6.3.2.2.3. Results

6.3.2.2.3.1. Study Centers, Enrollment, and Disposition

The study was conducted at 65 study centers, 29 in US and 36 ex-US including 22 countries in Africa, Asia, Europe, North American, and South America. The study enrolled 256 patients (randomized 2:1, montelukast:placebo), 175 to the montelukast group and 81 to placebo, with a breakdown of patient dispositions listed in Table 25. Also outlined in this table are the minimum enrollment requirements outlined in the pediatric Written Request.

Table 25. Study P176, Patient disposition

Disposition of Patients	Montelukast 4 mg oral granules		Placebo		Totals	
	n	(%)	n	(%)	n	(%)
WR Requirements for completed patients	100		50		150	
6 months to <12 months	25		13			
12 months to <2 years						
Entered (baseline): Totals:	175		81		256	
Boys (age range, months) [1]	116 (6 to 23) [2]		59 (6 to 24) [2]		175 (6 to 24)	
Girls (age range, months) [1]	59 (6 to 24) [2]		22 (6 to 23) [2]		81 (6 to 24)	
Age at Randomization:						
6 to 11 months	51	(29.1)	33	(40.7)	84	(32.8)
Boys	35		24		59	
Girls	16		9		25	
12 to 23 months	124	(70.9)	48	(59.3)	172	(67.2)
Boys	81		35		116	
Girls	43		13		56	
Completed:	169	(96.6)	74	(91.4)	243	(94.9)
Discontinued:	6	(3.4)	7	(8.6)	13 [3]	(5.1)
Clinical adverse experience	3	(1.7)	3	(3.7)	6	(2.3)
Protocol deviation	2	(1.1)	1	(1.2)	3	(1.2)
Lost to follow-up	1	(0.6)	1	(1.2)	2	(0.8)
Patient moved	0	(0.0)	1	(1.2)	1	(0.4)
Patient withdrew consent	0	(0.0)	1	(1.2)	1	(0.4)

[1] The age range for the study was 6 months to <2 years at the Prestudy Visit (Visit 1). Patient's age in the clinical database was based on age at randomization (Visit 2), not age at the Prestudy Visit. A total of 2 patients turned 24 months of age between Visits 1 and 2.

[2] Number of patients <1 year old: 51 in the montelukast treatment group, 35 boys and 16 girls; 33 in the placebo treatment group, 24 boys and 9 girls.

[3] Number of patients <1 year old: 3 in the montelukast treatment group, 1 clinical adverse experience, 1 protocol deviation, 1 lost to follow-up; 2 in the placebo treatment group, 1 clinical adverse experience, 1 lost to follow-up.

Sources: Clinical, Reference p176, Table 11, page 51; p176.pdf; and Pediatric Written Requests with amendments

6.3.2.2.3.2. Demographics and family history

Demographics, patient history, and family history information were provided in the study report with little explanatory information. These data are summarized in the discussion below and in Table 26, Table 27, and Table 28. Questions regarding the information presented in the study report were directed to the applicant to better elucidate how the

information was collected as well as about the population that was enrolled. These are discussed in the sections that follow this one.

Mean age of enrollment was 14.6 months, with 84 patients (32.8%) less than 12 months at randomization. As shown in Table 26, there was a higher proportion of boys than girls enrolled within both age groups and both treatment groups. Patient demographics were similar for height, and weight. While the montelukast 6-11 month group was similar to both montelukast and placebo 12 to 23 month groups, the placebo 6-11 month group enrolled patients with fewer missed day care or play group days (22.18 for montelukast, 14.13 for placebo), and less courses (1.41 for montelukast, 0.67 for placebo) and less days (7.51 for montelukast, 3.42 for placebo) of oral corticosteroid use in the last year than the other groups. However, the placebo 6-11 month group was similar to other groups in frequency of unscheduled visits to health care provider, ER, and hospital visits due to worsening asthma in past year, whereas the 6-12 month montelukast group enrolled patients who were lower than the other groups in these parameters.

Comment: Within the demographic tables, there appear to be subtle differences noted between the groups enrolled, particularly between the 6 to 11 month old montelukast and placebo groups. These differences are punctuated by differences in exploratory efficacy outcomes for these groups, and the discovery during the review process of a randomization imbalance between treatment groups, primarily in the 6 to 11 month age range. Please see further sections that discuss the randomization imbalance between the placebo and montelukast groups.

Table 26. Study P176, Patient demographics by age category

Demographics of Patients	6 to 11 months				12 to 23 months			
	Montelukast		Placebo		Montelukast		Placebo	
Age at Randomization **Totals**	**51**	(29.1%)	**33**	(40.7%)	**124**	(70.9%)	**48**	(59.3%)
Boys	35	(68.6%)	24	(72.7%)	81	(65.3%)	35	(72.9%)
Girls	16	(31.4%)	9	(27.3%)	43	(34.7%)	13	(27.1%)
Race								
Black	10	(5.7%)	5	(6.2%)	9	(7.3%)	3	(6.3%)
Hispanic	31	(17.7%)	17	(21.0%)	22	(17.7%)	10	(20.8%)
Other *	34	(19.4%)	12	(14.8%)	21	(16.9%)	7	(14.6%)
White	100	(57.1%)	47	(58.0%)	72	(58.1%)	28	(58.3%)
Weight (kg) (mean, range)	9.38	(6.86 - 11.91)	9.14	(7 50 - 14.06)	11.46	(8.20 - 17.01)	11.64	(9.10 - 14.29)
Height (cm) (mean, range)	72.85	(65.00 - 80.64)	71.50	(65.00 - 82.55)	80.71	(69.00 - 90.60)	81.95	(73.50 - 91.44)
Missed days at day care or play group in past year								
n	17		15		58		24	
Mean (SD, range)	22.18	(19.13, 0-60)	14.13	(18.80, 0-64)	20.62	(21.39, 0-70)	24.35	(27.57, 0-100
Days asthma affected performance at day care or play group in past year								
n	17		15		57		24	
Mean (SD, range)	20.82	(28.76, 0-84)	19.20	(23.56, 0-80)	31.21	(46.78, 0-300)	20.38	(24.18, 0-90
Total courses of oral corticosteroid in past year								
n	51		33		124		47	
Mean (SD, range)	1.41	(1.63, 0-8)	0.67	(0.96, 0-4)	1.63	(2.55, 0-15)	2.00	(1.53, 0-5)

Demographics of Patients	6 to 11 months				12 to 23 months			
	Montelukast		Placebo		Montelukast		Placebo	
Total days of oral corticosteroid in past year								
n	51		33		123		46	
Mean (SD, range)	7.51	(9.48, 0-42)	3.42	(5.12, 0-20)	7.52	(11.10, 0-60)	10.20	(8.96, 0-42)
Unscheduled visits to health care provider due to worsening asthma in past year								
n	50		33		123		47	
Mean (SD, range)	4.66	(4.99, 0-25)	6.94	(10.82, 0-50)	7.27	(7.67, 0-48)	6.23	(6.99, 0-30)
ER visits w/o admission due to worsening asthma in past year								
n	51		33		124		47	
Mean (SD, range)	1.12	(2.25, 0-12)	1.52	(2.25, 0-10)	2.33	(6.17, 0-60)	1.66	(2.71, 0-12)
Hospital visits due to worsening asthma in past year								
n	51		33		124		47	
Mean (SD, range)	0.41	(0.78, 0-3)	0.61	(0.93, 0-4)	0.79	(1.32, 0-7)	0.74	(0.99, 0-3)
* Other includes Asian, Eurasian, European, Micronesian, Multi-racial, and Native American								

Sources: Clinical, Reference p176, Category 4: Data, Appendix 4.4, Tables, 4.4.1-4.4.4, pages 831-3, 838-40; p176.pdf

Treatment and age groups were not significantly different in other patient history parameters, as outlined in Table 27. Incidence of other secondary diagnoses were similar between groups [Clinical, Reference p176, pages 58-9; p176.pdf]. Except for minor differences in frequency of inhaled corticosteroid use (ICS), incidence of other drug therapies was similar between groups [Clinical, Reference p176, pages 61-2; p176.pdf]. Although roughly similar percentages of patients were receiving controller therapy for asthma at randomization, including about 50% receiving ICS and about 10% receiving cromolyn, prior therapy with ICS was 48.4% for montelukast and 56.3 % for placebo in the 12-24 month age range, and 52.9% for montelukast and 42.4% for placebo in the 6-11 month age range. Many patients were diagnosed as having allergic rhinitis, even in the 6-11 month age range, and a significant percentage had a history of atopic dermatitis. While listing of may childhood diseases and immunizations were given, no data were included regarding frequency of bronchiolitis or RSV disease.

Table 27. Study P176, Patient history by age category

Patient History	6 to 11 months				12 to 23 months			
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48	
	n	(%)	n	(%)	n	(%)	n	(%)
Year asthma diagnosed								
Same year	36	(70.6%)	23	(69.7%)	55	(44.4%)	19	(39.6%)
First year *	15	(29.4%)	10	(30.3%)	67	(54.0%)	27	(56.3%)
Second year *					2	(1.6%)	2	(4.2%)
Concomitant Medication								
ICS	27	(52.9%)	14	(42.4%)	60	(48.4%)	27	(56.3%)
None	21	(41.2%)	15	(45.5%)	51	(41.1%)	16	(33.3%)
Cromolyn	3	(5.9%)	4	(12.1%)	13	(10.5%)	5	(10.4%)
Asthma exacerbations limit normal physical activity								
Not at all	13	(25.5%)	2	(6.1%)	25	(20.2%)	21	(43.8%)
Slightly	21	(41.2%)	15	(45.5%)	56	(45.2%)	15	(31.3%)

Patient History	6 to 11 months				12 to 23 months			
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48	
	n	(%)	n	(%)	n	(%)	n	(%)
Moderately	16	(31.4%)	15	(45.5%)	39	(31.5%)	9	(18.8%)
Severely	1	(2.0%)	1	(3.0%)	4	(3.2%)	3	(6.3%)
History of AR	21	(41.2%)	8	(24.2%)	44	(35.8%)	25	(52.1%)
AR sx in past year								
All year long without seasonal flares	8	(38.1%)	4	(50.0%)	11	(25.0%)	9	(37.5%)
Seasonal flares	5	(23.8%)	3	(37.5%)	20	(45.5%)	11	(45.8%)
All year with seasonal flares	8	(38.1%)	1	(12.5%)	13	(29.5%)	4	(16.7%)
History of atopic dermatitis	19	(37.3%)	9	(27.3%)	47	(37.9%)	18	(37.5%)
Atopic dermatitis sx in past year								
All year long without seasonal flares	7	(38.9%)	4	(57.1%)	18	(40.0%)	3	(17.6%)
Seasonal flares	9	(50.0%)	0	(0.0%)	23	(51.1%)	12	(70.6%)
All year with seasonal flares	2	(11.1%)	3	(42.9%)	4	(8.9%)	2	(11.8%)
Skin tested for allergies	6	(11.8%)	5	(15.2%)	27	(21.8%)	9	(18.8%)
History of disease:								
Prematurity	0		0		1	(0.8%)	0	
GERD	1	(2.0%)	0		4	(3.2%)	1	(2.1%)
RSV	1	(2.0%)	1	(0.8%)	0		1	(2.1%)
Bronchiolitis	4	(7.8%)	2	(6.1%)	14	(11.3%)	10	(20.8%)
Measles	0		0		1	(0.8%)	0	
Mumps	0		0		1	(0.8%)	0	
Rubella	0		0		1	(0.8%)	0	
Varicella	0		1	(3.0%)	13	(10.6%)	2	(4.2%)
Fifths disease	0		1	(3.0%)	2	(1.6%)	1	(2.1%)
Vaccine for:								
MMR	10	(19.6%)	8	(24.2%)	93	(75.0%)	33	(68.8%)
DTP/DTaP	50	(98.0%)	33	(100.0%)	123	(99.2%)	47	(97.9%)
Polio	49	(96.1%)	33	(100.0%)	123	(99.2%)	47	(97.9%)
Varicella	1	(2.0%)	4	(12.1%)	34	(27.4%)	16	(33.3%)
Average asthma sx in the past month:								
Never					4	(3.2%)	1	(2.1%)
Up to 2 times/week	12	(23.5%)	2	(6.1%)	24	(19.4%)	13	(27.1%)
>2 times/week, but not daily	31	(60.8%)	24	(72.7%)	81	(65.3%)	23	(47.9%)
Every day	7	(13.7%)	6	(18.2%)	12	(9.7%)	9	(18.8%)
Continuously	1	(2.0%)	1	3.0%)	3	(2.4%)	2	(4.2%)
Awakenings due to asthma sx in the past month:								
Never	7	(13.7%)	4	(12.1%)	17	(13.8%)	11	(22.9%)
≤2 times/month	7	(13.7%)	4	(12.1%)	22	(17.9%)	11	(22.9%)
>2 times/month	24	(47.1%)	12	(36.4%)	48	(39.0%)	13	(27.1%)
>1 time/week	11	(21.6%)	8	(24.2%)	27	(22.0%)	11	(22.9%)
Every day	2	(3.9%)	5	(15.2%)	9	(7.3%)	2	(4.2%)
Asthma sx affected performance in day care in the past year								

Patient History	6 to 11 months				12 to 23 months			
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48	
	n	(%)	n	(%)	n	(%)	n	(%)
n	17		12		57		24	
No	5	(29.4%)	2	(16.7%)	8	(14.8%)	3	(12.5%)
Yes	12	(70.6%)	10	(83.3%)	46	(85.2%)	21	(87.5%)
Asthma sx affected performance in play group in the past year								
n	47		32		118		46	
No	30	(63.8%)	17	(53.1%)	60	(50.8%)	22	(47.8%)
Yes	17	(36.2%)	15	(46.9%)	58	(49.2%)	24	(52.2%)
Frequency of bronchodilator in past 4 weeks:								
No days or 1 day	1	(2.0%)	0		1	(0.8%)	0	
2 or more days	50	(98.0%)	33	(100.0%)	122	(99.2%)	48	(100.0%)
Frequency of oral prednisone, ER, hospital or doctor visits in past 2 weeks:								
No oral prednisone	49	(96.1%)	33	(100.0%)	122	(99.2%)	48	(100.0%)
One or more oral prednisone	2	(3.9%)	0	(0.0%)	1	(0.8%)	0	
* "Year asthma first diagnosed" was based on the calendar year, where year of birth was the first year, etc.								

Sources: Clinical, Reference p176, Category 4: Data, Appendix 4.4, Table 4.4.2, pages 833-7, and Table 4.4.4, pages 840-4; p176.pdf
Response of 6/4/02, pages 28, 31-33; response.pdf

Family history of enrolled patients is listed in Table 28. Age and treatment groups were similar for family history parameters. Of interest is that significant percentages of patients had at least one smoker in the household.

Table 28. Study P176, Family history by age category

Family History	6 to 11 months				12 to 23 months			
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48	
	n	(%)	n	(%)	n	(%)	n	(%)
Mother with:								
Asthma	12	(23.5%)	10	(30.3%)	28	(22.8%)	8	(16.7%)
Allergic Rhinitis	16	(31.4%)	10	(30.3%)	36	(29.3%)	26	(54.2%)
Atopic dermatitis	8	(15.7%)	7	(21.2%)	11	(8.9%)	9	(18.8%)
Unknown	0		0		0		0	
Father with:								
Asthma	7	(14.0%)	8	(24.2%)	26	(21.8%)	6	(12.5%)
Allergic Rhinitis	14	(28.0%)	10	(30.3%)	40	(33.6%)	15	(31.3%)
Atopic dermatitis	4	(8.0%)	3	(9.1%)	12	(10.1%)	6	(12.5%)
Unknown	1	(2.0%)	0		5	(4.0%)	0	
Sibling with:	n = 43		n = 29		n = 104		n = 36	
Asthma	11	(26.2%)	13	(44.8%)	45	(44.6%)	16	(45.7%)
Allergic Rhinitis	6	(14.3%)	10	(34.5%)	22	(21.8%)	7	(20.0%)
Atopic dermatitis	9	(21.4%)	8	(27.6%)	15	(14.9%)	6	(17.1%)
Unknown	1	(2.3%)	0		3	(2.9%)	1	(2.8%)
Other biological family member * with:								
Asthma	27	(55.1%)	21	(67.7%)	68	(61.3%)	31	(70.5%)

Family History	6 to 11 months				12 to 23 months			
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48	
	n	(%)	n	(%)	n	(%)	n	(%)
Allergic Rhinitis	18	(36.7%)	11	(35.5%)	33	(29.7%)	16	(36.4%)
Atopic dermatitis	8	(16.3%)	11	(35.5%)	16	(14.4%)	7	(15.9%)
Unknown	2	(3.9%)	2	(6.1%)	12	(9.8%)	4	(8.3%)
Smoker in household	16	(31.4%)	10	(30.3%)	50	(40.3%)	18	(37.5%)
* Definition of "Other biological family member" was left up to the interpretation of the parent/guardian, and specification of the relationship was neither required nor requested.								

Source: Clinical, Reference p176, Category 4: Data, Appendix 4.4, pages 833-4, 840-1; p176.pdf
Response of 6/4/02, page 28; response.pdf

6.3.2.2.3.3. Further information regarding demographics and family history

The study report provided no information on how the information regarding demographic information was obtained. It was not clearly stated whether this was based on a parent-completed questionnaire, or on information completed by the primary caretaker. The study report provided no information on how the information regarding who made the diagnosis of allergic rhinitis and other diagnoses listed in the demographic tables. The Division requested Merck to provide this information. Merck responded that the patient demographic information, including diagnoses, were obtained by the study coordinator or investigator during a parent/guardian interview and/or by review of the patient's medical record (if available). [Response of 6/4/02, page 26; response.pdf]

It is clear from the demographic tables that enrolled patients had a much higher proportion of positive family history for allergic diseases than the average population. While many carried the diagnosis of "asthma," the diagnostic criteria used were that of recurrent episodes of airway obstruction. Diagnostic evaluations for recurrent wheezing, if done, were not part of the study report. Therefore, the Division requested Merck to provide information on the numbers of patients who were evaluated and the results the following tests:

- chest x-rays
- sweat chlorides
- swallowing studies
- sinus radiography, including sinus CT

Merck responded that they believe the inclusion criteria were sufficient to enroll patients with chronic asthma rather than other syndromes associated with the signs and symptoms of asthma. There was no protocol requirement to perform the above diagnostic evaluations in order to document the absence of other clinical syndromes. Therefore, no information was available regarding prior evaluations preformed on enrolled patients. Nevertheless, the clinical database was examined to identify randomized patients who underwent any of these diagnostic evaluations during the study. No patients had a sweat chloride or swallowing evaluation during the study. Seven patients had a total of 9 chest x-rays, and one patient had a sinus x-ray during the study. No results of the studies were provided. [Response of 6/4/02, pages 29-30; response.pdf]

In addition, the study report provided no listing for the diagnoses of prematurity (between 29-38 weeks gestation, since there was an exclusionary criterion for < 28 weeks gestation), gastroesophageal reflux disease (GERD), bronchiolitis, or respiratory syncytial virus (RSV) disease. Since these are crucial to the understanding of the recurrent reversible bronchospasm in these infants, the Division requested Merck to provide this information as well as how the diagnosis was made (e.g. by laboratory confirmation of RSV disease versus clinical diagnosis alone). Merck responded that they believe the inclusion criteria were sufficient to enroll patients with chronic asthma rather than other syndromes associated with the signs and symptoms of asthma. At our request, they searched the clinical database for the requested diagnoses of prematurity, GERD, bronchiolitis, and RSV disease. Thirty-nine patients had a history of at least one of these conditions, only two of which were considered "active" at study entry. These diagnoses are included within Table 27. [Response of 6/4/02, pages 31-3; response.pdf]

The study report provided no listing for results of skin testing for those patients with history of having undergone skin testing. The Division requested Merck to provide this information. Merck responded that, while skin testing was not specified in the protocol, history of skin testing was collected in the patient profiles, and parent/guardian reported results of positive tests were also recorded. Skin testing had been performed in 47/256 (18.4%) of randomized patients (18.9% in montelukast , 17.3% in placebo) prior to participation in the study. In the montelukast group, 15 of the 33 tested patients (45%) had a positive response. In the placebo group, 6 of 14 tested patients (43%) had a positive response. [Response of 6/4/02, pages 34-5; response.pdf]

The study report provided a listing of eosinophil counts at baseline and treatment (Report page 95-6), but no breakdowns by age. The Division requested Merck to provide this information. Merck responded with several tables showing ANCOVA analyses of total eosinophil counts for each age group. No differences were seen, either between treatment groups or age groups. [Response of 6/4/02, pages 36-8; response.pdf]

6.3.2.2.3.4. Compliance rates

Compliance rates were similar for both treatment groups.

Table 29. Study P176, Compliance rates*

	Montelukast	Placebo	Total
N	175	81	256
Mean %	95.9	94.3	95.4
Median %	100	100	100
SD	11.2	13.2	11.9
Range %	4.3 to 104.8	33.3 to 104.7	4.3 to 104.8
* Compliance rate = 100 x (actual number of doses taken / total number of doses than should have been taken)			

Source: Clinical, Reference p176, page 65; p176.pdf

6.3.2.2.3.5. Extent of exposure

The extent of exposure was comparable between treatment groups [Clinical, Reference p176, pages 65-6; p176.pdf]. As shown in Table 25, there were 169 patients (96.6%) in the montelukast treatment group and 74 patients (91.4%) in the placebo treatment group who completed the 6-week study.

6.3.2.2.3.6. Safety outcomes

6.3.2.2.3.6.1. Clinical adverse experiences

Clinical adverse events were reported for 194 (75.8%) of the 256 patients and are shown in Table 30. While the montelukast group experienced more serious adverse events, there was no difference in drug-related adverse events between treatment groups.

Table 30. Study P176, Clinical adverse events

	Montelukast 4-mg oral granules (N = 175)	Placebo (N = 81)
Number (%) of patients:	n (%)	n (%)
One or more adverse events *	132 (75.4)	62 (76.5)
No adverse event	43 (24.6)	19 (23.5)
Drug-related adverse events **	15 (8.6)	6 (7.4)
Serious adverse events	7 (4.0)	1 (1.2)
Serious drug-related adverse event	0 (0.0)	0 (0.0)
Died	0 (0.0)	0 (0.0)
Discontinued from therapy due to an adverse event	3 (1.7)	3 (3.7)
Discontinued from therapy due to a drug-related adverse event	3 (1.7)	2 (2.5)
Discontinued from therapy due to a serious adverse event	0 (0.0)	0 (0.0)
Discontinued from therapy due to a serious drug-related adverse event	0 (0.0)	0 (0.0)

* Although a patient may have had 2 or more clinical adverse events, the patient was counted only once per category .
** Determined by the investigator to be possibly, probably, or definitely drug related

Source: Clinical, Reference p176, page 65; p176.pdf

Specific adverse events with an incidence of ≥3% in either treatment group are listed in Table 31. The montelukast group experienced more upper respiratory infections but less influenza-like disease and digestive disease. Overall there were no significant differences between the groups. The study report points out less episodes of worsening asthma in the montelukast group. However, as seen in Table 32, when 'wheezing' and 'bronchospasm' are added, the percentages for each group are almost equal. This is discussed under the section discussing exploratory efficacy evaluations in the study. Oral candidiasis was uncommon, but only experienced in patients receiving inhaled corticosteroids. [Clinical, Reference p176, page 68; p176.pdf]

Table 31. Study P176, Adverse events with an incidence ≥3%

Adverse Event	Montelukast n = 175 n (%)	Placebo n = 81 n (%)
Body as a Whole	72 (41.1)	28 (34.6)
Fever	23 (13.1)	11 (13.6)
Influenza-like disease	0 (0.0)	3 (3.7)
Upper respiratory infection	56 (32.0)	17 (21.0)
Digestive System	38 (21.7)	22 (27.2)
Diarrhea	19 (10.9)	10 (12.3)
Gastroenteritis	3 (1.7)	3 (3.7)
Vomiting	15 (8.6)	9 (11.1)
Eyes, Ears, Nose and Throat	52 (29.7)	26 (32.1)
Conjunctivitis	4 (2.3)	5 (6.2)
Otitis	5 (2.9)	3 (3.7)
Otitis media	15 (8.6)	5 (6.2)
Pharyngitis	14 (8.0)	6 (7.4)
Rhinitis	8 (4.6)	3 (3.7)
Nervous System	4 (2.3)	4 (4.9)
Respiratory System	57 (32.6)	26 (32.1)
Asthma	33 (18.9)	18 (22.2)
Bronchitis	7 (4.0)	5 (6.2)
Cough	8 (4.6)	2 (2.5)
Skin	22 (12.6)	11 (13.6)
Rash	9 (5.1)	5 (6.2)
Other skin conditions	6 (3.4)	0 (0.0

Source: Clinical, Reference p176, Table 22, page 69; p176.pdf
Summary, Table 15, page 91; summary.pdf

Table 32. Study P176, Adverse events of respiratory tract and eyes, ears, nose, and throat

Adverse Event	Montelukast n = 175 n (%)	Placebo n = 81 n (%)
Upper respiratory infection	56 (32.0)	17 (21.0)
Viral infection	1 (0.6)	2 (2.5)
Influenza-like disease	0 (0.0)	3 (3.7)
Allergic conjunctivitis	1 (0.6)	0 (0.0)
Bacterial conjunctivitis	0 (0.0)	1 (1.2)
Conjunctivitis	4 (2.3)	5 (6.2)
Viral conjunctivitis	0 (0.0)	1 (1.2)
Allergic rhinitis	5 (2.9)	2 (2.5)
Rhinitis	8 (4.6)	3 (3.7)
Nasal congestion	2 (1.1)	1 (1.2)
Epistaxis	1 (0.6)	1 (1.2)
Nasal secretion	3 (1.7)	0 (0.0)
Upper airway obstruction	1 (0.6)	0 (0.0)
Nasopharyngitis	0 (0.0)	1 (1.2)
Otitis	5 (2.9)	3 (3.7)
Otitis media	15 (8.6)	5 (6.2)
Serous otitis media	1 (0.6)	0 (0.0)

Adverse Event	Montelukast n = 175 n (%)	Placebo n = 81 n (%)
Sinusitis	3 (1.7)	2 (2.5)
Oral candidiasis	2 (1.1)	1 (1.2)
Pharyngitis	14 (8.0)	6 (7.4)
Tonsillitis	4 (2.3)	0 (0.0)
Aspiration	1 (0.6)	0 (0.0)
Cough	8 (4.6)	2 (2.5)
Tachypnea	1 (0.6)	0 (0.0)
Asthma	33 (18.9)	18 (22.2)
Bronchospasm	1 (0.6)	0 (0.0)
Wheezing	5 (2.9)	1 (1.2)
Bronchiolitis	0 (0.0)	1 (1.2)
Bronchitis	7 (4.0)	5 (6.2)
Obstructive bronchitis	1 (0.6)	0 (0.0)
Tracheobronchitis	1 (0.6)	1 (1.2)
Tracheitis	0 (0.0)	1 (1.2)
Lower respiratory infection	2 (1.1)	1 (1.2)
Pneumonia	1 (0.6)	0 (0.0)
Respiratory infection	2 (1.1)	1 (1.2)
Pulmonary congestion	1 (0.6)	0 (0.0)

Sources: Clinical, Reference p176, Table 23, page 71; p176.pdf
Clinical, Reference p176, pages 976-8, 1218; p176.pdf

6.3.2.2.3.6.2. Drug-related clinical adverse events

As shown in Table 33, there were no significant differences in adverse events judged to be drug-related.

Table 33. Study P176, Drug related clinical adverse events (Incidence >0%)

	Montelukast 4-mg oral granules (N = 175) n (%)	Placebo (N = 81) n (%)
Patients with no drug-related adverse event	160 (91.4)	75 (92.6)
Patients with one or more drug-related adverse event	15 (8.6)	6 (7.4)
Digestive System	5 (2.9)	1 (1.2)
Constipation	1 (0.6)	0 (0.0)
Diarrhea	3 (1.7)	1 (1.2)
Vomiting	1 (0.6)	0 (0.0)
Metabolism and Nutrition	1 (0.6)	0 (0.0)
Anorexia	1 (0.6)	0 (0.0)
Body as a whole / Nervous System / Psychiatric Disorder	5 (2.9)	5 (6.2)
Asthenia / fatigue	0 (0.0)	1 (1.2)
Restlessness (Akathisia)	1 (0.6)	0 (0.0)
Hyperkinesia	2 (1.1)	0 (0.0)
Insomnia	0 (0.0)	2 (2.5)
Sleep disorder	1 (0.6)	2 (2.5)
Irritability	1 (0.6)	0 (0.0)
Respiratory System	2 (1.1)	0 (0.0)

	Montelukast 4-mg oral granules (N = 175)	Placebo (N = 81)
	n (%)	n (%)
Asthma	2 (1.1)	0 (0.0)
Skin	5 (2.9)	1 (1.2)
Eczema	2 (1.1)	0 (0.0)
Exanthema	0 (0.0)	1 (1.2)
Rash	2 (1.1)	0 (0.0)
Urticaria	1 (0.6)	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 events, the patient is counted only once in a category. The same patient may appear in different categories.

Sources:Clinical, Reference p176, Table 24, pages 72-3; p176.pdf

6.3.2.2.3.6.3. Serious adverse events, Deaths, and Discontinuations

There were no deaths in this study. There were 9 serious adverse events in 8 patients, 7 in the montelukast group and 1 in the placebo group. As shown in Table 34, these events spanned a wide variety of clinically unrelated areas. Four events related to the respiratory tract: one patient with worsening asthma 4 days after ending montelukast (11 month BF, AN6139), one patient with pneumonia associated with wheezing on Day 11 of montelukast (18 month multi-racial M, AN6525), one patient with bronchiolitis on Day 30 of placebo (17 month WM, AN6172), and one patient with aspiration of a walnut while on montelukast (18 month WM, AN6711). Close review reveals no relationship between the pattern of these serious clinical adverse events and use of montelukast.

Table 34. Study P176, Serious clinical adverse events (Incidence >0%)

Reason	Montelukast 4-mg oral granules (N = 175)	Placebo (N = 81)
	n (%)	n (%)
Patients with no serious adverse events	168 (96.0)	80 (98.8)
Patients with one or more serious adverse events	7 (4.0)	1 (1.2)
Aspiration (walnut)	1 (0.6)	0 (0.0)
Asthma (worsening asthma 4 days after study completion)	1 (0.6)	0 (0.0)
Bronchiolitis (30 days into study)	0 (0.0)	1 (1.2)
Diarrhea and	1 (0.6)	0 (0.0)
Dehydration (hospitalized for Shigella D infection)	1 (0.6)	0 (0.0)
Drug overdose (8 mg of montelukast without associated symptoms)	1 (0.6)	0 (0.0)
Inguinal hernia (congenital)	1 (0.6)	0 (0.0)
Pneumonia (associated with wheezing, 10 days into study)	1 (0.6)	0 (0.0)
Urinary tract infection (recurrence)	1 (0.6)	0 (0.0)

Sources: Summary, page 90; summary.pdf
Clinical, Reference p176, pages 74-8; p176.pdf

Six patients were discontinued (3 montelukast, 3 placebo) due to a clinical adverse event, three from each group. These are summarized in Table 35.

In the montelukast group, the adverse events included one patient with exacerbation of asthma associated with an upper respiratory infection and otitis media after one dose of montelukast (11 month WM, AN6144), one patient with vomiting on Day 7 that continued for 3 days post-D/C of montelukast (15 month WF, AN6136), and one patient with onset a rash on Day 26 (14 month Native American, AN6642). The rash was described as macular, erythematous, and blotchy, and present on the face, extremities, and abdomen, and lasted 10 days. The rash was concurrent to the patient having oral thrush. Concurrent medications included fluticasone propionate, albuterol and ferrous sulfate. The investigator felt that the rash was either a viral exanthema or secondary to study drug (montelukast), however the description of the rash is also consistent with an id reaction to the thrush. All three of the adverse events in the montelukast group were considered possibly drug related, and all patients recovered uneventfully after study drug (montelukast) withdrawal.

In the placebo group, the adverse events included one patient with bronchitis on Day 5 (22 month M, AN6096), one patient with lethargy (23 month M, AN6101), and one patient with poor sleeping (6 month M, AN6324). The episode of lethargy began on Day 8, study drug was discontinued on Day 12, and the episode lasted for 9 days (5 days beyond discontinuation of study drug). The episode of poor sleeping lasted 25 days, and appears to have been associated with irritability and wheezing, which were noted at the discontinuation visit. Two of the three events were considered related to the study drug (the episode of bronchitis was not considered related to study drug), and all patients recovered uneventfully after study drug (placebo) withdrawal.

Table 35. Study P176, Discontinuations from therapy due to a clinical adverse event

Reason	Montelukast 4-mg oral granules (N = 175) n (%)	Placebo (N = 81) n (%)
Patients not discontinued from therapy due to an adverse event	172 (98.3)	78 (96.3)
Patients discontinued from therapy due to an adverse event	3 (1.7)	3 (3.7)
Asthenia/fatigue (Lethargy at Day 8) *	0 (0.0)	1 (1.2)
Asthma (worsening asthma at Day 2 along with URI and OM at Day 4, montelukast d/c at 6 days) *	1 (0.6)	0 (0.0)
Bronchitis (at Day 5, lasting 13 days) **	0 (0.0)	1 (1.2)
Rash (at Day 26, lasting 10 days [*see text for description*]) *	1 (0.6)	0 (0.0)
Sleep disorder (Poor sleep at Day 11) *	0 (0.0)	1 (1.2)
Vomiting (at Day 7, resolved 3 days after d/c of montelukast) *	1 (0.6)	0 (0.0)

* Determined by the investigator to be possibly drug related: montelukast = asthma (AN 6144), rash (AN 6642), vomiting (AN 6136); placebo = asthenia/fatigue (AN 6101), sleep disorder (AN 6324).

** Determined by the investigator to be definitely not drug related: placebo = bronchitis (AN 6096).

Sources: Summary, page 97; summary.pdf
Clinical, Reference p176, pages 78-81; p176.pdf

6.3.2.2.3.6.4. Laboratory adverse events

Eight patients (3.2%) had at least one laboratory adverse event (7 montelukast {4.1%}, 1 placebo {1.3%}) (Table 36). Of these, four patients had 15 events determined to be drug

related, accounting for 15 separate laboratory adverse events. There were no serious laboratory adverse events, and no patients were discontinued due to a laboratory adverse event. [Clinical, Reference p176, pages 81-6; p176.pdf]

> *Comment: The protocol notes that variance within 10% of the upper or lower limits of normal will not be considered clinically abnormal for bilirubin, BUN, glucose, WBC, and platelets [Clinical, Reference p176, Appendix 3.3, page 460 ; p176.pdf]. An adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body or worsening of a preexisting condition temporally associated with the use of study drug [Clinical, Reference p176, Appendix 3.3, page 402; p176.pdf].*

While there was a trend toward more frequent drug-related laboratory adverse events in the montelukast group several patients experienced other clinical adverse events that may have influenced the results. Therefore no clear picture emerges. A brief summary of each of the four patients with drug-related adverse events follows. [Clinical, Reference p176, pages 81-6; p176.pdf]

- Patient AN 6041, a 23 month old boy on montelukast had a blood glucose of 60 and a platelet count of 250 $x10^3/\mu L$ on Day 47. All were felt to be drug related.
- Patient AN 6526, a 21 month old boy on montelukast had an ALT of 192 IU/L (normal range = 6 to 34 IU/L) an AST of 75 IU/L (normal range = 10 to 69 IU/L), an albumin of 5.4 g/dL, and a creatinine of 0.7 mg/dL on Day 42. All were felt to be drug related. Two weeks later, ALT and AST were normal, but repeat creatinine was 0.8 mg/dL, and Epstein-Barr antibody was positive at Day 68. Based on additional lab data, the creatinine was not felt to be an adverse event, but this was reported after the cutoff date.
- Patient AN 6654, a 10 month old girl on montelukast was hospitalized on Day 23 for a serious clinical adverse event of a UTI. At the post study visit on Day 37 (11 days after discharge), and while on Amoxacillin, WBC was 5.68 $x10^3/\mu L$, neutrophils 1.17 $x10^3/\mu L$, platelets 196 $x10^3/\mu L$, and AST of 42 IU/L (normal range = 6 to 56 IU/L). All were determined to be possibly related to study drug, and all but the neutrophil county were resolved 12 days later.
- Patient AN 6658, a 20 month old boy on montelukast had an ALT of 51 IU/L (normal range = 6 to 34 IU/L), an AST of 79 IU/L (normal range = 10 to 69 IU/L), an albumin of 5.4 g/dL, leukocytes (WBC) of 5.62 $x10^3/\mu L$, and lymphocytes of 3.1 $x10^3/\mu L$. All were felt to be drug related. Repeat measurements 9 days later were normal.

Table 36. Study P176, Laboratory adverse events

Reason	Montelukast 4-mg oral granules (N = 175) n/m * (%)	Drug-related n %	Placebo (N = 81) n/m * (%)	Drug-related n %
Patients with no lab adverse events	163/170 (95.9)		78/79 (98.7)	
Patients with one or more lab adverse events	7/170 (4.1)	4 (2.4)	1/79 (1.3)	0 (0.0)
Patients with Serum Chemistry AE	5/169 (3.0)	4	0/78 (0.0)	0
↑ Alanine aminotransferase (ALT)	2/168 (1.2)	2	0/75 (0.0)	0
↑ Aspartate aminotransferase (AST)	3/169 (1.8)	3	0/75 (0.0)	0
Hyperglycemia	1/165 (0.6)	0	0/75 (0.0)	0
Hypoglycemia	1/165 (0.6)	1	0/75 (0.0)	0
↑ Albumin	1/169 (0.6)	1	0/75 (0.0)	0
↑ Creatinine	2/169 (1.2)	1	0/77 (0.0)	0
↑ Total protein	1/169 (0.6)	1	0/76 (0.0)	0
Patients with Hematology AE	5/168 (3.1)	3	1/74 (1.4)	0
↓ Leukocytes (WBC)	2/163 (1.2)	2	0/73 (0.0)	0
↑ Leukocytes (WBC)	1/163 (0.6)	0	0/73 (0.0)	0
↓ Lymphocytes	1/163 (0.6)	1	0/74 (0.0)	0
↓ Neutrophils	1/163 (0.6)	1	1/74 (1.4)	0
↓ Platelets	2/155 (1.3)	2	0/71 (0.0)	0
↑ Platelets	1/155 (0.6)	0	0/71 (0.0)	0

* n/m = number of patients with the lab AE / number of patients with one or more post-baseline lab tests

Sources: Summary, page 97; summary.pdf
Clinical, Reference p176, Tables 28-9, pages 81-4; p176.pdf

The study report presents a type of shift table for certain (but not all) laboratory results with "predefined limits of change" for these laboratory tests that identify the number and percent of results that exceeded these limits and the differences between treatment groups. Merck does not explain why the particular laboratory tests in this table were selected, nor is an explanation given for the predefined limits of change, which are not present in the protocol. Nevertheless, the choice of tests seems reasonable, and review of other laboratory results does not yield further data of relevance. Some trends are noted, as shown in Table 37.

In the montelukast group there was a trend to have more patients cross the threshold of lower WBCs, along with a trend to have fewer patients experience an increase of WBC above the predefined limit (montelukast baseline 10.21 with –0.9 mean change, placebo baseline 10.35 with 1.02 mean change). However, analysis of the baseline and mean changes for each the lab values for each treatment group (as shown in parenthesis) was not revealing . Similar trends with montelukast treatment occurred for Hematocrit (montelukast baseline 12.10 with 0.0 mean change, placebo baseline 12.24 with 0.1 mean change) and Platelet counts (montelukast baseline 369.69 with –1.51 mean change, placebo baseline 357.03 with 17.02 mean change). A trend was noted in increased AST (montelukast baseline 22.55 with 0.58 mean change, placebo baseline 22.27 with 0.66 mean change) and increased ALT (montelukast baseline 41.34 with 0.25 mean change, placebo baseline 41.41

with 0.11 mean change) above the "predefined" threshold of change, but no trend was noted for total bilirubin.

Table 37. Study P176, Laboratory results exceeding predefined limits of change

Laboratory Test	Predefined limit of change	Treatment	Number / Total	%	Delta %
WBC ($10^3/\mu L$)	↓ ≥20% and value <1xLLN	Montelukast Placebo	9/159 1/71	5.7 1.4	4.3
	↑ ≥20% and value <1xULN	Montelukast Placebo	27/159 16/71	17.0 22.5	-5.6
Hematocrit (%)	↓ ≥20% and value <1xLLN	Montelukast Placebo	2/155 0/70	1.3 0.0	1.3
	↑ ≥20% and value <1xULN	Montelukast Placebo	0/155 1/70	0.0 1.4	-1.4
Platelet count ($10^3/\mu L$)	↓ ≥25% and value <1xLLN	Montelukast Placebo	2/151 0/67	1.3 0.0	1.3
	↑ ≥50% and value <1xULN	Montelukast Placebo	10/151 5/67	6.6 7.5	-0.8
ALT (IU/L)	↑ ≥100% and value <1xULN	Montelukast Placebo	6/164 1/75	3.7 1.3	2.3
AST (IU/L)	↑ ≥50% and value <1xULN	Montelukast Placebo	3/165 1/75	1.8 1.3	0.5
Bilirubin (mg/dL)	↑ ≥100% and value <1xULN	Montelukast Placebo	0/165 0/75	0.0 0.	0.0

Sources: Clinical, Reference p176, Table 30, pages 88; p176.pdf
Clinical, Reference p176, Appendix 4.16.8, pages 946-8; p176.pdf

6.3.2.2.3.6.5. Vital Signs and Physical Examinations

There were no clinically meaningful differences between treatment groups in change from baseline related to vital signs or physical examinations.

6.3.2.2.3.7. Exploratory efficacy outcomes

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.

Exploratory outcomes are summarized in Table 38, with subgroups for each endpoint explored in Table 39 through Table 43 and Figure 11 through Figure 13, and summarized by age group in Table 46. Several trends appear to favor the montelukast treatment group. These include a higher mean percentage of days without beta-agonist use, lower number of beta-agonist treatments per day, and lower percentage of unscheduled visits for asthma. Nevertheless, the montelukast group experienced about equal percentages of asthma attacks, and they required more oral corticosteroid rescues than the placebo group. Trends toward the need for oral corticosteroid rescue and for the subgroup of concomitant cromolyn use are discussed in further detail below. In particular, the trend toward higher corticosteroid use paired with the demographic differences noted between treatment groups, and raised the

suspicion of a randomization imbalance. A concern was also raised for the subgroup of patients receiving concomitant treatment with cromolyn. These issues are discussed below.

Table 38. Study P176, Exploratory efficacy outcomes

Exploratory Efficacy Outcomes	Montelukast n = 174		Placebo n = 81	
Days without beta-agonist use (mean %, SD)	66.52%	± 33.13	59.53%	± 33.10
Beta-agonist treatments per day (mean, SD)	0.75	± 0.90	0.87	± 0.80
Unscheduled visits for asthma (rate [%], #)	9.77%	17	14.81%	12
Oral corticosteroid rescues (rate [%], #)	14.94%	26	7.41%	6
Asthma attacks (rate [%], #)	16.67%	29	18.52%	15
Discontinuations due to worsening asthma (rate [%], #)	1.15%	2	2.47%	2
Total peripheral eosinophil counts (mean change from baseline, 1000/μL)	0		-0.01	

Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

The rate of corticosteroid rescue for the montelukast group (Table 43) was double the rate for the placebo group (14.94% for montelukast, 7.41% for placebo). The Kaplan-Meier plot of the rate of corticosteroid rescue for asthma (Figure 13) graphically represents this trend in favor of placebo over the course of the study. While the study was of 6 weeks duration, data points in the Kaplan-Meier plot for placebo end earlier than montelukast (38 days versus 44 days). The final data point for montelukast on day 44 is not reflected in Table 43. If that data point were used, the data might suggest a wider and continued separation of the two treatment groups, except that no data for the placebo group is available to that same timepoint.

This tend appears to have been driven by differences in the subgroup patients under 12 months of age where 22% of the patients in the montelukast group and none of the placebo group required oral corticosteroid rescue . The differences are greater in the subgroup of males than for females under 12 months of age . Although many subgroups enrolled too few patients to draw any conclusions, the differences appeared to span all subgroups of concomitant medications and races. . In addition, review of demographic data from Table 26 for the subgroup of patients ages <12 months reveals that the group who received placebo had fewer use of oral corticosteroids prior to study entry, both for total courses of oral corticosteroids days of corticosteroid use, than their counterparts who received montelukast. Even though much of the rest of their baseline characteristics appeared similar to the other groups, it was speculated that there may have been some baseline difference between the montelukast and placebo groups <12 months of age that was simply reflected in their overall need to corticosteroids and was unaffected by the montelukast use during the study. This is addressed in the paragraphs below.

While the numbers of patients enrolled who were using concomitant cromolyn were too small to draw any conclusions , the separation between montelukast and placebo appears to be most prominent for these patients. For patients using concomitant cromolyn, use of montelukast along with cromolyn appeared to make it more likely for patients to need rescue oral corticosteroids (25.0% for montelukast, 0% for placebo). This group also had higher number of beta-agonists per day (1.05/day for montelukast, 0.77/day for placebo), higher

rates for asthma attacks (25.0% for montelukast, 11.1% for placebo), higher rates for unscheduled visits for asthma (18.8% for montelukast, 11.1% for placebo), but equal percent of days without beta-agonist use (55.26% for montelukast, 56.63% for placebo).

As noted above, the trend toward increased need for corticosteroid rescue in favor of placebo over montelukast was of enough concern that further data was requested of the applicant in an effort to evaluate whether the differences seen were real or related to a suspected randomization imbalance. Information was requested relating oral corticosteroid use for each subgroup prior to, up to, and during the study. Specifically, the Division requested information regarding the patients who required oral corticosteroid rescue during the study, to evaluate whether the use of oral corticosteroids was also higher prior to the study. This information was submitted in a response dated June 4, 2002, and is shown in Table 44 and Table 45. For the age group of 6 to 11 months, 11 of 51 patients in the montelukast group required rescue, whereas none of the 33 patients in the placebo group required rescue. Of these 11 patients, nine required oral corticosteroids within the previous year, and two had received a rescue shortly prior to randomization. These differences are highlighted in yellow in Table 44, and reflect the fact that there was a randomization disparity between the two groups below the age of 12 months.

From the data presented, it appears likely that the subgroup of patients who required oral corticosteroid rescue in the 6 to 11 month age group skewed the results in favor of placebo regarding oral corticosteroid use for that 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.

As is seen in Table 46, the group of patients 12 to 23 months of age who did not experience a randomization imbalance did have equal numbers of corticosteroid rescues. In this subgroup there were trends to fewer asthma attacks, fewer unscheduled visits for asthma, and less albuterol use. 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.

Table 39. Study P176, Days without beta-agonist use

Exploratory Efficacy Outcome	Montelukast			Placebo		
	n	Mean	± SD	n	Mean	± SD
Days without beta-agonist use	174	66.52%	± 33.13	81	59.53%	± 33.10
Females	58	69.45%	± 31.05	22	58.53%	± 31.62
Males	116	65.05%	± 34.16	59	59.91%	± 33.90
6 to 11 months	50	63.13%	± 32.64	33	57.29%	± 31.62
12 to 23 months	124	67.88%	± 33.36	48	61.07%	± 32.29
Concomitant: ICS	87	58.70%	± 33.91	41	54.93%	± 34.40
Concomitant: Cromolyn	16	55.26%	± 36.88	9	56.63%	± 32.62
Concomitant: None	71	78.64%	± 27.47	31	66.46%	± 31.29
Black	10	59.11%	± 35.07	5	64.40%	± 40.40
Hispanic	31	83.64%	± 27.13	17	74.35%	± 31.71
Other	33	75.31%	± 29.19	12	70.09%	± 24.00
White	100	59.05%	± 33.59	47	50.96%	± 32.99

Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

Table 40. Study P176, Beta-agonist treatments per day

Exploratory Efficacy Outcome	Montelukast			Placebo		
	n	Mean	± SD	n	Mean	± SD
Beta-agonist treatments per day	174	0.75	± 0.90	81	0.87	± 0.80
Females	58	0.68	± 0.91	22	0.93	± 0.70
Males	116	0.78	± 0.90	59	0.85	± 0.83
6 to 11 months	50	0.79	± 0.83	33	0.90	± 0.86
12 to 23 months	124	0.73	± 0.93	48	0.86	± 0.76
Concomitant: ICS	87	0.99	± 1.00	41	1.03	± 0.89
Concomitant: Cromolyn	16	1.05	± 1.14	9	0.77	± 0.57
Concomitant: None	71	0.38	± 0.54	31	0.70	± 0.70
Black	10	1.04	± 1.11	5	0.66	± 0.82
Hispanic	31	0.38	± 0.66	17	0.63	± 0.80
Other	33	0.55	± 0.76	12	0.63	± 0.51
White	100	0.90	± 0.95	47	1.05	± 0.83

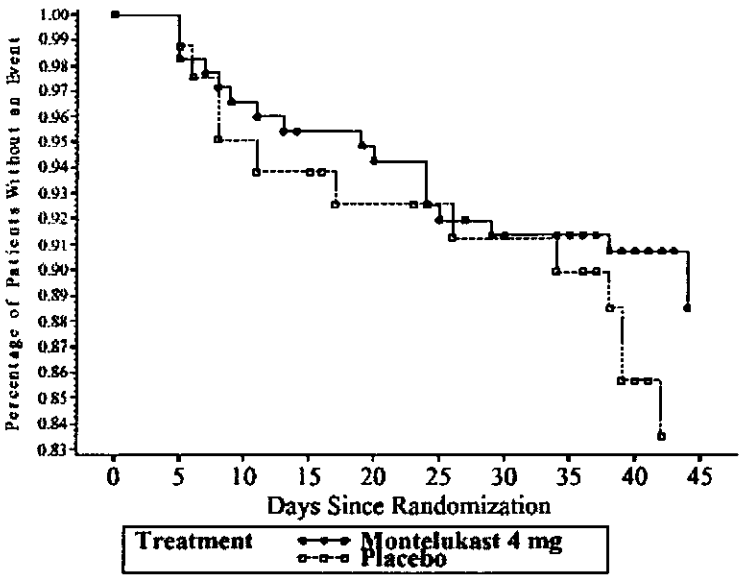
Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

Table 41. Study P176, Unscheduled visits for asthma

Exploratory Efficacy Outcome	Montelukast		Placebo	
	#/n	rate (%)	#/n	rate (%)
Unscheduled visits for asthma	17/174	9.77	12/81	14.81
Females	5/58	8.6	2/22	9.1
Males	12/116	10.3	10/59	16.9
6 to 11 months	6/50	12.0	4/33	12.1
12 to 23 months	11/124	8.9	8/48	16.7
Concomitant: ICS	10/87	11.5	5/41	12.2
Concomitant: Cromolyn	3/16	18.8	1/9	11.1
Concomitant: None	4/71	5.6	6/31	19.4
Black	2/10	20.0	1/5	20.0
Hispanic	2/31	6.5	3/17	17.6
Other	6/33	18.2	3/12	25.0
White	7/100	7.0	5/47	10.6

Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

Figure 11. Study P176, Kaplan-Meier Plot of Unscheduled Visits for Asthma



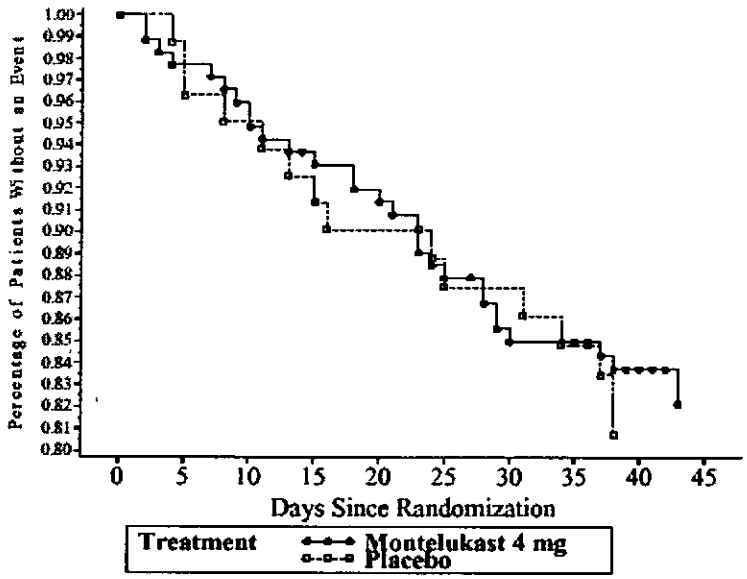
Source: Clinical, Reference P176, Category 4: Data, Appendix 4.9, page 867; p176.pdf

Table 42. Study P176, Asthma attacks

Exploratory Efficacy Outcome	Montelukast		Placebo	
	#/n	rate (%)	#/n	rate (%)
Asthma attacks	29/174	16.67	15/81	18.52
Females	11/58	19.0	4/22	18.2
Males	18/116	15.5	11/59	18.6
6 to 11 months	12/50	24.0	4/33	12.1
12 to 23 months	17/124	13.7	11/48	22.9
Concomitant: ICS	15/87	17.2	7/41	17.1
Concomitant: Cromolyn	4/16	25.0	1/9	11.1
Concomitant: None	10/71	14.1	7/31	22.6
Black	2/10	20.0	1/5	20.0
Hispanic	2/31	6.5	317	17.6
Other	7/33	21.2	3/12	25.0
White	18/100	18.0	8/47	17.0

Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

Figure 12. Study P176, Kaplan-Meier Plot of Asthma Attacks



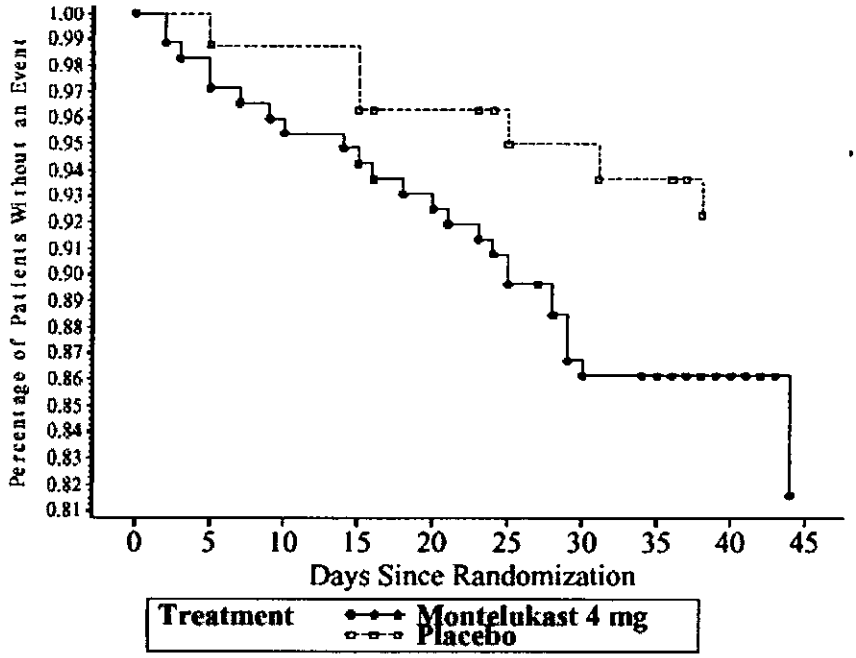
Source: Clinical, Reference P176, Category 4: Data, Appendix 4.9, page 869; p176.pdf

Table 43. Study P176, Oral corticosteroid rescues

Exploratory Efficacy Outcome	Montelukast		Placebo	
	#/n	rate (%)	#/n	rate (%)
Oral corticosteroid rescues	26/174	14.94	6/81	7.41
Females	10/58	17.2	3/22	13.6
Males	16/116	13.8	3/59	5.1
6 to 11 months	11/50	22.0	0/33	0.0
12 to 23 months	15/124	12.1	6/48	12.5
Concomitant: ICS	15/87	17.2	5/41	12.2
Concomitant: Cromolyn	4/16	25.0	0/9	0.0
Concomitant: None	7/71	9.9	1/31	3.2
Black	2/10	20.0	0/5	0.0
Hispanic	1/31	3.2	0/17	0.0
Other	5/33	15.2	0/12	0.0
White	18/100	18.0	6/47	12.8

Source: Clinical, Reference p176, pages 89-96 and Appendices 4.11-4.14, pages 883-910; p176.pdf

Figure 13. Study P176, Kaplan-Meier Plot of Oral Corticosteroid Rescues



Source: Clinical, Reference P176, Category 4: Data, Appendix 4.9, page 868; p176.pdf

Table 44. Study P176, Summary of need for oral corticosteroid (OCS) rescue during the active treatment period for ages 6 to 11 months

Age 6 to 11 months	OCS rescue during active treatment period		No OCS rescue during active treatment period	
	Montelukast	Placebo	Montelukast	Placebo
	n / m rate(%)	n / m rate(%)	n / m rate(%)	n / m rate(%)
Patients	11/51 21.6	0/33 0.0	40/51 78.4	33/33 100.0
Concomitant controller Rx	7/11 63.6	0/0 0.0	23/40 57.5	18/33 54.5
OCS rescues over the previous year	9/11 81.8	0/0 0.0	23/40 57.5	15/33 45.5
Number of OCS courses per patient	2 to 8	0	1 to 4	1 to 4
Mean	3.4	0	1.8	1.5
Median	2.0	0	2.0	1.0
Number of days on OCS per patient	4 to 40	0	3 to 42	3 to 20
Mean	16.5	0	10.2	7.5
Median	15.0	0	8.0	5.0
Recent OCS Rescue prior to randomization	5/11 45.5	0/0 0.0	5/40 12.5	2/33 6.1

Source: Response of 6/4/02, Table R2-1, page 3; response.pdf

Table 45. Study P176, Summary of need for oral corticosteroid (OCS) rescue during the active treatment period for ages 12 to 23 months

Age 12 to 23 months	OCS rescue during active treatment period		No OCS rescue during active treatment period	
	Montelukast	Placebo	Montelukast	Placebo
	n / m rate(%)	n / m rate(%)	n / m rate(%)	n / m rate(%)
Patients	15/124 12.1	6/48 12.5	109/124 87.9	42 /48 87.5
Concomitant controller Rx	12/15 80.0	5/6 83.3	61/109 56.0	27/42 64.2
OCS rescues over the previous year	11/15 73.3	6/6 100.0	56/109 51.4	29/42 69.0
Number of OCS courses per patient	1 to 15	1 to 5	1 to 12	1 to 5
Mean	3.4	3.2	2.9	2.6
Median	2.0	3.0	2.0	3
Number of days on OCS per patient	3 to 45	5 to 42	3 to 60	3 to 22
Mean	12.8	20.8	14.0	11.8
Median	10	17.5	10.0	12.0
Recent OCS Rescue prior to randomization	2/15 13.3	0/6 0.0	8/109 7.3	5/42 11.9

Source: Response of 6/4/02, Table R2-1, page 3; response.pdf

Table 46. Study P176, Summary of exploratory efficacy outcomes by age group

Exploratory Efficacy Outcome	Montelukast		Placebo	
	#/n	rate (%)	#/n	rate (%)
Oral corticosteroid rescues	26/174	14.94	6/81	7.41
6 to 11 months	11/50	22.0	0/33	0.0
12 to 23 months	15/124	12.1	6/48	12.5
Asthma attacks	29/174	16.67	15/81	18.52
6 to 11 months	12/50	24.0	4/33	12.1
12 to 23 months	17/124	13.7	11/48	22.9
Unscheduled visits for asthma	17/174	9.77	12/81	14.81
6 to 11 months	6/50	12.0	4/33	12.1
12 to 23 months	11/124	8.9	8/48	16.7
Beta-agonist treatments per day	0.75	± 0.90	0.87	± 0.80
6 to 11 months	0.79	± 0.83	0.90	± 0.86
12 to 23 months	0.73	± 0.93	0.86	± 0.76
Days without beta-agonist use	66.52%	± 33.13	59.53%	± 33.10
6 to 11 months	63.13%	± 32.64	57.29%	± 31.62
12 to 23 months	67.88%	± 33.36	61.07%	± 32.29

Note: Eosinophil counts are not presented in this table

6.3.2.2.4. Conclusions

Study P176 evaluated the safety and tolerability of montelukast when administered to patients age 6 to 23 months with a history of recurrent reversible airflow obstruction. The dosage of 4 mg for the entire age range was selected, as per the Written Request, in study P136C1. Just as for study P136C1, study design was based on the pediatric Written Request. All efficacy measures were exploratory endpoints, including 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. Steady-state levels of montelukast were not performed in this study.

In general, a multiple doses of montelukast oral granules for up to six weeks were 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. There were no significant differences in incidence of clinical adverse events, drug-related clinical adverse events, or adverse events of the ear, nose or throat area or respiratory tract. 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.

Eight patients (3.2%) had at least one non-serious laboratory adverse event (7 montelukast {4.1%}, 1 placebo {1.3%}), of whom four patients on montelukast had (a total of 15) events determined to be drug related. Several patients on montelukast experienced mild, transient changes in laboratory values, including elevations in serum transaminases (AST and/or AST), decreased white blood cell counts, or decreased platelet counts. Most of these laboratory adverse events, including the elevations in serum transaminases, occurred in patients with other clinical adverse events that may have been associated with those

laboratory events (one patient with +EB virus, and one patient with a urinary tract infection, and one patient with an upper respiratory infection).

In the laboratory shift tables, several trends were noted to cross the "predefined" threshold of change for several laboratory values. More patients in the montelukast-treated group experienced a 20% decrease in WBCs, and more patients in the placebo group experienced a 20% increase in WBC count. Both of these trends might suggest that montelukast tends to depress or prevent elevation of the WBC in a minimal fashion that does not seem to translate into any clinical concern. Alternatively, these trends may have resulted from the higher use of oral corticosteroids in the montelukast group (randomization inequality), although oral corticosteroids would be expected to increase rather than decrease the WBC count, so a corticosteroid effects is unlikely. Similar non-significant trends were noted for a decrease in Hematocrit and Platelet counts . A trend was noted in increased AST (delta of 2.3 percentage points) and increased ALT (delta of 0.5 percentage points) above the "predefined" threshold of change, but no trend was noted for total bilirubin.

The exploratory efficacy results from study population taken as a whole appeared to trend in different directions depending upon the endpoint. While the montelukast group had a higher number of days without beta agonist use, fewer beta agonist treatments per day, and fewer unscheduled visits for asthma, the oral corticosteroid rescue rate in the montelukast group was double the rate for the placebo group. Beta-agonist use and unscheduled visit results may all be explained by the higher use of oral corticosteroids in the montelukast group, since higher use of oral corticosteroids might have obviated the need for beta agonists.

Efficacy data for this study are made extremely difficult to interpret by the fact that there was a randomization imbalance between treatment groups below the age of 12 months. For the subgroup of patients age 6 to 11 months, 11 of 51 patients in the montelukast group required rescue, whereas none of the 33 patients in the placebo group required rescue. Of these 11 patients, nine required oral corticosteroids within the previous year, and two had received a rescue shortly prior to randomization. These differences are highlighted in yellow in Table 44. 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.

Nevertheless, differences in the subgroup of patients age 6 to 11 months who were receiving concomitant cromolyn are of some concern, since there was a marked disparity between the groups who received cromolyn in favor of the placebo group with regard to oral corticosteroid use. These differences may or may not be explained by the randomization imbalance that affected corticosteroid use. The 6 to 11 month group enrolled fewer patients on concomitant cromolyn in the montelukast than in the placebo group (montelukast 5.9%, placebo 12.1%), but it is not known if there was a prior association between cromolyn use and corticosteroid use in the 6 to 11 month group randomized to montelukast.

As is seen in Table 46, 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.

6.4. Efficacy Discussion and Conclusions

6.4.1. Conclusions 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 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 (Table 12), 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 (Table 13, Table 16).

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 (Table 17). 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.

There were no safety trends of concern in these single-dose adult studies.

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.

6.4.2. Discussion and Conclusions for Indication of Age — 23 Months

Two studies, P136C1 and P176, were submitted supporting the use of montelukast 4mg oral granules for pediatric patients 6 to 23 months of age.

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6.4.2.1. The diagnosis of asthma in young children

As noted in the introduction to this review, Merck's rationale for a oral granule formulation of montelukast with an indication —— is that asthma is a significant public health concern, including —— 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]. This section of the review will discuss the terminology, diagnosis, and phenotypes of asthma and wheezing disorders of infants and young children.

6.4.2.1.1. Terminology, diagnosis, natural history, and "phenotypes" of asthma

The terminology of asthma is complex and not precise, causing the use of multiple names. Indeed, the term is used in several different ways, either generally to describe reversible airway obstruction, of specifically, to describe the atopic asthma phenotype described

below. This section will attempt to provide a description of asthma, which will be used in the more specific sense.

The *Guidelines for the Diagnosis and Management of Asthma* published by the National Asthma Education and Prevention Program (NAEPP) state that asthma is a "chronic inflammatory disorder of the airways" [NAEPP, 1997 #42] [American Academy of Allergy, 1999 #43]. The hallmark of asthma is recurrent episodes of airway obstruction clinically characterized by "wheezing, chest tightness, and coughing" "associated with airway obstruction" [NAEPP, 1997 #42]. But there are a number of other diseases that may also present with wheezing, and even recurrent wheezing, that must be distinguished from asthma. Characteristically these diseases also present in the infant and toddler age group, the same time that many cases of asthma begin. These diseases include sinusitis, cystic fibrosis, anatomic abnormalities (including vascular rings, mediastinal masses and tracheoesophageal fistulas), foreign body aspiration, GERD, bronchopulmonary dysplasia, cardiac abnormalities, as well as several respiratory viral and bacterial infections (tuberculosis, pertussis, bronchiolitis, and croup) [Strunk, 2002 #8]. Because these diseases often present with asthma-like symptoms, many pediatricians have used the term 'reactive airway disease' prior to making a specific diagnosis. The term 'recurrent reversible bronchospasm' may also be used when a clinically positive response to a bronchodilator is noted. However, neither is synonymous with asthma, since other diagnoses have not been ruled out.

As noted above, the diagnosis of asthma depends on recurrent episodes of symptoms and variable reversible airflow obstruction. Critical to the diagnosis is a careful clinical history, eliciting the nature and duration of symptoms, exacerbating factors, and family history. Appropriate diagnostic tests vary depending upon the clinical history and presentation, but most often include the consideration of a chest x-ray, sweat chloride, and (in older children) allergy skin testing [Strunk, 2002 #8]. Although pulmonary functions may confirm a diagnosis in older individuals, it is difficult to perform pulmonary function studies on preschool children as part of a diagnostic evaluation, and therefore this is often overlooked by the clinician. As a consequence, asthma is difficult to diagnose definitively in the youngest children, and the criteria are often expressed operationally as recurrent episodes of wheezing. However, as discussed below, this is not sufficient for establishment of a firm diagnosis.

As part of the study protocol for study P176, evaluation of the enrollees did not include a diagnostic evaluation to rule out other causes of wheezing. If carried out previous to the study, the results of such a diagnostic evaluation were not sought or presented in the study report. This is a major drawback of study P176, as the diagnosis of asthma was never firmly established for the patients participating in the study. On the other hand, entry criteria limited entry to patients previously diagnosed with or a history of prematurity <28 weeks, mechanical ventilation, bronchopulmonary dysplasia, cystic fibrosis, gastroesophageal reflux, tracheoesophageal fistula, pertussis, congenital heart disease, or allergy to apple sauce. Therefore most of the confounding diseases presumably were previously ruled out prior to study entry.

In 1995, Martinez et al published a the longitudinal study of children 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. In addition, therapy with anti-inflammatory drugs did not significantly diminish the risk of developing the disease [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, 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].

This brings up a discussion about 'asthma phenotypes' or 'wheezing phenotypes'. [*Note: this discussion of asthma phenotypes paraphrases information found in the two cited articles published by Dr Martinez as well as information provided directly by Dr. Martinez by telephone. Readers are encouraged to read these articles to gain further information.*] Three major wheezing phenotypes have been described in younger children based on the longitudinal study from Tuscon [Martinez, 2002 #3]. These include 'transient wheezing of infancy' or 'transient early wheezing', 'non-atopic wheezing', and 'atopic wheezing/asthma'. In the broad sense, the term 'asthma' includes all of the phenotypes. However, in the narrow sense of the typical asthmatic at or after age six years of age, it will be noted that only the last phenotype fits this narrower description or definition of 'asthma'.

- Transient early wheezing typically peaks early in life and resolves by 3 years of age. Risk factors include prematurity, exposure to other children in day care, and history of maternal smoking during pregnancy. In this group there appears to be no increased family history of asthma. Children with this phenotype were found to have reduced $V_{max}FRC$ in infancy prior to wheezing episodes, and at age six years this group continued to have reduced $V_{max}FRC$ compared to other groups [Martinez, 1995 #4]. This suggests that the primary risk factor for this phenotype is reduced pulmonary function, which functionally becomes less significant as airway size increases with age. Other risk factors include prematurity and exposure to illness, particularly from day care. Risk factors also include a history of maternal smoking, either during pregnancy or postnatally, presumably predisposing the infants to smaller airway growth.
- The peak incidence of non-atopic wheezing is 3 to 6 years of age, but this form may also begin in infancy. These children develop airway obstruction when exposed to viral illnesses, particularly respiratory syncytial virus (RSV), during the first few years of life. When compared to children who have not had lower respiratory tract infections with RSV, children with a history of RSV infection before age 3 years have significantly lower FEV_1 (adjusted for length and gender). These children also respond more readily to bronchodilators. It is not clear if these findings are acquired secondary to the RSV infection, or predate the infection. [Martinez, 1995 #4] [Martinez, 2002 #3].
- The atopic wheezing / asthma phenotype includes the majority of older children who carry the diagnosis of persistent asthma, particularly at and above age 6. As a group, these children exhibit higher IgE levels than children who never wheezed. They are sensitized to allergens early in life, and have genetic factors that predispose them toward atopy. Environmental factors are also felt to play a role in tipping theTh1/Th2 balance

toward the asthma phenotype (the so-called hygiene hypothesis). More than half of this group starts to have episodes of wheezing before age 3, and 80% begin before age 6 [Martinez, 2002 #3]. Of concern in this group is that lung function declines over time, and while (in the CAMP study) use of inhaled glucocorticoids altered symptoms they did not influence the progression of decline in lung function [Zeiger, 1999 #45] [The Childhood Asthma Management Program Research Group, 2000 #46].

While some physicians call patients with any of these phenotypes asthmatic, the group traditionally called "asthma" is the third group of atopic wheezers. Of significance is that publications in older children and adults which discuss asthma are actually discussing this group. Although all exhibit airway obstruction and wheezing, the pathogenesis and pathophysiology of each group clearly differs. Hence, the potential response to specific controller mediations may differ as well. This topic is discussed in the next section.

In particular, for study P176, and assuming that all enrollees actually carried a diagnosis of asthma in the broader sense of the term, no effort was made to distinguish patients with different wheezing phenotypes. While this might be very hard to do, and might require long-term follow-up to clarify, this information might be critical to a compete evaluation of efficacy for montelukast in this age group. Efficacy was not evaluated except as exploratory measures in study P176, and will be discussed further in the sections that follow. Note that the approval for Pulmicort Respules was based on enrollment of all-comers with airway obstruction, presumably enrolling all three wheezing phenotypes as long as patients satisfied the enrollment criteria. A similar approach for entry criteria was taken for study P176. The difference is that Pulmicort enrolled over 1000 patients in three efficacy studies in children 6 months to 8 years of age.

6.4.2.1.2. Pathogenesis / Airway inflammation

Merck argues that there is a need for controller therapy — . an argument that this reviewer does not disagree with. Merck argues that since the pathogenesis of asthma (presumably they are discussing the atopic asthma phenotype) 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, 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 glucocorticoids, they argue that there is a place for an oral controller (montelukast) in the treatment armamentarium. However, it is not clear that this is the case.

The mechanism of action of controller medications such as leukotriene antagonists and glucocorticoids differ significantly. While it well-known that leukotrienes are potent bronchospastic agents, and it is accepted that wheezing is a hallmark of airway obstruction, it does not follow that all children who exhibit wheezing have elevated levels of leukotrienes as a cause of the airway obstruction. Therefore, treatment with a leukotriene receptor antagonist may or may not be appropriate.

Airway inflammation is the hallmark of asthma, both in children and in adults, and most experts agree that in general from a pathophysiologic point of view asthma is a similar disease in children and adults [Busse, 1995 #22] [Larsen, 1992 #33] [Lemanske, 2002 #14].

However, these publication are considering the atopic wheezer phenotype of persistent asthma discussed above. It is this phenotype that airway remodeling occurs, and it is in this phenotype that montelukast has demonstrated efficacy (in children, adolescents and adults six years of age and above). It is reasonable to accept that the pathophysiological mechanisms and therefore, treatment modalities would be similar in all age ranges for each phenotype. Therefore, based on efficacy data in older children and adults it is reasonable to accept that montelukast would be efficacious in the treatment of the atopic asthma phenotype in children of all ages. However, consideration must be given as to whether from a theoretical as well as practical level montelukast might be effective for the other wheezing phenotypes of transient early wheezing and non-atopic wheezing. If one were to accept the use of montelukast in the treatment of these conditions, this would broaden the diagnosis from the specific asthma phenotype to any form of reversible obstructive airway disease (all three wheezing phenotypes) in this age group.

Although the relationship between inflammatory infiltrates and airway remodeling is complex, is not fully understood, and will not be discussed here, eosinophils are felt to play a pivotal role in this inflammatory process by the release of cytokines and active recruitment of inflammatory mediators. Leukotrienes are released by inflammatory cells including eosinophils and mast cells. It has been shown that inflammatory cells including mast cells, eosinophils and lymphocytes are present in the airway of young patients with even mild asthma [Lemanske, 2002 #14]. Nevertheless, the levels of eosinophils in lavage fluid of non-atopic wheezers are not elevated, implying the pathophysiologic processes are different [Lemanske, 2002 #14].

On the other hand, infants with RSV bronchiolitis have been shown to have elevated levels of cysteinyl leukotrienes in their respiratory secretions [van Schaik, 1999 #50] [Welliver, 1999 #47] [Welliver, 2001 #10]. In addition, broncho-alveolar lavage (BAL) has revealed elevations of leukotriene B_4 and thromboxane A_2 in patients who have wheezing without asthma [Lemanske, 2002 #14]. Leukotriene levels in respiratory secretions have also been shown to be elevated with passive smoke exposure. Since there is a confluence of increased severity of RSV disease in infants exposed to second-hand smoke, some researchers have hypothesized that elevations of leukotrienes are responsible, and treatment with a leukotriene receptor antagonist might have theoretical benefit.

On the other hand, if recurrent or persistent wheezing is based primarily on anatomical differences that result in reduced pulmonary function, there is no reason to expect that montelukast (or any other controller medication, for that matter) would be of significant benefit for these patients.

Since each of the three wheezing phenotypes found in infants and younger children appears to be distinct, each must involve a different pathophysiologic process. While leukotriene levels may be elevated in the various phenotypes, it is not clear that leukotrienes play a similar or significant role in the pathogenesis of airway obstruction for each wheezing phenotype. This makes it far more difficult to extrapolate efficacy from older age ranges to younger age ranges, where the disease process may differ. At this point in time there simply is not enough known about the different phenotypes to make a statement either way as to whether montelukast would be beneficial to these patients.

6.4.2.2. Literature on use of montelukast in children under 2 years of age

A PubMed search revealed only one article by Ng et al regarding the use of montelukast in early childhood under the age of 2 years [Ng, 2000 #1]. This discussed the clinical experience with montelukast in three infants 5 to 20 months of age, including a 5 month old boy with adenovirus type 3 infection, a 20 month old boy with bronchopulmonary dysplasia, GERD, and both RSV and adenovirus type 3 infection, and a 20 month old girl with chronic lung problems after a severe episode of E. Coli pneumonia at age 1 month. All three had complex clinical courses and required high dose glucocorticoids. All were treated with "2.5 mg *nocte*" of montelukast. The report suggests that all experienced clinical improvement within one week of starting montelukast, and states that for at least two of the patients the improvement was dramatic. No adverse events attributable to the montelukast were described. CBC and liver functions were normal in follow-up of these patients while on montelukast.

This literature does not provide information sufficient to support the use of montelukast in this age range.

6.4.2.3. Study P136C1

Study P136C1used 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 study P136C1, 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 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, and therefore that the dosage in terms of AUC exposure would be the same. 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. There were no serious drug-related adverse experiences and no deaths. There were no trends in frequency of adverse events noted. 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. 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 may be true, implications of the higher individual C_{max} exposure have not been explored.

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 35-40% greater than that for adults, with a breakdown of 34% higher in 12 to 23 months and 48% higher in the 6 to 11 month olds (Data from Dr. Suarez. Merck's figures are lower at 18% and 35% respectively for the two age groups). 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, 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 is seen graphically in Figure 10.

Specifically, no trend in the relationship between $AUC_{0-\infty}$ 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 correlation of AUC to weight or age 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).

Review of the data from 2 to 5 year old pharmacokinetic study previously submitted for approval of Singulair 4 mg chewable tablets shows a relatively narrow variance in AUCs that are comparable to those seen in adults. This is not the case in either the 6 to 11 month old or the 12 to 23 month old age groups, but far more so in the youngest age range.

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. Pharmacokinetic evaluations at steady-state are recommended for future efficacy studies to further evaluate the relationship of clearance and exposure to efficacy.

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. This information must be placed into perspective from what is already known about the safety and efficacy of montelukast. 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. Doses of up to 50 mg to 300 mg were evaluated in adult multiple-dose studies before the dose of 10 mg was chosen. These doses produced exposures far higher those seen in the 6 to 11 month old population. 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. Merck argues that since there is a wide safety margin for montelukast in older individuals, these differences in C_{max}, T_{max}, and AUC are not significant either with regard to safety or to potential for efficacy of montelukast in this younger population. While it is likely that the margin of safety encompasses the variability of exposure seen in this study, one cannot assume that this same margin exists in successively younger age groups that may not be able to metabolize the drug as efficiently. In particular, this applies to the population below age 12 months where variability of exposure is highest and the diagnosis is less certain. Nevertheless, this study did support use of montelukast in 12 to 23 month age ranges by providing pharmacokinetic data regarding exposure after single doses. Whether the study supported use in patient 6 to 11 months of age will be discussed in the sections below.

6.4.2.4. Study P176

With the dose of 4 mg selected from study P136C1, study P176 evaluated the safety and tolerability of montelukast when administered to patients age 6 to 23 months with a history of recurrent wheezing. Just as for study P136C1, study design was based on the pediatric Written Request. This was not an efficacy study, although efficacy endpoints were evaluated on a exploratory basis.

6.4.2.4.1. Patient enrollment and demographics

As part of the study protocol for study P176, evaluation of the enrollees did not include a diagnostic evaluation to rule out other causes of wheezing discussed in the sections above). If carried out previous to the study, the results of such a diagnostic evaluation were not sought or presented in the study report. This is a major drawback of study P176, as the diagnosis of asthma was never firmly established for the patients participating in the study. On the other hand, entry criteria limited entry to patients previously diagnosed with or a history of prematurity <28 weeks, mechanical ventilation, bronchopulmonary dysplasia, cystic fibrosis, gastroesophageal reflux, tracheoesophageal fistula, pertussis, congenital heart disease, or allergy to apple sauce. Therefore most of the confounding diseases presumably were previously ruled out prior to study entry.

In this study, no effort was made to distinguish patients with different wheezing phenotypes. While this might be difficult to do, and require long-term follow-up, this information might be critical to a compete evaluation of efficacy for montelukast in this age group. The alternative approach would be to accept 'all-comers' with recurrent episodes of wheezing,

representing all three wheezing phenotypes. The approval for Pulmicort Respules was based on this type of enrollment and similar approach to entry criteria was taken for study P176. The difference is that Pulmicort enrolled over 1000 patients in three efficacy studies.

What is not clear from the demographic and family history information is the likelihood of these children progressing from recurrent airway obstruction to asthma later in childhood. There is at least one published article by Castro-Rodriguez et al suggesting a clinical index to define the risk of future development of persistent asthma in young children with recurrent wheezing [Castro-Rodriguez, 2000 #2]. Two indexes were proposed, a "stringent index for the prediction of asthma", and a "loose index for the prediction of asthma." Both indices use the same combination of meeting one of two major criteria or two of three minor criteria, as shown in Table 47. The difference in the indices is that the "stringent" index includes children defined as early frequent wheezers during the first three years of life , and the "loose" index includes early wheezers (not early frequent wheezers) during the first three years of life. The different indices provide different degrees of sensitivity, but both have a high degree of specificity and negative predictive value for identifying children who will have the atopic phenotype of asthma at school age.

Table 47. Criteria for clinical indices to define asthma risk

Major Criteria	Minor Criteria
Parental MD diagnosed asthma	MD diagnosed allergic rhinitis
MD diagnosed eczema	Wheezing apart from colds
	Eosinophilia ≥4%

Source: Table 1, [Castro-Rodriguez, 2000 #2]

Therefore, the Division requested Merck to provide information to complete a table regarding a clinical index for asthma in a format suggested by Castro-Rodriguez et al. These data are presented in Table 48. Because the request was post-hoc, and other data was not available, the information to complete the table was based on the baseline profile for each patient that had been provided by a parent. Therefore, the diagnoses could not be confirmed to have been physician diagnosed. In addition, a specific assessment of "wheezing apart from upper respiratory infections" was not performed during the study. Merck argues that most patients were categorized as having this criterion based on the entry criteria which included a history of a least 3 distinct episodes of asthma or asthma-like symptoms plus the use of beta agonists 2 or more times per week in the month prior to the study.

Merck states that in their retrospective analysis 74% of the patients met either the "stringent" or "loose" predictive criteria described by Castro-Rodriguez et al. This value was not broken down by treatment group, but as shown in Table 48, there was little difference between the two groups with regard to individual criteria within the predictive index. Based on this analysis, it appears that this safety study enrolled a high proportion of patients who might progress to a diagnosis of asthma at school age.

Table 48. Study P176, Clinical index for asthma risk (atopic phenotype) *

Family History	6 to 11 months				12 to 23 months				Total				Frequency of traits used by Castro-Rodriquez to develop indices
	Montelukast n = 51		Placebo n = 33		Montelukast n = 124		Placebo n = 48		Montelukast n = 175		Placebo n = 81		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Parent with MD Dx asthma	19	(37.2)	18	(54.5)	54	(43.5)	14	(29.1)	73	(41.7)	32	(39.5)	22.7%
MD Dx eczema	19	(37.2)	9	(27.2)	47	(37.9)	18	(37.5)	66	(37.7)	27	(33.3)	12.0%
MD Dx allergic rhinitis	21	(41.1)	8	(24.2)	44	(35.8)	25	(52.0)	65	(37.4)	33	(40.7)	16 9%
Wheeze apart from colds	50	(98.0)	33	(100.0)	123	(99.1)	48	(100.0)	173	(98.8)	81	(100.0)	14.9%
Eosinophilia ≥4 **%	9/48	(18.7)	6/33	(54.5)	8/123	(22.7)	8/47	(17 0)	37/171	(21.6)	14/80	(17.5)	10.3%

* Based on criteria described by Castro-Rodriguez, et al. [Castro-Rodriguez, 2000 #2]
** Presented as the number of patients with eosinophils = 4% at baseline / number of patients with pre-randomization eosinophil measurements

Sources: 6/4/02, Table R11-1, page 41; response.pdf

6.4.2.4.2. Safety endpoints

In general, a multiple doses of montelukast oral granules for up to six weeks were well tolerated, and there were no significant safety trends noted in this review. There were no serious drug-related adverse experiences and no deaths.

There were no significant differences in incidence of clinical adverse events, drug-related clinical adverse events, or adverse events of the ear, nose or throat area or respiratory tract. 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.

Eight patients (3.2%) had at least one non-serious laboratory adverse event (7 montelukast {4.1%}, 1 placebo {1.3%}), of whom four patients on montelukast had (a total of 15) events determined to be drug related. Several patients on montelukast experienced mild, transient changes in laboratory values, including elevations in serum transaminases (2 AST, 3 AST), decreased white blood cell counts (2 leukocytes, 1 lymphocytes, 1 neutrophils), or decreased platelet counts (2). Most of these laboratory adverse events, including the elevations in serum transaminases, occurred in patients with other clinical adverse events that may have been associated with those laboratory events (one patient with +EB virus, and one patient with a urinary tract infection, and one patient with an upper respiratory infection).

Of specific interest is that there was no higher incidence of diarrhea in the montelukast treatment group than in the placebo group. This concern was raised because the formulation includes about [redacted] mannitol in each packet of montelukast. 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. While there was a concern that this dose might cause diarrhea, or accentuate diarrhea in a susceptible infant, this was not found to be the case in this study.

In the laboratory shift tables, several trends were noted wherein several laboratory values crossed the "predefined" threshold of change in a particular value. More patients in the montelukast-treated group experienced a 20% decrease in WBCs, and more patients in the placebo group experienced a 20% increase in WBC count. Both of these trends suggest that montelukast tends to decrease or dampen elevations in the WBC in a minimal fashion that does not seem to translate into any clinical concern. Similar non-significant trends were noted for a decrease in Hematocrit and Platelet counts. A trend was noted in increased AST (delta of 2.3 percentage points) and increased ALT (delta of 0.5 percentage points) above the "predefined" threshold of change, but no trend was noted for total bilirubin.

Since there was a randomization imbalance in this study, the montelukast group received more rescues with oral corticosteroids both before and during the study. It is not clear whether the trends in the laboratory values noted above were related more to the higher use of oral corticosteroids or to the use of montelukast. While further data could have been requested to see if there were a relationship between the use of oral corticosteroids and the laboratory trends, this reviewer felt that there would be insufficient information gleaned from this endeavor to make any safety statements. In addition, oral corticosteroids would be

expected to increase the WBC counts rather than dampen them, so an association with oral corticosteroid use is unlikely. At any rate, such a breakdown of the safety data was not requested of the applicant. The trends should be evaluated in further efficacy studies.

Brief information ongoing study P232, an open extension to P176, was reviewed. The information provided is not in sufficient detail to add to the safety evaluation of study P176 itself, but no further instances of elevations in serum transaminases were reported..

For comparison, the clinical review of study P072 was examined. Study P072 was a six-week safety and tolerability study of the montelukast 4mg chewable tablet in children 2 to 5 years of age. In that study, "no patient on montelukast therapy had elevated ALT but 4 patients had mild (> 1 and ≤ 1.25 ULN) elevation in AST which resolved without intervention. Three patients on placebo had elevations in AST and/or ALT > 2 ULN. One patient had mononucleosis with secondary non-icteric hepatitis, while the other two patients had hepatitis A. These three patients were discontinued from the study because of the infectious nature of their illness." The reviewer concluded that montelukast therapy did not cause clinically significant derangement in serum transaminases or eosinophil counts in these patients.

6.4.2.4.3. Exploratory efficacy endpoints

All efficacy for this study was considered as exploratory endpoints, the main endpoint being safety. Efficacy measures included 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.

Of note is that in the previously submitted 2 to 5 year old safety and tolerability study with an almost identical study design, exploratory efficacy endpoints were all trending in favor of montelukast. For informational and comparative purposes, these trends are discussed in the next section, with the results shown in Table 49.

As a whole, the exploratory efficacy data from study P176 appeared to trend in different directions depending upon the endpoint. While the montelukast group had a higher number of days without beta agonist use, fewer beta agonist treatments per day, and fewer unscheduled visits for asthma, the oral corticosteroid rescue rate in the montelukast group was double the rate for the placebo group. Efficacy inferences by age or other subgroups were never declared, and are considered post-hoc analyses.

For the subgroup of patients 6 to 11 months, these results may be explained by the higher use of oral corticosteroids in the montelukast group, since higher use of oral corticosteroids might have obviated the need for beta agonists. This higher oral corticosteroid use in the montelukast group was directly related to a randomization imbalance between treatment groups in the groups below the age of 12 months. The randomization imbalance resulted from enrolling fewer patients with a history of oral corticosteroid rescues in the placebo than in the montelukast 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, and making analysis of clinical safety endpoints difficult.

As is seen in Table 46, the group of patients 12 to 23 months of age who did not experience a randomization imbalance did have equal numbers of corticosteroid rescues. In this group there were trends to fewer asthma attacks, fewer unscheduled visits for asthma, and less albuterol use. 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 (*Note: see the next section for a brief overview of the results from study P072*).

6.4.2.5. Secondary efficacy from study P072 in 2-5 year olds

For information and comparison purposes, this section presents a brief outline of efficacy outcomes from the 12-week safety study evaluating the use of Singulair 4 mg chewable tablets in 2 to 5 year old patients with asthma. Efficacy outcomes are shown in Table 49, and Kaplan-Meier plot of time to first oral corticosteroid rescue is shown in Figure 14. Efficacy supplement to NDA 20-830, SE1-008 (submitted May 6, 1999) for Montelukast Sodium (Singulair ® 4-mg chewable tablet) was for the indication of use in 2- to 5- year old children with asthma. Supplemental application 20-830, SE8-011 (submitted May 5, 2000) contained data from the completed chronic Asthma Study (study P072) in 2-5 year old children submitted in interim form to the original efficacy supplement. The reader should keep in mind that approval of the 4 mg chewable tablet formulation was based on safety from an interim study report for the first six weeks of the 12-week study, a population PK study showing pharmacokinetics in this age similar to that found in adults, and extrapolated efficacy from older children and adults.

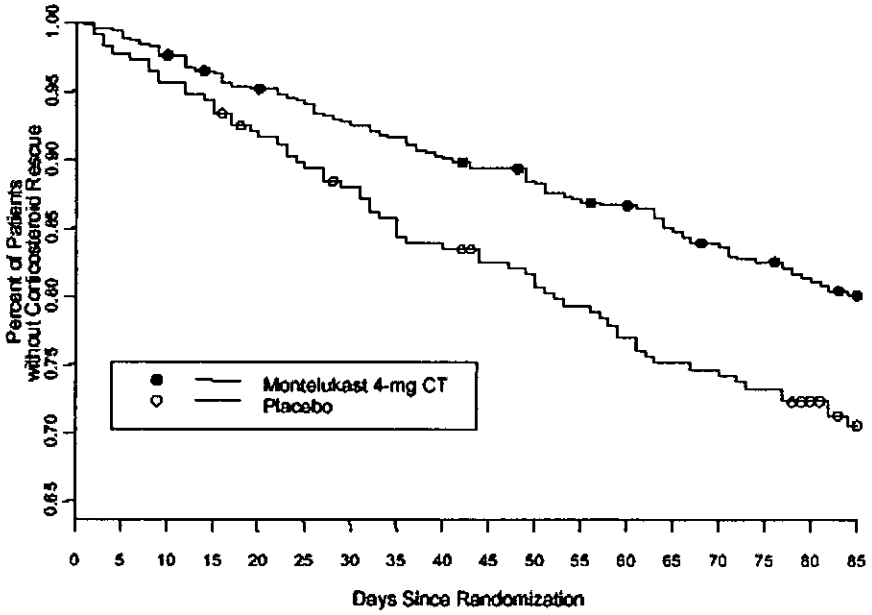
The design of this study was almost identical to the design for study P176 described above, as both were performed in response to the pediatric Written Request. All efficacy endpoints were secondary endpoints, and all were similar to those described above for study P176. The trend for time to oral corticosteroid rescue in study P072 was significantly in favor of montelukast over placebo (log rank test statistic=8 and p-value = 0.005). Other exploratory outcomes also followed trends in favor of montelukast. [NDA 20-830, SE8-011 {Submitted 3/25/00}, Clinical, Reference P072, Category 4: Data, Appendix 4.4.7, page 1037; p072.pdf]

Table 49. Study P072, Secondary efficacy outcomes

Efficacy Outcome	Montelukast	Placebo
	LS mean	LS mean
Days With Daytime Asthma Symptoms (%)	63.23%	68.80%
Daytime Asthma Symptom (Score)	-0.37	-0.25
Days With Beta-Agonist Use (%)	50.09%	56.63%
Corticosteroid Rescue (% of Patients)	19.09%	28.07%
Days Without Asthma (%)	30.50%	23.63%
Physician's Global (Score)	1.22	1.49
Average of Physician's and Caregiver's Global (Score)	1.17	1.40
Total Blood Eosinophil Counts (103/TL)	-0.09	-0.05
Overnight Asthma Symptom (Score)	-0.41	-0.30

Source: Clinical, Reference 56, P072 Study Report Synopsis, page 3; 0056.pdf

Figure 14. Study P072 (Ages 2-5 years), Kaplan-Meier Plot of Time to First Oral Corticosteroid Rescue



Source: NDA 20-830, SE8-011, {Submitted 3/25/00}, Clinical, Reference P072, Category 4: Data, Appendix 4.4.7, page 1037; p072.pdf]

6.4.2.6. Extrapolation of efficacy to younger age ranges

Extrapolation of efficacy to younger age ranges is based on the presumption that the disease process is the same in all age ranges, and the drug will exhibit the same pharmacodynamic effect in all age ranges. Under this model, a pharmacokinetic study showing similar exposure and a safety study showing safety are sufficient for extrapolation to a younger age range. 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 because the pathophysiology of asthma as a disease was accepted to be the same, the pharmacokinetics showed similar exposure, and safety data were supportive. In addition, efficacy trends in favor of montelukast were also supportive.

Based on the same assumptions, Merck is requesting extrapolation to younger children ages [redacted] 23 months, presuming that AUCs that are efficacious in older children and adults may be extrapolated to younger children. Accepting that the use of montelukast may be efficacious in the treatment of the atopic asthma phenotype in children of all ages, the question of the correct dose still arises. In adults there was no dose-ordering to efficacy, implying that the dosage of 10 mg is at the top of the dose curve. This would allow a range of doses around the AUCs achieved in adults to remain efficacious if the disease remains the same. Pharmacokinetic data were presented above, and support the use of montelukast in the 12 to 23 month old population, where variability is not unusually high, and AUCs are 18% (by Merck's figures) to 34% higher (by Dr. Suarez's figures) higher than that in adults. In the 6 to 11 month age range, variability is significantly higher, but probably still within the comparable ranges studied in adults.

The question of treatment of different wheezing phenotypes needs to be addressed. In successively younger age groups, wheezing phenotypes other than the atopic phenotype occur more frequently, and it may be impossible to separate children with different phenotypes at the time of diagnosis. Although Castro-Rodriguez has offered a clinical index to define the risk of asthma in young children with recurrent wheezing, the actual diagnosis often can only be made retrospectively. Therefore, with successively younger ages, it becomes harder to extrapolate efficacy from older populations. But at exactly what age it becomes impossible to extrapolate efficacy is a matter of debate, with no firm answer.

Because of confusion over this issue, the Division consulted Dr. Fernando Martinez of the University of Arizona, a leading expert in the field. He was consulted by teleconference regarding the more general issue of asthma phenotypes and the relationship to treatment, and no reference to this specific NDA was made. He stressed that the disease pathogenesis is different for different phenotypes, and that clinical trials should try to identify and separate efficacy by phenotype. In particular, he felt that this applied to age groups below age 2 years, where the transient wheezing phenotype predominates. Of significance, the enrollment criteria for study P176 allowed successful enrollment of patients who had a high likelihood of having the atopic phenotype. However, there is no retrospective or longitudinal evidence to confirm the diagnosis in these patients.

Accepting that an efficacious dose for atopic asthma phenotype may be extrapolated to all age groups with atopic asthma, one must question whether the same doses or exposure (AUC) given to older children and adults can be extrapolated to efficacy in the other wheezing phenotypes. However, as noted previously, it is likely that the dosage of montelukast is at the top of the dose curve. As long as leukotrienes play a role in the manifestation of symptoms, regardless of phenotype, it is not unreasonable to assume that a dosage effective for one phenotype will work in another. In other words, if leukotrienes play a role in pathogenesis of a particular phenotype, it may not matter whether the phenotype is atopic (for which efficacy is accepted) or another phenotype, and distinguishing between phenotypes may be a moot point.

By far the best scenario would be that the use of montelukast in children with a diagnosis of recurrent/persistent airway obstruction characterized by recurrent episodes of wheezing (cough, etc) would be supported by efficacy studies in this population rather than by extrapolation from use in asthmatics above six years of age. In addition, the use of montelukast in children without a clear diagnosis of asthma (other wheezing phenotypes) would also be supported by efficacy studies in this population where extrapolation from use in asthmatics above six years of age is more problematic.

In practice, however, separation of patients (or efficacy, for that matter) by phenotype extremely difficult to accomplish, and may not be a practical approach. A drug company may enroll 'all-comers' with recurrent wheezing who are candidates for controller therapy, and if efficacy is shown, it may or may not matter for approval which patients had which phenotype. The difficulty is in showing efficacy in this young age group where all efficacy is obtained through the intermediary of the parent, introducing subjective interpretation by the parent into the equation. For most such studies, the efficacy data is often not much better than the exploratory efficacy data in study P176.

Therefore, one is left with either accepting or rejecting the limited data available as supportive of extrapolation to age groups below two years of age. The next sections discuss the conclusions from the pharmacokinetic and safety studies, and how they support or do not support extrapolation to lower ages.

6.4.2.7. Conclusions (6 to 23 months)

6.4.2.7.1. Safety

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.

6.4.2.7.2. Efficacy

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 46).

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 46). 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.

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-Rodriguez) 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. 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.

6.4.2.7.3. Final conclusions

As a primary formulation for the prophylaxis and chronic treatment of pediatric "asthma" patients ages 12 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, but well within the exposures studied in adults. There is no relationship between exposure and either weight or age. Since efficacy for this age range has not been demonstrated, a clearly positive risk/benefit ratio has not been established.

Since stability testing was done in only four foods for a period of up to 30 minutes, information with regard to methodology for dosing should be clearly stated in the label. Merck suggests labeling that 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 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." For the 2 to 5 year old age group, use of montelukast immediately should not be an issue, but it may be an issue for younger age groups.

Please refer to the Conclusions and Recommendations section of this review for recommendation and labeling recommendations.

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7. INTEGRATED REVIEW OF SAFETY

7.1. Summary and Conclusions

Although several minor laboratory trends were noted, no significant safety signals were found in the safety review of the five studies provided in this NDA. There were no deaths. 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. In study P176, minor trends were noted in laboratory shift tables for WBC, Hematocrit, Platelet counts, and ALT. It was not determined whether these trends were related more to the higher use of oral corticosteroids due to the randomization imbalance than to the use of montelukast. 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). The evidence is insufficient to conclude that there is a safety concern from these findings.

Information provided from the open-label extension of the safety study as well as other studies in the Safety Update Report did not provide sufficient information to add much to the safety evaluation of study P176 itself.

7.2. Methods and Content

Adverse event tables presented in the 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. The following data were reviewed in the preparation of this overview of safety:

- Safety data from five pivotal clinical studies included in this submission through the cutoff date of May 31, 2001 [Summary, page 67; clinsum.pdf]. Data for each these studies were reviewed, with an evaluation of subgroups defined by gender, age, and ethnic origin.
- The Summary of Safety, included within the Worldwide Clinical Summary, which included worldwide post-marketing patient exposure data for montelukast through the cutoff date of May 31, 2001 [Summary, page 67; clinsum.pdf].
- MRL Report: Montelukast Sodium – 2-5 year old patients: Worldwide Pediatric Extension Report (PER), 22 June 2000 [Clinical, Reference 58; 0058.pdf].
- The Safety Update Report (SUR), submitted January 28, 2002, covering 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 Averse Experience Reporting System, the SUR included patients enrolled in studies P072-10, P219, and P232 described below.

7.3. Description of Patient Exposure

Of the five submitted studies, three were single-dose pharmacokinetic studies in adult subjects, yielding no new safety information. A total of 71 adults were exposed to single

doses of 2, 4 or 6 mg of montelukast in these studies. Two studies were in infants and toddlers ages 6 to 23 months with recurrent episodes of wheezing. One of these was a single-dose population pharmacokinetic dose-selection study, and one was a six-week safety and tolerability study. Thirty two patients were exposed to single doses of 4 mg in the dose selection study. In the six-week study, 175 patients age 6 to 23 months received montelukast and 81 received placebo. Of the total of 207 6 to 23 month old patients exposed to montelukast, a total of 33 were exposed for 1 day, 3 for 2 to20 days, 49 for 21 to 39 days, and 122 for 40 or more days. [Summary, page 87; summary.pdf]

In addition to the submitted studies, safety information was provided in a Safety Update Report for the following studies:

- P072-10, an open extension to P072-02, a multicenter, open-label, controlled extension to the 2 to 5 year old asthma study. This study enrolled 407 patients, 288 in the montelukast group and 119 in the usual care group.
- P219, a multicenter, double-blind, parallel group study comparing montelukast with placebo in SAR patients 2 to 14 years of age. This study enrolled 413 patients, 280 in the montelukast group and 133 in the placebo group. Of these, 145 patients were age 2 to 5 years (100 montelukast, 45 placebo).
- P232, an open extension to P176, a multicenter, open-label, controlled extension to the 6 to 23 month old study. As of November 29, 2001, this study enrolled 113 patients, 94 in the montelukast group and 19 in the usual care group.

7.4. Specific Findings of Safety Review

7.4.1. AEs, Laboratory AEs, SAEs, Deaths, and Withdrawals

Safety data for each study may be found within the review of each trial in the Integrated Summary of Efficacy Section of this review, and will not be repeated here. There were no deaths in any of the studies submitted. No safety signals were seen in any of the three single-dose adults pharmacokinetic studies or in the single-dose pharmacokinetic study in 6 to 23 month old patients with recurrent wheezing. The rest of this discussion therefore focuses on information from multidose studies.

In general, a multiple doses of montelukast oral granules for up to six weeks in 6 to 23 month olds were well tolerated in study P176 , and there were no clinical AE safety trends noted in this review. There were no significant differences in frequency of adverse events by age group, gender or ethnic origin. While there were more serious adverse events in the montelukast arm, there were no safety signals in the review of serious adverse events.

Table 50 shows adverse events from study P176 with an incidence of ≥3%. For comparison, the same table also contains information regarding AEs from adults studies as presented in the Singulair Product Label. There is a clear difference between the AEs in the 6 to 23 month age group and in adults, but these differences are expected based on age alone. In general, these AEs relate primarily to the gastrointestinal and respiratory tracts and to the skin. Except for the incidence of upper respiratory infections (montelukast 33%, placebo 22%) there are no clear differences between the montelukast and placebo groups.

Table 50. Adverse events for Study P176 with an incidence ≥3%, compared with PI with an incidence ≥1%, regardless of causality

	Study P176 ≥3%		Approved Package Insert ≥1%	
Adverse Event	Montelukast 4 mg/day n = 175 %	Placebo n = 81 %	Montelukast 10 mg/day n = 1955 %	Placebo n = 1180 %
Body As a Whole				
Asthenia / fatigue	0	1.2	1.8	1.2
Fever	13.1	13.6	1.5	0.9
Pain			2.9	2.5
Trauma (trauma + contusion in P176)	1.7	1.2	1.0	0.8
Digestive System				
Diarrhea	10.9	12.3		
Dyspepsia			2.1	1.1
Gastroenteritis, infectious	1.7	3.7	1.5	0.5
Pain, dental			1.7	1.0
Vomiting	8.6	11.1		
EENT				
Conjunctivitis	2.3	6.2		
Otitis	2.9	3.7		
Otitis media	8.6	6.2		
Pharyngitis	8.0	7.4		
Rhinitis	4.6	3.7		
Nervous System / Psychiatric	2.3	4.9		
Dizziness			1.9	1.4
Headache			18.4	18.1
Respiratory System				
Asthma	18.9	22.2		
Bronchitis	4.0	6.2		
Congestion, nasal	1.1	1.2	1.6	1.3
Cough	4.6	2.5	2.7	2.4
Influenza	0	3.7	4.2	3.9
URI	32.0	21.0		
Skin				
Rash	5.1	6.2	1.6	1.2
Other skin conditions	3.4	0.0		
Laboratory Adverse Events				
↑ ALT			2.1	2.0
↑ AST			1.6	1.2
Pyuria			1.0	0.9

Source: PI
Clinical, Reference p176, Table 22, page 69; p176.pdf
Summary, Table 15, page 91; summary.pdf

There were no episodes of seizures in patients 6 to 23 months of age in study P176, but there were two patients enrolled in the open-label extension studies who experienced an afebrile seizure, one each in study P232 and study P072-10.

- A 5 year old with a history of a seizure disorder and a 2-3 day history of a barky cough experienced an afebrile, generalized clonic seizure after being on montelukast for approximately one year. Concomitant medications included chlorpheniramine maleate, dextromethorphan hydrobromide, and pseudoephedrine HCl. In the ER, a CAT scan

was negative for any acute processes. EEG on follow-up was negative. There was a strong family history of seizures, including the mother with temporal lobe epilepsy, a paternal aunt and paternal great-grandparent with seizures. [2002-01-28, SUR, Reference 8, WAES for AEs in 6 month to 5 year old patients, 31 May 2001 through 30 Sep 2001, pages 7-9; 0008.pdf]

- This was a 2 year Hispanic male with a history of pre-term delivery and neonatal hypoxia requiring oxygen therapy, and asthma (AN2045). Three months after starting montelukast therapy, the patient experienced an afebrile seizure. The AE report states that the patient was hospitalized and a CAT scan and "ECG" were performed, both of which were reported as normal. *Comment: No information is provided regarding whether an EEG was performed. The reviewer surmises that an EEG was done rather than a ECG, but this was not confirmed.* [2002-01-28, SUR, Reference 7, WAES for SAEs in 6 month to 5 year old patients, 31 May 2001 through 30 Sep 2001, page 5; 0007.pdf]

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

In the laboratory shift tables, several trends were noted wherein several laboratory values crossed the "predefined" threshold of change in a particular value. More patients in the montelukast-treated group experienced a 20% decrease in WBCs, and more patients in the placebo group experienced a 20% increase in WBC. Both of these trends suggest that montelukast tends to decrease or dampen elevations in the WBC in a minimal fashion that does not seem to translate into any clinical concern. Similar non-significant trends were noted for a decrease in Hematocrit and Platelet counts. A trend was noted in increased AST (delta of 2.3 percentage points) and increased ALT (delta of 0.5 percentage points) above the "predefined" threshold of change, but no trend was noted for total bilirubin.

Since there was a randomization imbalance in this study, the montelukast group received more rescues with oral corticosteroids both before and during the study. It is not clear whether the trends in the laboratory values noted above were related more to the higher use of oral corticosteroids or to the use of montelukast. While further data could have been requested to see if there were a relationship between the use of oral corticosteroids and the laboratory trends, this reviewer felt that there would be insufficient information gleaned from this endeavor to make any safety statements. Therefore, such a breakdown of the safety data was not requested of the applicant. The trends should be evaluated in further efficacy studies.

For comparison, the Medical Officer reviews for study P072 were examined. Study P072 was a 12-week safety and tolerability study of the montelukast 4mg chewable tablet in children 2 to 5 years of age. In the original review of interim data through 6 weeks, no patient on montelukast had elevated ALT but 4 patients had mild (> 1 and ≤ 1.25 ULN)

elevation in AST which resolved without intervention. The reviewer concluded that montelukast therapy did not cause clinically significant derangements in serum transaminases in these patients. In the follow-up submission containing the full study report for study P072, three patients on montelukast had small transient increases in AST up to 50 U/L (normal 0 –42).

While the evidence is insufficient to conclude that there is a safety concern for elevations in transaminases, there is a trend apparent in both the 6 to 23 month old (clinically as well as in the shift tables) and the 2 to 5 year old age group for mild, transient elevations in AST levels. In individual patients, these elevations are often manifested at the time of a concurrent illness.

7.5. Adequacy of Safety Testing

Safety testing done for the five submitted studies was adequate.

7.6. Summary of Critical Safety Findings and Limitations of Data

No safety signals were found in the safety review of the studies. No new or significant safety information was generated that would need to be added to the labeling.

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.

Data from study P232, an open extension to P176, were in summary fashion only, since the study is not yet completed. Information provided in the Safety Update Report did not provide sufficient safety information to add much to the safety evaluation of study P176 itself.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

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, but approvable for the 23 month 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 for 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 of 24 hours. 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.

While two studies evaluated use of the oral granule formulation in infants and toddlers age 6 to 23 months, use of the oral granule formulation was not evaluated in children age 2 to 5 years. These issues are addressed in the Integrated Review of Efficacy.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

There is insufficient information to fully evaluate the effects of gender on safety or efficacy in this application. In study P176, the six-week safety and tolerability study in 6 to 23 month old infants, more patients in the montelukast group ages 6 to 11 months required oral corticosteroid rescue, with a higher in frequency in male patients than female patients. However, study P176 had a randomization imbalance, enrolling more infants ages 6 to 11 months into the montelukast group who had a history of need for corticosteroid rescue. Therefore, no statements may be made with regard to gender effects in 6 to 23 month olds except that there were no other safety trends related to gender noted.

9.2. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

There is insufficient information in this application to fully evaluate the effects of race or ethnicity on safety or efficacy.

Since studies for the oral granule formulation in the age range of 2 to 5 years were single-dose studies in adults, evidence with regard to the effects of age on safety or efficacy was not evaluated in the studies submitted for this age range. Efficacy was previously extrapolated from older ages for approval of the 4 mg chewable tablets in this age range. Safety was previously assessed as part of the evaluation of the 4 mg chewable tablet application. Except for formulation and stability in foods issues discussed above and in the Chemistry/Manufacturing and Controls section, it is reasonable to accept that an extrapolation of both efficacy and safety may be made for the 4 mg oral granules in the 2 to 5 year old age range.

Evaluation of evidence with regard to the effects of age on safety was part of the two studies submitted to support the new age range of . One was a single-dose population pharmacokinetic study, and one was a six-week safety and tolerability study. The single-dose population pharmacokinetic study in 6 to 23 month olds yielded little safety information, and no specific efficacy information, except that it clearly showed significant variability in AUCs that did not relate either to age or weight. In study P176, the six-week study, efficacy evaluations were secondary to safety and tolerability evaluations. Efficacy and Safety trends are discussed fully in the Integrated Review of Efficacy and Integrated Review of Safety sections of this review, and are not presented here.

Both of these studies were done in response to, and following the recommendations of a pediatric Written Request. That request did not specifically ask for an efficacy study, and an efficacy study was neither attempted nor submitted.

9.3. Evaluation of Pediatric Program

The application was submitted as part of Merck's pediatric program for montelukast. As noted above, the program was done in response to, and following the recommendations of a pediatric Written Request. That request did not specifically ask for an efficacy study, and an efficacy study was neither attempted nor submitted. Adequacy of this program is discussed fully in the Integrated Review of Efficacy and in the Conclusions and Recommendations sections of this review, and will not be discussed here. However, efficacy evaluations are considered essential for approval for the age range of 6 to 23 months.

9.4. Comments on Data Available or Needed in Other Populations

Not applicable.

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions

A full review of the conclusions of the integrated review of safety and efficacy will be found within the Integrated Review of Efficacy, and are not repeated here. A summary follows.

Merck did not submit stability data in various foods extending to beyond 30 minutes, or any stability data when mixed in formulas. Merck states that "after opening the packet, the full dose...must be administered immediately (within 15 minutes). If mixed with food, Singulair [redacted] must not be stored for future use. Singulair [redacted] are not intended to be dissolved in liquid for administration." It is recommended that this information be incorporated into the labeling.

10.1.2. Conclusions for age 2 to 5 years

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.

10.1.3. Conclusions for age 6 to 23 months

10.1.3.1. Safety

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.

10.1.3.2. Efficacy

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 51).

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 51). 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 51. 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-Rodriguez) 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 — 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 — 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 — 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. 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.

10.1.3.3. Conclusions

As a primary formulation for the prophylaxis and chronic treatment of pediatric "asthma" patients ages — 12 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 — but well within the exposures studied in adults. There is no relationship between exposure and either weight or age. Since efficacy for this age range has not been demonstrated, a clearly positive risk/benefit ratio has not been established.

10.2. Recommendations

10.2.4. 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.

[redacted]

10.2.6. Labeling Recommendations

10.2.6.1. 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. [redacted]
- 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 [redacted]
- ADVERSE REACTIONS: Extensively reworked to combine the 2 to 5 year old information with the 6 to 14 year old information into one section. [redacted]
- DOSAGE AND ADMINISTRATION: As an alternative formulation for pediatric patients 2 to 5 years of age, as a primary formulation : [redacted] information regarding mixing with food and need to administer the dose immediately.
- HOW SUPPLIED: Description of Singulair 4 mg oral granules.

10.2.6.2. 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 so high that neither safety nor efficacy may be assured. 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.

11. CITATIONS

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Welliver, R. C. and P. L. Ogra (2001). "RSV, IgE, and wheezing." J Pediatr **139**(6): 903-5.

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/s/

Peter Starke
7/26/02 12:50:18 PM
MEDICAL OFFICER

Badrul Chowdhury
7/26/02 12:53:55 PM
MEDICAL OFFICER
See my memorandum dated July 26, 2002

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	NDA 21-409	**PROPRIETARY NAME:**	Singulair™ ———
SPONSOR:	Merck Research Laboratories PO Box 2000, RY33-720 Rahway, NJ 07065	**USAN NAME:**	Montelukast sodium oral granules
CATEGORY:	Cysteinyl leukotriene receptor antagonist	**ROUTE:**	Oral
MEDICAL OFFICER:	Peter Starke, MD, FAAP	**REVIEW DATE:**	16 November 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
28 September 2001	1 October 2001	N-000	Pediatric and adult PK study reports Pediatric Exclusivity determination request

REVIEW SUMMARY:

This NDA is an efficacy supplement for *Singulair*™ ——— (Montelukast Sodium Oral Granules). Merck is submitting five clinical studies to support *Singulair* 4 mg ——— as an alternate formulation to the 4 mg chewable tablet in ages 2 to 5 years, and as a primary formulation for pediatric asthma patients ages ——— Efficacy for this population is to be extrapolated from older age groups.

Two studies provide pharmacokinetic, safety, and limited efficacy data using of the 4 mg oral granule formulation in patients ages >6 months to <2 years. 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.

On March 4, 1999, the Agency issued a Written Request (WR) for four clinical studies with montelukast in pediatric patients. There have been three amendments to the Written Request, dated April 18, 2000, September 28, 2000, and September 7, 2001. Four studies were requested as part of the Written Request, for pediatric information regarding 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. Therefore, with this application Merck is requesting a determination of Pediatric Exclusivity under Section 505A of the Food, Drug, and Cosmetic Act. Information regarding completion of the requirements for the WR is given in Item 20 of the application.

One CRF is missing, for one patient who discontinued due to an AE in Study P136C1. This information should be requested of the applicant. Since the application is primarily pharmacokinetic material, and not evidence of efficacy, and since Singulair is not a new molecular entity, a DSI audit is not needed for this NDA submission.

OUTSTANDING ISSUES:

One CRF is missing, for one patient who discontinued due to an AE in Study P136C1. This should be submitted. The rationale for giving an indication down to ——— will be a major area of consideration for this NDA.

RECOMMENDED REGULATORY ACTION

__X__ FILEABLE _____ NOT FILEABLE

I. General Information

This NDA is an efficacy supplement for Singulair™ ———(Montelukast Sodium Oral Granules). Merck is submitting five clinical studies to support Singulair 4 mg ——— as an alternate formulation to the 4 mg chewable tablet for ages 2 to 5 years, and as a primary formulation for pediatric asthma patients ages ———to <2 years. Efficacy for this population is to be extrapolated from older age groups.

Two studies provide pharmacokinetic, safety, and limited efficacy data using the 4 mg oral granule formulation in patients ages >———to <2 years. 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.

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II. Background and Rationale [Worldwide Clinical Summary]

As rationale for a ——— formulation of montelukast with an indication ———, Merck argues that asthma is a significant public health concern, including ———. 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 between 0-4 years of age. Airway inflammation is the hallmark of asthma, both is children and in adults, and most experts agree that asthma is a similar disease in children and adults (Busse, 1995). 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 has an episode of wheezing within the first 2 years of life (Martinez, 1995). Of these children, at age 6 years 41% had persistent wheezing and decreased lung function consistent with asthma. Of children hospitalized for wheezing in the first 2 years of life, approximately 50% are ultimately diagnosed with asthma (Wilson, 1997; Reijonen, 1998). 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; Strachan, 1996; Oswald, 1994). [Worldwide Clinical Summary, pages 56-7]

They argue that based on this evidence there is a need for controller therapy ——— 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.

III. Regulatory and Foreign Marketing History

A. Regulatory History

Table 1. List of related INDs and NDAs [Cover letter]

Product	IND	NDA	Approval Date
Singulair 10 mg film-coated tablets		20-829	February 20, 1998
Singulair 5 mg chewable tablets		20-830	February 20, 1998
Singulair 4 mg chewable tablets		20-830, S-008	March 3, 2000

B. 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, 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:

[redacted]

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

[redacted]

IV. Items Required for Filing and Reviewer Comments

A. Reviewer Comments

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 ———: 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.

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 include six patients, all from study P176, who were discontinued due to AEs. However, one CRF is missing, for one patient who discontinued due to an AE in Study P136C1.

B. Necessary Elements (21 CFR 314.50)

Table 2. Necessary Elements

Type	Status	Location (*paper*/electronic)
Application Form (FDA 356h):	Present	*Volume 1.1* Item 1, NDA TOC; 356h.pdf
Electronic Filing Requirements: Format: Table of Contents / Indexes:	 OK Present	 ndatoc.pdf

Type	Status	Location (paper/electronic)
Labeling:	Present in pdf format Word documents sent on separate diskette.	Item 2, Ten pdf files for history, proposed, current, approved, carton and container labeling
Investigator Debarment Certification:	Present	*Volume 1.1, Item 16* Item 16; debar.pdf
Financial Disclosure:	Present	*Volume 1.1, Item 19* Item 19; finandis.pdf
Statements of Good Clinical Practice:	Present on front page of each Study Report	Items 8 and 10, Clinical/Statistical/clinstat; 5 Study Report pdf files
Environmental Assessment:	Request for Exclusion Present	Item 4, Chemistry; environ.pdf
Proposed labeling changes:	Present in pdf format Word documents sent on separate diskette.	Item 2; multiple pdf files for proposed, carton and container labeling Two Word files
Integrated Summary of Effectiveness (subsets for age, gender, and race):	Part of Worldwide Clinical Summary	Item 8, Clinical/clinstat, Summaries; clinsum.pdf
Integrated Summary of Safety:	Part of Worldwide Clinical Summary	Item 8, Clinical/clinstat, Summaries; clinsum.pdf
Integrated Summary of Benefits and Risks:	Part of Worldwide Clinical Summary	Item 8, Clinical/clinstat, Summaries; clinsum.pdf
Statement that all clinical studies were conducted in accordance with IRB and Informed Consent procedures:	Present within each Study Report	Items 8 and 10, Clinical/Statistical/clinstat; 5 Study Report pdf files
Clinical/Statistical Analyses:	Worldwide Clinical Summary, 4 Uncontrolled and 1 Controlled Study Reports Clinical Study Report Errata (Study P090)	Items 8 and 10, Clinical/Statistical/clinstat; clinsum.pdf Items 8 and 10, Clinical/Statistical/clinstat; 5 Study Report pdf files errata.pdf
Pediatric Use Section:	N/A	N/A
Case Report Tabulations:	Present for all 5 studies	Item 11, Case Report Tabulations, Datasets; crt/datasets/datatoc.pdf
Case Report Forms (for patients who died or did not complete studies):	Present only for patients discontinued due to AEs, and only for 6 patients in P176, not for 1 patient in P136C1.	Item 12, Case Report Forms, crf/crftoc.pdf

Type	Status	Location (*paper*/electronic)
Patent Information:	Present	*Volume 1.1, Item 13* Item 13; PatInfo.pdf
Other:		
Written Request information:	Present	*Volume 1.1A, Item 20* Item 20; otherinfo.pdf
Field copy Certification:	Present	*Volume 1.1, Item 17* Item 17; otherinfo.pdf
User Fee Cover Sheet:	Present	*Volume 1.1, Item 18* Item 18; otherinfo.pdf

C. Decision

One CRF is missing, for one patient who discontinued due to an AE in Study P136C1. This information should be requested of the applicant. This application is fileable.

V. Clinical Studies

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 studies provide pharmacokinetic, safety, and limited efficacy data using the 4 mg oral granule formulation in patients ages 6 months to <2 years. Two of the adult studies also provide food-effect bioavailability data for the 4 mg ——— formulation.

Table 3. Summary of Studies

Study	Design	Treatment Groups	Duration	Dosage	Subjects n / Sex	Evaluations / Materials Submitted
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 ——— 4 mg ——— + 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	3 single doses	4 mg ——— 4 mg ——— + high-fat meal 4 mg chewable tab	20 M 11 F	PK: AUC_{0-} C_{max} T_{max} $t_{1/2}$ Safety
P127	Single-center, open-	Healthy, non-smoking	3 single	2 mg	10 M	PK:

Study	Design	Treatment Groups	Duration	Dosage	Subjects n / Sex	Evaluations / Materials Submitted
	label, randomized, 3-period crossover fasted single-dose, dose-proportionality PK study	men and women between 18-45 years 96 hours between treatments	doses with water	——— 4 mg ——— 6 mg ———	6 F	AUC_{0-} C_{max} T_{max} $t_{1/2}$ Safety
P136C1	Multi-center, open-label, randomized, single-dose PK study	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	1 single dose	4 mg ——— in applesauce	Total: 26 evaluable 14 M 18 F 6-11m: 14 12-23m: 18	Pop PK: AUC_{pop} C_{max} T_{max} $t_{1/2}$ C_{24hr} Cl/F Safety
P176	Multi-center, randomized, double-blind, placebo-controlled, parallel group safety and tolerability study	Boys and girls, ages ≥6 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	6 weeks	4 mg ——— Placebo mixed in applesauce QD hs	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
* Enrolled/Completed number of patients						

VI. DSI Review / Audit

Since the application is primarily pharmacokinetic material and not evidence of efficacy, and since Singulair is not a new molecular entity, a DSI audit is not needed for this NDA submission.

VII. Timeline for Review

Table 4. Timeline for Review

Milestone	Target Date for Completion
Stamp Date	October 1, 2002
Pediatric Exclusivity Determination	December 5, 2001
Studies P090, P127, P183	February 1, 2002
Studies P136C1, P176	March 1, 2002
Draft Review	May 1, 2002
Label Review	June 1, 2002
Wrap-up Meeting	July 1, 2002

Milestone	Target Date for Completion
Due Date	August 1, 2002

VIII. Comments to Applicant

1. One Case Report Form is missing, for one patient who discontinued due to an AE in Study P136C1. Please supply this Case Report Form.

IX. References

Busse W, Banks-Schlegel SP, Larsen GL. Childhood-versus adult-onset asthma. Am J Respir Crit Care Med 1995;151:1635-9.

Martinez FD, Wright AL, Taussig LM, et al. Asthma and wheezing in the first six years of life. N Engl J Med 1995;332(3):133-8.

Wilson NM, Doré CJ, Silverman M. Factors relating to the severity of symptoms at 5 yrs in children with severe wheeze in the first 2 yrs of life. Eur Respir J 1997;10:346-53.

Reijonen TM, Korppi M. One-year follow-up of young children hospitalized for wheezing: the influence of early anti-inflammatory therapy and risk factors for subsequent wheezing and asthma. Pediatr Pulmonol 1998;26:113-9.

Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994;309:90-3.

Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 1996;312:1195-9.

Oswald H, Phelan PD, Lanigan A, Hibbert M, Bowes G, Olinsky A. Outcome of childhood asthma in mid-adult life. BMJ 1994;309:95-6.

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/s/

Peter Starke
11/16/01 04:25:46 PM
MEDICAL OFFICER

Badrul Chowdhury
11/16/01 04:39:50 PM
MEDICAL OFFICER
I concur

APPEARS THIS WAY
ON ORIGINAL