PRIMARY EFFICACY VARIABLES

The primary efficacy analyses were performed on the following variables in order of descending priority. Interestingly, the concept of ordered importance for these variables was not addressed in the final protocol version, but seems to have been added later [11/19/98 1:29-31, 34, 9:45-51].

1. office visit spirometry, units and comparison point unspecified but $FEV_{1.0}$ was referenced as both percent predicted and as an absolute value in liters; the latter measure was used to define sample size, though the former would probably be more reasonable for children of very different ages and sizes; that the primary analysis was to be done at endpoint was also added after the final revision of the protocol; the timing of spirograms relative to treatment was unspecified but the spirograms were to be performed at least 6 hours after the last dose of albuterol [11/19/98 1:29-30, 56]
2. morning PEFR (expressed as percent change from baseline and in L/min) prior to beta-2 agonist use or trial medication administration
3. beta-2 agonist use (before exercise, for asthma symptoms or low PEFR, and total daily)
4. asthma-episode score consisted of one or more signs of asthma (wheezing, coughing, chest tightness, shortness of breath) occurring during the course of a 24-hour period, recorded at bedtime and rated on a 0-3 scale, as follows [11/19/98 1:31, 9:57]:

   0 = none

   1 = 1-3 mild coughing or wheezing spells

   2 = >3 spells, or spells that interfere with activity, play, school or sleep

   3 = spells > 3 hours or spells causing stay-at-home or seeing doctor
5. number of nights awakened with asthma defined as (7x(#nights awakened/#nights with data)) recorded each morning as a binary, "yes" or "no" response [11/19/98 1:34, 9:57]
6. evening PEFR (expressed as percent change from baseline and in L/min) prior to beta-2 agonist use, although how this measure was timed relative to beta-2 agonist use earlier in the day is not clear
7. peak flow variability (PFV) defined as ((PM PEFR - AM PEFR)/average daily PEFR) expressed as an unsigned percent; the baseline for this was the last 7 days of the run-in period [11/19/98 1:35]

SECONDARY EFFICACY VARIABLES

Analyses were performed on the following variables in the intent-to-treat sample:

1. school absenteeism for asthma was assessed as if school were in session each day [11/19/98 1:31, 36]
2. doctor or hospital contacts for asthma
3. treatment failures defined as the number of patients withdrawn from the trial because of asthma exacerbations [11/19/98 1:31, 36]

4. [redacted] Quality of Life (QOL) Questionnaire; 23 questions were divided into 3 domains and given to children of age ≥ 7 years [11/19/98 1:36-7]
5. health economics questionnaire which was apparently an ad hoc interview of patients and care givers [11/19/98 1:37]
6. Child Health Questionnaire - Parent Form (CHQ-PF50) was constructed to assess the physical and psychosocial well-being of children of age ≥ 5 years [11/19/98 1:37]

SAFETY VARIABLES

Adverse events (AE's), physical examinations, vital signs, electrocardiograms (EKG's) and Tanner staging were all recorded. The sampling times were presented under the 'Protocol' section of this review. The following clinical laboratory parameters were determined [11/19/98 1:42-6]:

1. Hematology: hemoglobin, hematocrit, total and differential white blood cell (WBC) count, and platelet count
2. Clinical Chemistry: creatinine, blood urea nitrogen (BUN); calcium; total protein; glucose; total bilirubin; alkaline phosphatase; lactate dehydrogenase (LDH); aspartate transaminase (AST); alanine transaminase (ALT); creatine kinase (CK); potassium; sodium; chloride; and, carbon dioxide
3. Coagulation: prothrombin time (PT) and partial thromboplastin time (PTT)
4. Urinalysis: color; appearance; specific gravity; ketones; pH; bilirubin; urine protein; urine glucose; and a microscopic examination of the sediment to determine the presence of WBC's, red blood cells (RBC's), bacteria, and casts

PHARMACOKINETIC PARAMETERS

A plasma sample was obtained for determination of the zafirlukast concentration at visits 1 or 2 and at visit 5. The dates and times blood samples were obtained and similar information about administration of the last dose of trial medication were all recorded [11/19/98 9:37].

DEMOGRAPHICS

A total of 413 pediatric patients with asthma from 41 research centers in the United States were randomized and entered the double-blind portion of this trial and 379 (91.8%) patients completed the trial. One patient (0025/4601) was dispensed trial treatment (zafirlukast 20 mg BID) and subsequently relocated to another area. This patient did not provide any efficacy data after receipt of trial treatment and was not included in any of the efficacy analyses, leaving 412 randomized patients who were evaluable for efficacy. Characteristics of the study participants are presented in the table below [11/19/98 1:47-8].

sNDA #20-547 9188IL/00139: BASELINE DEMOGRAPHIC PARAMETERS [11/19/98 1:48-9]				
Parameters/Characteristics	Placebo (n=105)	10 mg (n=104)	20 mg (n=105)	40 mg (n=99)
Age in years				
5 through 8; count (%)	45 (42.9)	40 (38.5)	52 (49.5)	49 (49.5)
> 8 through 12; count (%)	60 (57.1)	64 (61.5)	53 (50.5)	50 (50.5)
mean (SD)	8.7 (1.9)	8.8 (1.9)	8.4 (1.9)	8.4 (2.0)
range	5 - 11	5 - 11	5 - 11	5 - 11
Sex				
females; count (%)	47 (44.8)	35 (33.7)	43 (41.0)	39 (39.4)
males; count (%)	58 (55.2)	69 (66.3)	62 (59.0)	60 (60.6)
Weight in kilograms				
mean (SD)	33.5 (9.9)	35.7 (12.3)	32.9 (8.9)	34.2 (11.5)
range	17 - 65	17 - 68	17 - 56	16 - 68
Race; count (%)				
white	75 (71.4)	63 (60.6)	76 (72.4)	61 (61.6)
black	14)13.3)	22 (21.2)	14 (13.3)	21 (21.2)
hispanic	10 (9.5)	16 (15.4)	14 (13.3)	12 (12.1)
other	6 (5.7)	3 (2.9)	1 (1.0)	5 (5.1)
$FEV_{1.0}$ % predicted				
< 65%; count (%)	11 (10.5)	15 (14.4)	15 (14.3)	16 (16.2)
65% through 80%; count (%)	53 (50.5)	44 (42.3)	50 (47.6)	51 (51.5)
> 80%; count (%)	40 (38.1)	44 (42.3)	39 (37.1)	32 (32.3)
mean (SD)	76.0 (8.2)	75.8 (10.1)	75.6 (10.7)	74.3 (9.2)
range				
number of recorded values	104	103	104	99
Asthma Episode Scores				
mean (SD)	10.6 (2.5)	11.0 (2.6)	10.4 (2.3)	11.1 (2.8)
range				
number of recorded values	105	104	105	99

There do not appear to be any notable differences between treatment groups by the baseline categorizations indicated above. Trial 0139 has some minor baseline differences from study 079 such as enrollment of greater proportions of non-Caucasians and patients with $FEV_{1.0} < 65\%$ predicted.

EFFICACY

PRIMARY ENDPOINTS

A half dozen variables were all considered as 'primary' and each was analyzed several ways resulting in an unwieldy number of comparisons. No adjustments for multiple comparisons were made to the Type I Errors nor were exhaustive pairwise comparisons protected by significant 'F' statistics. Two measures were considered to be important endpoints by this reviewer. The first of these was the $FEV_{1.0}$ expressed as a percent predicted. The sponsor referred to this as the primary endpoint and it seemed the fairest way to summarize and compare children of vastly different ages and sizes. The second of these was the $FEV_{1.0}$, expressed in liters. This is one of the measures by which sample size was determined. Exactly which derivative of these measures was to serve (e.g., final visit value expressed as percent change from baseline) was never

prospectively defined. However, the most common analyses were exhaustive pairwise between-treatment comparisons of change from baseline.

$FEV_{1.0}$ (PERCENT PREDICTED)

The following table presents this parameter at baseline, as change from baseline to 'endpoint' (LVCF = last value carried forward for missing data), by treatment group and by pairwise difference of the change from baseline between each treatment and placebo groups adjusted for center effect [11/19/98 1:57, 2:13].

sNDA #20-547 9188IL/0139: ITT FEV1.0 (PERCENT PREDICTED) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT [11/19/98 1:57, 2:13]

Treatment	N	Baseline	Mean Change	LS Mean Diff.	p-Value
Placebo	102	76.20	4.63		
10 mg BID	100	76.08	6.52	1.87	0.254
20 mg BID	98	76.07	7.93	3.20	0.052
40 mg BID	94	74.19	7.69	2.04	0.221

FEV1.0 (percent predicted) was adjusted for size, age, sex and race of the patient. The LS Mean Difference of change from baseline from placebo was adjusted for center effects. 'Endpoint' employs the last value carried forward (LVCF). 'p-Value' applies to the LS Mean Difference.

This measure failed to achieve statistical significance from placebo even under analytic conditions that underestimate the true Type I Error. The placebo effect was prominent and no dose ordering was apparent. Though the primary comparison was between placebo and the 10 mg BID treatment, the 20 mg BID treatment produced the largest mean effect by both absolute change from baseline and change from baseline in excess of placebo. The per protocol analyses produced similar findings. The $FEV_{1.0}$ (percent predicted) data for each treatment group and at each visit are shown in the table below to provide a comparison of point estimates, data variability and changes over time [11/19/98 2:9-10].

sNDA #20-547 9188IL/0139: ITT FEV1.0 (PERCENT PREDICTED) DURING TRIAL, MEAN (SE) [11/19/98 2:9-10]

		40 mg BID	20 mg BID	10 mg BID	Placebo
Screen	n = 99, 103, 102, 104	71.65 (0.96)	74.73 (0.97)	72.83 (1.02)	73.54 (0.86)
End Run-In	n = 99, 104, 103, 104	74.32 (0.92)	75.62 (1.05)	75.75 (1.00)	75.99 (0.81)
End DB Week 3	n = 90, 95, 99, 99	79.71 (1.51)	82.41 (1.46)	82.44 (1.39)	79.65 (1.15)
End DB Week 6	n = 87, 79, 94, 85	82.20 (1.39)	83.85 (1.57)	81.94 (1.28)	81.48 (1.15)
Endpoint (LVCF)	n = 94, 98, 100, 102	81.88 (1.39)	84.00 (1.24)	82.60 (1.28)	80.83 (1.07)

LVCF = Last Value Carried Forward

This table differs from similar tables that pertain to this trial and to Trial #079 elsewhere in this review. The measure of data variability here is the Standard Error of the Mean (SE). The Standard Deviation (SD) of sample data has been the usual measure of data variability. These two measures are related by the following equation:

$$SD = SE \times \text{SQUARE ROOT}(N)$$

As an example, take the values for the 40 mg BID treatment at endpoint. It has an SE = 1.39 with a sample of 94 patients and yields an SD = 13.48. The end of the run-in period

is the last measure of baseline placebo treatment for all treatment groups. The table entry, End DB Week 3 & 6, refers to the double-blind treatment period and corresponds to the ends of weeks 5 and 8, or visits 4 and 5, on the flow chart [7/28/99 Telecon, 1:20]. The endpoint is the last treatment, as defined in the protocol, with the last value carried forward (LVCF). This measure shows improvement between screening and run-in periods and further improvement with treatment in all groups that are very similar in magnitude.

$FEV_{1.0}$ (LITERS)

The following table presents this parameter at baseline, as change from baseline to endpoint, by treatment group and by pairwise difference of the change from baseline between each treatment and placebo groups corrected for center effects [11/19/98 1:59, 306].

sNDA #20-547 9188IL/0139: ITT FEV1.0 (LITERS) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT [11/19/98 1:59, 306]

Treatment	N	Baseline	Mean Change	LS Mean Diff.	p-Value
Placebo	102	1.50	-0.09		
10 mg BID	100	1.50	0.14	0.05	0.138
20 mg BID	98	1.47	0.17	0.08	0.025
40 mg BID	94	1.43	0.16	0.07	0.067

The LS Mean Difference of change from baseline from placebo was adjusted for center effects. 'Endpoint' employs the last value carried forward. 'p-Value' applies to the LS Mean Difference.

By this analysis, a dose and variable that were not designated as the most important finally achieved a value below 0.05, with the usual caveat about this grossly underestimating the true Type I Error. Dose ordering of effect magnitude was not apparent. The per protocol analyses were similar to the intent-to-treat analyses, shown above. The $FEV_{1.0}$ (liters) data for each treatment group and at selected visits are shown in the table below [11/19/98 1:302-3].

sNDA #20-547 9188IL/0139: ITT FEV1.0 (LITERS) DURING TRIAL, MEAN (SD) [11/19/98 1:302-3]

		40 mg BID	20 mg BID	10 mg BID	Placebo
Screen	n = 99, 103, 102, 104	1.37 (0.38)	1.44 (0.37)	1.42 (0.38)	1.44 (0.42)
End Run-In	n = 99, 104, 103, 104	1.42 (0.41)	1.46 (0.37)	1.48 (0.39)	1.49 (0.42)
End DB Week 3	n = 90, 95, 99, 99	1.54 (0.44)	1.61 (0.47)	1.63 (0.43)	1.55 (0.42)
End DB Week 6	n = 87, 79, 94, 85	1.60 (0.49)	1.63 (0.48)	1.62 (0.43)	1.62 (0.41)
Endpoint (LVCF)	n = 94, 98, 100, 102	1.59 (0.49)	1.64 (0.45)	1.64 (0.45)	1.58 (0.42)

LVCF = Last Value Carried Forward

OTHER COPRIMARY ENDPOINTS

These included morning and evening PEFR, peak flow variability (PFV) mean asthma episode score, total nighttime awakenings and concomitant total daily beta-2 agonist use. The liberal definition of statistical significance was achieved for both morning and evening PEFR in the LS mean comparison of change from baseline between

the placebo and the 10 mg BID treatment. Other intent-to-treat analyses of these many variables and permutations of them were not 'significant' [11/19/98 1:61, 64].

The AM PEFR was performed before the morning dose of trial treatment was administered. Both AM and PM PEFR's were performed before the use of beta-2 agonists, though how 'before the use' is interpreted with respect to the evening PEFR is open to speculation. These were measured by _____ peak flow meters provided for each patient. Patients were instructed to record the best of three forced exhalations on their diary card on each occasion [11/19/98 1:30, 9:57].

The AM PEFR was the only flow measurement that had a known relation to preceding treatments (trough, performed before the morning dose of trial medication and use of the albuterol inhaler). Frequent (daily) recordings of it allowed for examination of treatment effects and the variability of them over time. For these reasons, values for every week of the treatment are presented in the table below. The placebo group baseline (run-in) was about midpoint among the means of the active treatment groups. Most of the improvement in all groups occurred by the first week, including the placebo group. The range of weekly means during treatment (DB Week-1-6) were as high as about 15 L/min (20 mg BID group). The 10 mg and 20 mg BID groups showed the most improvement over baseline at endpoint. About equal improvement over baseline was seen in the placebo and 40 mg BID treatment groups. Among active treatments, the change from baseline appeared to follow an inverse dose ordering. That is, the lowest dose was associated with the greatest improvement and the highest dose with the least.

sNDA #20-547 9188IL/0139: ITT DAILY AM PEFR (L/min) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:143-4]

		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 99, 105, 103, 105	225.96 (74.75)	241.61 (74.15)	242.17 (71.06)	235.43 (68.88)
DB Week 1	n = 96, 102, 98, 102	236.14 (70.98)	246.74 (71.86)	259.05 (74.33)	243.44 (71.66)
DB Week 2	n = 96, 99, 96, 98	237.98 (72.83)	251.40 (70.37)	258.12 (73.06)	245.50 (71.15)
DB Week 3	n = 96, 97, 99, 97	241.04 (73.57)	255.28 (73.03)	263.61 (71.44)	246.27 (75.84)
DB Week 4	n = 94, 94, 98, 97	238.46 (74.35)	253.99 (70.41)	262.15 (68.38)	245.27 (73.12)
DB Week 5	n = 93, 91, 97, 95	237.71 (74.98)	253.38 (67.57)	260.24 (64.85)	244.39 (71.85)
DB Week 6	n = 89, 85, 96, 91	234.42 (74.87)	261.75 (69.70)	266.05 (68.94)	246.93 (74.22)
Endpoint (LVCF)	n = 96, 96, 95, 101	233.30 (76.27)	257.40 (69.46)	265.00 (67.79)	243.03 (71.87)

LVCF = Last Value Carried Forward

The PM PEFR at selected weeks is shown in the table below. The PM PEFR weekly means were higher than the AM PEFR at all time points shown for all treatments including placebo. The placebo group baseline (run-in) value of PM PEFR was comparable to the baseline values of the three active treatment arms. As was true of the AM PEFR, change from run-in to endpoint among the active treatments was inversely dose ordered.

sNDA #20-547 9188IL/0139: ITT DAILY PM PEFR (L/min) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:175-6]					
		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 99, 105, 103, 105	240.43 (73.05)	253.44 (73.15)	256.02 (71.82)	251.03 (69.84)
DB Week 1	n = 96, 102, 98, 102	249.52 (74.06)	257.06 (70.59)	265.79 (72.36)	254.67 (68.97)
DB Week 4	n = 94, 94, 98, 97	249.18 (76.91)	263.80 (70.24)	270.39 (69.91)	258.54 (74.13)
Endpoint (LVCF)	n = 96, 97, 93, 99	245.81 (76.21)	264.94 (69.01)	270.00 (67.48)	251.37 (69.16)
LVCF = Last Value Carried Forward					

The rationale behind the following variable is not entirely clear. Comparable daily mean peak flow variability (PFV) was seen in all groups at baseline. PFV declined in all groups and the decline in the placebo group was about equal to that seen in the 40 mg BID treatment group.

sNDA #20-547 9188IL/0139: ITT DAILY PEFR VARIABILITY (%) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:295-6]					
		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 99, 105, 103, 105	13.68 (9.85)	13.33 (10.58)	13.53 (8.76)	13.85 (10.58)
DB Week 1	n = 96, 102, 97, 102	13.67 (11.97)	10.42 (8.85)	10.21 (7.14)	11.37 (8.53)
DB Week 4	n = 94, 94, 98, 95	11.50 (8.92)	9.95 (7.29)	10.83 (8.75)	11.34 (8.58)
Endpoint (LVCF)	n = 95, 95, 93, 99	11.33 (9.86)	9.39 (7.46)	10.60 (8.96)	11.91 (11.35)
LVCF = Last Value Carried Forward PEFR Variability = ((PM PEFR - AM PEFR)/average daily PEFR) expressed as an unsigned percent					

Patients rated the severity of asthma symptoms once daily at bedtime, over the preceding 24 hours, on a 0-3 scale by criteria presented previously. The table below shows daily means estimated from seven-day periods with the last value carried forward (LVCF). All groups showed a reduction of mean daily symptoms, form run-in to endpoint, as the study progressed. The placebo and 20 mg BID groups showed very comparable reductions. The 10 and 40 mg BID groups demonstrated comparable reductions in mean from run-in to endpoint. Recall that in order to enter the double-blind portion of the trial, each patient had to demonstrate a total asthma episode score ≥ 8 over the last seven consecutive days of the placebo run-in period. This translates into a daily score of ≥ 1.143 in order to qualify for the trial. By this criterion applied to treatment means at endpoint, every group except the 20 mg group would still qualify for study inclusion because of the continued severity of symptoms. Dose ordering was not demonstrated by this measure.

sNDA #20-547 9188IL/0139: ITT DAILY ASTHMA EPISODE SCORE ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:49-50]					
		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 99, 105, 104, 105	1.58 (0.40)	1.48 (0.33)	1.57 (0.38)	1.52 (0.35)
DB Week 1	n = 96, 102, 100, 102	1.27 (0.61)	1.25 (0.53)	1.28 (0.57)	1.36 (0.58)
DB Week 4	n = 93, 94, 99, 97	1.13 (0.62)	1.17 (0.68)	1.16 (0.61)	1.24 (0.60)
Endpoint (LVCF)	n = 97, 97, 95, 101	1.18 (0.67)	1.13 (0.64)	1.15 (0.59)	1.21 (0.63)
LVCF = Last Value Carried Forward					

Nighttime awakenings specifically because of asthma were recorded on arising each morning as a daily 'yes' or 'no' response. Therefore, the maximum score over one week was 7. Every group, including placebo, reported fewer nighttime awakenings as the study progressed. The placebo, 10 and 20 mg BID groups all showed a reduction from run-in to endpoint of approximately the same amount. The 40 mg BID group, with the largest mean number of total nighttime awakenings during run-in, showed the smallest reduction. This measure did not reflect dose ordering at endpoint or as a difference of means from run-in to endpoint.

sNDA #20-547 9188IL/0139: ITT TOTAL NIGHTS AWAKENED WITH ASTHMA PER WEEK ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:75-6]					
		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 95, 104, 102, 103	1.27 (1.86)	1.21 (1.65)	1.04 (1.63)	1.19 (1.64)
DB Week 1	n = 90, 99, 97, 98	1.03 (1.92)	0.83 (1.36)	0.80 (1.57)	0.99 (1.75)
DB Week 4	n = 87, 93, 94, 92	0.99 (1.72)	0.87 (1.60)	0.58 (1.44)	0.71 (1.39)
Endpoint (LVCF)	n = 90, 94, 91, 97	0.93 (1.71)	0.76 (1.55)	0.53 (1.22)	0.70 (1.56)
LVCF = Last Value Carried Forward Nights Awakened With Asthma = (7x(#nights awakened/#nights with data)); Maximum Score is '7.'					

The preceding data differ from prior efficacy measures in having larger variability. The standard deviation of nighttime awakenings was about twice as large as the mean. For other measures presented earlier, the standard deviation was usually 1/4 to 1/2 of the mean.

Beta agonist use was a difficult measure to interpret because some use was 'prescribed,' either before exercise or for low PEFR's. These 'prescribed' uses were not standardized between patients and clinicians nor were they retrospectively tracked to assure consistent adherence within each patient. This leaves the beta agonist use purely for rescue as an unknown quantity. With these caveats, the mean daily beta agonist use declined throughout the double-blind treatment period, for each treatment including placebo. The greatest reductions were in the active treatment arms, but were not dose ordered.

sNDA #20-547 9188IL/0139: ITT DAILY BETA-2 AGONIST USE IN PUFFS PER DAY ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [11/19/98 2:259-60]					
		40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In	n = 99, 105, 104, 104	3.13 (1.94)	2.89 (1.96)	3.15 (2.05)	2.93 (2.36)
DB Week 1	n = 96, 102, 99, 101	2.47 (2.04)	2.41 (1.98)	2.59 (2.12)	2.92 (3.12)
DB Week 4	n = 93, 94, 99, 95	2.35 (2.02)	2.41 (2.24)	2.45 (2.32)	2.45 (2.43)
Endpoint (LVCF)	n = 97, 96, 95, 99	2.29 (2.00)	2.22 (2.10)	2.40 (2.19)	2.59 (2.99)
LVCF = Last Value Carried Forward					

SECONDARY ENDPOINTS

These included school absenteeism because of asthma, doctor or hospital contacts for asthma, early withdrawals because of asthma (treatment failures),

[redacted]Quality of Life Questionnaire (QOL), the health economics questionnaire, the Child Health Questionnaire and post hoc responder analysis.

School absenteeism was either actual or was presumed given the following hypothetical condition: if school were in session, would the child have been absent because of asthma. This judgement was recorded daily at bedtime [11/19/98 9:37, 57]. Absenteeism is shown for all groups in the table below. The most absenteeism was reported in the placebo group and the next most, in the 10 mg BID arm. The 20 mg BID group was associated with the least absenteeism. Dose ordering was also not apparent by this measure.

sNDA #20-547 9188IL/0139: DAYS REPORTED ABSENT FROM SCHOOL BECAUSE OF ASTHMA [11/19/98 6:285]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Median	0.00	0.00	0.00	0.00
Mean	0.39	0.34	0.52	0.59
Standard Deviation	1.22	0.84	1.63	1.73

The table below shows healthcare contacts (physician or hospital) for asthma and most contacts were reported for the 10 and 40 mg BID treatment groups. The 20 mg BID group reported the lowest mean contacts. Dose ordering was also not found in this variable.

sNDA #20-547 9188IL/0139: PHYSICIAN OR HOSPITAL CONTACTS FOR ASTHMA [11/19/98 6:285]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Median	0.00	0.00	0.00	0.00
Mean	0.30	0.09	0.31	0.25
Standard Deviation	0.83	0.32	1.59	0.67

Total early withdrawals and premature withdrawals due specifically to asthma are shown in the table below. The greatest number and frequency of premature discontinuations for asthma were found in the placebo arm. The lowest number and frequency were in the 10 mg BID treatment group and no dose ordering was seen. Total withdrawals were greatest in the placebo and 20 mg BID groups and there was no dose ordering by this measure either.

sNDA #20-547 9188IL/0139: ITT WITHDRAWALS - TOTAL AND DUE TO ASTHMA, COUNT (%) [11/19/98 1:300]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Due to asthma	2 (2.0)	3 (2.9)	2 (1.9)	5 (4.8)
Total withdrawals	6 (6.1)	11 (10.5)	6 (5.8)	11 (10.5)
Number in treatment group	99	105	104	105

The [redacted] Quality Of Life Questionnaire was retrospectively limited to children seven years of age and older. The rationale was that this instrument was only validated for this age range, but the post hoc age restriction for any reason is suspicious. The overall scores are shown in the table below. Note that the minimum important difference (MID) for most of [redacted] other QOL instruments is 0.5.

sNDA #20-547 9188IL/0139: QUALITY OF LIFE QUESTIONNAIRE - OVERALL SCORE [11/19/98 6:333-4]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In				
Mean	4.75	4.90	4.63	4.85
Standard Deviation	1.162	1.018	1.077	1.132
Number	76	83	89	88
Endpoint				
Mean	5.57	5.63	5.30	5.37
Standard Deviation	1.014	1.060	1.133	1.157
Number	74	81	90	88
Difference: Run-In to Endpoint				
In means	0.82	0.73	0.67	0.52

All treatments showed a change in means from the placebo run-in period to endpoint that exceeded the MID, including the placebo group. However, the largest active-treatment-to-placebo difference between run-in-to-endpoint differences was well below the MID.

The health economics questionnaire appears to be a summary of absenteeism and healthcare contacts (hospitals and doctors), both of which have been individually-reviewed earlier and will not be presented again. The Child Health Questionnaire (CHQ-PF50) consisted of 14 'concepts' and 2 'summary' variables. These two summary variables, Physical Summary and Psychosocial Summary, are reproduced in the two tables below [11/19/98 1:37].

sNDA #20-547 9188IL/0139: CHILD HEALTH QUESTIONNAIRE (PARENT REPORT) - PHYSICAL SUMMARY [11/19/98 7:13]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In				
Mean	44.4	44.6	44.1	45.1
Standard Deviation	8.61	9.95	8.29	9.71
Number	85	97	93	98
Endpoint				
Mean	47.7	46.8	45.8	47.4
Standard Deviation	8.17	8.39	10.06	9.25
Number	95	99	101	95
Difference: Run-In to Endpoint				
In means	3.3	2.2	1.7	2.3

Most improvement in the Physical Summary index was seen in the 40 mg BID treatment group. The placebo arm showed greater improvement in run-in-to-endpoint difference of means than the other two active treatments.

sNDA #20-547 9188IL/0139: CHILD HEALTH QUESTIONNAIRE (PARENT REPORT) - PSYCHOSOCIAL SUMMARY [11/19/98 7:14]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Run-In				
Mean	49.4	49.7	48.1	48.8

sNDA #20-547 9188IL/0139: CHILD HEALTH QUESTIONNAIRE (PARENT REPORT) - PSYCHOSOCIAL SUMMARY [11/19/98 7:14]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Standard Deviation	10.76	8.11	9.43	9.58
Number	85	97	93	98
Endpoint				
Mean	50.2	51.5	49.9	49.8
Standard Deviation	9.89	7.88	8.98	11.00
Number	95	99	101	95
Difference: Run-In to Endpoint				
In means	0.8	1.8	1.8	1.0

By the Psychosocial Summary index, the 10 and 20 mg BID groups showed the most improvement from run-in to endpoint. The placebo and 40 mg BID groups showed the least. There was no dose ordering by either Physical or Psychosocial Summaries.

Though not technically a secondary endpoint, post hoc 'responder analysis' figured prominently in the approval of zafirlukast for adults under this NDA and was carried out in this pediatric trial as a post hoc additional analysis [11/19/98 1:38, 87]. A 'responder' was defined by a patient who met any of the following criteria [11/19/98 18:6]:

6. 50% decrease in number of nighttime awakenings without an increase in beta agonist use
7. 50% decrease in mean asthma symptom score without an increase in beta agonist use
8. 30% increase in morning PEFR without an increase in beta agonist use
9. 30% increase in evening PEFR without an increase in beta agonist use
10. 50% decrease in daily beta agonist use without an increase in asthma episode score

sNDA #20-547 9188IL/0139: ITT RESPONDER ANALYSIS AT ENDPOINT [11/19/98 6:295, 1:87**]				
	40 mg BID	20 mg BID	10 mg BID	Placebo
Number of responders/	50	55	53	45
% responders	51.5	56.7	55.2	44.6
Number in treatment group	97	97	96	101
**these two sources of the same information differ in the number of patients in the placebo treatment group (100 vs. 101)				

This measure did not show dose ordering. Neither the intent-to-treat nor the per protocol samples achieved statistical significance from placebo, though the interpretation of prospective inferential testing in post hoc analyses is undefined.

SAFETY

ADVERSE EVENTS (AE'S)

About 40% of randomized patients reported at least one AE and an average of 1.7 AE's were reported by each. That is, 167 patients reported one or more AE's and a total

of 279 AE reports were filed. The following table presents a breakdown of these data [11/19/98 1:93-5, 2:1].

sNDA #20-547 9188IL/0139: OUTCOME BY PATIENTS AND BY EVENTS [11/19/98 1:93-5, 3:1]								
	40 mg BID		20 mg BID		10 mg BID		Placebo	
	Events	Patients	Events	Patients	Events	Patients	Events	Patients
Patients at risk, n (% total = 413)		99 (24.0)		105 (25.4)		104 (25.2)		105 (25.4)
Patients with AE n (% group)		39 (39.4)		42 (40.0)		40 (38.5)		46 (43.8)
AE's n (% total = 279)	65 (23.3)		59 (21.1)		79 (28.3)		76 (27.2)	
Deaths	0	0	0	0	0	0	0	0
W/D, SAE's	0	0	0	0	0	0	0	0
W/D, non-serious AE's	2	2	3	3	3	3	6	6
W/D, other than AE		4		8		3		5
W/D = withdrawals	SAE's = Serious Adverse Events							

Review of AE's by COSTART term and arrayed by body system uncovered only seven that showed possible dose ordering, The frequencies of patients reporting an AE in the groups were either level or monotonically increasing as follows: placebo $\leq$ 10 mg BID $\leq$ 20 mg BID $\leq$ 40 mg BID. These were 'neck rigidity,' 'gastroenteritis,' 'myalgia,' 'bronchitis,' 'herpes simplex,' 'blepharitis,' and 'lacrimation disorder.' Five of these seven were reported by only one patient in the highest dose group. Two of these, 'gastroenteritis' and 'bronchitis,' were each reported by three patients, two in the 40 mg BID group and one in the 20 mg BID group [11/19/98 3:2-5].

DEATHS

None [11/19/98 1:99].

SERIOUS ADVERSE EVENTS (SAE'S)

None [11/19/98 1:104-5].

WITHDRAWALS BECAUSE OF ADVERSE EVENTS

Fourteen patients discontinued prematurely because of AE's: six were in the placebo group; three each were in the 10 and 20 mg BID groups; and, two were in the 40 mg BID group. Twelve of these early terminators were because of asthma exacerbations, COSTART coded as an 'aggravation reaction.' In one of the twelve, the exacerbation was associated with pharyngitis and an upper respiratory infection. One of the remaining two patients suffered from a rash over the trunk and withdrew. The last patient was withdrawn because of severe hyperactivity, without a preceding history, which was COSTART coded as 'hyperkinesis' [11/19/98 1:99-104].

CLINICAL LABORATORY

These will be completely reviewed as a part of the Integrated Safety Summary, but salient points will be mentioned here. Five hematology lab results were reported as AE's: leukopenia (WBC = $3.5x10^9$ on 20 mg BID); eosinophilia (20% on placebo); and, three reports of minimally abnormal findings. These were low hematocrit (31% on placebo), marginally elevated PT (13.4 on placebo) and PTT (45 on placebo). One chemistry lab result was reported as an AE. A single patient had two hyperglycemic blood samples during the double-blind portion of the trial (7.4 & 7.6 mmol/L on 20 mg BID). The normal range of blood glucose in these units of mmol/L was 3.331 to 6.106 mmol/L [11/19/98 1:105-113].

VITAL SIGNS

These will be evaluated in the Integrated Safety Summary. No consistent differences in systolic or diastolic blood pressure changes between baseline, week 3 or week 6 were noted for active treatments compared with placebo [11/19/98 1:113-5].

ELECTROCARDIOGRAMS (EKG'S)

These too will be evaluated in the Integrated Safety Summary. Mean values and shift tables for quantitative variables (PR interval, QRS interval and QTc interval, QT interval, RR interval) were generally similar among the three groups and among treatment visits during the trial. Changes from baseline for these were also generally similar among the three treatment groups [11/19/98 1:115-7, 3:94-108].

PHARMACOKINETICS

A range of blood collection times occurred because collection times were not controlled and no measure of efficacy was compared with plasma zafirlukast levels. After randomization, five placebo-treated patients had quantifiable plasma zafirlukast concentrations at the end of week 6. The highest of these was 158.7 ng/mL. Two more of these had measurable trough plasma levels. Trough was defined as 10-12 hours after administration of the last treatment, which, in this case, was supposedly a placebo. The following table shows the trough zafirlukast concentrations at the end of double-blind week 6, the time point for which most data were available [11/19/98 1:88, 3:116-7].

sNDA #20-547 9188IL/0139: TROUGH PLASMA CONCENTRATIONS (ng/mL) FOR ZAFIRLUKAST-TREATED PATIENTS [11/19/98 1:88, 3:116-7]

Treatment Groups	Number of Patients/Samples		Summary Statistics		
	Sampled	Quantifiable	Mean (SD)	Median	Range
Placebo	18	2	NC	NQ	
10 mg BID	20	18	18.92 (18.34)	14.63	
20 mg BID	20	18	50.59 (57.71)	39.07	
40 mg BID	7	7	251.49 (361.76)	140.34	

NQ = Not Quantifiable NC = Not Calculated

In the table above, if ≥ 50% of data were not quantifiable, then summary statistics were not calculated (NC). If < 50% were not quantifiable (NQ), then ____ng/mL, the limit of quantification (LOQ) was substituted for NQ patients. The mean was consistently higher than the median for each active treatment group indicating that the sample distribution was skewed to higher values, hence asymmetric. This was particularly true of the 40 mg BID group, where the standard deviation, as a symmetric measure of data variability, did not reflect these salient characteristics of the sample distribution. A surprisingly small number of patients contributed to these data (45 samples from close to 400 patients). This was not a prospectively defined sub-sample so the possibility of bias exists in those few patients who contributed to the sample. A graph of plasma concentration, plotted against time from last dose at the end of week 6, for each active treatment group showed data from all groups co-mingled over all time points (up to 24 hours). There was a trend to slightly lower plasma concentrations at later times for all groups. A box-and-whisker plot over two-hour intervals post-dosing indicated dose ordering by summary measures [11/19/98 1:154-5, 3:116-7].

9188IL/0075 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, SINGLE-DOSE, MULTI-CENTER TRIAL TO ASSESS THE ANTAGONISM OF ORAL ZAFIRLUKAST (ACCOLATE™) ON EXERCISE-INDUCED BRONCHOCONSTRICTION IN PEDIATRIC PATIENTS WITH EXERCISE-INDUCED ASTHMA

PRINCIPLE INVESTIGATOR	STUDY DATES
David S Pearlman M.D. Colorado Allergy & Asthma Clinic 1450 South Havana Street Aurora, CO 80012	First patient recruited: 29 August 1995 Last patient completed: 11 June 1996

SUMMARY

Thirty-six pediatric (6-14 years old) exercise-induced asthma patients who could be maintained on inhaled beta-2 agonist alone were the subjects of this randomized, multi-center, single-dose, double-blind, placebo-controlled trial. They were stratified by weight, randomized into two 'treatment groups' within each of which three single-dose crossover treatments were studied. The three treatments in treatment group I were placebo, 5 mg and 20 mg of zafirlukast. In treatment group II, the treatments were placebo, 10 mg and 40 mg of zafirlukast. Four hours after taking the blinded treatment on an empty stomach, an exercise challenge was performed and various efficacy and safety parameters and plasma zafirlukast concentrations were measured. Many inferential tests were carried out without the benefit of correction for multiple comparisons or 'protection' by an overall significant 'F' statistic, thus grossly underestimating true Type I Errors.

Zafirlukast provided partial relief from exercise induced falls in $FEV_{1.0}$ by three measures, maximum decline in $FEV_{1.0}$, $FEV_{1.0}$ AUC and $FEV_{1.0}$ recovery time to within 5% of baseline. Single zafirlukast doses associated with the most protective effect by different measures were 20 and 40 mg. The next most effective dose, by these same measures, was 5 mg, underscoring the absence of dose ordering. Efficacy analyses were also carried out over three weight classes, ignoring crossover treatment group membership. The 5 and 10 mg treatments were classified as "low dose" and 20 and 40 mg, as "high dose." No differences between high and low dose active treatments were found in any weight class by any measure. There was no consistent dose ordering within weight classes by maximum effect or by $FEV_{1.0}$ AUC. Mean plasma zafirlukast concentrations generally increased with increasing dose, however, no linear associations between plasma levels and maximum exercise effect on $FEV_{1.0}$, $FEV_{1.0}$ AUC or recovery time were found.

One case of gastroenteritis was reported one day after the patient received 40 mg of zafirlukast and was considered to be 'probably related' to treatment, by the clinical investigator.

OBJECTIVE

Determine the following in pediatric patients: 1)antagonism of exercise-induced bronchoconstriction by single oral doses (5 mg to 40 mg) of zafirlukast 4 hours after dosing; 2)time to recovery after exercise-induced bronchoconstriction; 3)estimates of plasma concentrations of zafirlukast obtained after single oral doses of zafirlukast; and, 4)the safety of single oral doses of zafirlukast during exercise challenges [12:9].

PROTOCOL

This was a randomized, multi-center, single-dose, double-blind, placebo-controlled trial in 2 parallel groups of pediatric patients with exercise-induced asthma. Before being assigned to a treatment group and a randomized treatment sequence, pediatric patients with exercise-induced asthma were stratified by weight into 1 of 3 weight ranges (25.0 kg through 32.0 kg, 32.1 kg through 45.0 kg, or 45.1 kg through 70.0 kg). Each group underwent a balanced 3-period crossover design with a separation of 4 to 14 days between trial periods [12:16].

During each treatment period, patients underwent exercise-challenge testing 4 hours after trial medication was administered, eight hours after the last albuterol usage and only if the $FEV_{1.0}$ was $\geq$ 70% of predicted. During each trial period, spirometry was measured before dosing, immediately before exercise challenge, immediately after exercise challenge, and at 5, 10, 15, and 30 minutes after exercise challenge. For each pulmonary function test, the highest $FEV_{1.0}$ of 3 expiratory maneuvers, with its corresponding FVC, was recorded on the appropriate case report forms (CRF's) [12:10, 24].

For the screening exercise challenge (visit 1), patients exercised on an electronically driven treadmill. Heart rate and ventilation were monitored throughout exercise. The treadmill gradient and speed were gradually increased until the patient's heart rate reached 80% of maximum (maximum heart rate = 220 beats per minute minus the patient's age in years). Exercise then continued for 6 to 8 minutes at between 80% and 90% of the maximum heart rate. Spirometry was measured immediately before and after exercise and at 5, 10, 15, and 30 minutes after exercise. Patients whose $FEV_{1.0}$ after exercise challenge decreased by at least 20% from the value obtained before exercise were eligible to continue participation in the randomized, double-blind portion of the trial [12:24-5].

Randomization occurred when a patient successfully completed all required screening assessments. The actual treatment given to individual patients was determined at each center. Patients were randomized to one of two treatment groups and one of six treatment sequences within a weight range. The randomization ensured that patients in each weight range were divided equally between two treatment groups and that each treatment sequence within a treatment group was represented. Within each weight range patient numbers were allocated sequentially. Each of the 3 clinical research centers was to enroll 4 patients per weight range. In treatment group I, patients were given single doses of placebo and two zafirlukast doses. The two active treatment doses (trial periods) were different for each treatment group. Within each treatment group, the three trial periods permuted to six treatment sequences. The three trial periods for each group were separated by a 4 to 14-day washout period [12:10, 16].

PATIENTS

The study was to enroll 36 children aged 6 to 14 years with exercise-induced asthma, evenly divided between two treatment groups within each of which three crossover treatments would be administered. During the screening period there was to be documentation of a history of exercise-induced asthma treated with only beta-2 agonists; demonstrated $FEV_{1.0}$ of at least 70% of predicted without medication (8 hours after beta-2 agonist); and, no requirement of long-term concomitant asthma medications other than beta-2 agonists administered as required (PRN). To be randomized required demonstrated exercise-induced bronchoconstriction (at screening visit 1) by achieving at least a 20% reduction in $FEV_{1.0}$ after exercise challenge when compared with the pre-exercise baseline. Key exclusion criteria were: 1)any clinically significant deviation from reference range laboratory results except for abnormalities related to asthma or allergy; and, 2)any history of illness or use of medication that might confound the results of the trial or place the patient at risk [12:10].

TREATMENT

Zafirlukast and matching placebo were supplied as tablets for oral use. During each of the three trial periods patients received a single oral dose (2 tablets) of either placebo or zafirlukast and underwent exercise-challenge testing approximately 4 hours after dosing. Trial medication was taken either 1 hour before or 2 hours after eating food. Additionally, patients did not have a major meal within 2 hours of exercise challenge. The date and time of dosing were recorded on the appropriate CRF [12:22].

The following trial medications were supplied (formulation number followed by the lot and batch numbers):

sNDA #20-547 9188IL/0075: TRIAL MEDICATIONS BY DOSE. FORMULATION, LOT AND BATCH [12: 21]			
Dose	Formulation	Lot	Batch
5 mg	[redacted]	T53036A	ST70124-012-FA01
10 mg	[redacted]	T53037A	ST70125-016-FA01

sNDA #20-547 9188IL/0075: TRIAL MEDICATIONS BY DOSE. FORMULATION, LOT AND BATCH [12: 21]			
Dose	Formulation	Lot	Batch
20 mg		T53038A, T53038B	ST70126-051-FA02
matching placebo		N53033A	ST70255-027-FA01

Treatment group I was given single oral doses of 5 mg and 20 mg of zafirlukast and matching placebo in a 3-period crossover design and treatment group II was given single oral doses of 10 mg and 40 mg of zafirlukast and matching placebo.

The use of prescription or nonprescription medications for allergy was standardized for each patient at screening and for the duration of the trial and was used only by agreement between the investigator and the sponsor. The use of these medications might subsequently decrease but not increase. Other prescription or nonprescription medication could be used only with prior agreement between the investigator and the sponsor. Astemizole, nedocromil sodium, theophylline, or beta-2 agonists (other than albuterol) could not be prescribed or continued during the trial. The use of inhaled or oral corticosteroids during the screening or double-blind periods necessitated withdrawal from the trial. Long-term treatment with cromolyn sodium was discontinued 4 weeks before screening. Desensitization was not to be initiated or discontinued during the trial; however, injections could continue at maintenance levels. Aspirin (and aspirin-containing products) and nonsteroidal anti-inflammatory drugs (NSAIDs) were not permitted during the trial. Acetaminophen was the sole nonprescription medication allowed for analgesia. [12:23]

PARAMETERS

Four co-primary pharmacodynamic efficacy endpoints were defined based on the response to the exercise challenge [12:17, 23-4]:

1. $FEV_{1.0}$, maximum percent fall from baseline
2. $FEV_{1.0}$ AUC, maximum percent change from baseline
3. time to achieve maximum effect
4. heart rate, maximum percent change from baseline

Five additional endpoints were considered to be secondary measures of pharmacodynamic efficacy [12:17, 24]:

1. recovery time, $FEV_{1.0}$ returns to within 5% of baseline
2. number of patients with maximum effect $< 20\%$ and $\geq 20\%$
3. percent of patients with maximum effect $< 20\%$ and $\geq 20\%$
4. number of patients with maximum effect $< 15\%$ and $\geq 15\%$
5. percent of patients with maximum effect $< 15\%$ and $\geq 15\%$

Safety variables included adverse events (AE's), clinical laboratory evaluations of blood and urine, 12-lead electrocardiograms (EKG's), physical examinations and vital

signs. AE's were solicited by investigators at each visit, described in the investigator's terms and coded with COSTART terms. Laboratories consisted of routine screening tests, obtained at each visit, of hematology, blood chemistry, coagulation and routine and microscopic urinalysis. EKG's were recorded before dosing and immediately following peak response to exercise challenge at each visit. Physical examinations were performed at screening, at check-in and discharge during each visit or upon early trial withdrawal. Blood pressure, heart rate and respiratory rate were recorded during each physical examination, 3 hours after trial medication administration, just before each exercise challenge test, immediately following the peak response and just before discharge [12:17, 27, 29].

Plasma concentrations of zafirlukast were obtained at the conclusion of the exercise challenge at visits 2, 3 and 4. [redacted] that utilized [redacted] was developed and validated by the sponsor for this analysis [12:17, 25].

DEMOGRAPHICS

Thirty-nine patients entered the trial from three U.S. research centers, 36 patients were randomized evenly to both treatment groups and completed the trial. The numbers of patients at entry included three more patients than those who actually completed the trial. These three extra patients were early withdrawals, two because of asthma and one because of pharyngitis. Two of these patients were in treatment group I and received zafirlukast 10 and 20 mg BID. The third, was in treatment group II and received placebo [12:33, 51-2]. Descriptive statistics of the patients who entered are shown in the table below. Parenthesized entries refer to patients who completed the trial, unless the left most column indicates that they represent standard deviations (SD's) [12:31-2].

sNDA #20-547 9188IL/0075: BASELINE DEMOGRAPHIC PARAMETERS OF 39 PATIENTS AT ENTRY (AT TRIAL COMPLETION) [12:32-3, 51-2]

Characteristic	Treatment Group I	Treatment Group II	All Entered
Number of patients at entry	20 (18)	19 (18)	39 (36)
Gender			
Male	10 (8)	7	17 (15)
Female	10	12 (11)	22 (21)
Age (years)			
6 through 8	3 (2)	3	6 (5)
9 through 12	8	12 (11)	20 (19)
12 through 14	9 (8)	4	13 (12)
Mean (SD)	11.1 (2.0)	10.3 (1.9)	10.7 (2.0)
Range	8 - 14	6 -14	6 - 14
Race (number)			
white	14 (12)	16 (15)	30 (27)
black	3	1	4
hispanic	3	1	4
other	0	1	1
Weight (kilograms)			
Mean (SD)	39.6 (9.5)	39.3 (11.0)	38.9 (10.1)

sNDA #20-547 9188IL/0075: BASELINE DEMOGRAPHIC PARAMETERS OF 39 PATIENTS AT ENTRY (AT TRIAL COMPLETION) [12:32-3, 51-2]			
Characteristic	Treatment Group I	Treatment Group II	All Entered
Range	24 - 55	23 - 59	23 - 59
Screening FEV1.0 (percent predicted)			
Mean (SD)	87.80 (11.04)	91.21 (11.89)	89.47 (11.44)
Range			
SD = Standard Deviation			

EFFICACY

Many inferential tests (140) were carried out without the benefit of correction for multiple comparisons or 'protection' by an overall significant 'F' statistic. Therefore, the probabilities shown grossly underestimate the true Type I Errors. For this reason, the misleading probabilities were omitted from this review [12:169-199, 201, 203, 205, 207]. The table below presents some of the efficacy endpoints by treatment group (patients given the same crossover treatments) and by treatment received. Shaded cells represent measures of most protection against exercise induced asthma.

sNDA #20-547 9188IL/0075: EFFICACY MEASURES BY TREATMENT GROUP, MEAN (SD) [12:37]						
Group	I	I	II	I	II	II
Treatment	PBO	5 mg	10 mg	20 mg	40 mg	PBO
Max. Effect (%)	-17.4 (11.9)	-8.9 (10.2)	-11.1 (12.2)	-8.7 (8.2)	-10.2 (11.0)	-16.3 (12.0)
AUC (% x min)	-268.1 (301.9)	-16.7 (201.8)	-39.3 (215.6)	-72.1 (179.7)	-8.5 (177.7)	-140.6 (220.1)
Time to effect (min)	7.8 (8.0)	4.3 (4.6)	8.9 (10.7)	6.6 (9.8)	5.5 (8.9)	2.1 (2.5)
HR (% change)	46.8 (27.4)	44.0 (36.1)	42.9 (40.4)	37.0 (34.0)	67.6 (128.0)	39.2 (28.6)
Recovery time (min)	14.6 (10.5)	5.1 (6.7)	6.2 (8.1)	7.2 (8.9)	4.8 (7.4)	11.4 (9.5)
SD = Standard Deviation						

The maximum effect was the largest exercise-related drop in the $FEV_{1.0}$, expressed in units of percent predicted. Placebo treatments in both treatment groups were associated with the largest mean declines of 16-17% predicted. Active treatments resulted in lesser mean declines or 9-11% predicted. There was no dose ordering over all treatments or within treatment groups I, but was seen in treatment group II. The $FEV_{1.0}$ AUC was determined by subtracting the baseline $FEV_{1.0}$ from successive determinations done at 0, 5, 10, 15 and 30 minutes after exercise and expressing the result as a negative area of percent predicted reduction from baseline multiplied by time. Placebo treatments were again associated with the largest mean negative area and dose ordering was again absent over all treatments and within treatment group I, but was found in treatment group II. The mean time to maximum effect (time to minimum $FEV_{1.0}$ after exercise) provided no useful summary information to separate active treatments from placebo. It is not readily apparent if a beneficial effect would be associated with a longer or shorter time to maximum fall in $FEV_{1.0}$. The mean heart rate changes were dose ordered in treatment group II, inversely dose ordered in treatment group I, and showed no dose ordering over all treatments. The mean time to recovery (time until $FEV_{1.0}$ returned to within 5% of

baseline) was longest in both placebo groups, showed dose ordering in treatment group II and none in treatment group I or over all treatments.

Zafirlukast provided partial relief from exercise induced falls in $FEV_{1.0}$ by three measures, maximum decline in $FEV_{1.0}$, $FEV_{1.0}$ AUC and $FEV_{1.0}$ recovery time. Doses associated with the most protective effect by these measures were 20 mg (Max. Effect) and 40 mg (AUC, Recovery Time) and are represented by shaded cells in the table above. The second most effective dose, by each of these same two measures, was 5 mg, underscoring the absence of dose ordering.

Efficacy analyses were also carried out by weight class (25-32 kg, 32.1-45 kg, 45.1-70 kg) over both treatment groups. The 5 and 10 mg treatments were classified as "low dose" and 20 and 40 mg, as "high dose." No difference between high and low dose active treatments were found in any weight class by any measure. There was no consistent dose ordering within weight classes by maximum effect or by $FEV_{1.0}$ AUC [12:43, 69-70].

SAFETY

ADVERSE EVENTS (AE'S)

Twenty-eight patients reported 49 AE's. About 57% of the AE's were reported during or after zafirlukast treatment and 43% were reported during or after placebo [12:47]. This was unexpectedly high for placebo treatment because the relative exposure times were 1/3 for placebo and 2/3 for zafirlukast. No liver function test abnormalities, decreased white blood cell counts, hemoglobin or hematocrit abnormalities or EKG abnormalities were reported as AE's. Moderate gastroenteritis lasting one day was reported by one patient one day after receiving 40 mg of zafirlukast and was considered to be 'probably related' to treatment [12:47, 49].

DEATHS

None [12:47].

SERIOUS ADVERSE EVENTS (SAE'S)

A 6-year old white male was prematurely withdrawn for an SAE. He was hospitalized for an asthma exacerbation 10 days after receiving 10 mg of zafirlukast. An upper respiratory infection developed one day after the exacerbation and he recovered [12:51].

WITHDRAWALS BECAUSE OF ADVERSE EVENTS

Three patients withdrew early and were replaced. One was an SAE (asthma exacerbation) and the other two were for the AE's, asthma exacerbation and pharyngitis.

These cases were also discussed earlier in this review under the heading, DEMOGRAPHICS [12:51-2].

CLINICAL LABORATORY

These will be reviewed in the Integrated Safety Summary, but salient items will be mentioned here. Two patients had high eosinophil percentages of 8-15% after zafirlukast and placebo. Five patients had low WBC counts and 4 had received zafirlukast. The lowest of these was $2.6x10^9$ after placebo. Three patients had increased ALT values, all after receiving zafirlukast. The highest of these was 32 U/L which had decreased from a baseline of 38 (normal < 26)). Two patients had increased AST values, all after receiving zafirlukast. The highest of these was 54 U/L (normal < 38). Urinalysis abnormalities were rare. There were three findings of high pH (by > 0.5 pH units) in three patients, one who received placebo. Two zafirlukast treated patients had "3-7 or more" RBC in the microscopic analysis [12:52-4, 226].

VITAL SIGNS

Vital signs will be reviewed in the Integrated Safety Summary. These included systolic blood pressure (BP), diastolic BP and respiratory rate were recorded at the time of physical examination, three hours after receiving medication, immediately before exercise challenge, at the time of peak effect, or peak response, and at discharge. Temperature, height and weight were recorded at the time of the physical examination. Nothing of interest was apparent when these data were presented as a variety of descriptive statistics arrayed by treatment group or by treatment [12:54, 228-48]. Parenthetically, the time of 'peak effect' or 'peak response' was never clarified as maximum exercise, peak decline in $FEV_{1.0}$ or something else entirely.

ELECTROCARDIOGRAMS (EKG'S)

These too will be reviewed in the Integrated Safety. Various intervals (PR, QRS, QT, QTc, RR) were at baseline and peak effect and were summarized by treatment group, by treatment and as shift tables. Nothing unique was discovered [12:54, 249-60].

PHARMACOKINETICS

Mean plasma zafirlukast concentrations generally increased with increasing dose and are represented in the table below. However, no linear associations between plasma levels and maximum exercise effect on $FEV_{1.0}$, $FEV_{1.0}$ AUC or recovery time were found [12:45, 211].

sNDA #20-547 9188IL/0075: PLASMA CONCENTRATIONS OF ZAFIRLUKAST (ng/mL) BY DOSE [12:211]					
	PBO	5 mg	10 mg	20 mg	40 mg
Media	NQ	32.1	56.9	104.0	271.6
Mean	NQ	37.3	67.3	103.6	271.6

sNDA #20-547 9188IL/0075: PLASMA CONCENTRATIONS OF ZAFIRLUKAST (ng/mL) BY DOSE [12:211]					
	PBO	5 mg	10 mg	20 mg	40 mg
Standard Deviation	NC	15.0	31.6	51.7	214.3
Range	NQ	18.2 - 80.7	20.3 - 150.0	40.7 - 259.0	76.3 - 799.0
Number	37	19	18	19	18
NQ = Not Quantifiable	NC = Not Calculated				

The rules for these calculations followed the same form as for the two pivotal trials. If ≥ 50% of the data were not quantifiable (NQ), then summary statistics were not calculated (NC). If < 50% of the data were NQ, then the lower limit of quantification was substituted for NQ patients. The 37 placebo patients suggest that these data summarized all patients enrolled who generated data, not just the 36 who contributed to the efficacy analysis.

INTEGRATED SAFETY SUMMARY (9/17/98 ISS) & 4-MONTH SAFETY UPDATE (1/12/99 SU1)

SUMMARY

As of the 1/12/99 submission of the 4-Month Safety Update, 811 subjects were exposed to zafirlukast in clinical trials. Of these 788 subjects were 5-11 years of age and these included 470 who were given zafirlukast for less then six months, 200 who were administered zafirlukast for more than six months but less than one year and 113 subjects who received the drug for at least one year. The mean age of all patients was 8.7 years, there was a slight male preponderance and two thirds of the patients were Caucasian. Patients had mild-to-moderate asthma and were evenly divided between baseline $FEV_{1.0}$'s 65-80% predicted and > 80% predicted. Only 12% of patients had baseline $FEV_{1.0}$'s < 65% predicted.

Adverse events more frequently reported by patients taking zafirlukast than placebo and considered to be drug-related by the clinical investigator were coded under the COSTART terms 'headache,' 'nausea,' 'gastroenteritis' and 'epistaxis.' Open-label extension trials, without placebo controls, reported 'headache' and a variety of respiratory adverse events most commonly. These respiratory adverse events included the COSTART terms 'aggravation reaction,' 'flu syndrome,' 'pharyngitis' and 'sinusitis.' Serious adverse events and withdrawals due to adverse events were mostly due to asthma exacerbations. There were no deaths.

Clinical laboratory findings were assessed by shift tables of values that were 'low,' 'normal' or 'high' before and at the end of treatment. Hematology laboratory findings showed no disproportionate shifts to higher or lower categories during treatment that were large or were not also found in patients who received placebo. Small shifts during treatment to lower categories were found for eosinophils and for the activated partial thromboplastin time. The significance of these are unknown but presumably unimportant. Small shifts to higher categorical values during treatment were found for AST and ALT but only two values greater than 100 U/L were recorded and one of these occurred two months after treatment had ceased. Four patients with elevated ALT's in open-label trials were judged to be drug-related. Shifts to higher categories were also found for alkaline phosphatase.

Zafirlukast in children 5-11 years of age seemed to have a safety profile that was relatively benign and similar to that found in the adult trial program. This observation must be considered in light of emerging spontaneous reports in adults of hepatic impairment, including death, and of eosinophilic vasculitis, including Churg-Strauss Syndrome.

EXPOSURE

This section contains information on total exposure to zafirlukast during completed controlled trials and during open-label extension (OLE) trials. To date, 811 subjects have been exposed to zafirlukast in clinical trials; 601 in completed controlled trials and 210 who received the drug for the first time in OLE trials. Twenty-three subjects who enrolled in these trials were 12-14 years of age and excluding them leaves 788 subjects of ages 5-11 years. Of these 470 were given zafirlukast for less then six months, 200 received zafirlukast for more than six months but less than one year and 113 subjects got the drug for at least one year. The duration of treatment for the remaining five patients is unknown because no 'end of treatment' date was provided [1/12/99 1:59]. The following table shows exposure of subjects in single and multiple dose, completed and controlled trials, with and without asthma, listed by daily dose received.

sNDA #20-547-7 ISS & 4-Month SU: EXPOSURE TO ZAFIRLUKAST IN COMPLETED, CONTROLLED TRIALS [1/12/99 1:60]

Trial Category	Single-Dose	Multiple-Dose		Grand
	Asthmatics	Asthmatics	Non-Asthmatics	Totals
Daily Dose: n (%)				
< 15 mg	2 (3.5)	99 (19.5)	0 (0.0)	101 (16.8)
20 - 30 mg	31 (54.4)	205 (40.4)	16 (44.4)	252 (41.9)
>30 - 60 mg	23 (40.4)	105 (20.7)	20 (55.6)	148 (24.6)
>60 mg	1 (1.8)	99 (19.5)	0 (0.0)	100 (16.6)
Total (% Grand Total)	57 (9.5)	508 (84.5)	36 (6.0)	601 (100.0)
Duration of Treatment (days)				
Mean	1.9	36.9	11.4	32.0
Median	2	42	15	33
Range	1 - 2	1 - 60	7 - 15	1 - 60

N.B. shaded cells represent modal categories (rows) in each column

Although 210 patients received zafirlukast for the first time in OLE trials, almost an equal number of patients (250) received the drug in preceding blinded clinical trials, 9188IL/0079 and 9188IL/0139 prior to entering the OLE. OLE trial participation was broken down as follows with each successive indented entry a subset of the iesser indented preceding entry.

OLE participation: 460
- Entered directly from screening: 118
- Previously participated in trial: 342
  - Received zafirlukast: 250
  - Received placebo: 92

The patients exposed to zafirlukast in OLE trials, irrespective of previous exposure, all were given either 10 mg (179 = 38.9%) or 20 mg (281 = 61.1%) BID during the OLE [1/12/99 1:61, 64].

DEMOGRAPHICS

Baseline characteristics of patients who received zafirlukast in completed, controlled clinical trials are displayed in the table below:

sNDA #20-547-7 ISS & 4-Month SU: DEMOGRAPHICS OF SUBJECTS GIVEN ZAFIRLUKAST IN COMPLETED, CONTROLLED TRIALS [1/12/99 1:52, 55]

Characteristics	Single-Dose	Multiple-Dose		Grand
	Asthmatics	Asthmatics	Totals	Totals
Number (% Grand Total)	57 (9.5)	508 (84.5)	36 (6.0)	601 (100.0)
Age (years)				
Mean	10.0	8.5	8.8	8.7
Median	10	9	9	9
Range	6 - 14	5 - 12	6 - 11	5 - 14
Age Category: n (%)				
≤ 8 years	16 (28.1)	236 (46.5)	14 (38.9)	266 (44.3)
> 8 years	41 (71.9)	272 (53.5)	22 (61.1)	335 (55.7)
Gender: n (%)				
Females	26 (45.6)	205 (40.4)	21 (58.3)	252 (41.9)
Males	31 (54.4)	303 (59.6)	15 (41.7)	349 (58.1)
Race: n (%)				
White	30 (52.5)	353 (69.5)	21 (58.3)	404 (67.2)
Black	22 (38.6)	84 (16.5)	1 (2.8)	107 (17.8)
Other	5 (8.8)	71 (14.0)	14 (38.9)	90 (15.0)
Baseline FEV1.0 % predicted				
Mean	85.7	76.3	Not Collected	77.3
Range			Not Collected	
Baseline FEV1.0 Category: n (%)				
< 65%	1 (1.8)	67 (13.2)	Not Collected	68 (11.3)
65% - 80%	20 (35.1)	237 (46.7)	Not Collected	257 (42.8)
> 80%	36 (63.2)	199 (39.2)	Not Collected	235 (39.1)
Not Collected	0 (0.0)	5 (1.0)	36 (100.0)	41 (6.8)

N.B. shaded cells represent modal characteristic in each column

There was a slight preponderance of subjects greater than 8 years of age, of males, of Caucasians and of subjects with baseline $FEV_{1.0} \leq 80\%$ predicted in those who received the active drug. The distribution of these same demographic characteristics was very similar in the 260 patients who received placebo in the completed, controlled clinical trials and in the patients who participated in the OLE [1/12/99 1:53-4, 56, 58].

ADVERSE EVENTS (AE'S)

COMPLETED CONTROLLED TRIALS

There were 601 patients treated with zafirlukast in completed, controlled, clinical trials. A total of 229 (38.1%) of these reported at least one AE. Of the 259 placebo-treated patients in these same trials, 100 (38.6%) reported one or more AE's. COSTART designations for AE's with a report frequency ≥ 0.5% from the zafirlukast-exposed patients and that were more frequently reported for zafirlukast than for placebo are shown in the table below [1/12/99 1:75-7]. The table is confusing because the entries are the numbers of AE reports, not numbers of patients reporting them, and the parenthesized

percentages represent the number of reports for a given COSTART term divided (normalized) by the number of patients at risk (in each treatment group or column).

sNDA #20-547-7 ISS & 4-Month SU: AE's IN COMPLETED CONTROLLED TRIALS WITH A REPORT FREQUENCY ≥ 0.5% IN THE ZAFIRLUKAST GROUP AND MORE FREQUENTLY REPORTED BY PATIENTS ON ZAFIRLUKAST THAN ON PLACEBO [1/12/99 1:75-7]		
Body System & Adverse Event	**Zafirlukast (n = 601 patients)**	**Placebo (n = 259 patients)**
ANY AE	229 (38.1)	100 (38.6)
WHOLE BODY		
Headache	27 (4.5)	11 (4.2)
Abdominal Pain	17 (2.8)	6 (2.3)
Fever	10 (1.7)	2 (0.8)
Pain	7 (1.2)	2 (0.8)
Viral Infection	4 (0.7)	1 (0.4)
DIGESTIVE		
Nausea	10 (1.7)	2 (0.8)
Gastroenteritis	5 (0.8)	0 (0.0)
HEMIC & LYMPHATIC		
Lymphadenopathy	3 (0.5)	1 (0.4)
RESPIRATORY		
Epistaxis	10 (1.7)	1 (0.4)
Bronchitis	5 (0.8)	1 (0.4)
SKIN & APPENDAGES		
Rash	10 (1.7)	3 (1.2)
Urticaria	4 (0.7)	0 (0.0)
Herpes Simplex	3 (0.5)	0 (0.0)
SPECIAL SENSES		
Otitis Media	7 (1.2)	2 (0.8)
Conjunctivitis	3 (0.5)	1 (0.4)

Parenthesized numbers are percentages and were derived by the number of AE reports for a given COSTART term divided by the number of patients in the treatment group.

Shaded cells are common between this table and the next and were AE's considered to be drug-related by the investigator.

The numbers of individual AE reports for each COSTART term were relatively small, as were the differences in report frequencies between zafirlukast and placebo groups. In the table above, 'headache,' 'abdominal pain,' 'fever,' 'nausea,' 'epistaxis' and 'rash' were the individual AE's with the largest report frequencies [1/12/99 1:79]. Shaded cells represent those AE's in the table above that were also thought to be drug-related by the investigator.

The following table shows the most frequent AE's considered to be drug-related by the investigator and which showed a greater report frequency in zafirlukast-treated patients than for patients who received placebo [1/12/99 1:86].

sNDA #20-547-7 ISS & 4-Month SU: AE's IN COMPLETED CONTROLLED TRIALS CONSIDERED TO BE DRUG-RELATED BY THE INVESTIGATOR AND MORE FREQUENTLY REPORTED BY PATIENTS ON ZAFIRLUKAST THAN ON PLACEBO [1/12/99 1:86]		
Body System & Adverse Event	**Zafirlukast (n = 601 patients)**	**Placebo (n = 259 patients)**
WHOLE BODY		
Headache	5 (0.8)	1 (0.4)
DIGESTIVE		
Nausea	2 (0.3)	0 (0.0)
Gastritis	1 (0.2)	0 (0.0)
Gastroenteritis	1 (0.2)	0 (0.0)
Vomiting	1 (0.2)	0 (0.0)
NERVOUS		
Dizziness	3 (0.5)	1 (0.4)
Anxiety	1 (0.2)	0 (0.0)
RESPIRATORY		
Epistaxis	1 (0.2)	0 (0.0)
Parenthesized numbers are percentages and were derived by the number of AE reports for a given COSTART term divided by the number of patients in the treatment group. Shaded cells are common between this table and the last and were AE's reported by ≥ 0.5% of zafirlukast-treated patients regardless of putative drug-relatedness.		

Ignoring 'headache,' the perpetually most common AE in almost all drug trials, the last two tables share the AE's 'nausea,' 'gastroenteritis' and 'epistaxis.' These AE's were more common in zafirlukast-treated patients than in those who received placebo and more frequently thought to be drug-related.

OPEN-LABEL EXTENSION (OLE) TRIALS

AE's reported in OLE trials are displayed in the table below if the report frequency was ≥ 1.0%. This quantity has the same definition as in previous tables. That is, it is the number of AE reports normalized by the total number of exposed patients (460) and reported as a percentage.

sNDA #20-547-7 ISS & 4-Month SU: AE's IN OLE TRIALS WITH A REPORT FREQUENCY ≥ 1.0% [1/12/99 1:94-7]	
Body System & Adverse Event	**Zafirlukast (n = 460 patients)**
Subjects with AE's	265 (57.6)
WHOLE BODY	
Abdominal Pain	17 (3.7)
Accidental Injury	9 (2.0)
Aggravation Reaction	68 (14.8)
Fever	19 (4.1)
Flu Syndrome	31 (6.7)
Headache	36 (7.8)
Infection	18 (3.9)
Pain	5 (1.1)
Viral Infection	12 (2.6)
DIGESTIVE	
Diarrhea	12 (2.6)
Gastroenteritis	14 (3.0)
Nausea	9 (2.0)

sNDA #20-547-7 ISS & 4-Month SU: AE's IN OLE TRIALS WITH A REPORT FREQUENCY ≥ 1.0% [1/12/99 1:94-7]	
Body System & Adverse Event	**Zafirlukast (n = 460 patients)**
Vomiting	26 (5.7)
MUSCULOSKELETAL	
Pathological Fracture	6 (1.3)
NERVOUS	
Hypertonia	5 (1.1)
RESPIRATORY	
Bronchitis	15 (3.3)
Cough Increased	23 (5.0)
Pharyngitis	140 (30.4)
Pneumonia	7 (1.5)
Rhinitis	16 (3.5)
Sinusitis	45 (9.8)
SKIN & APPENDAGES	
Rash	13 (2.8)
Urticaria	10 (2.2)
SPECIAL SENSES	
Ear Pain	5 (1.1)
Otitis Media	18 (3.9)

Parenthesized numbers are percentages and were derived by the number of AE reports for a given COSTART term divided by the number of patients in the treatment group.
Shaded cells represent the five most frequently reported AE's in OLE trials.

The five most common of the AE's in the table above (shown in shaded cells) are the ever-present 'headache' and four respiratory complaints; 'aggravation reaction,' 'flu syndrome,' 'pharyngitis' and 'sinusitis.' The only 'DIGESTIVE' AE that was in the ten most frequently reported was 'vomiting.' 'Epistaxis,' previously found to be more associated with zafirlukast than placebo and frequently considered to be drug-related, was only reported by 3 patients (0.7%) and is not shown in the table above.

Thirteen (2.8%) patients had AE's that the investigator considered to be drug-related. Four patients had elevated ALT values and one of these had an elevated AST. Three patients reported 'abdominal pain.' One patient each reported 'aggravation reaction,' 'migraine,' 'gastroenteritis,' 'hyperkinesia,' 'alopecia' and 'accidental injury' [1/12/99 1:98].

POST-MARKETING REPORTS

Zafirlukast was approved by this agency for adults and adolescents, ages 12 years old and above, 26 September 1996 and launched by Zeneca 3 November 1996. Between this launch date and 30 September 1998, spontaneous AE reports were received for 1495 cases of 3049 AE's. Most troubling among these were reports of hepatic impairment of varying degrees and eosinophilic conditions including Churg-Strauss Syndrome. There have been 105 cases of 133 AE's involving the liver which include the following [1/12/99 1:170-1]:

77 reports of liver function test abnormalities or impairment

31 reports of hepatomegly or hepatitis

17 reports of icterus or hyperbilirubinemia

8 reports of liver failure, cirrhosis or liver necrosis

At the present time (8/1/99), there have been two death equivalents associated with this drug found in spontaneous reports. A 67-year old female died of liver failure in Norway (#[redacted]00953) and 49 year old female underwent liver transplantation because of failure of that organ (#[redacted]48388).

There have been 90 reports of systemic eosinophilia and vasculitis. Thirty of these could be considered as cases of Churg-Strauss Syndrome, using criteria developed by consultants. Chart reviews indicated that many of these reports were associated with withdrawal of systemic corticosteriods. However, not all cases involved corticosteroid withdrawal and a labeling change was affected to reflect this emerging safety concern. There have been no reports of systemic eosinophilic conditions from the clinical trial program in adult or pediatric subjects and there have been no reports of systemic eosinophilic conditions in pediatric patients from the post-marketing experience [1/12/99 1:171].

DEATHS

None [1/12/99 1:118].

SERIOUS ADVERSE EVENTS (SAE's)

COMPLETED CONTROLLED TRIALS

No SAE's were reported by 259 patients exposed to placebo. Three SAE's were reported by two of the 601 patients administered zafirlukast in completed controlled trials. Brief narratives are presented below with leading identifiers presented as a trial/center/patient number designation followed by the treatment received [30:100-1, 1/12/99 1:119-20]:

1. 0075/0001/1111 (10 mg BID) This 6 year old Caucasian boy was withdrawn and hospitalized with an asthma exacerbation 10 days after starting treatment. One day later his course was complicated by a URI. Both 'aggravation reaction' and 'pharyngitis' were considered SAE's.
2. 0079/004/0407 (5 mg BID) A 6 year old girl had an asthma exacerbation and a seizure after seven days of treatment and was hospitalized overnight. She was withdrawn for the 'aggravation reaction.'

OPEN-LABEL EXTENSION (OLE) TRIALS

Twenty-nine SAE's were reported by 17 of the 460 OLE trial patients, but only 25 SAE's were enumerated in the narrative summaries below. Although the exact number of SAE's in the OLE trials is not certain, the most frequent was asthma exacerbation (COSTART = 'aggravation reaction'). Pneumonia was the second most

frequent SAE. The first three of the seventeen total cases that follow were withdrawn because of SAE's [30:101, 1/12/99 1:120-6]:

0079/0024/2403 (10 mg BID) A 7 year old Caucasian boy was withdrawn and hospitalized for an asthma exacerbation after he completed the double-blind period (28 days) and 142 days of the OLE. He was discharged after five days. He previously had another SAE, pneumonia that did not lead to withdrawal.

0079/0028/2854 (10 mg BID) This 10 year old Caucasian boy was withdrawn and hospitalized for hemoptysis after 105 days of OLE therapy which resolved in four days. This patient had pre-existing congenital malformation of the ear canals, antra of the ear micrognathia and repaired anomalous venous return of the heart.

0079/0028/2857 (10 mg BID) A 6 year old Caucasian female with past history of seizures that were under control entered the OLE directly and had an SAE, a seizure, after 114 days of treatment that did not lead to withdrawal. After 199 days of treatment, she had a grand mal seizure that was also an SAE and she was withdrawn.

0139/0010/1003 (20 mg BID) This 6 year old Caucasian male completed the double-blind part of the trial (28 days) and 137 days of the OLE before being hospitalized and withdrawn for an asthma exacerbation and pneumonia.

0079/0009/0959 (10 mg BID) A 6 year old Caucasian boy entered the OLE directly and after 155 days on treatment he was hospitalized for asthma and recovered within two days.

0079/0027/2705 (10 mg BID) A 6 year old Caucasian female was hospitalized after 178 days in the OLE and after completing the double-blind part of the trial for tonsillectomy and tympanoplasty tube placement.

0079/0027/2751 (10 mg BID) This 9 year old Caucasian female entered the OLE directly. After 353 days on treatment, she received antibiotics for a strep throat and recovered after 16 days.

0079/0028/2860 (10 mg BID) A 9 year old Caucasian female directly entered the OLE portion of the study. After 17, and again after 123 days of treatment, she was twice hospitalized for asthma exacerbations. After a total of 181 days of treatment, she was hospitalized for pneumonia.

0079/0029/2907 (10 mg BID) A 7 year old Caucasian male completed the double-blind part of the trial. After 350 days in the OLE part of the study, he was hospitalized for surgical repair of a broken arm.

0079/0029/2954 (10 mg BID) This 6 year old Caucasian male entered the OLE part of the study directly. After 344 days of treatment he was treated for an asthma exacerbation and received corticosteroids.

0079/0036/3608 (10 mg BID) A 7 year old Caucasian female completed the double-blind portion of the trial, then entered the OLE part. After 168 days on OLE treatment she was hospitalized for abdominal pain, received IV fluids and acetaminophen and recovered in one day.

0079/0036/3609 (10 mg BID) This 10 year old Black female completed the double-blind part of the trial before entering the OLE portion. After 353 days of OLE therapy, she was treated for a lacerated finger.

0079/0038/3808 (10 mg BID) An 8 year old Caucasian male entered the OLE section of the study directly. He was hospitalized about two months into treatment for a upper respiratory infection.

0079/0040/4001 (10 mg BID) A 9 year old Native American female directly entered the OLE part of the trial and, after 234 days, she was hospitalized for flu syndrome.

0079/0040/4002 (10 mg BID) A 9 year old Caucasian male completed the double-blind part of the study before entering the OLE section of it. After 313 days of OLE treatment, the patient received corticosteroid treatment for an asthma exacerbation.

0079/0043/4352 (10 mg BID) An 8 year old Black female entered the OLE portion of the study directly. After 238 days of OLE treatment, she was hospitalized for an asthma exacerbation.

0139/0013/1351 (20 mg BID) This 11 year old Caucasian male entered the OLE part of the trial directly. After 9 days of OLE treatment, he was hospitalized for an asthma exacerbation.

Reviews of case report forms (CRF's) added no pertinent information to the narrative summaries of patients who reported SAE's shown above.

WITHDRAWALS BECAUSE OF ADVERSE EVENTS

COMPLETED CONTROLLED TRIALS

The two subject who withdrew because of SAE's were covered in that section of this review. Twenty-four patients withdrew from controlled clinical trials because of non-serious AE's and they were evenly divided between zafirlukast and placebo groups, at 12 withdrawals from each. The patient identifiers, AE's associated with premature discontinuation and the treatment group in which the patient was enrolled are shown in the table below [1/12/99 1:127-34]:

sNDA #20-547-7 ISS & 4-Month SU: PATIENT IDENTIFIERS* OF EARLY WITHDRAWALS DUE TO NON-SERIOUS AE's IN COMPLETED CONTROLLED CLINICAL TRIALS [1/12/99 1:127-34]

COSTART Term For AE	Zafirlukast Treatment	Placebo Treatment
Pharyngitis		0075/0002/2123 0079/0025/2502
Aggravation Reaction	0075/0001/1132 (20 mg BID) 0079/0027/2701 (5 mg BID) 0079/0001/0103 (10 mg BID) 0079/0005/0506 (10 mg BID) 0139/0013/4654 (10 mg BID) 0139/0017/1711 (10 mg BID) 0139/0027/2707 (20 mg BID) 0139/0048/4729 (20 mg BID) 0139/0016/1606 (40 mg BID) 0139/0023/2302 (40 mg BID)	0079/0003/0304 0079/0003/4126 0079/0017/1703 0139/0008/0805 0139/0013/4685 0139/0021/2106 0139/0030/3002 0139/0041/4112
Pharyngitis & Aggravation Reaction	0139/0026/2609 (20 mg BID)	0079/0027/2709
Rash		0139/0026/2612
Hyperkinesia	0139/0008/0802 (10 mg BID)	

sNDA #20-547-7 ISS & 4-Month SU: PATIENT IDENTIFIERS* OF EARLY WITHDRAWALS DUE TO NON-SERIOUS AE's IN COMPLETED CONTROLLED CLINICAL TRIALS [1/12/99 1:127-34]		
COSTART Term For AE	Zafirlukast Treatment	Placebo Treatment
* Patient Identifiers = Trial Number/Center Number/Patient Number (assigned active treatment dose)		

'Aggravation reaction' led to most withdrawals in both treatment groups and reviews of patient narrative summaries were not revealing.

OPEN-LABEL EXTENSION (OLE) TRIALS

Three patients withdrew prematurely from OLE trials because of SAE's and were covered in that section of this review. Twelve patients withdrew early from these OLE studies for a variety of reasons, the most frequent of which was 'aggravation reaction' [1/12/99 1:135-9].

sNDA #20-547-7 ISS & 4-Month SU: PATIENT IDENTIFIERS* OF EARLY WITHDRAWALS DUE TO NON-SERIOUS AE's IN OLE TRIALS [1/12/99 1:135-9]	
COSTART Term For AE	Zafirlukast Treatment
Aggravation Reaction	0079/0004/0451 (10 mg BID) 0079/0033/3302 (10 mg BID) 0079/0036/3604 (10 mg BID) 0139/0011/1111 (10 mg BID) 0139/0017/1751 (10 mg BID)
Pharyngitis	0079/0036/3605 (10 mg BID)
Hyperkinesia	0079/0006/0605 (10 mg BID)
Pneumonia	0079/0014/1408 (10 mg BID)
Alopecia	0079/0023/2304 (10 mg BID)
SGPT increased	0079/0028/2853 (10 mg BID)
Abdominal Pain	0139/0007/0704 (10 mg BID)
Sinusitis	0139/0035/3503 (10 mg BID)
* Patient Identifiers = Trial Number/Center Number/Patient Number (assigned active treatment dose)	

CLINICAL LABORATORY

Shift tables presented laboratory values before and at the end of treatment which were divided into gradations of 'low,' 'normal' and 'high' values. All sub-categories were combined by this reviewer into one of the three mentioned in the prior sentence. This 3-category before-and-after-treatment display resulted in a 3x3 table of nine joint events. The three categories were mutually exclusive, but not necessarily all inclusive and were retrospectively defined by the sponsor with different criteria for different age ranges of patients even within the same shift table. Numbers in the cells representing shifts up or down one or more categories between baseline and end of treatment were scrutinized.

The evaluation of OLE trials relied on observed values from active treatment recipients only. The assumption on which interpretation of these OLE shift tables was based was that baseline-to-end-treatment shifts to higher categories should be about equal to shifts to lower categories. If these shifts reflected random events, they would be

equally likely to occur in both directions. Completed, placebo-controlled trials offered more powerful information by comparing directional shifts in actively-treated and placebo-treated patients. A shift in variable values to lower or higher categories may be unequal, hence unlikely to reflect random error. However, this unequal shift may be plausibly ascribed to the active treatment only if a shift in the same direction was not found in the placebo group. Shift tables comparing zafirlukast- and placebo-treated groups were first examined in completed controlled trials. If a differential shift was found that was not apparent in the placebo group, further confirmation was sought in OLE trials. Thereafter, the pathological implications of the shift were taken into consideration.

HEMATOLOGY

The first of these was blood leukocytes, inflammatory cells that might be effected by a treatment that is supposed to act on mediators of inflammation. A slightly greater percent of patients treated with zafirlukast shifted to lower categories than shifted to higher ones. This same phenomenon was seen in the placebo group. No effect of zafirlukast treatment on leukocyte count could be inferred. Neutrophil shifts were slightly more common toward lower categories (63 = 11.5%) than higher (53 = 9.7%). This small differential was not found in placebo patients or in actively treated patients from OLE trials and was considered unlikely to be a real effect. Eosinophils also showed unequal shifts to lower categories between the pretreatment baseline and the end of treatment. This was also found in the placebo group, to a lesser degree, and in the OLE actively treated patients [1/12/99 1:183-7, 164-5]. The concern surrounding eosinophils was the emergence of eosinophilia during treatment, so the slight trend of shifts to lower categories was not considered worrisome.

Hemoglobin levels showed shifts to lower categories in actively treated patients and this was also found in patients who received placebo. Platelet counts shifted slightly to lower categories during treatment in both zafirlukast- and placebo-treated patients. No directional shifts of prothrombin times were found in patients who received zafirlukast in completed controlled trials. The activated partial thromboplastin time (aPTT) did show a shift to lower categories in patients receiving zafirlukast. This was not seen in patients given placebo but was confirmed in OLE trials. This reviewer knows of no pathological correlates to a shortened aPTT so this finding was not considered to be clinically important [1/12/99 1:190-4, 211-3, 224].

CHEMISTRY

Safety considerations in adults have been colored by the post-marketing experience, which has shown a number of cases of hepatic enzyme elevations, frank hepatitis, and liver failure. Two of the worst outcomes in the last category were death and liver transplantation to avert death from complete organ failure. This was barely suggested from the review of over 3000 of adult subjects in the original NDA, over 500 of who had received the drug for at least one year. The only hints of hepatic toxicity emanating from the adult NDA trial program were: 1)the AE 'increased ALT' showed

dose-ordering; 2)a small excess percentage of zafirlukast-treated patients, compared with placebo, showed ALT shifts from ≤ 2 times the upper limit of normal (2xULN) to higher values between beginning and end of treatment; and, 3)three zafirlukast-treated patients withdrew prematurely because of abnormal liver enzymes [6/26/95 NDA Submission; Medical Reviewer Safety Summary:12, 21].

AST values in zafirlukast-treated pediatric patients from completed controlled trials showed slightly more shifts to higher categories than to lower. This was not found in the placebo group and this upward shift was confirmed in OLE trials. However, numbers were very small with two more patients in completed controlled trials shifting to higher categories than to lower. In OLE studies, only five more patients shifted to higher than to lower categories. In the tables below, 'high' was anything greater than 'normal' and the criteria for 'normal' at various labs had upper limits of normal at 40-50 UL. The highest value for any patient in completed controlled or OLE trials was 78 U/L [1/12/99 1:202-3, 214]. Darkly shaded cells contain shifts to lower categories and the lighter shaded cells contain shifts to higher categories.

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT AST VALUES IN COMPLETED CONTROLLED TRIALS: n (% total) [1/12/99 1:202]

Before Treatment Value	End of Treatment Value		
	Low	Normal	High
ZAFIRLUKAST			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	539 (98.4)	5 (0.9)
High	0 (0.0)	3 (0.5)	1 (0.2)
PLACEBO			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	223 (99.1)	0 (0.0)
High	0 (0.0)	2 (0.9)	0 (0.0)

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT AST VALUES IN OLE TRIALS: n (% total) [1/12/99 1:214]

Before Treatment Value	End of Treatment Value		
	Low	Normal	High
ZAFIRLUKAST			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	435 (97.8)	7 (1.5)
High	0 (0.0)	2 (0.4)	1 (0.2)

The ALT values in zafirlukast-treated patients in completed controlled trials showed unequal shifts toward lower categories, which were also found in patients receiving placebo. OLE studies of ALT shifts paralleled the findings for AST, that is they showed small shifts to higher categories (lightly shaded cells) during treatment.

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT ALT VALUES IN OLE TRIALS: n (% total) [1/12/99 1:216]

Before Treatment Value	End of Treatment Value		
	Low	Normal	High
ZAFIRLUKAST			

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT ALT VALUES IN OLE TRIALS: n (% total) [1/12/99 1:216]			
	End of Treatment Value		
Before Treatment Value	Low	Normal	High
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	428 (96.8)	10 (2.3)
High	0 (0.0)	4 (0.9)	0 (0.0)

The upper limit of normal for ALT at various labs ranged from 30-48 U/L. The maximum value during treatment was 126 U/L and was the only value from any patient during treatment that was greater than 100 U/L. One patient had a maximum value during treatment of 81 U/L which rose to 108 U/L two months after treatment ceased [1/12/99 1:204-6, 216-7].

The alkaline phosphatase values in zafirlukast-treated patients showed small disproportionate shifts to higher categories in completed controlled trials that were not found in patients receiving placebo. OLE trials confirmed the shift to higher categories [1/12/99 1:206-7, 218].

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT ALKALINE PHOSPHATASE VALUES IN COMPLETED CONTROLLED TRIALS: n (% total) [1/12/99 1:206]			
	End of Treatment Value		
Before Treatment Value	Low	Normal	High
ZAFIRLUKAST			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	460 (84.1)	20 (3.7)
High	0 (0.0)	12 (2.2)	54 (9.9)
PLACEBO			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	178 (79.1)	8 (3.6)
High	0 (0.0)	7 (3.1)	32 (14.2)

sNDA #20-547-7 ISS & 4-Month SU: SHIFT TABLE OF BEFORE-TO-END-TREATMENT ALKALINE PHOSPHATASE VALUES IN OLE TRIALS: n (% total) [1/12/99 1:218]			
	End of Treatment Value		
Before Treatment Value	Low	Normal	High
ZAFIRLUKAST			
Low	0 (0.0)	0 (0.0)	0 (0.0)
Normal	0 (0.0)	393 (88.5)	17 (3.8)
High	0 (0.0)	12 (2.7)	22 (5.0)

The shifts in AST paralleled those seen in the adult NDA trial program and were of about the same magnitude, as reported in the original medical officer Safety Summary. ALT shifts to higher categories during treatment were also found in adult placebo-controlled trials, but were not found in children. Disproportionate shifts of ALT to higher categories were found in both children and adults in OLE trials. It appears as if responses of hepatic enzymes to this drug in children is similar to that seen in adults.

URINALYSIS

Completed controlled and OLE trials failed to show any suspicious findings. The only minor discrepancies reported were of pH changes and the presence of urine ketones, neither of which seemed particularly ominous [1/12/99 1:225-6].

VITAL SIGNS

Systolic and diastolic blood pressures, heart rate and respiratory rate before and at the end of treatment in both completed controlled and OLE trials were presented as means, medians, standard deviations and ranges for treatment groups. No consistent or large differences were noted in any group as a concomitant of treatment [1/12/99 1:233-5, 9:151-62].

ELECTROCARDIOGRAMS (EKG'S]

Shift tables of PR, QRS and QTc intervals, normal and prolonged, failed to show any directional changes that were unique to zafirlukast in completed controlled or OLE trials. Various benign rhythm disturbances were found including sinus tachycardia, sinus bradycardia, junctional and ectopic atrial rhythms. The most common of these was sinus tachycardia and it was a more frequent finding before treatment than at the end of treatment. This same pattern was observed in patients who received placebo and in active treatment recipients in OLE trials [1/12/99 1:226-34].