CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary Drug Products (HFD-570)

APPLICATION #:	20-547-7	**APPLICATION TYPE:**	NDA Supplement
SPONSOR:	Zeneca	**PROPRIETARY NAME:**	Accolate
CATEGORY:	leukotriene antagonist	**USAN NAME:**	zafirlukast
		ROUTE:	oral
MEDICAL OFFICER:	R. F..Anthracite, MD	**REVIEW DATE:**	9/2/99

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
9/17/98	9/18/98	pediatric supplement	original submission
9/17/98	9/18/98	recalc 79 omit Center 22	called "Addendum"
11/19/98	11/20/98	Trial #0139	final study report
1/12/99	1/13/99	4-Month Safety Update	integrated safety

RELATED APPLICATIONS (if applicable)

Document Date	Application Type	Comments
6/26/95	original NDA	adult application
12/21/95	safety update	resubmitted

REVIEW SUMMARY:

This supplement provides exploratory efficacy data analyses from two large, randomized, placebo-controlled, double-blind, parallel-group trials in 5 to 11 year old children, studies 0079 and 0139. It also includes one small dose-finding, crossover, challenge trial in children, 6 to 14 years of age, with exercise-induced bronchospasm, study 0075. 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. Efficacy findings in children were unconvincing, contradictory and did not establish an appropriate dose or dosing interval. Neither adults nor children have shown any pharmacokinetic-pharmacodynamic relationship for efficacy. In fact, dose ordering of efficacy was not apparent or was even inverted. Dose ordering did seem to be related to certain gastrointestinal and hepatic adverse events in adults. In order to approve this drug for children we will need sufficient evidence of efficacy to choose a dose and treatment interval.

OUTSTANDING ISSUES: None.

RECOMMENDED REGULATORY ACTION

New Clinical Studies:	_____	**HOLD**	_____	**MAY PROCEED**
NDA/Efficacy/Label Supplements:	XXX	**APPROVABLE**	_____	**NOT APPROVABLE**

SIGNATURES

Reviewer: /S/ **Date:** 9/2/99

Team Leader: /S/ (Note: See TL Memo) **Date:** 9/14/99

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APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

This supplement provides exploratory efficacy data analyses from two large, randomized, placebo-controlled, double-blind, parallel-group trials in 5 to 11 year old children, studies 0079 and 0139. It also includes one small dose-finding, crossover, challenge trial in children, 6 to 14 years of age, with exercise-induced bronchospasm, study 0075.

The pivotal trials, 0079 and 039, enrolled children (5-11 years of age) with mild-to-moderate asthma ($FEV_{1.0}$ 50 to 85 or 90% of predicted). Patients demonstrated reversible airways disease or bronchial hyper-reactivity to provocative challenge and received beta-2 agonist therapy. Orally inhaled cromones and corticosteroids were not permitted. These two pivotal trials differed in the double-blind period duration, the number of parallel arms and the doses of zafirlukast studied. Trial 0079 had a four-week double-blind period and included three groups, placebo, 5 and 10 mg of zafirlukast BID. Study 0139 with a six-week double-blind period had four groups; placebo and 10 mg, 20 mg and 40 mg of zafirlukast BID. Various measures of $FEV_{1.0}$, PEFR, nighttime awakenings, daytime asthma symptoms, beta-2 agonist use, school absenteeism, medical contacts for asthma and withdrawals due to asthma were all evaluated with multitudinous statistical comparisons. In no case was a single efficacy endpoint declared as primary, nor was the measure and comparison of any efficacy endpoint completely and prospectively identified. No adjustment of the Type I Error was made for these multiple tests of inference, rendering 'statistical significance' a concept of limited meaning that grossly underestimated Type I Error probabilities in these studies.

With this liberal definition in mind, statistical significance in trial 0079 was achieved only for $FEV_{1.0}$ (percent predicted) in the 5 mg group, and for the Mean Total Daily Beta-2 Agonist Use, in the 10 mg group, in the modified intent-to-treat sample. By most measures, efficacy endpoints did not show dose ordering. Comparing the two active treatments, the 5 mg BID dose of zafirlukast showed the most evidence of effect by many measures. It also resulted in the most absenteeism from school for asthma, the most physician and hospital contacts for asthma and the most study withdrawals due to asthma, exceeding even that found with placebo. Statistical significance in study 0139 was achieved only for $FEV_{1.0}$ (liters), in the 20 mg group, and for both AM and PM PEFR, in the 10 mg group, in the modified intent-to-treat sample. Again, efficacy endpoints did not show dose ordering. In fact, inverse dose ordering was a frequent finding. Among the three active treatments, the 10 mg BID dose of zafirlukast showed the greater evidence of efficacy by several measures. It also showed the highest beta-2 agonist use at endpoint, resulted in the most absenteeism from school for asthma and the most physician and hospital contacts for asthma of the three active treatments.

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, study 0075. They were stratified by weight, randomized into two 'treatment groups' within each of which three

single-dose crossover treatments were studied (Group I: placebo, 5 mg and 20 mg of zafirlukast; Group II: placebo, 10 mg and 40 mg of zafirlukast). Four hours after taking the single dose of the blinded treatment on an empty stomach, an exercise challenge was performed. Zafirlukast provided partial relief from exercise induced falls in $FEV_{1.0}$ by three highly correlated 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. 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.

As of the 1/12/99 submission date 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 upper and lower respiratory adverse events most commonly. 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. 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. Small shifts to higher categories were also found for alkaline phosphatase.

Zafirlukast in children 5-11 years of age seems to have a safety profile that is 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.

Efficacy findings in children were unconvincing, contradictory and did not establish an appropriate dose or dosing interval. Neither adults nor children have shown any pharmacokinetic-pharmacodynamic relationship for efficacy. In fact, dose ordering of efficacy was not apparent or was even inverted. Dose ordering did seem to be related to certain gastrointestinal and hepatic adverse events in adults. In order to approve this drug for children we will need sufficient evidence of efficacy to choose a dose and treatment interval. I suggest a more rigorously conducted efficacy study of doses lower than, and including, [redacted] be undertaken. It should include completely and prospectively defined endpoints with appropriate Type I Error correction if multiple comparisons or endpoints are invoked, measurement of those endpoints at specified times after verified dosing, and monitored timing of blood samples for pharmacokinetic studies.

/S/

Raymond F. Anthracite, M.D.
Medical Review Officer

cc:
NDA #20-547 Supplement 7
HFD-570/Division Files
HFD-570/Team Leader/Chowdhury
HFD-570/Medical Reviewer/Anthracite
HFD-570/Statistical Reviewer/Gebert
HFD-570/BioPharm Reviewer/Hunt
HFD-570/PharmTox Reviewer/Sancilio
HFD-570/Chemistry Reviewer/Khorshidih
HFD-570/Project Manager/Jani

GENERAL INFORMATION

NOTE TO READERS

This review has a bottom-up construction. References in each section are enclosed in square brackets ([....]) and include the submission, meeting or telephone conversation dates followed by optional descriptors, volume, page(s) and table and figure numbers; e.g., [6/26/95 ISS 109:149 Table 4-16]. Descriptors include: 'ISS' for integrated safety summary; 'SU' for safety update; 'Telecon' is self explanatory; and, 'Addendum' for recalculated efficacy data omitting the contribution of Dr. Edwards and Center 22 that was submitted on the same date as the pediatric supplement to the NDA. References that do not begin with a date are to the original 9/17/98 submission of this supplement. At the beginning of each clinical study review is a summary. A summary also precedes the integrated review of safety. The executive summary draws from the individual section summaries.

PRECLINICAL SAFETY

Fat necrosis has been reported in neonatal rats and dogs at doses of 400 mg/kg/d and 500 mg/kg/d, respectively. AE's associated with panniculitis were assumed to include erythema nodosum, panniculitis and subcutaneous nodules. None of these AE's was reported by any patient. The mean exposure (AUC) in humans is five-fold less than the minimum exposure associated with fat necrosis in neonatal animals [6/26/95 ISS 109:143-4]. Currently, neonatal humans are not candidates for this drug at any dose, but this preclinical issue should be revisited if zafirlukast is ever proposed for use in a population of very young children.

Microscopic findings suggestive of estrus/metestrus were found in a six-month toxicity study of dogs receiving 150 mg/kg/d of zafirlukast. Ovarian and uterine weights were normal. At the suggestion of the agency, all women of child-bearing age kept menstrual diaries in all thirteen-week trials. A greater percentage of placebo-treated than zafirlukast-treated patients reported any change in cycle length (Pbo = 15/110 = 13.6%; Z = 31/279 = 11.1%). Of those reporting a cycle-length change, a greater percentage of placebo-treated patients reported that change to be $\geq$ 7 days than zafirlukast-treated patients (Pbo = 5/15 = 33.3%; Z = 9/31 = 29.0%). Nine post-menopausal women had pelvic examinations and Pap smears before and at the end of therapy. One Pap smear showed "atypical squamous cell of undetermined significance" and a repeat Pap smear was normal. Nine women became pregnant during a clinical trial and five of these had received zafirlukast. None of the five reported taking hormones for any indication. The outcome of these pregnancies was not reported [6/26/95 ISS 109:144-7]. These findings do not implicate zafirlukast in causing significant hormonal imbalances or ovarian/uterine dysfunction.

Granulomatous infiltrates, consisting predominantly of enlarged histiocytic cells, were observed in dogs given zafirlukast in doses $\geq$ 75 mg/kg/d. These infiltrates

occurred in the parenchyma and adjacent adipose tissue of a range of organs, were not associated with functional changes, did not appear to be a result of primary tissue degeneration or necrosis and were not found after a period of withdrawal. The overall incidence of the COSTART term "infection" was slightly greater in the zafirlukast-treated patients compared with those receiving placebo (Z = 142/3332 = 4.3%; Pbo = 69/1677 = 4.1%), but the difference was small [6/26/95 ISS, 12/21/95 SU resubmitted by the sponsor, Tables 5-3]. A breakdown of infection by type, organ and inciting agent did not show a large difference from placebo for any subset [6/26/95 ISS 109:149 Table 4-16]. This negative finding in humans is a comforting addition to the species-specific nature of the animal finding, suggested by the sponsor.

Neoplasms were seen in two rodent species. A 76-week study at a dose of 2000 mg/kg in rats showed urinary bladder tumors. Hepatic tumors were found in male mice exposed to 300 mg/kg and were presumed to be secondary to prolonged fatty degeneration. No urinary bladder tumors or hepatic tumors have been reported in humans, though none were specifically sought [6/26/95 ISS 109:150-2].

9188IL/0079 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING, PARALLEL-GROUP, MULTICENTER, SAFETY AND EFFICACY TRIAL OF ZAFIRLUKAST (ACCOLATE™) IN THE TREATMENT OF PEDIATRIC PATIENTS WITH MILD-TO-MODERATE ASTHMA

PRINCIPLE INVESTIGATOR	STUDY DATES
Kathi Lampl. M.D. Rockville, MD	First patient recruited: 17 October 1995 Last patient completed: 6 June 1997

SUMMARY

About 300 pediatric patients (5-11 years of age) with asthma were given zafirlukast (5 mg or 10 mg) or placebo twice daily on an empty stomach over four weeks. They had mild-to-moderate disease ($FEV_{1.0}$ 50-90% of predicted), had reversible airways disease or bronchial hyper-reactivity to provocative challenge and had been given beta-2 agonist therapy. Orally inhaled cromones or corticosteroids were not permitted. This was a three-arm, 1:1:1 randomized, double-blind, placebo-controlled, dose-ranging, parallel-group multicenter study. Various measures of $FEV_{1.0}$, PEFR, daytime and nighttime asthma symptoms, beta-2 agonist use, school absenteeism, medical contacts for asthma and withdrawals due to asthma were all evaluated with multitudinous statistical comparisons. Interim analyses of safety and efficacy variables were also performed. No adjustment of the Type I Error was made for these multiple tests of significance in the final or the interim analyses, rendering 'statistical significance' a concept of limited meaning, that grossly underestimated Type I Error probabilities in this study.

With this liberal definition, statistical significance was achieved only for $FEV_{1.0}$ (percent predicted), in the 5 mg group, and for the Mean Total Daily Beta-2 Agonist Use, in the 10 mg group, in the modified intent-to-treat sample. By most measures, efficacy endpoints did not show dose ordering. Comparing the two active treatments, the 5 mg BID dose of zafirlukast showed the greater evidence of effect by several measures. It also resulted in the most absenteeism from school for asthma, the most physician and hospital contacts for asthma and the most study withdrawals due to asthma. Plasma zafirlukast concentrations were reported in a minority of patients in which they were collected. The levels were very variable, skewed toward higher plasma concentrations and tended to decline slightly over the double-blind period.

There were no deaths. The single patient with serious adverse events (seizures, asthma) and eight patients withdrawn due to adverse events were overwhelmingly

associated with exacerbations of asthma. Adverse events of leukopenia ($3.6x10^9$) and eosinophilia (21%) were each reported once in zafirlukast-treated patients. The mean hematocrit declined slightly in all three groups, with the largest drops found in the active treatment arms. The mean alkaline phosphatase increased slightly in both active treatment arms and declined in the placebo group.

OBJECTIVES

In pediatric patients (5-11 years of age) with mild-to-moderate asthma ($FEV_{1.0}$ 50-90% of predicted), determine the effect of 5 and 10 mg tablets of zafirlukast reflected by changes in the $FEV_{1.0}$, PEFR, daytime and nighttime asthma symptoms and daily beta-2 agonist usage. Also, determine plasma zafirlukast concentrations following twice-daily oral administration [14:11, 19].

PROTOCOL

This was a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group multicenter study. The trial included four periods: 1)one week of screening; 2) one-to-two weeks of single-blind placebo run-in; 3)four weeks of double-blind efficacy and safety; and, 4)a 52-week open-label safety extension which will be summarized separately. Following the screening and placebo run-in periods, eligible patients were assigned to 1 of 3 treatment groups according to a 1:1:1 randomization: 5 or 10 mg of oral zafirlukast BID or placebo BID for the four-week double-blind period [14:12, 20]. The flow-chart for the protocol and procedures is shown below.

sNDA #20-547 9188IL/0079: SCHEDULE OF EVENTS [14:21]					
	Screen	Single Blind Run-In		Double Blind Treatment	
Week	0	1	2 to 3	4 to 5	6 to 7
Visit	1	2	3	4	5
Vital Signs	X		X	X	X
Laboratories		X			X
EKG's	X		X	X	X
PFT's	X		X	X	X
$FEV_{1.0}$ Reversal	X				
Randomization			X		
History	X				
Physical Exam	X		X	X	X
Sample for PK					X
Tanner Staging					X

PATIENTS

Randomization of 311 pediatric patients with mild-to-moderate asthma resulted in 288 (92.6%) patients who completed the trial [14:12].

SCREENING PERIOD CRITERIA

Pediatric patients were eligible for screening if they provided written informed consent (parent or legal guardian also signed the patient's consent form) and met the following additional criteria [14:23]:

1. nonsmoking boys or girls aged 5 through 11 years (sexually active girls of childbearing potential were eligible if they a practiced reliable method of contraception, i.e., double-barrier method or hormonal contraceptives)
2. documented clinical history of asthma that included one of the following:
   a. reversible airway disease as shown by at least a 12% increase in $FEV_{1.0}$ after inhaled beta-2 agonist
   b. nonspecific bronchial hyper-reactivity to methacholine or histamine challenge within 6 months of screening; the provocative concentration of methacholine that produced a 20% decrement in $FEV_{1.0}$ (PC_{20} $FEV_{1.0}$) was at least 0.25 mg/ml but not greater than 8.0 mg/ml or the PC_{20} $FEV_{1.0}$ of histamine was less than or equal to 8.0 mg/ml
3. was given beta-2 agonist therapy for asthma
4. demonstrated a $FEV_{1.0}$ greater than or equal to 50% and less than or equal to 90% of predicted without medication, i.e., 6 hours after inhaled beta-2 agonist, 8 hours after oral beta-2 agonist, or 48 hours after salmeterol
5. performed three acceptable forced expiratory maneuvers with one reproducible $FEV_{1.0}$ within 10% of the largest $FEV_{1.0}$
6. stature-to-weight ratio within the normal range
7. weighed greater than 20 kg (for the first 30 patients enrolled in the trial)
8. able to swallow tablets

DOUBLE-BLIND PERIOD CRITERIA

For inclusion into the randomized, double-blind portion of the trial, pediatric patients had to meet the following criteria [14:23-4]:

1. demonstrated a $FEV_{1.0}$ greater than or equal to 50% and less than or equal to 90% of predicted without medication (at least 6 hours after inhaled beta-2 agonist or 8 hours after oral beta-2 agonist) on the day of randomization (subjects who were within this range on the 1st day of screening, but out of this range on the day of potential randomization were not eligible to continue in the trial.)
2. demonstrated clinically mild-to-moderate asthma as defined by an asthma episode score totaling at least 8 (0-3 daily; maximum 7-day score = 21) during the last 7 consecutive days of the 7-14-day single-blind placebo run-in period [18:273]
3. performed three acceptable forced expiratory maneuvers with one reproducible $FEV_{1.0}$ within 10% of the largest $FEV_{1.0}$
4. complied with dosing regimen, proper use of peak-flow meter, and diary recording

5. demonstrated compliance with trial medication of at least 85% during the placebo run-in period

EXCLUSION CRITERIA

Any of the following was regarded as a criterion for exclusion from the trial [14:24-5]:

1. patients would be placed at undue risk by a temporary postponement of initiating long-term asthma therapy, according to the investigator's judgement
2. laboratory results with a clinically significant deviation from the reference range, except for abnormalities related to asthma or allergy
3. evidence of hepatic disease other than evidence of isolated hyperbilirubinemia associated with a diagnosis of Gilbert's Syndrome
4. evidence of chronic lung disease other than asthma, including cystic fibrosis or bronchopulmonary dysplasia
5. evidence from physical examination or medical history of any disease that affects gastrointestinal absorption
6. evidence of cardiovascular disease
7. immunization with a live viral vaccine (e.g., measles-mumps-rubella, varicella) within 3 weeks of screening
8. use of astemizole within 3 months of screening
9. use of oral or inhaled corticosteroids (nasal corticosteroids were permitted), or barbiturates within 4 weeks of screening
10. use of cromolyn or theophylline within 4 weeks of screening
11. new use or changing regimen (dose and frequency) of cromolyn nasal solution or nasal corticosteroids within 4 weeks of screening; patients whose regimen did not change during the 4 weeks before screening were eligible, and their regimen could not change during the screening and double-blind trial periods
12. use of salmeterol within 48 hours of screening or any use during the trial
13. upper or lower respiratory tract infection with a significant asthma flair requiring additional or increased amounts of asthma medication within 4 weeks of screening
14. acute illness within 1 week of screening
15. history of drug or alcohol abuse
16. vaccination with hepatitis B surface antigen within 6 weeks of screening
17. entry into the single-blind lead-in period of this trial on a previous occasion
18. seasonal asthma as defined by symptoms or therapy confined to less than 2 months per year
19. participation in another trial with an investigational drug within 4 weeks of screening in this trial
20. positive urine drug screen for substances that indicate abuse

21. history of convulsive disorders or any significant central nervous system disorder; attention deficit disorder was acceptable if a patient did not require treatment or was being treated with an established dose of medication
22. inability to perform 3 acceptable forced expiratory maneuvers with one reproducible $FEV_{1.0}$ within 10% of the largest $FEV_{1.0}$
23. inability to take tablets
24. participation in a previous trial involving zafirlukast

WITHDRAWAL CRITERIA

Patients were withdrawn from the trial if any of the following circumstances occurred [14:25-6]:

1. had a significant adverse event
2. developed a significant concurrent illness unrelated to asthma
3. patient chose to withdraw from the trial, or the patient's parent or legal guardian wished the patient to withdraw
4. patient did not adhere to the rules and procedures for this trial
5. any other situation in which the investigator considered continued participation in the trial would not be in the best interest of the patient
6. patient was lost to follow-up

A patient was removed from the trial as a treatment failure and noted as "asthma became worse" if any of the following occurred:

1. more than one emergency room visit was made for asthma during the double-blind period or the patient required hospitalization
2. deterioration of asthma required chronic treatment with medications that were not permitted

All withdrawals from the trial were documented with reasons for the withdrawal. If a patient withdrew from the trial or if the investigator chose to terminate a patient's participation before the scheduled completion of the trial, the patient was given a complete physical examination, a standard battery of laboratory tests, the standard set of pulmonary function tests, and a 12-lead EKG examination at the time of withdrawal [14:25-6].

TREATMENT

Formulations and lot numbers of the active treatments, placebo controls and the rescue medication are shown in the table below [14:12, 27].

sNDA #20-547 9188IL/0079: TREATMENT FORMULATIONS & LOT NUMBERS [14:12, 27]		
Treatment	Formulation	Lot
5 mg Zafirlukast		T53036B, N63131A

sNDA #20-547 9188IL/0079: TREATMENT FORMULATIONS & LOT NUMBERS [14:12, 27]		
Treatment	Formulation	Lot
10 mg Zafirlukast	[redacted]	T53037B, T63122A, N63123A, T63137A, T63137B
Placebo Zafirlukast	[redacted]	N53033B, N53033C
Ventolin Inhalers	[redacted]	Z1045, Z1045A, ZPA177, ZPO177, ZPO261, ZPO612, ZPO755

Zafirlukast and placebo tablets appeared identical and were packaged in foil blisters during the double-blind and open-label periods. Each supply of medication was contained in a sealed box. Four blisters (10 tablets each, total 40 tablets) were provided for visit 2 of the single-blind placebo run-in period and each week during the double-blind period. Eight blisters (10 tablets each, total 80 tablets) were provided for visit 5.

During the double-blind period of the trial, patients were given placebo or one of the two doses of zafirlukast (5 or 10 mg) BID for 4 weeks. The trial medication was taken either one hour before food or, if that was not possible, two hours after food. It was acceptable for the trial medication to be hidden in a light snack (e.g., tablespoon of applesauce, placed in a "fruit roll-up"). The date and time of dosing were recorded on the appropriate case report form (CRF) as part of each patient's permanent record.

Albuterol inhalers (Formulation [redacted]) were dispensed to each prospective patient following qualification for screening at visit 1 and as needed, throughout the trial. The investigator maintained records that accounted for the dispensing of albuterol inhalers. The albuterol inhaler canister was weighed (without the spacer or actuator) before dispensing and again at each visit during the double-blind period and the weights were recorded on the CRF [14:27-8].

Prescription or nonprescription medication could be used only with prior agreement between the investigator and the sponsor. Antihistamines were not permitted for at least 48 hours before pulmonary function testing. Astemizole, inhaled cromolyn sodium or nedocromil sodium, methylxanthines, or beta-2 agonists other than rescue albuterol could not be prescribed or used during the trial. The use of inhaled or oral corticosteroids during the screening or double-blind periods necessitated withdrawal from the trial. New use or changing regimen of cromolyn nasal solution or nasal corticosteroids within 4 weeks of screening was not permitted. Patients whose regimen did not change during the 4 weeks before screening were eligible, and their regimen could not change during the screening and double-blind periods. Desensitization to allergens was not to be initiated or discontinued during the trial; however, allergy injections could continue at maintenance levels. The influenza vaccine was allowed during this trial. Acetaminophen was the sole nonprescription medication allowed for analgesia [14:29-30].

PARAMETERS

Though hosts of parameters was listed as coprimary, the difference between treatments, measured as the absolute $FEV_{1.0}$ in liters and PEFR in L/min, seem to have

been used to calculate sample size. The time point in the study at which this comparison was to be made was at the final visit if the final visit was within three days of the last dose of randomized trial medication. Otherwise, data from the preceding visit was used for the endpoint analysis (LVCF = last value carried forward).

Rather than basing approval on the statistical significance of all declared coprimary endpoints, it seems more reasonable to use the $FEV_{1.0}$ (liters) difference between treatments, on which sample size determination was based, or the $FEV_{1.0}$ (percent predicted), a more reasonable measure of children with large size variability, as the primary efficacy endpoint. Modified intent-to-treat, per-protocol, stratification and responder analyses were all performed on many of these endpoints and various measures of them [14:30-5, 37-41, 18:261].

Interestingly, a blinded interim analysis was performed after the first thirty patients completed the double-blind portion of the trial. The rationale for this appeals to reasons of both safety and efficacy parameter estimation. The two reasons given were: 1)to identify "increased susceptibility to adverse effects of zafirlukast;" and, 2)to estimate the variability of efficacy variables to power Trial 0139 [14:48]. The adverse effect signal would have to be huge to be seen in 30 patients, only 20 of whom received active treatment. Variance estimates could certainly be made from such a small number of patients but would not be very stable [7/13/99 conversation with Dr. J. Gebert, Statistical Reviewer]. The final protocol, dated 30 June 1997, cites the reason for this interim evaluation as testing the adequacy of initial sample size estimates in children based on adult data and does not appeal to any safety rationale [18:263]. Both sources agree that the interim analyses were global for all safety and efficacy parameters, were initially blinded but could be unblinded "if required" by safety findings, could not result in any prospectively defined action and that no statistical penalty was paid for the peek. This interim analysis was added in a revision dated 15 September 1995 [18:320].

PRIMARY EFFICACY VARIABLES

1. spirometry (parameters and comparison point unspecified but $FEV_{1.0}$ was referenced as both percent predicted normal 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; except for the baseline spirometry at visit 3 performed before the first dose of randomized treatment, the timing of subsequent spirograms relative to treatment was unspecified [14:31-4, 37, 7/20/99 Telecon]
2. morning and evening PEFR before the use of albuterol inhaler; exactly what was meant by performing evening test 'before the use of the inhaler' is not clear; the morning randomized treatment was to be given after the AM PEFR had been done; there was no specified temporal relation between receiving the randomized treatment in the evening and performing the PM PEFR at bedtime [14:31, 18:273, 7/20/99 Telecon]

3. rescue medication use was encouraged for exercise, low PEFR and symptoms; PEFR criteria were not specified nor were these necessarily the same for all patients [14:32, 34, 7/20/99 Telecon]
4. night time awakenings, recorded on waking in the morning [18:273]
5. asthma episode scores consisted of one or more signs of asthma (wheezing, coughing, chest tightness, shortness of breath) occurring during the course of a 24-hour period and rated on a 0-3 scale at bedtime by reflection [14:31, 18:273]

   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 > 2 hours or spells causing stay-at-home or seeing doctor

SECONDARY EFFICACY VARIABLES

1. school absenteeism for asthma; if school was not in session, this was to be answered as if each day were a school day [14:32]
2. doctor or hospital contacts for asthma
3. treatment failures (withdrawals due to asthma)

SAFETY VARIABLES

Adverse events were recorded on CRF's, if brought to the attention of the investigator, or if voiced in response to a general question asked at clinic visits, "Has anything bothered you since your last visit?" [14:46, 18:252] The following laboratory determinations were made at visits 1 (start of placebo run-in) and 5 (end or double-blind treatment):

1. hemoglobin, hematocrit, WBC, differential, platelet count, PT, PTT
2. creatinine, BUN, calcium, total protein, glucose, total bilirubin, alkaline phosphatase, LDH, AST, ALT, CPK, potassium, sodium, chloride, bicarbonate, total carbon dioxide
3. routine and microscopic urinalyses

Vital signs were taken at the end of the placebo run-in and at each visit during treatment. Twelve-lead EKG's were taken at each visit except 2 [14:45-7].

PHARMACOKINETIC PARAMETERS

Patients had blood samples drawn to determine plasma zafirlukast concentrations at visits 3, 4 and 5 according to the original protocol. The first 30 patients had two blood samples drawn 45 minutes apart at visit 4. After the final protocol revision, samples were drawn only at visit 5. The timing of samples had no predetermined relation to the timing of treatment. If, at a given time point $\leq$ 50% of the samples were not quantifiable (NQ), the mean and standard deviation were calculated by substituting the limit of

quantification (LOQ) [redacted] ng/mL. If > 50% of the samples were not quantifiable, the mean and standard deviation were reported as not calculable (NC) [14:42-3, 16:10-1]. This practice may lead to some precise numbers that are questionably related to any precise data.

DEMOGRAPHICS

After 557 patients were screened, 311 patients with asthma from 37 research centers in the United States were randomized to enter the double-blind portion of this trial and 288 (92.6%) completed the trial. One investigator, Dr. Edwards of Center 22, was placed on a 'restricted investigators' list because of discrepancies in the performance of clinical investigations for drug development under another sponsor. The data presented in this segment of the review are corrected by removal of Dr. Edwards' data. One patient never returned for any visit after the initial treatment was dispensed and was not included in some analyses. Some baseline parameters comparing the treatment groups are shown in the following table [14:49-51, 57, Addendum:Cover Letter, 27-9, 31, 34].

sNDA #20-547 9188IL/0079: BASELINE DEMOGRAPHIC PARAMETERS [14:51, Addendum:27-9, 31, 34]			
Parameters/Characteristics	**Placebo (n=101)**	**5 mg BID (n=99)**	**10 mg BID (n=101)**
Age in years			
5 through 8; count (%)	44 (43.6)	48 (48.5)	47 (46.5)
> 8 through 12; count (%)	57 (56.4)	51 (51.5)	54 (53.5)
mean (SD)	8.8 (1.7)	8.5 (1.8)	8.4 (1.9)
range	5-11	5-11	5-12
Sex			
females; count (%)	44 (43.6)	38 (38.4)	50 (49.5)
males; count (%)	57 (56.4)	61 (61.6)	51 (50.5)
Weight in kilograms			
mean (SD)	35.5 (11.1)	34.4 (11.2)	31.6 (8.2)
range	19-68	17-67	16-58
Race; count (%)			
white	76 (75.2)	76 (76.8)	77 (76.2)
black	14 (13.9)	12 (12.1)	15 (14.9)
hispanic	8 (7.9)	9 (9.1)	7 (6.9)
other	3 (3.0)	2 (2.0)	2 (2.0)
$FEV_{1.0}$ % predicted			
< 65%; count (%)	11 (11.2)	9 (9.4)	13 (12.9)
65% through 80%; count (%)	45 (45.9)	46 (47.9)	47 (45.5)
> 80%; count (%)	42 (42.9)	41 (42.7)	44 (43.6)
mean (SD)	77.6 (9.8)	79.0 (9.9)	74.8 (10.3)
range	[redacted]	[redacted]	[redacted]
number with recorded values	98	96	101
Asthma Episode Scores			
mean (SD)	10.8 (2.6)	10. (2.5)	10.8 (2.6)
range	[redacted]	[redacted]	[redacted]
number with recorded values	101	98	101

The only minor between-group imbalance was a male preponderance in the placebo and 5 mg BID groups that was not as prominent in the 10 mg BID group. These 301 patients

excluded the ten who withdrew prematurely but did not further exclude patients from Dr. Edwards' data (Center 22).

EFFICACY

PRIMARY ENDPOINTS

Six variables were all considered as 'primary' and each was analyzed several ways resulting in an unwieldy number of comparisons. Exhaustive pairwise comparisons were performed and were not 'protected' by statistically significant 'F' Tests. None of these tests for multiple comparisons of multiple endpoints was corrected for the gross underestimation of Type I Error that resulted. Two measures were considered important endpoints by this reviewer. The first of these was the $FEV_{1.0}$, expressed as a percent predicted. The final report 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 (e.g., final visit value expressed as percent predicted) was to serve was never prospectively defined. However, the most common published analyses were of pairwise between-treatment comparisons of change from baseline. Per protocol analyses were carried out in a more restricted patient sample which had been retrospectively checked for strict protocol adherence [14:35-6]. The results of per protocol and stratification analyses did not add to the findings of the intent-to-treat analyses and will be mentioned only briefly. For historical reasons, responder analysis will be more completely reviewed.

$FEV_{1.0}$ (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 between each treatment and the placebo group [14:60, 15:20].

sNDA #20-547 9188IL/0079: ITT FEV1.0 (PERCENT PREDICTED) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT [14:59-60, 15:20]

Treatment	N	Baseline	Mean Change	LS Mean Diff.	p-Value
Placebo	97	77.52	3.04		
5 mg BID	97	78.57	6.52	4.02	0.033
10 mg BID	103	76.98	5.96	3.07	0.097

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

These same data are presented below with Dr. Edwards' data (Center 22) removed to assess efficacy without a possibly corrupted influence [Addendum:49].

sNDA #20-547 9188IL/0079: ITT FEV1.0 (PERCENT PREDICTED) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT OMITTING CENTER 22 [Addendum:49]					
Treatment	N	Baseline	Mean Change	LS Mean Diff.	p-Value
Placebo	96	77.55	3.08		
5 mg BID	94	78.87	6.75	4.20	0.029
10 mg BID	100	77.12	5.93	2.96	0.117
FEV1.0 (percent predicted) was adjusted for size, age, sex and race of the patient. The LS Mean Difference from placebo was adjusted for center effects. 'Endpoint' employs the last value carried forward (LVCF). 'p-Value' applies to the LS Mean Difference.					

The intent-to-treat $FEV_{1.0}$ (percent predicted) change from baseline showed a small effect of about 4% as a difference from placebo. This achieved statistical significance (without adjustment for multiple comparisons or the interim analysis) for the 5 mg BID treatment but not for the 10 mg BID treatment [Addendum:6]. The point estimates of this measure were not dose ordered; i.e., the lower dose was associated with the greater improvement. Per protocol analyses showed similar results of less magnitude and not statistically significant for either dose. The following table presents summary data of this variable at different times during the study. 'End DB Week 2' refers to the end of the second week of the double-blind period. The term 'endpoint' differs from an entry for visit 4 in that the former uses the LVCF for missing data [14:36, 140, 15:18].

sNDA #20-547 9188IL/0079: ITT FEV1.0 (PERCENT PREDICTED) DURING TRIAL, MEAN (SD) [15:18]				
		10 mg BID	5 mg BID	Placebo
Screen	n = 105, 102, 104	74.56 (10.23)	77.31 (8.49)	75.38 (9.79)
End Run-In	n = 104, 99 100	76.99 (9.97)	78.69 (9.95)	77.57 (9.67)
End DB Week 2	n = 104, 99, 99	82.99 (15.26)	84.83 (13.96)	80.86 (13.83)
Endpoint (LVCF)	n = 104, 100, 101	82.84 (15.79)	84.85 (13.08)	80.57 (15.11)
LVCF = Last Value Carried Forward				

The mean change over time in all groups showed improvement, even before randomization and blinded treatment. This effect was substantial in the placebo group, relative to the two active treatment arms. A comparable table (Table T5.4.1) excluding Dr. Edwards' data was not supplied and was not available for inclusion in this report, but it should differ very little from the data presented above [Addendum:21-6].

$FEV_{1.0}$ (LITERS)

The following table presents this parameter at baseline, as change from baseline to endpoint, by treatment group and by pairwise difference between each treatment and placebo group [14:62, 15:4].

sNDA #20-547 9188IL/0079: ITT FEV1.0 (LITERS) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT [14:62, 15:4]					
Treatment	N	Baseline	Mean Change	LS Mean Diff.	p-Value
Placebo	97	1.57	0.06		
5 mg BID	97	1.53	0.13	0.07	0.056
10 mg BID	103	1.42	0.10	0.04	0.316

sNDA #20-547 9188IL/0079: ITT FEV1.0 (LITERS) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT [14:62, 15:4]					
Treatment	**N**	**Baseline**	**Mean Change**	**LS Mean Diff.**	**p-Value**
The LS Mean Difference from placebo was adjusted for center effects. 'Endpoint' employs the last value carried forward. 'p-Value' applies to the LS Mean Difference.					

The same data is presented with Dr. Edwards' data (Center 22) removed to assess efficacy without possibly corrupt data [Addendum:49].

sNDA #20-547 9188IL/0079: ITT FEV1.0 (LITERS) AT BASELINE, CHANGE AT ENDPOINT AND LS MEAN DIFFERENCE FROM PLACEBO IN CHANGE FROM BASELINE TO ENDPOINT OMITTING CENTER 22 [Addendum:43]					
Treatment	**N**	**Baseline**	**Mean Change**	**LS Mean Diff.**	**p-Value**
Placebo	96	1.58	0.06		
5 mg BID	94	1.53	0.14	0.07	0.050
10 mg BID	100	1.43	0.10	0.03	0.356
The LS Mean Difference from placebo was adjusted for center effects. 'Endpoint' employs the last value carried forward. 'p-Value' applies to the LS Mean Difference.					

Statistical significance was not achieved for either dose with or without Dr. Edwards' data nor was the effect of treatment dose ordered by this measure. As was true of the $FEV_{1.0}$ (percent predicted), the per protocol analyses of the $FEV_{1.0}$ (liters) were of smaller magnitude and not statistically significant [Addendum:7]. The table below shows that the mean $FEV_{1.0}$ (liters) improved in all groups, even before randomization and blinded treatment.

sNDA #20-547 9188IL/0079: ITT FEV1.0 (LITERS) DURING TRIAL, MEAN (SD) [15:2]				
		10 mg BID	**5 mg BID**	**Placebo**
Screen	n = 105, 102, 104	1.38 (0.38)	1.51 (0.42)	1.52 (0.39)
End Run-In	n = 104, 99, 100	1.43 (0.38)	1.53 (0.43)	1.57 (0.44)
End DB Week 2	n = 104, 99, 99	1.53 (0.41)	1.66 (0.48)	1.64 (0.46)
Endpoint (LVCF)	n = 104, 100, 101	1.52 (0.41)	1.67 (0.49)	1.63 (0.49)
LVCF = Last Value Carried Forward				

A comparable table (Table T5.4.1) excluding Dr. Edwards' data was not supplied and so was not available for inclusion in this report, but it should differ very little from the data presented above [Addendum:21-6].

OTHER COPRIMARY ENDPOINTS

These included morning and evening PEFR, mean asthma episode score, total nighttime awakenings and concomitant total daily beta-2 agonist use. The intent-to-treat analyses of these paralleled the results of the $FEV_{1.0}$'s. Generally, the 5 mg BID dose performed better than the 10 mg BID dose and the per protocol analyses did not provide clear and consistently superior evidence of a treatment effect over the intent-to-treat analyses. Selected representative weeks are shown in the tables below. The placebo run-in period was described earlier; week 1 was the first week of treatment; and, the endpoint consisted of the last seven days of randomized treatment with LVCF [14:31-3]. Tables

comparable to the ones shown below, but excluding data from Dr. Edwards and Center 22 were not supplied, but the data in them should be very similar ($FEV_{1.0}$ liters T5.1.1; $FEV_{1.0}$ % predicted T5.4.1; Asthma Episode Score T7.1.1; Nighttime Awakenings T8.1.1; AM PEFR T9.1.1; PM PEFR T10.1.1; Beta Agonist Use T13.1.1) [Addendum:21-6].

The AM and PM PEFR were performed with ( ) peak flow meter at the patient's home. Each morning and evening, PEFR measurements were made before the use of the albuterol inhaler. The best of three forced exhalations were recorded on the diary card. Baseline and endpoint values were defined as the summary values from the last seven days of the run-in period before the first dose of trial treatment and from the last seven days of randomized treatment, respectively. The notation, 'DB Week 1', refers to the first week of the double-blind period and subsequent numbers refer to successive weeks.

The AM PEFR was the only flow measurement that had a known temporal relation to preceding treatments. This was a 'trough' measurement, which was performed before the morning dose of trial medication and before the morning use of the albuterol inhaler. Frequent (daily) recordings of it allowed for examination of treatment effects and the variability of them over time. Values summarized for every week of the treatment are presented in the table below.

sNDA #20-547 9188IL/0079: ITT MEAN DAILY AM PEFR (L/min) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [15:110]				
		10 mg BID	5 mg BID	Placebo
Run-In	n = 105, 101, 104	231.01 (60.45)	247.43 (73.77)	248.71 (76.68)
DB Week 1	n = 103, 97, 100	242.18 (65.26)	258.10 (73.97)	248.66 (76.68)
DB Week 2	n = 102, 96, 96	241.11 (67.60)	257.96 (75.57)	252.18 (79.12)
DB Week 3	n = 99, 94, 91	243.52 (67.81)	261.36 (76.19)	255.13 (81.21)
DB Week 4	n = 96, 90, 90	247.45 (68.17)	265.09 (77.98)	256.94 (76.75)
Endpoint (LVCF)	n = 103, 98, 98	244.45 (67.86)	262.09 (77.18)	252.69 (73.79)
LVCF = Last Value Carried Forward				

The baseline mean value of the AM PEFR for the placebo group was between that of the two active treatment groups. A 3.5 L/min increase from baseline in means occurred in the placebo group at the second week with a maximum increase from baseline of 8 L/min at week 4. The two active treatment arms showed a difference of means between placebo run-in and the first double-blind week of 11 L/min and a maximum increase from baseline of 16 to 18 L/min at the fourth week. Both active treatment arms showed a small improvement from baseline to endpoint that exceeded the placebo group and that was inversely dose ordered.

sNDA #20-547 9188IL/0079: ITT PM PEFR (L/min) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [15:128]				
		10 mg BID	5 mg BID	Placebo
Run-In	n = 105, 101, 104	242.59 (61.77)	256.98 (73.72)	263.27 (74.20)
DB Week 1	n = 103, 97, 99	249.63 (65.45)	266.83 (73.25)	261.15 (74.72)

sNDA #20-547 9188IL/0079: ITT PM PEFR (L/min) ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [15:128]			
	10 mg BID	5 mg BID	Placebo
Endpoint (LVCF) n = 102, 98, 97	252.49 (68.40)	271.03 (73.28)	268.45 (72.42)
LVCF = Last Value Carried Forward			

In the table above, the daily mean PM PEFR was generally higher than the AM PEFR for the same treatment group and over comparable times, including the run-in period. The PM PEFR difference in means between run-in and endpoint was higher for the active treatments than for placebo and were inversely dose ordered among active treatments.

During screening, run-in and randomized periods, patients/caregivers scored the severity of asthma symptoms over the past 24-hour period on a 0-3 scale, the criteria for which were presented previously. As was the case with summary statistics for the PEFR, the means given below are daily means calculated from one week of data with the LVCF. Recall that inclusion in the double-blind portion of the trial required a total (7-day) asthma symptom score of ≥ 8, which is equivalent to a daily mean score ≥ 1.143 [14:24, 31-3].

sNDA #20-547 9188IL/0079: ITT DAILY ASTHMA EPISODE SCORE DURING TRIAL ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [15:44]			
	10 mg BID	5 mg BID	Placebo
Run-In n = 105, 101, 104	1.53 (0.38)	1.53 (0.36)	1.55 (0.37)
DB Week 1 n = 103, 97, 100	1.28 (0.55)	1.31 (0.58)	1.32 (0.58)
Endpoint (LVCF) n = 103, 98, 95	1.21 (0.64)	1.18 (0.71)	1.25 (0.66)
LVCF = Last Value Carried Forward			

By this measure, improvement occurred when scores were lower. All treatment groups were associated with a reduction in daily mean asthma episode score of approximately the same magnitude. It is interesting that at endpoint none of the treatments showed a point estimate (mean) sufficiently low to have excluded untreated patients from entering the trial.

Nighttime awakenings specifically because of asthma were recorded on arising each morning as a daily 'yes' or 'no' response [18:273]. Therefore, the maximum score over one week was 7. Every group experienced fewer nighttime awakenings for asthma. The largest reduction in awakenings for asthma was found in the 10 mg BID group and the smallest reduction occurred in the 5 mg BID group. The placebo arm showed a reduction in awakenings that was midway between the two active treatments.

sNDA #20-547 9188IL/0079: ITT TOTAL NIGHTTIME AWAKENINGS PER WEEK, MEAN (SD) [15:60]			
	10 mg BID	5 mg BID	Placebo
Run-In n = 104, 99, 99	1.14 (1.72)	0.71 (1.46)	0.82 (1.30)
DB Week 1 n = 100, 92, 94	0.71 (1.48)	0.84 (1.43)	0.72 (1.42)
Endpoint (LVCF) n = 101, 94, 91	0.55 (1.33)	0.61 (1.51)	0.67 (1.42)
LVCF = Last Value Carried Forward			

These 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 with each treatment including placebo and declined most in the 10 mg BID group.

sNDA #20-547 9188IL/0079: ITT DAILY BETA-AGONIST USE IN PUFFS ESTIMATED OVER 7-DAY PERIODS, MEAN (SD) [15:180]				
		10 mg BID	5 mg BID	Placebo
Run-In	n = 105, 99, 104	3.04 (2.13)	2.95 (2.14)	3.11 (2.52)
DB Week 1	n = 103, 95, 100	2.49 (2.06)	2.59 (1.93)	2.88 (2.45)
Endpoint (LVCF)	n = 103, 95, 94	2.26 (1.90)	2.58 (2.35)	2.76 (2.50)
LVCF = Last Value Carried Forward				

SECONDARY ENDPOINTS

The first of these three was school absenteeism, either actual or 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 [14:32, 16:286, 18:273]. Ironically, the only group so far showing any hint of efficacy, the 5 mg BID treatment, was associated with the most absenteeism, though data variability was large. Data excluding Dr. Edwards' patients at Center 22 were not supplied for any of the secondary endpoints [Addendum:21-6]

sNDA #20-547 9188IL/0079: DAYS REPORTED ABSENT FROM SCHOOL BECAUSE OF ASTHMA [16:286]			
	10 mg BID	5 mg BID	Placebo
Median	0.00	0.00	0.00
Mean	0.23	0.47	0.36
Standard Deviation	0.63	1.10	0.99

Physician or hospital contacts for asthma were also recorded at bedtime each day as a binary response [18:273]. Again, the 5 mg BID treatment group reported the most medical contacts for asthma. Data variability (standard deviation) was again large relative to the mean [16:286].

sNDA #20-547 9188IL/0079: PHYSICIAN OR HOSPITAL CONTACTS FOR ASTHMA [16:286]			
	10 mg BID	5 mg BID	Placebo
Median	0.00	0.00	0.00
Mean	0.09	0.18	0.14
Standard Deviation	0.35	0.62	0.45

The last secondary endpoint was withdrawals specifically due to asthma. These were defined as: 1)hospitalization; 2)more than one Emergency Room visit for asthma during the double-blind period; or, 3)deterioration of asthma requiring chronic treatment with medications that were not permitted [14:26, 287]. Nothing particularly striking emerges from this analysis, though the 5 mg BID treatment appears less effective than the other two in terms of percent withdrawals due to asthma.

sNDA #20-547 9188IL/0079: ITT WITHDRAWALS - TOTAL AND DUE TO ASTHMA, COUNT (%) [14:287]			
	10 mg BID	5 mg BID	Placebo
Due to asthma	2 (1.9)	4 (3.9)	4 (3.8)
Total withdrawals	5 (4.8)	7 (6.9)	11 (10.6)
Number in treatment group	105	102	104

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 [14:41, 18:261-3]. A 'responder' was defined by a patient who met any of the following criteria:

1. 50% decrease in number of nighttime awakenings without an increase in beta agonist use
2. 50% decrease in mean asthma symptom score without an increase in beta agonist use
3. 30% increase in morning PEFR without an increase in beta agonist use
4. 30% increase in evening PEFR without an increase in beta agonist use
5. 50% decrease in daily beta agonist use without an increase in asthma episode score

sNDA #20-547 9188IL/0079: RESPONDER ANALYSIS [14:97]			
	10 mg BID	5 mg BID	Placebo
Number of responders	42	48	37
% responders	40.8	48.5	37.8
Number in treatment group	103	99	98

Though statistical significance is of unknown meaning in a retrospectively defined sample, neither the intent-to-treat nor the per protocol analyses approached it. Dose ordering by this measure was again absent.

SAFETY

ADVERSE EVENTS (AE'S)

About one third of the randomized patients reported at least one AE and an average of 1.6 AE's were reported by each. That is 113 patients reported one or more AE's and a total of 179 AE reports were filed. The following table provides a breakdown of these data excluding those from Dr. Edwards at Center 22 [15:224, Addendum:117].

sNDA #20-547 9188IL/0079: OUTCOME BY PATIENTS AND BY EVENTS [14:104, 109-11,15:224, Addendum:117]						
	10 mg BID		5 mg BID		Placebo	
	Events	Patients	Events	Patients	Events	Patients
Patients at risk, n (% of total patients)		101 (33.6)		99 (32.9)		101 (33.6)
Patients with AE's (% of patients in grp)		35 (31.0)		40 (35.4)		38 (33.6)
Adverse events, n (% of total AE's)	44 (24.6)		74 (41.3)		61 (34.1)	
Deaths	0	0	0	0	0	0
Withdrawal - Serious adverse events	0	0	2	1	0	0
Withdrawal - Non--serious AE's	2	2	1	1	6	5

Review of AE's by COSTART term and arrayed by body system uncovered only four that showed possible dose ordering. The frequencies of patients reporting an AE in the groups were either level or monotonically increasing as follows: placebo $\leq$ 5 mg BID $\leq$ 10 mg BID. These were 'viral infection,' 'hemorrhage,' 'leukopenia' and 'eczema,' and each was reported by only one patient in the highest active treatment group [15:225-8].

DEATHS

None [14:104, 109, 15:224].

SERIOUS ADVERSE EVENTS (SAE'S)

This 8-year old Caucasian female had an acute exacerbation of asthma and a seizure after 17 days of randomized treatment with zafirlukast 5 mg BID. She was hospitalized overnight and released the following day on corticosteroids. She had no history of seizures, received no treatment for them and was withdrawn for these two SAE's. This patient was not from the Dr. Edwards' data set at Center 22 [14:112].

WITHDRAWALS BECAUSE OF ADVERSE EVENTS

Eight patients discontinued from the study prematurely because of non-serious AE's. Five of these patients had six events and received placebo; one patient had one event and had been part of the 5 mg BID group; and, two patients had two events and received 10 mg of zafirlukast BID. One of the placebo group withdrawals was coded as 'pharyngitis' but was described as a persistent URI. Another placebo group withdrawals was coded as 'pharyngitis' and 'aggravation reaction.' The narrative described it as a coexisting viral URI and asthma exacerbation. All of the remaining AE's causing early discontinuation from the trial were for asthma exacerbations [14:109-11]. This section of the review has been corrected to exclude two patients from Center 22 withdrawn for asthma exacerbations.

CLINICAL LABORATORY

These will be completely reviewed as a part of the Integrated Safety Summary, but salient points will be mentioned here. Two hematology findings were considered as AE's; leukopenia (WBC = 3.6×10^9/L) and eosinophilia (Eosinophils = 21%) both in

patients treated with zafirlukast [14:112-3]. The mean hematocrit dropped from baseline to week 4 for all groups, but the largest drops were in the two active treatment groups (PBO = -1.54%; 5 mg = -2.55%; 10 mg = -2.32%) [14:114]. The mean alkaline phosphatase dropped in the placebo group (-3.42%) between baseline and week 4, but rose in the two active treatment groups (5 mg = +1.64%; 10 mg = +1.37%) [14:117]. These data include Dr. Edwards' contributions from Center 22.

VITAL SIGNS

These will be more extensively evaluated in the Integrated Safety Summary. Minor group mean changes in systolic and diastolic blood pressure suggested a trend toward changes between baseline and week 4 that were lesser increases, or even pressure drops, in the active treatments compared with placebo. This trend was more apparent in the higher (10 mg BID) zafirlukast group [14:121-2]. These data include Dr. Edwards' patients from Center 22.

ELECTROCARDIOGRAMS (EKG'S)

These too will be more extensively evaluated in the Integrated Safety Summary. Before treatment, EKG data were available for 101, 97 and 104 patients treated with placebo, 5 mg and 10 mg of zafirlukast, respectively. Mean values and shift tables for quantitative variables (PR interval, QRS interval, 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 [14:123-4].

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. Two placebo patients had quantifiable plasma zafirlukast concentrations at the ends of weeks 2 and 4 and the highest concentration was 3.14 mg/mL. Drug accountability records indicated that the patients were given only placebo. There was no reason to implicate incorrect randomization or dosing. At the end of the placebo run-in period, one patient in each of the active treatment arms also had measurable zafirlukast levels (6.13 and 9.19 ng/mL) and these cases were not further elucidated in the report. The plasma trough concentration were considered as those that had been drawn 10-12 hours after treatment administration and the following presents these data in summary [14:98, 16:8].

sNDA #20-547 9188IL/0079: TROUGH PLASMA CONCENTRATIONS (ng/mL) FOR ZAFIRLUKAST-TREATED PATIENTS [14:98, 16:10-11]

Time Point	Number of Patients/Samples		Summary Statistics		
	Sampled	Quantifiable	Mean.	Median	Range
End DB Week 2					
5 mg BID	16	15	11.39	9.99	
10 mg BID	11	10	22.16	17.10	

sNDA #20-547 9188IL/0079: TROUGH PLASMA CONCENTRATIONS (ng/mL) FOR ZAFIRLUKAST-TREATED PATIENTS [14:98, 16:10-11]					
Time Point	Number of Patients/Samples		Summary Statistics		
	Sampled	Quantifiable	Mean.	Median	Range
End DB Week 4					
5 mg BID	17	15	12.62	7.59	
10 mg BID	20	18	14.70	9.45	
Trough = samples drawn 10 to 12 hours after treatment administration					

In the table above, if $\geq$ 50% of data were not quantifiable, then summary statistics were not calculated. Apparently, this did not occur. If < 50% were not quantifiable, then 0.75 ng/mL was substituted for NQ patients, which may have occurred without any specific knowledge of how this estimation might have contributed to the summary statistics. The mean was consistently higher than the median indicating a distribution skewed to higher plasma concentrations. The ranges for both doses at both time points were very wide raising the possibility of incomplete compliance. None of the three summary statistics was particularly stable over time with both doses mostly trending downward between End Week 2 and End Week 4. This may represent improved catabolism, decreased compliance or (less likely) decreased absorption. These data are from less than 40 patients sampled at visits 3, 4 and 5. Data from the remainder of the patients are incomplete (many patients missing), not well described and presented only in tabular form [16:6-9].

9188IL/0139 A DOSE-RANGING, SAFETY, AND EFFICACY TRIAL WITH ZAFIRLUKAST (ACCOLATE™) IN THE TREATMENT OF PEDIATRIC SUBJECTS WITH MILD-TO-MODERATE ASTHMA

PRINCIPLE INVESTIGATOR	STUDY DATES
James W. Baker, M.D. 545 NW 47th Avenue #310 Portland, Oregon, 97213	First patient recruited: 28 February 1997 Last patient completed: 23 February 1998

SUMMARY

About 400 pediatric patients (5-11 years of age) with asthma were given zafirlukast (10, 20 or 40 mg) or placebo twice daily on an empty stomach over six weeks. They had mild-to-moderate disease ($FEV_{1.0}$ 50-85% of predicted), had reversible airways disease or bronchial hyper-reactivity to provocative challenge and had been given beta-2 agonist therapy. Orally inhaled cromones or corticosteroids were not permitted. This was a four-arm, 1:1:1:1 randomized, double-blind, placebo-controlled, dose-ranging, parallel-group multi-center study. Various measures of $FEV_{1.0}$, PEFR, daytime and nighttime asthma symptoms, beta-2 agonist use, school absenteeism, medical contacts for asthma and withdrawals due to asthma were all evaluated with multitudinous statistical comparisons. No adjustment of the Type I Error significance criterion was made for these multiple tests that were also unprotected by overall significance of 'F' statistics. 'Statistical significance,' as it applied to findings in this study, grossly underestimated the true situation.

With this liberal definition, statistical significance was achieved only for $FEV_{1.0}$ (liters), in the 20 mg group, and for both AM and PM PEFR, in the 10 mg group, all in the modified intent-to-treat sample. By most measures, efficacy endpoints did not show dose ordering. In fact, inverse dose ordering was a frequent finding. Among the three active treatments, the 10 mg BID dose of zafirlukast showed the greater evidence of effect by several measures (AM and PM PEFR, asthma episode score and nighttime awakenings). It also showed the highest beta-2 agonist use at endpoint, resulted in the most absenteeism from school for asthma and the most physician and hospital contacts for asthma among the active treatments. Plasma zafirlukast concentrations were reported in a minority of patients in which they were collected. The levels were very variable and skewed toward higher plasma concentrations.

There were no deaths or serious adverse events. The majority of early withdrawals were due to exacerbations of asthma. One patient who received active drug developed leukopenia ($3.5x10^9$) and another had two hyperglycemic blood samples

during the double-blind portion of the trial. Several other technical abnormalities of laboratory results were less impressive.

OBJECTIVES

The objective of this trial was to assess the effect of zafirlukast on asthma in a pediatric population compared with placebo as reflected by changes in forced expiratory flows, daytime and nighttime asthma symptoms, daily beta agonist usage and determination of plasma concentrations of zafirlukast following twice-daily oral dosing. An additional objective was to assess whether the response to zafirlukast treatment increased with increasing doses across the dose range studied [11/19/98 1:9, 18].

PROTOCOL

This was a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group, multicenter, trial in which zafirlukast was given twice daily to pediatric patients with mild-to-moderate asthma. The trial included the following 4 parts: a one-week observation and screening period; a 7- to 14-day single-blind placebo run-in period; a 6-week double-blind treatment period to assess efficacy and safety; and. a 52-week open-label safety-extension period which will be reviewed separately. Patients were also allowed to enter the open-label portion of the trial directly without having participated in the double-blind portion of the trial [11/19/98 1:10, 19]. The flow chart of the protocol and procedures is shown below:

sNDA #20-547 9188IL/0139: SCHEDULE OF EVENTS [11/19/98 1:20]					
	Screen	Single Blind Run-In		Double Blind Treatment	
Week	0	1	2	5	8
Visit	1	2	3	4	5
Vital Signs	X		X	X	X
Laboratories		X			X
ECG's	X				X
PFT's	X		X	X	X
$FEV_{1.0}$ Reversal	X				
Randomization			X		
History	X				
Physical Exam	X		X	X	X
QOL		X			X
Sample for PK		X			X
Tanner Staging	X				

PATIENTS

Randomization of 413 pediatric patients with mild-to-moderate asthma resulted in 379 (91.8%) patients who completed the trial [11/19/98 1:47].

SCREENING PERIOD CRITERIA

Pediatric patients were eligible for screening if they provided written informed consent (parent or legal guardian also signed the patient's consent form) and met the following additional criteria [11/19/98 1:22]:

1. were boys or girls aged 5 through 11 years (girls could not be sexually active)
2. were nonsmokers
3. had a documented clinical history of asthma that included one of the following:
   a. reversible airway disease as shown by at least a 12% increase in $FEV_{1.0}$ after inhaled beta agonist (within 4 weeks of screening)
   b. nonspecific bronchial hyper-reactivity to methacholine or histamine challenge within 6 months of screening, where the provocative concentration of methacholine that produced a 20% decrease in $FEV_{1.0}$ (PC_{20} $FEV_{1.0}$) was at least 0.25 mg/ml but not greater than 8.0 mg/ml, or the PC_{20} $FEV_{1.0}$ of histamine was less than or equal to 8.0 mg/ml
4. were given beta-2 agonist therapy for asthma
5. demonstrated an $FEV_{1.0}$ of at least 50% and no greater than 85% of predicted without medication, i.e., 6 hours after inhaled beta-2 agonist, 8 hours after oral beta-2 agonist, or 48 hours after salmeterol treatment
6. performed 3 acceptable forced expiratory maneuvers with 1 reproducible $FEV_{1.0}$ within 10% of the largest $FEV_{1.0}$
7. had a stature-to-weight ratio within the normal range
8. were able to swallow tablets

DOUBLE-BLIND PERIOD CRITERIA

For inclusion into the randomized, double-blind portion of the trial, pediatric patients must have met the following criteria [11/19/98 1:23]:

1. demonstrated an $FEV_{1.0}$ of at least 50% and no greater than 85% of predicted without medication (at least 6 hours after inhaled beta-2 agonist) on the day of randomization, visit 3 (patients who were within this range on the first day of screening, but out of this range on the day of potential randomization were not eligible to continue in the trial)
2. demonstrated clinically mild-to-moderate asthma, as defined by an asthma-episode score totaling at least 8 (scale 0 to 3 daily) during the last 7 consecutive days of the 7- to 14-day single-blind placebo run-in period
3. performed 3 acceptable forced expiratory maneuvers, with 1 reproducible $FEV_{1.0}$ within 10% of the largest $FEV_{1.0}$
4. complied with dosing regimen, proper use of peak flow meter, and diary recording
5. demonstrated compliance with trial medication of at least 85% during the placebo run-in period

EXCLUSION CRITERIA

Any of the following was regarded as a criterion for exclusion from the trial [11/19/98 1:23-4]:

1. patients would be placed at undue risk by a temporary postponement of initiating long-term asthma therapy, according to the investigator's judgement
2. laboratory results with a clinically significant deviation from the reference range, except for abnormalities related to asthma or allergy
3. evidence of hepatic disease other than evidence of isolated hyperbilirubinemia associated with a diagnosis of Gilbert's Syndrome
4. evidence of chronic lung disease other than asthma, including cystic fibrosis or bronchopulmonary dysplasia
5. evidence from physical examination or medical history of any disease that affects gastrointestinal absorption
6. evidence of cardiovascular disease
7. immunization with a live viral vaccine (e.g., ~~measles-mumps-rubella~~, varicella) within 3 weeks of screening
8. use of oral or inhaled corticosteroids within 4 weeks of screening
9. use of barbiturates within 4 weeks of screening
10. use of salmeterol within 48 hours of screening (salmeterol use was not permitted during the trial)
11. use of cromolyn sodium, nedocromil sodium, or theophylline within 4 weeks of screening
12. use of astemizole within 3 months of screening
13. new use or changing regimen (dose and frequency) of cromolyn sodium nasal solution or nasal corticosteroids within 4 weeks of screening (patients whose regimen did not change during the 4 weeks before screening were eligible, and their regimen could not change during the screening and double-blind trial periods)
14. upper or lower respiratory tract infection with a significant asthma flair requiring additional or increased amounts of asthma medication within 4 weeks of screening
15. acute illness within 1 week of screening
16. history of drug or alcohol abuse
17. vaccination with hepatitis A and B surface antigen within 6 weeks of screening
18. entry into the single-blind lead-in period of this trial on a previous occasion
19. seasonal asthma as defined by symptoms or therapy confined to less than 2 months per year
20. participation in another trial with an investigational drug within 4 weeks of screening in this trial
21. history of convulsive disorders or any significant central nervous system disorder (attention deficit disorder was acceptable if a patient did not require treatment or was being treated with an established dose of medication)

22. inability to take tablets
23. participation in a previous trial involving zafirlukast
24. use of cisapride within 1 week of screening

WITHDRAWAL CRITERIA

Patients were withdrawn from the trial if any of the following circumstances occurred [11/19/98 1:25]:

1. had a significant adverse event
2. developed a significant concurrent illness unrelated to asthma
3. chose to withdraw from the trial, or the patient's parent or legal guardian wished the patient to withdraw
4. did not adhere to the rules and procedures for this trial
5. any other situation in which the investigator considered continued participation in the trial would not be in the best interest of the patient
6. was lost to follow-up

TREATMENT

Randomization to treatment took place at the end of the screening period, after patients had qualified for the trial. Formulations and lot numbers of the active treatments, placebo controls and the rescue medication are shown in the table below [11/19/98 1:25-6].

sNDA #20-547 9188IL/0139: TREATMENT FORMULATIONS & LOT NUMBERS [11/19/98 1:26]		
Treatment	**Formulation**	**Lot**
5 mg Zafirlukast		T53036, N63131
10 mg Zafirlukast		T63122, T63137
20 mg Zafirlukast		N63128, T63138, T63129, T63132, T73046
Placebo Zafirlukast		N53033, N53039
Albuterol Inhalers		ZPA024, ZPO318, ZPO527

Zafirlukast and placebo tablets appeared identical and were packaged in foil blisters. Each supply of medication was contained in a sealed box. Four blisters (10 tablets each, total 40 tablets) were provided for each week.

During the double-blind period of the trial, patients were given placebo or 1 of the 3 doses of zafirlukast (10, 20, or 40 mg) BID for 6 weeks. The trial medication was taken as two tablets twice daily, either 1 hour before or two hours after food. It was acceptable for the trial medication to be hidden in a light snack (e.g., tablespoon of applesauce, "fruit roll-up"). The date and time of dose administration were recorded in the case report form (CRF). Patients were allocated to treatment in balanced blocks of four. The protocol didn't explicitly state how the daily doses were comprised of the available formulations. For example, the dose 10 mg BID, administered as two tablets twice daily, may be given

as two 5 mg tablets twice daily or one placebo and one 10 mg tablet twice daily, though the former is assumed.

Albuterol (Ventolin™, Glaxo Wellcome) inhalers [redacted] were dispensed to each prospective patient following qualification for screening at visit 1. Additional inhalers were dispensed to each patient, as needed, throughout the trial. The albuterol inhaler canister was weighed (without the spacer or actuator) before dispensing and again at each visit during the double-blind period. The weights were recorded on the CRF as a measure of compliance [11/19/98 1:26-7].

Prescription or nonprescription medications for allergy were used only by agreement between the investigator and the sponsor. Antihistamines were not permitted for at least 48 hours before pulmonary function testing. Acetaminophen was the sole medication allowed for analgesia. Aspirin and aspirin-containing compounds and nonsteroidal anti-inflammatory drugs were not permitted during the trial. Astemizole, inhaled cromolyn or nedocromil sodium, methylxanthines, or beta-2 agonists, other than the albuterol rescue medication, were not prescribed or used during the trial. Beta-2 agonists were administered with an [redacted] spacer. The use of inhaled or oral corticosteroids during the screening or double-blind period necessitated withdrawal from the trial. Treatment with cromolyn was discontinued 4 weeks before screening. Desensitization was not initiated or discontinued during the trial; however, allergy injections could continue at maintenance levels. The influenza vaccine was allowed during this trial. Use for the first time or a change in treatment (dose and frequency) of cromolyn nasal solution or nasal corticosteroids within 4 weeks of screening were not permitted. Patients whose regimen did not change during the 4 weeks before screening were eligible; their regimen could not change during the screening and double-blind periods. The specific type and amount of all medication was documented fully on the Prior and Concurrent Treatment CRF [11/19/98 1:28].

PARAMETERS

Though a host of efficacy parameters was listed as coprimary, only the absolute $FEV_{1.0}$ (liters) and PEFR (L/min) were used to calculate sample size. No adjustment of the Type I Error significance criterion was made for these multiple tests that were also unprotected by overall significance of 'F' statistics. The 'primary focus' was the endpoint, defined as the last observed $FEV_{1.0}$ (percent predicted) taken no later than 24 hours after the last day patients were administered trial medication, carried forward in the intent-to-treat patient group. The intent-to-treat comparison between placebo and the 10 mg BID treatment was designated as the 'primary contrast' to 'confirm' findings from study 0079. Per-protocol, stratification and responder analyses were also performed [11/19/98 1:32, 35, 37-8, 9:45].