in multiple-dose safety and tolerability studies. Assuming that single-dose data may be extrapolated to what might occur with multiple dosing, some patients may have exposures significantly under the expected exposure, while others might have levels significantly higher than expected. In adults there is a wide margin of safety above the dose of 10 mg that achieves the AUCs to which the pediatric AUCs are being compared. The margin of safety in adults extends to doses above 50 mg, which were evaluated before the dose of 10 mg was chosen. However, it remains to be demonstrated that the disease and dose range for efficacy and safety in this population are the same as in older populations.

6.3.2.1.2. Study Design

6.3.2.1.2.1. Description

This was a 5-center, open-label, single-dose study to determine the population pharmacokinetics of the 4 mg oral granule formulation (administered in 1 tablespoon of applesauce) of montelukast in 32 patients ages 6 to 23 months. Plasma drug concentrations were obtained at four time points over the 24 hours post-dosing via one of two collection schedules, and population pharmacokinetic analysis was performed based on the limited blood sampling. [Clinical, Reference p136c1, pages 16-7, 182, 185; p136c1.pdf]

6.3.2.1.2.2. Objectives

1. To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUC_{pop} , C_{max} , T_{max} , estimated $C_{24\text{ hr}}$, and apparent elimination $t_{1/2}$) obtained from 6 to 11 month, 12 to 23 month, and 6 to 23 month old children after administration of a 4 mg (and possibly a 2 mg or 6 mg) dose of the — formulation of montelukast with historical data from adult subjects administered a 10 mg dose of the film-coated tablets of montelukast.
2. To evaluate and compare montelukast plasma concentration profiles and pharmacokinetic parameters (AUC_{pop} , C_{max} , T_{max} , estimated $C_{24\text{ hr}}$, and apparent elimination $t_{1/2}$) between 6 to 11 month and 12 to 23 month old children after administration of a 4 mg (and possibly a 2 mg or 6 mg) dose of the — formulation of montelukast.
3. To evaluate the safety and tolerability of a 4 mg (and possibly a 2 mg or 6 mg) dose of the — formulation of montelukast in 6 to 23 month old children. [Clinical, Reference p136c1, pages 16, 233-4, 332; p136c1.pdf]

6.3.2.1.2.3. Population

At least 24 patients male and female patients ages ≥ 6 months and < 24 months at the first visit within 5th to 95th percentile for height and weight for age were required to participate in this study. The Study Report states that there was the requirement for at least 12 patients each in the 6 to < 12 month and 12 to < 24 month old age-specific subgroups. However, each Protocol states that 24 patients are to be enrolled (same as the Study Report), but also states that only 6 (rather than the 12 stated in the Study Report) were required per age group. [Clinical, Reference p136c1, pages 16-7, 236, 334; p136c1.pdf]

Comment: Merck does not account for the differences between the Protocols (which have identical statements) and the Study Report. Since the Protocols do not refer to each other. Therefore, one cannot infer that the numbers could be added to achieve the numbers stated in the Study Report, especially since the overall planned enrollment numbers stated in the Protocols and the Study Report were the same.

6.3.2.1.2.4. Inclusion / Exclusion Criteria

Entry criteria included patients with a history of “at least 3 episodes of physician-diagnosed asthma or ‘asthma-like’ symptoms (i.e., ≥ 3 discrete episodes of wheezing after 8 weeks of age with episodes separated by a symptom-free interval of at least 7 days.” [Clinical, Reference p136c1, pages 22-4, 234-6, 332-4; p136c1.pdf]

Comment: The Study Report states that waivers were granted to include patients with a history of “asthma-like” symptoms who had a history of bronchiolitis and that entry into the study was based on a revised criterion contained in the waiver [Clinical, Reference p136c1, pages 23, 39; p136c1.pdf]. However, this criterion was not found in a review of the original protocols, and the waiver letter to the investigators is not included with the documentation of the study:

“Male or female patients aged 6 months to < 2 years with a history of physician-diagnosed asthma or ‘asthma-like’ symptoms consistent with the need for chronic anti-asthma controller therapy (in the judgment of the physician), including, but not limited to, cough, wheezing, and shortness of breath.”

This is not considered a significant issue, since the point of the entry criteria was to select patients who might be candidates for controller therapy rather than in healthy subjects, and this was accomplished.

Exclusion criteria included patients with history of prematurity, mechanical ventilation, cystic fibrosis, bronchopulmonary dysplasia, tracheomalacia, tracheoesophageal fistula, gastroesophageal reflux, pertussis, congenital heart disease, and history of allergy to apple sauce. Also excluded were patients with a history of any clinically significant disease of the gastrointestinal, cardiovascular, hepatic, neurological, renal, genitourinary, or hematological systems or has a pulmonary disease other than asthma, as well as patients with unusual or extreme dietary habits and patients with unresolved signs and symptoms of an upper respiratory tract infection (URI), or had a URI within 1 week of drug administration..

Permitted therapy included inhaled albuterol, cromolyn, and corticosteroids. Excluded medications included theophylline, terfenadine, loratadine, and/or oral or parenteral

corticosteroids (within 10 days), beta-agonists (within 24 hours), astemizole (within 3 months), and other non-asthma mediations (within 10 days). [Clinical, Reference p136c1, pages 22-4, 234-6, 332-4; p136c1.pdf]

6.3.2.1.2.5. Safety Variables

Safety was assessed by history and physical examinations, blood and urine tests, electrocardiograms, and measurements of vital signs. Laboratory tests included CBC and serum chemistries (ALT, AST, bilirubin, BUN, creatinine, glucose, calcium, total protein, electrolytes). [Clinical, Reference p136c1, pages 17-9; p136c1.pdf]

6.3.2.1.2.6. Conduct

Patients were randomized according to one of two sample allocation schedules (A and B) shown in Table 18. Following the predose procedures, the oral granule formulation was mixed with 1 tablespoon of applesauce and administered as quickly and completely as possible, and the time was recorded. Patients were allowed to consume water ad lib, and apple juice 1 hour after study drug administration. There were no limitations on food, as long as meals did not interfere with the clinical procedures. Patients were discharged at either 12 (Schedule A) or 24 hours (Schedule B) after dosing. [Clinical, Reference p136c1, page 25; p136c1.pdf]

Table 18. Protocol P136C1, Study flow chart

Procedures	Day 1 (Hours)							Day 2	Post-study (3-5 days)
	Pre-dose	0	2.5	3	5	8	12	24	
Informed consent	✓								
Medical history	✓								
Physical exam (incl Ht / Wt)	✓								✓
Vital signs (BP, HR, RR, temperature)	✓		✓		✓	✓		✓	✓
Laboratory safety tests	✓						✓ A*	✓ B*	✓
Montelukast administration		✓							
Montelukast assay Schedule A	✓		✓		✓		✓		
Montelukast assay Schedule B	✓			✓		✓		✓	

* Lab safety tests at 12 hours for Schedule A and 24 hours for Schedule B

Source: Clinical, Reference p136c1, page 18, and Appendix 3.3 pages 221, 320, 394; p136c1.pdf

6.3.2.1.2.7. Parameters, Dose selection, Interim analysis, and Sample size

Blood samples (3 mL per sampling time) for determination of montelukast plasma concentrations were collected at 0, 2.5, 5, and 12 hours for Schedule A, and at 0, 3, 8 and 24 hours for Schedule B [Clinical, Reference p136c1, page 30; p136c1.pdf]. Montelukast plasma concentrations were determined using a ξ

}] [Clinical, Reference p136c1, page 25; p136c1.pdf].

Population pharmacokinetic analyses included area under the concentration-time curve (AUC_{pop}), maximum concentration (C_{max}), time of maximum observed plasma concentration

(T_{max}), and apparent elimination half-life ($t_{1/2}$). Except for $t_{1/2}$ (linear mixed-effects model) all estimations used a nonlinear mixed-effects model. For patients who had sampling at 24 hours, a mean C_{24hr} was also reported. Results were reported for the entire group and broken down by subset of age group.

Dose selection of a 4 mg dose was based on a least squares regression analysis of the plotted AUC ($AUC_{0-\infty}$ or AUC_{pop}) versus weight data from three previous pharmacokinetic studies (P036, P039, and P066) in older patients to obtain predicted AUC values for 6 to 23 month age-appropriate weights of 6 to 15 kg. The predicted AUC adjusted for a 4 mg dose was then compared with the potency-normalized mean $AUC_{0-\infty}$ in adults after a 10 mg film0-coated tablet (P034). For a 4 mg dose, the predicted AUC and 95% CI was slightly greater than 1 SD above the reference mean $AUC_{0-\infty}$, but was felt to give a reasonable estimate of the appropriate dose for the 6 to <24 month age group. [Clinical, Reference p136c1, pages 27-8; p136c1.pdf]

To evaluate whether the estimated dose was in the correct range, the protocols called for an interim analysis at ≥ 12 patients to determine whether the subsequent patients would be studied at the 2, 4, or 6 mg dose, with at least 12 patients to be studied at the chosen dose level. The interim analysis was performed after 18 patients had completed pharmacokinetic analysis. The interim analysis confirmed the 4 mg dose, and all 32 patients were studied at this dosage. [Clinical, Reference p136c1, pages 16-7, 236, 334; p136c1.pdf]

6.3.2.1.3. Results

6.3.2.1.3.1. Patient disposition and demographics

Thirty-two (32) patients were entered, and one patient discontinued due to an AE. One patient (AN203) was lost to follow-up after completion of the pharmacokinetic sampling, but before the post-study visit, and was included in the pharmacokinetic result. [Clinical, Reference p136c1, page 38-40; p136c1.pdf] Fourteen patients were in the 6 to 11 month age group, and 18 were in the 12 to 23 month age group. Patient distribution as well as demographic breakdowns are listed in Table 19. Other patient baseline characteristics are presented in Table 20. [Clinical, Reference p136c1, page 38-45; p136c1.pdf]

Seven patients had a history of “asthma-like” symptoms diagnosed as bronchiolitis rather than as asthma. These patients were enrolled based on the waiver that Merck states was sent to investigators allowing study entry for patients who had “a history of physician-diagnosed asthma or ‘asthma-like’ symptoms consistent with the need for chronic anti-asthma controller therapy (in the judgment of the physician), including, but not limited to, cough, wheezing, and shortness of breath.” [Clinical, Reference p136c1, page 39; p136c1.pdf]

According to Table 8 on pages 42-4, the status of these patients symptoms was “not active,” and the text implies that these patients were not required to have ongoing symptoms to be considered as candidates for chronic anti-asthma ongoing therapy.

Comment: It is also not clear if these 7 patients satisfied the inclusion criteria for ≥ 3 discrete episodes of wheezing after 8 weeks of age with episodes separated by a symptom-free interval of at least 7 days. . Since the inclusion criteria of ‘asthma’ or

'asthma-like' symptoms were set to justify the blood draws rather than chronic treatment, these are moot issues.

Table 19. Study P136C1, Patient distribution and demographics

	Ages:	6 to 11 months	12 to 23 months	Totals
WR Requirement (completed)		12	12	24
Entered		14	18	32
Boys		9 (6 to 11)	5 (17 to 23)	
Girls		5 (8 to 11)	13 (12 to 23)	
Black		1	4	
Hispanic		6	3	
Multiracial		3	5	
White		4	6	
Completed		13	17	30
Discontinued		1	1	2
Data used / available for pharmacokinetic analysis		12	14	26

Source: Clinical, Reference p136c1, pages 10, 41; p136c1.pdf

Table 20. Study P136C1, Patient baseline characteristics

Mean (range)	Age (months)	Weight (kg)	Height (cm)
Combined	14 (6 to 23)	10.4 (7.9 to 13.4)	77.0 (67.0 to 86.6)
Boys	13 (6 to 23)	10.2 (7.9 to 13.4)	75.9 (67.0 to 86.6)
Girls	16 (8 to 22)	10.5 (8.2 to 12.7)	77.9 (69.0 to 85.0)

Source: Clinical, Reference p136c1, page 41; p136c1.pdf

Prior therapy included six patients with asthma (4 albuterol, 1 beclomethasone dipropionate, and 1 prednisolone). Ongoing therapy included 27 patients with treatments for asthma (10 albuterol, 1 salmeterol, 1 fenoterol, 6 fluticasone propionate, 6 beclomethasone dipropionate, 2 budesonide, and 1 ipratropium bromide). Concomitant therapy to treat an adverse experience included one patient treated with albuterol for asthma. [Clinical, Reference p136c1, pages 10, 41; p136c1.pdf]

6.3.2.1.3.2. Pharmacokinetic parameters

This section contains data from the pharmacokinetic analysis of Study P136C1 as presented by Merck in the study report for this study. For convenience and to allow comparison with previous studies and age ranges, historical population and/or actual pharmacokinetic data from Study P034 in adults (with the 10mg film-coated tablet), and P066 in children ages 2 to 5 years (with the 4mg chewable tablet) are also presented. Please refer to the Biopharmaceutics review of Dr. Sandra Suarez for a report of her independent analysis of the data, which shows higher exposure than Merck calculates. The reason for the differences is that Merck pooled the data prior to doing the pharmacokinetic calculations, whereas Dr. Suarez did pharmacokinetic calculations for each patient prior to pooling the data.

Pharmacokinetic analysis was done on 26 of the 32 enrolled patients. Six patients were excluded for the following reasons. One patient (AN109) did not consume the entire dose.

One patient (AN227) was discontinued due to the AE of vomiting 10 minutes after study drug administration. Two patients (AN104 and 131) did not have a 12-hour sample drawn. Additionally, two patients (AN101 and 132) were excluded from the population pharmacokinetic analysis “due to conversion issues” (i.e. they were outliers). Merck states that the analysis could not be performed using a fixed absorption rate constant when these patients were included due to the relatively low 3-hour and high 8-hour postdose concentrations. Other analyses were done, including use of a random absorption rate and a fixed elimination rate, and all results were similar. Individual model fits of the results montelukast plasma concentrations for each patient are shown in Figure 8. [Clinical, Reference p136c1, page 38-40, 47; p136c1.pdf]

Except for results of the two outliers, a 1-compartment model provided a reasonable fit for the data. Results are shown in Table 21 and Table 22. For comparison, these tables include both the adult population pharmacokinetic (pop-PK) model and the regular pharmacokinetic (non-pop-PK) model of the data from the same adult study (P034) as well as data from the population pharmacokinetic study P066 in children 2 to 5 years of age. Also included for comparison is some of the data from P039 for the 5 mg chewable tablets in 6-8 year old children.

Estimates for AUC_{pop} were 3226.6 ng·hr/mL (SE: 250.0) after the 4 mg oral granules in the 6 to 23 month old patients taken as a group, as compared to 2569.0 ng·hr/mL (SE: 165.7) after the 10-mg FCT in adults (historical data from study P034). The ratio for AUC_{pop} was 1.26 with 95% CI of (1.02, 1.54), within the prespecified primary study hypothesis interval of (0.50, 2.00). The data is broken down by age sub-group is quite revealing. For 6 to 11 month olds, the AUC_{pop} estimates was 3470.9 ng·hr/mL with a SE of 499.3, and for the 12 to 23 month olds, the AUC_{pop} estimates was 3039.3 ng·hr/mL (SE: 212.5). Ratios of AUC_{pop} for each of these age groups compared to adults were 1.35 (0.97, 1.87) and 1.18 (0.97, 1.44), respectively. The 95% CIs were also within the (0.50, 2.00) interval, although this was not prespecified. Therefore, the AUC_{pop} data show a higher mean exposure for the youngest population 6 to 11 months of age which is outside the proposed limits of the AUC ratios. In addition, in the 6 to 11 month old group there is a very high standard error, implying a much wider variability to the pharmacokinetic data in this group than in any other age group. Even the 12 to 23 month old group has a higher standard error (212) than the adults (165), again implying higher variability of exposure.

Evaluation of the individual pharmacokinetic data support this variability of exposure. Scatter plots for the individual $AUC_{0-\infty}$ values versus age and versus weight obtained by Bayes estimates which were derived from the pharmacokinetic model are presented in Figure 6 and Figure 7. The horizontal line in each figure represents the AUC_{pop} estimated from adults in study P034. While the AUC_{pop} estimate was 3226.6 ng·hr/mL for the entire age group, the range of individual $AUC_{0-\infty}$ was from 1000 to 6000 ng·hr/mL. Patients experienced $AUC_{0-\infty}$ values of anywhere from 31% to 186% of the mean value, or about 39% to 233% of the adult target value, implying that some patients will be significantly underdosed, and some will be overdosed.

No trend in the relationship between $AUC_{0-\infty}$ values and weight or age was noted, with Pearson's coefficients of -0.07 for $AUC_{0-\infty}$ versus weight, and -0.14 for $AUC_{0-\infty}$ versus age. Nevertheless, children in the younger age range tended toward higher AUCs than older

children. This is consistent with the pediatric/adult AUC_{pop} ratio of 1.35 in the 6 to 11 month olds versus 1.18 in the 12 to 23 month olds and the overall ratio of 1.26 for the entire 6 to 23 month age range (Table 21). The lack of a trend in relationship of AUC to age or weight means that there is no way to predict which infant will experience an exposure below the expected AUC (down to 1/3 the expected AUC), and which infant will experience an exposure higher than the expected AUC (up to double the expected AUC).

Population estimates for clearance were about tree times lower in children (20.7 mL/min) than in adults (64.9 mL/min). These data are presented in Table 23, along with a breakdown by age subgroup. Clearance is slightly higher in the younger than the older children, but far less than in adults. For comparison, the clearance estimate for 2 to 5 year old patients in Protocol 066 was 24.5 (21.3, 27.7) [Clinical, Reference p136c1, page 52; p136c1.pdf].

Table 21. Comparative single-dose population pharmacokinetics for age 6 to 23 months. Studies P136C1, P066, and P034.

Population	N	Dose Formulation	AUC _{pop} GM ng*hr/mL	SE	Pediatric / Adult Ratio (95% CI)
All patients ages 6 to 23 months	26	4 mg oral granules	3226.6	250.0	1.26 (1.02, 1.54)
6 to 11 months	12	4 mg oral granules	3470.9	499.3	1.35 (0.97, 1.87)
12 to 23 months	14	4 mg oral granules	3039.3	212.5	1.18 (0.97, 1.44)
Historical data					
Ages 2-5 years (P066) *	15	4 mg CT	2721	164.39	1.05 (0.90, 1.22)
Ages 6-8 years (P039) **		5 mg CT	2928 ± 904		
Adults (P034) *	16	10mg FCT	2569.0	165.7	
Adults (P034) **	16	10mg FCT	2595	164.53	
* Population pharmacokinetic results					
** Actual pharmacokinetic results					
FCT = film-coated tablet					

Sources: Clinical, Summary, pages 80; summary.pdf

Clinical, Reference p136c1, Table 10, page 49; p136c1.pdf

* Clinical, Reference 54, Study P066, pages 3-8; 0054.pdf

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Table 22. Study P136C1, single-dose population pharmacokinetics for age 6 to 23 months. Comparative data from Studies P066, and P034.

Population	N	Dose Formulation	Pop Cmax ng/mL (95% CI)	Pop Tmax hours (95% CI)	Pop T½ hours (95% CI)	Observed C24 hr ng/mL Mean (95% CI)
All patients ages 6 to 23 months	26	4 mg oral granules	514.4 (425.2, 603.6)	2.24 (1.95, 2.53)	3.39 (2.98, 3.80)	8.2 (4.6, 11.8)
6 to 11 months	12	4 mg oral granules	583.5 (391.6, 775.4)	2.07 (1.43, 2.71)	3.24 (2.44, 4.05)	9.1 (2.1, 16.1)
12 to 23 months	14	4 mg oral granules	470.1 (380.4, 559.7)	2.34 (2.02, 2.66)	3.48 (3.03, 3.93)	7.3 (2.1, 12.5)
Historical data						
Ages 2-5 years (P066) *	15	4mg CT	471.0 (361.8, 580.2)	2.07 (1.57, 2.58)	3.17 (± 0.20)	
Ages 6-8 years (P039) **		4 mg CT	495 ± 129	2.0 ± 1.3	3.7	
Adults (P034) *	16	10mg FCT	279.0 (221.8, 336.3)	3.39 (2.95, 3.82)	4.09 (3.73, 4.45)	9.7 (7.6, 11.8)
Adults (P034) **	16	10mg FCT	283.7 (193.8, 373.6)	3.4 (2.37, 4.36)	4.1 (0.1)	
* Population pharmacokinetic results						
** Actual pharmacokinetic results						

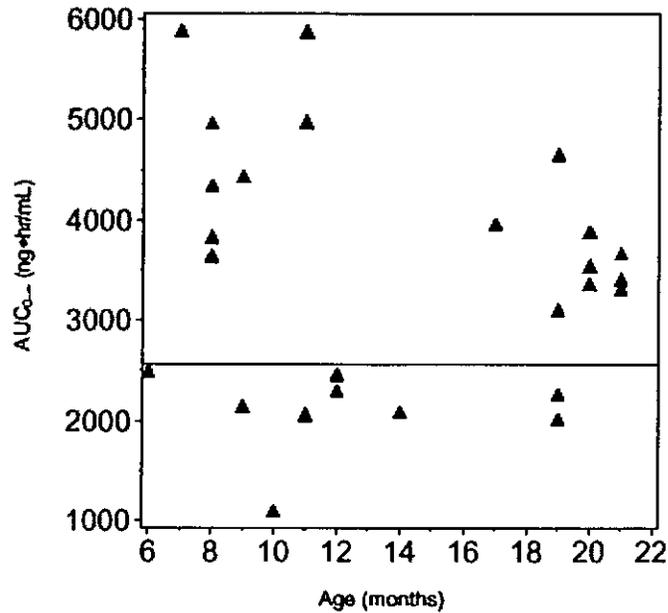
Sources: Clinical, Summary, pages 80, 81; summary.pdf
 Clinical, Reference p136c1, Tables 12-15, page 53-6, ; p136c1.pdf
 * Clinical, Reference 54, Study P066, pages 3-8; 0054.pdf
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Table 23. Population estimates for clearance after a single dose of montelukast . Studies P136C1, P066, and P034

Population	N	Dose Formulation	Population clearance mL/min	SE	(95% CI)
All patients ages 6 to 23 months	26	4 mg oral granules	20.7	1.6	(17.3, 24.0)
6 to 11 months	12	4 mg oral granules	19.2	2.8	(13.0, 25.5)
12 to 23 months	14	4 mg oral granules	21.9	1.5	(18.6, 25.3)
Historical data					
Ages 2-5 years (P066) **	15	4 mg CT	24.5	1.5	(21.3, 27.7)
Adults (P034) *	16	10mg FCT	64.9	4.2	(55.8, 73.9)
Adults (P034) **	16	10mg FCT	64.2	4.1	(55.4, 73.0)

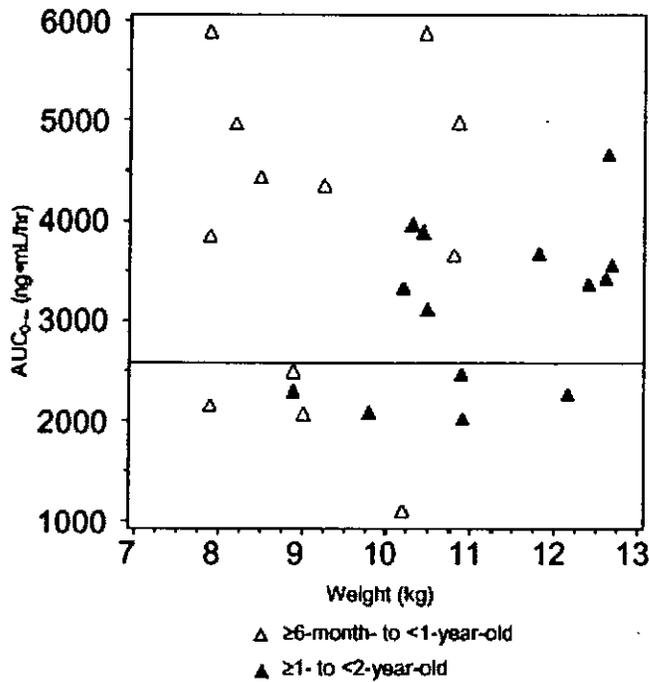
Sources: * Clinical, Reference p136c1, Table 11, page 52; p136c1.pdf
 ** Clinical, Reference p136c1, Appendix 4.3.4, page 558; p136c1.pdf

Figure 6. Study 136C1, Individual $AUC_{0-\infty}$ estimates of montelukast versus age



Horizontal line = AUC_{pop} estimated from adults in P034.
 Source: Clinical, Reference p136c1, page 50; p136c1.pdf

Figure 7. Study 136C1, Individual $AUC_{0-\infty}$ estimates of montelukast versus weight



Horizontal line = AUC_{pop} estimated from adults in P034
 Source: Clinical, Reference p136c1, page 51; p136c1.pdf

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6.3.2.1.3.3. Safety

In this single-dose study, there were no deaths and one serious adverse event. Thirteen patients experienced 22 clinical adverse events. Five AEs were determined by the investigator to be probably or possibly drug related, including two episodes of somnolence (probably), and three episodes of diarrhea (possibly). The remaining 17 adverse events were not felt to be drug related. The most common adverse event was diarrhea (6 of 22 AEs). The one serious adverse event was moderate dehydration (patient AN 108) and was admitted to the hospital 7 days following dosing with vomiting, diarrhea and dehydration. This AE was not determined to be related to study drug. Patient AN 227 was discontinued from therapy due to an adverse experience of vomiting, which occurred within 10 minutes of dosing. The investigator determined to this be definitely not drug related. [Clinical, Reference p136c1, pages 57-60; p136c1.pdf]

There were four laboratory adverse events in three patients (ANs 108, 112, and 203). The same patient who experienced moderate dehydration (AN 108) had an increase in blood urea nitrogen to 24 mg/dL at the post-study evaluation. One patient (AN 112) had a decrease in absolute neutrophil count, from 1120 cells/mL (total WBC 8,000, 14% PMN) to 663 cells/mL (total WBC 6500, 10.2% PMN) 24 hours after dosing, with a normal repeat laboratory test. This reduction was not associated with a clinical AE and was felt to be probably not drug related and likely secondary to normal variation of laboratory results. One patient (AN 203) had decrease in hemoglobin and Hematocrit 24 hours after dosing. The hemoglobin decreased from 11.3 to 9.9 g/dL, and the Hematocrit decreased from 33 to 30%. Both were considered to be related to blood sampling. [Clinical, Reference p136c1, pages 60-1; p136c1.pdf]

Study P136C1, Clinical Adverse Events

Number (%) of patients:	Montelukast 4-mg oral granules (N = 32)
	n (%)
With one or more adverse events	13 (40.6)
With no adverse events	19 (59.4)
With drug-related † adverse events	4 (12.5)
With serious adverse events	1 (3.1)
With serious drug-related adverse events	0 (0.0)
Who died	0 (0.0)
Discontinued from therapy due to an adverse event	1 (3.1)
Discontinued from therapy due to a drug-related adverse event	0 (0.0)
Discontinued from therapy due to a serious adverse event	0 (0.0)
Discontinued from therapy due to a serious drug-related adverse event	0 (0.0)
† Determined by the investigator to be possibly, probably, or definitely drug related. Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.	

Source: page 98; summary.pdf

6.3.2.1.4. Conclusions

The study used a population pharmacokinetic approach, comparing 4 sparse blood samples from 6 to 23 month olds with historical population pharmacokinetic data from adults. C_{max} , T_{max} , AUC_{pop} , and clearance were calculated, both by Merck, and by the Division, and are discussed below.

The purpose of this study, as defined in the Written Request, was to select a dose of montelukast oral granules appropriate for use in a six-week safety and tolerability study (Study P176) in children 6 to 23 months of age. Merck suggests [Clinical, Reference p136c1, page 61; p136c1.pdf] that the purpose of this study was to select an appropriate dose for treatment of patients with asthma in this age range. However, their rationale assumes that the clinical expression of asthma is similar in all age ranges. This approach was used and validated in several efficacy studies for the 5 mg CT dose in 6 to 14 year old patients. This approach was also used for dose selection of a 4 mg CT for ages 2 to 5 years (Study P066), although efficacy for asthma that age range was extrapolated from older ages. It is not confirmed that this approach is adequate to select an appropriate dose for this very young age range, where asthma is a far more difficult diagnosis to make, and other factors (including physical, genetic, environmental, and exposure to illness) in the etiology of wheezing may be at play.

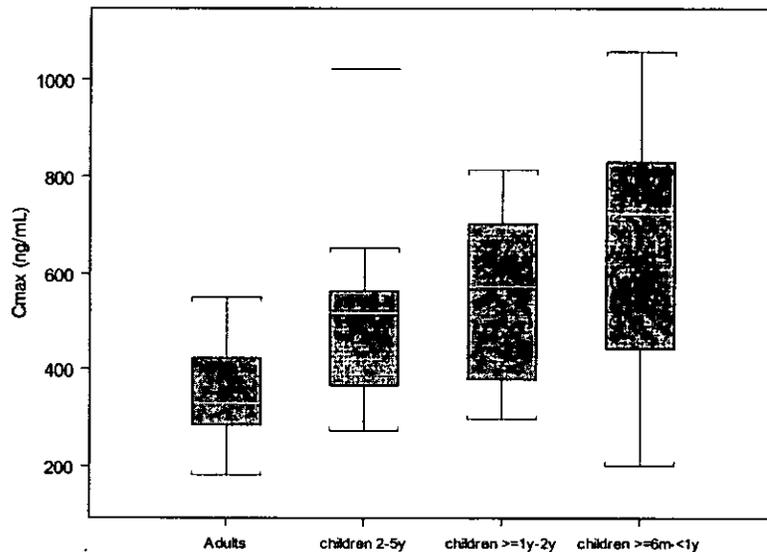
In general, a single dose of montelukast oral granules was well tolerated in this study, and there were no safety signals found in this review. There were no serious drug-related adverse experiences and no deaths. One patient had a serious adverse event of hospitalization for vomiting, diarrhea and dehydration, probably unrelated to study drug. One patient experienced vomiting 10 minutes after study drug administration. Five of 22 adverse experiences (2 somnolence/3 diarrhea) were mild and were rated as probably or possibly drug related. Three patients had 4 non-serious, non-drug-related laboratory adverse experiences.

Samples from two patients were outliers, did not fit into a one-compartment model, and were omitted from the population pharmacokinetic analysis. This is bothersome, since the cause of the outlying results from these two patients were largely unexplored.

Population estimates for clearance were about tree times lower in children (20.7 mL/min) than in adults (64.9 mL/min). Clearance was slightly higher in the younger than the older children, and both were slightly less than for 2 to 5 year old patients (24.5 mL/min in P066).

C_{max} in the 6 to 23 month olds is about double that in adults, roughly similar to that found in 2 to 5 year olds (Study P066), but higher in the 6 to 11 month old than in the 12 to 23 month old patients (see Figure 9). Dr. Suarez's figures are higher than Merck's figures, with mean values increased by 58% in 12 to 23 month olds and 79% in 6 to 11 month olds compared to adults. T_{max} was earlier (2.2 hours) than in adults (3.4 hours). Since there is a wide safety margin for montelukast in older individuals, Merck states that these differences in C_{max} and T_{max} are not significant either with regard to safety or to potential for efficacy of montelukast. While this statement is true, the implications of the higher individual C_{max} exposure have not been explored.

Figure 9. Box plot for population C_{max} (CL_{pop}) following single administration of Singulair oral granules 4 mg in children 6 months to 23 months of age, single dose of Singulair 4 mg chewable tablets to children 2y to 5 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. The C_{max} adult data was calculated using non-compartmental methods. Subjects 101 and 132 excluded from the 6-23m old group.



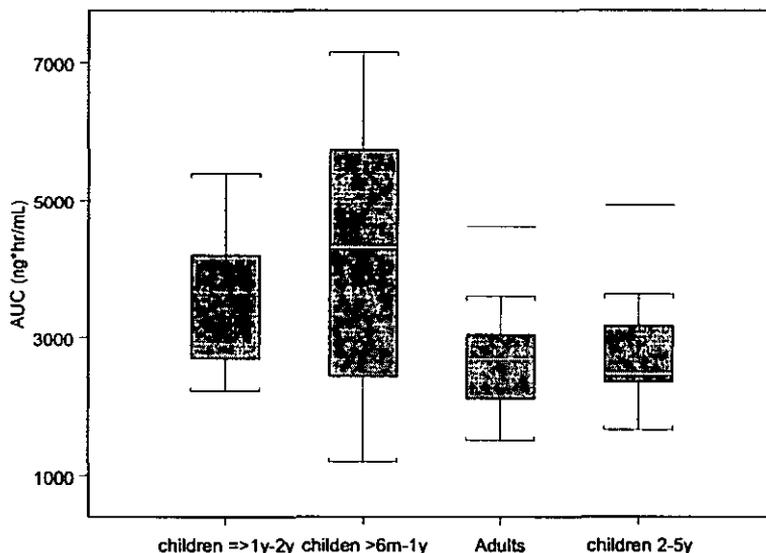
Source: Data calculated by Dr. Sandra Suarez, Biopharmacy reviewer, using NONMEM.

According to Merck's figures, the AUC_{pop} results show that the mean montelukast exposure from a 4 mg oral granule dose in the entire age range is on average approximately 25% greater than that for adults, with a breakdown of 18% higher in 12 to 23 months and 35% higher in the 6 to 11 month olds. Dr. Suarez's figures are higher than Merck's, with mean values of 34% in the 12 to 23 month olds and 48% higher in the 6 to 11 month olds. Of note, individual exposure varied significantly, from less than half to more than double the adult AUC_{pop}. This variability was largest in the 6 to 11 month old infants, with a range of 1200ng*hr/mL to 7153 ng*hr/mL, corresponding to a standard error of 499. The variability in the 6 to 11 month age group (SE: 499) was significantly higher than in the 12 to 23 month group (SE: 212), which was still higher than either in the 2 to 5 year olds (SE: 164) or in adults(SE: 165). These data imply patients will experience significant variations in exposure, particularly in the youngest age group of 6 to 11 months. This variability may be seen graphically in Figure 10.

No trend in the relationship between AUC_{0-∞} values and weight or age was noted, although there was a trend to higher AUCs in the 6 to 11 month old than in the 12 to 23 month old

population. The lack of a trend in relationship of AUC to age or weight means that there is no way to predict which infant will experience an exposure below the expected AUC (down to 1/3 the expected AUC), and which infant will experience an exposure higher than the expected AUC (up to double the expected AUC).

Figure 10. Box plot for population AUC (AUC_{pop}) following single administration of Singulair oral granules 4 mg in children 6 months to 23 months of age, single dose of Singulair 4 mg chewable tablets to children 2y to 5 years an single dose of Singulair 10mg film-coated tablets to adult volunteers. Subjects 101 and 132 excluded from the 6-23m old group.



Source: Data calculated by Dr. Sandra Suarez, Biopharmacy reviewer, using NONMEM.

Neither the cause nor the implications of this wide variance in exposure has been fully explored. The lower exposures are more easily explained than the higher exposures. Low exposures are likely secondary to concomitant food effects, poor absorption, or lack of completely taking the entire dose administered. Higher exposures can only be explained by differences in clearance (slower metabolism by CYP 3A4 and 2C9 or slower biliary excretion), but the cause is unclear. Pharmacokinetic evaluations at steady-state might have resolved some of these issues, but were not included in the multiple-dose safety and tolerability study.

Assuming that single-dose data may be extrapolated to what might occur with multiple dosing, some patients might have levels significantly lower than expected, while others might have levels significantly higher than expected. Merck argues that since there is a wide safety margin for montelukast in older individuals, differences in C_{max} , T_{max} , and AUC are not significant either with regard to safety or to potential for efficacy of montelukast.

This is likely the case. In addition, in adults the 10mg tablets provided efficacy that did not dose-order with higher doses, allowing that variations in exposure might more readily translate into efficacy without compromise to safety. This will be discussed further in the Discussion and Conclusions Sections below.

6.3.2.2. Study P176

Protocol #: 176
Title: A multicenter, double-blind, randomized, parallel-group study comparing montelukast with placebo in pediatric patients aged 6 to 24 months with asthma.
Study Dates: August 1, 2000 to February 27 2001
Sites: 65 study centers: 29 in US, 36 multinational including 22 countries in Africa, Asia, Europe, North and South America
IRB: IRB at each study site
Sources: Clinical, Reference p176, page 2 and Appendix 3.6, pages 520-29; p176.pdf

6.3.2.2.1. Summary

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 a history of at least 3 episodes of "asthma or asthma like symptoms." There were 175 patients randomized to montelukast, and 81 to placebo. Breakdown by age category was 84 patients 6 to 11 months (51 montelukast, 33 placebo), and 172 patients 12 to 23 months (124 montelukast, 48 placebo).

In general, a multiple doses of montelukast oral granules for up to six weeks were well tolerated, and there were no safety signals found in this review. While the incidence of serious clinical adverse events was higher in the montelukast group (7 montelukast {4.0%}, 1 placebo {1.2%}), the types of events were over a broad range with no clinical bearing to the study drug. Several patients on montelukast experienced transient elevations in AST and/or ALT, decreased white blood cell counts, or decreased platelet counts.

Exploratory evaluations included evaluation of the effects of montelukast in comparison with placebo in the exploratory efficacy endpoints of days without beta-agonist use, discontinuations from the study due to worsening asthma, oral corticosteroid rescues for worsening asthma symptoms, number of unscheduled physician or emergency room, or hospital visits due to worsening asthma symptoms, and total peripheral eosinophil counts. A randomization imbalance resulted from enrolling more patients with a history of more oral corticosteroid rescues in the montelukast than the placebo group. The randomization imbalance skewed the baseline as well as the results for patients 6 to 11 months of age, making all efficacy inferences (even exploratory ones) for this age group invalid.

The subgroup of patients 12 to 23 months of age who did not experience a randomization imbalance did have equal numbers of corticosteroid rescues. There were 124 patients randomized to montelukast, and 48 patients randomized to placebo in this age group. Efficacy trends for this group favor montelukast with fewer asthma attacks, fewer

unscheduled visits for asthma, and less albuterol use in the montelukast treatment arm. However, there was no trend toward less use of oral corticosteroids, as was seen in study P072, a similar safety study in 2 to 5 year olds

6.3.2.2.2. Study Design

6.3.2.2.2.1. Description

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”).

Study P176 was followed by study P232, a “— Extended Safety Study.” This was a 52-week, multicenter, open-label, controlled extended safety study enrolling patients who completed study P176, and comparing “usual care” with 4 mg montelukast once daily. Exploratory efficacy endpoints for this study were similar to those in study P176 described below. [2002/01/28, Reference 5; 0005.pdf]

6.3.2.2.2.2. Objectives

The primary objective was to evaluate the safety and tolerability of montelukast compared with placebo over the 6-week treatment period. The exploratory objective was to evaluate the effects of montelukast in comparison with placebo in the exploratory efficacy endpoints of days without beta-agonist use, discontinuations from the study due to worsening asthma, oral corticosteroid rescues for worsening asthma symptoms, number of unscheduled physician or emergency room, or hospital visits due to worsening asthma symptoms, and total peripheral eosinophil counts. [Clinical, Reference p176, Category 3: Study Documents, pages 383, 400, 409; p176.pdf]

6.3.2.2.2.3. Population

At least 250 male and female patients ages ≥ 6 months and < 24 months at the first visit within 5th to 95th percentile for height and weight for age were required to participate in this study. Study age requirements included at least 50% of patients 6 to 12 months old in order to have 75 patients in this age range complete the study, assuming that 150 patients will complete the study. [Clinical, Reference P716, Category 3, Appendix 3.3, page 387; p176.pdf]

6.3.2.2.2.4. Inclusion and Exclusion Criteria

Patients were required to have been fed solid foods for at least one month, and have been fed applesauce or other apple-containing products for at least one week prior to the prestudy visit.

Entry criteria included patients with a history of “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” and prior to the first visit., with at least one of the episodes having occurred within 6 months of the pre-study visit. Patients were also required to have “symptoms consistent with asthma at least at Step 2 of the GINA guidelines” (need for

controller therapy) as evidenced by an answer of *b* on each of the two questions in a parent/guardian Asthma Baseline Questionnaire. This questionnaire included the following questions:

- 1) On average over the past 4 weeks, how often in an average week did your child need to use their short-acting bronchodilator medication?
 - a) No days or 1 day with short-acting bronchodilator use in an average week.
 - b) Two or more days with short-acting bronchodilator use in an average week.
- 2) Over the past 2 weeks, how often did your child need to use oral prednisone or have emergency visit to a hospital or physician for an acute asthma attack?
 - a) One or more episodes of oral prednisone use or emergency visits to a hospital for asthma attack over the past 2 weeks.
 - b) No episodes of oral prednisone use or emergency visits to a hospital for asthma attack over the past 2 weeks.

Patients with history of prematurity (<28 weeks gestation), mechanical ventilation, cystic fibrosis, bronchopulmonary dysplasia, tracheomalacia, tracheoesophageal fistula, gastroesophageal reflux, pertussis, congenital heart disease, and history of allergy to apple sauce were excluded from the study. [Clinical, Reference p176, Category 3, Appendix 3.3, pages 384-6; p176.pdf]

Comments: The term "symptoms consistent with the need for chronic anti-asthmatic therapy" was not specifically used in this protocol. Instead, the term 'asthma-like' symptoms was used. Enrollees were patients who were required to have the need for recurrent bronchodilator treatment for respiratory symptoms. Many were on previous controller therapy, and the enrollment criteria were strict enough to meet the current NAEP/NHLBI guidelines of the need for controller therapy.

Diagnostic studies such as chest-rays, sinus radiography, sweat tests, and evaluation for gastroesophageal reflux were not included. While this is more of a real-world approach, the entry criteria were not strict enough to establish the diagnosis of asthma with certainty.

6.3.2.2.2.5. Safety Evaluations

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. [Clinical, Reference p176, page 21 and Category 3: Study Documents, pages 408-9; p176.pdf]

Comments: No chest x-ray was done as part of this study.

6.3.2.2.2.6. Conduct

Montelukast 4 mg oral granules or matching placebo oral granules were administered once daily in the evening mixed in one tablespoon of apple sauce. There was no treatment run-in period. Randomization was 2:1 montelukast:placebo. Patients were followed at 5 visits

before and during the study as outlined in the flow chart in Table 24. All patients used ‘as-needed’ beta-agonist therapy throughout the study, and maintained on any inhaled asthma medications if treatment had been initiated at least two weeks prior to the prestudy visit. At visit 2, eligible patients were randomized to receive six weeks of either montelukast or placebo. [Clinical, Reference p176, page 18; p176.pdf]

Table 24. Protocol P176, Study flow chart

Procedures	Period:	Prestudy		Treatment Period		
	Week:	-1	0	2	4	6 or early DC
	Visit:	1	2*	3	4	5
Informed consent		✓				
Assign screening number		✓				
Assign allocation number			✓			
Inclusion/exclusion review		✓	✓			
Baseline clinical review and asthma questionnaire		✓				
Review study procedures		✓	✓	✓	✓	
Parent/guardian demonstrates competence with study procedures			✓			
Review prior therapy		✓	✓			
Review concomitant therapy			✓	✓	✓	✓
Review adverse experiences		✓	✓	✓	✓	✓
Review action plan for worsening asthma		✓	✓	✓	✓	
Vital signs (HR, RR, temperature)		✓	✓	✓	✓	✓
Weight		✓				✓
Recumbent length		✓				✓
Blood pressure		✓				✓
Laboratory safety tests		✓				✓
Plasma sample for archive						✓
Review prestudy laboratory safety tests			✓			
Complete physical exam		✓				✓
Study medication Dispensed			✓	✓	✓	
Returned/reviewed				✓	✓	✓
Applesauce supplies dispensed/assessed			✓	✓	✓	✓
Beta-agonist dispensed/assessed		✓	✓	✓	✓	✓
Asthma calendar: Dispensed		✓	✓	✓	✓	
Returned/reviewed			✓	✓	✓	✓

* The procedure visit window between Visits 1 and 2 was 10 ± 3 days.

Source: Clinical, Reference p176, Category 3: Study Documents, pages 20, 368, 394; p176.pdf