

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-547/S007

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical

NDA #: 20-547 / SE1-007

SEP 13 1999

Applicant: Zeneca Limited

Name of Drug: Accolate (Zafirlukast) tablets 10 mg

Indication: Prophylaxis and chronic treatment of Asthma in children through 11 years of age.

Documents Reviewed: Volumes 1.1-1.76, dated September 17, 1998; an addendum also dated September 17, 1998; a submission dated November 4, 1999; volumes 1-37, dated November 19, 1998; volumes dated October 30, 1998 and February 15, 1999, and statistical analysis plans submitted December 2, 1998. CANDA dated September 17, 1998, updated November 19, 1998 and March 18, 1999.

This review pertains to two placebo-controlled, dose response studies in children 5 to 11 years of age.

The medical officer for the submission is R. Anthracite, M.D. (HFA-570) with whom this review was discussed.

Background

Accolate is a leukotriene receptor antagonist. Accolate was approved for the prophylaxis and chronic treatment of asthma for adults and adolescents on September 25, 1996.

The addendum dated September 17, 1998 contains analyses of Study 0079 deleting data from Dr. Edwards (Center 22) at the request of FDA's Division of Scientific Investigations. The efficacy results, with Dr. Edwards's patients deleted, will be discussed in this review.

This reviewer requested in a telephone conversation that the sponsor should submit statistical analysis plans for the two studies and indicate whether these plans had already been submitted to the agency. The sponsor provided these plans in their December 2, 1998 submission, along with the dates when the plans had been submitted to the agency.

This reviewer had trouble producing the output from the sponsor's CANDA running on our computer systems. It was discovered that the

sponsor had used PROC MIXED output from version 6.11 in their programs. Certain values outputted in that SAS version are not outputted in our SAS version 6.12. Therefore, the programs did not work properly. The sponsor provided, in their March 18, 1999 submission, a laptop containing their CANDA and SAS version 6.11 from which the sponsor's tables were produced.

Dose Response Studies

Studies 0079 and 0139 were placebo-controlled, randomized, parallel group studies in children 5 to 11 years of age with mild-to-moderate asthma. Both studies had a 7-14 day placebo run-in period. The treatment period for Study 0079 was 4 weeks, whereas it was 6 weeks for Study 0139.

Patients on Nasalcrom or nasal corticosteroids could continue on their regimen, if dosage was kept stable during the study.

To enter the study the pediatric patient had to demonstrate reversible airways disease, as shown by at least a 12% increase in FEV₁ after beta-agonist use (within 4 weeks of screening) or through a 20% decrease in FEV₁ during methacholine or histamine challenge (within 6 months of screening). He/she had to have an FEV₁ of 50 to 85% of predicted normal in Study 0139 (50 to 90% for Study 0079) and have 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 run-in period.

5mg Accolate BID, 10mg Accolate BID and placebo BID were compared in Study 0079. The patient took one tablet every 12 hours. 10mg Accolate BID, 20mg Accolate BID, 40mg Accolate BID, and placebo BID were compared in Study 0139. The patients in Study 0139 took two tablets (each half the dose) every 12 hours.

All patients in both studies were issued albuterol inhalers (Ventolin) and were told to use them in accordance with package labeling. The patient recorded albuterol usage in the asthma daily diary. This review will only focus on total daily usage. (The patient recorded the number used for exercise and number used for asthma symptoms or low peak flow.)

PFTs in both studies were performed at each clinic visit. The best of 3 maneuvers was used for FEV₁. The time of day that any given patient had pulmonary function testing was standardized throughout the trial. It was not standardized, however, between patients (the measurement could be taken at any time since their dose in the morning).

PEFRs in both studies were measured by the patient using a peak flow meter each morning and evening before usage of

the albuterol inhaler. Patients recorded the best of three PEFr determinations on each occasion on the asthma diary card.

During the screening, run-in, and randomized periods of the trial, patients in both studies recorded at bedtime whether asthma symptoms occurred during the day or night, and scored the severity of the asthma episodes according to the following system:

- | | |
|---|---|
| 0 | no wheezing, chest tightness, or coughing |
| 1 | 1,2 or 3 mild coughing or wheezing spells |
| 2 | more than 3 mild spells that interfere with activity, play, school, or sleep |
| 3 | spells longer than 2 hours or spells causing the patient to stay at home or to see a doctor |

An asthma spell (episode) is a single period of 1 or more of the following signs of asthma: wheezing, coughing, chest tightness, or shortness of breath. As noted above, a score of 8 or greater during the last 7 days of placebo run-in was needed to enter the trial.

The patients in both studies also recorded the number of nighttime awakenings in the asthma daily diary.

The sponsor defined peak flow variability as $100\% * \frac{|PM\ PEFr - AM\ PEFr|}{(\text{average daily PEFr})}$.

Baseline diary assessments, except for nighttime awakenings, were the means of the last 7 days of the placebo run-in period, before the first dose of trial medication. End point diary assessments, except for nighttime awakenings, were the mean value from the last 7 days of randomized treatment. For nighttime awakenings the weekly totals, rather than means, were used. Baseline FEV₁ was the assessment before receiving randomized treatment.

The protocols stated that the primary efficacy variables were

- (1) office-visit FEV₁ (expressed in liters and as a percent of predicted normal)
 - (2) morning PEFr
 - (3) B-agonist use (puffs per day before exercise, puffs per day for asthma symptoms or low PEFr, and total daily puffs)
 - (4) asthma episode score
 - (5) nights awakened by asthma
 - (6) evening PEFr
 - (7) peak flow variability
- (Peak flow variability was not included as a primary variable in Study 0079.)

The study report for Study 0139 stated that percent predicted FEV₁ was the primary efficacy measure. [The statistical analysis plan, dated May 6, 1998 and submitted to IND [redacted] on May 8, 1998, stated that percent predicted FEV₁ was the primary measure. This was after the last patient had completed on February 23, 1998.] The protocols of both studies stated that one hundred patients per treatment group was sufficient to detect a 0.20 liter difference in FEV₁ (SD=0.50 L) for pairwise comparisons between treatments at the 0.05 significance level with 80% power.

All variables were tested using an ANCOVA model, which included treatments, center, treatment-by-center interaction with baseline value as covariate. If the treatment-by-center interaction was insignificant at the 0.10 level, it was dropped from the model.

In Study 0139 the protocol stated that the primary comparison was 10mg versus placebo (to confirm the results of Study 0079). In Study 0079 the primary comparison in the study report was stated to be the combined doses against placebo. The statistical analysis plan of Study 0079 (dated August 22, 1997 and submitted to the agency on August 26, 1997) stated that a comparison of the combined doses versus placebo would be done to control experiment-wise error rate, that there would be no adjustment for multiple comparisons, and that percent predicted FEV₁ would be the primary efficacy measure. The last patient in this study completed on June 6, 1997, which was before the date of the statistical analysis plan. The protocol's sample size justification in Study 0079 gave no indication that both Accolate treatments would be combined.

The protocol of Study 0079 stated that there would be an interim analysis after 30 patients. The sponsor stated that there would be an assessment of variability and that there could be an adjustment of sample size after this look, but there would be no stopping for efficacy. The study report states that the primary purpose of the interim analysis was to assess the safety of Accolate. The study report did not address the assessment of variability and possibility that sample size might be adjusted. [Since this look is so early (relative to final sample size), there would be little effect on the p-value from this administrative look even if sample size had been increased for reasons other than variability.]

Results

In Study 0079, a total of 311 pediatric patients at 37 centers were randomized into the study. One patient on Accolate 10mg was immediately lost to follow-up and did not provide any efficacy or safety data. An additional 5 patients did not provide any efficacy data. Therefore, the ITT population contained 305

children (101 placebo, 100 5mg Accolate, and 104 10mg Accolate). 288 patients (93 placebo, 95 5mg Accolate, 100 10mg Accolate) completed this study.

In Study 0139, a total of 413 pediatric patients at 41 centers were randomized into the study. The ITT population contained 413 patients (105 placebo, 104 10mg Accolate, 105 20mg Accolate, and 99 40mg Accolate). One patient relocated and did not provide any efficacy data. 379 patients (94 placebo, 98 10mg Accolate, 94 20mg Accolate, and 93 40mg Accolate) completed the study.

In both studies the treatment groups were comparable at baseline in demographic and baseline efficacy variables.

In Study 0139 the sponsor pooled centers because of small sample sizes. Centers 0004, 0006, 0043, 0049, and 0050 were combined into 1 center (West coast); Centers 0010, 0023, and 0028 were combined (East coast); Centers 0020 and 0030 were combined (Midwest); and Centers 0018, 0034, and 0047 were combined (Southeast). There was no pooling of centers in Study 0079.

[The sponsor's study report for Study 0139 stated that the pooling of centers was different than was used in the CANDA and the sponsor's analyses. (The study report said that centers 0018 and 0034 were pooled into a "Midwest" center and centers 0020, 0030 and 0047 were pooled into a "Southeast" center.) The pooling of the CANDA was more appropriate and agreed with the geographic labels. The sponsor admitted the error in their study report in the March 18, 1999 submission.]

The table below provides the effect sizes and p-values comparing treatment groups with the respective placebo group of their study for most of the "primary" efficacy variables considered in the protocols. No adjustment has been made for multiple comparisons. (As noted above, the protocol for Study 0139 stated that the comparison of the 10mg Accolate group with placebo was primary.) The sample sizes differed for each variable, but were about 92-102 per treatment group. The subset analyses of the variables, mean number of nighttime awakenings (baseline ≥ 0) and mean change in mean total daily beta-agonist use (baseline greater than 2 puffs/day), were added to the list of primary variables because in Study 0079, the sponsor stated that these variables supported a 10mg dose of Accolate.

**APPEARS THIS WAY
ON ORIGINAL**

ITT Endpoint Analysis

Mean Changes and (p-values, uncorrected for multiple comparisons, comparing dose levels with respective placebo treatments). Center 22 (Dr. Edwards) has been excluded in Study 0079.

Variable	Study 0079			Study 0139			
	Placebo	Accolate Dose		Placebo	Accolate Dose		
		5mg	10mg		10mg	20mg	40mg
Mean Changes in Percent Predicted FEV ₁	3.08	6.75 (0.029)	5.94 (0.117)	4.63	6.52 (0.254)	7.93 (0.052)	7.69 (0.221)
Mean Changes in FEV ₁	0.06	0.14 (0.050)	0.10 (0.356)	0.09	0.14 (0.138)	0.17 (0.025)	0.16 (0.067)
Mean Changes in Morning PEFr	8.93	15.37 (0.088)	13.88 (0.270)	4.73	21.79 (0.001)	9.86 (0.223)	8.98 (0.581)
Mean Changes in Evening PEFr	6.30	14.31 (0.055)	11.14 (0.345)	-1.61	13.18 (0.003)	6.49 (0.064)	7.50 (0.121)
Mean Change in Peak Flow Variability	-0.92	-2.30 (0.114)	-3.29 (0.088)	-1.61	-3.21 (0.227)	-3.16 (0.084)	-2.37 (0.485)
Mean Changes in Weekly Nighttime Awakenings	-0.16	-0.15 (0.692)	-0.60 (0.146)	-0.45	-0.52 (0.424)	-0.46 (0.977)	-0.24 (0.316)
Mean Changes in Weekly Nighttime Awakenings (Baseline ≥ 0)	-0.68	-0.96 (0.755)	-1.66 (0.030)	-1.20	-1.52 (0.130)	-1.36 (0.566)	-1.08 (0.979)
Mean Changes in Asthma Episode Scores	-0.32	-0.40 (0.347)	-0.33 (0.817)	-0.31	-0.41 (0.298)	-0.36 (0.611)	-0.40 (0.375)
Mean Changes in Total Daily Beta Agonist Use	-0.45	-0.57 (0.435)	-0.76 (0.094)	-0.39	-0.85 (0.079)	-0.66 (0.280)	-0.84 (0.074)
Mean Changes in Total Daily Beta Agonist Use (Baseline Greater Than 2 Puffs/Day)	-0.55	-1.00 (0.096)	-1.20 (0.016)	-0.66	-1.28 (0.018)	-0.90 (0.242)	-1.19 (0.065)

The p-values for the combined treatment groups versus placebo in Study 0079 were 0.031 for percent predicted FEV₁ and 0.097 for FEV₁ in liters.

Reviewer's Comments

The testing of the combined doses (5 mg and 10 mg) versus placebo in Study 0079 is somewhat problematic. It is a test of whether the drug is effective, but it does not address the issue of which dose to use in children. The question of which dose to use is addressed by the individual pairwise comparisons with placebo.

The results described above are suggestive that Accolate is effective in children, in that almost all treatment groups effect sizes are larger numerically than placebo. However, it is doubtful that any statistical claim of effectiveness for any particular dose can be made. Since the statistical analysis plans are dated after the last patient completed, this reviewer must consider them as *post hoc*. Although both statistical analysis plans state that percent predicted FEV₁ was the primary efficacy

measure, the protocol used differences in FEV₁ in liters to calculate sample size. [This reviewer agrees, however, that percent predicted FEV₁ is the best primary efficacy measure in children, because of the differing lung sizes.] In light of these circumstances, this reviewer must consider multiple comparison and multiple endpoint issues to evaluate the effectiveness in both studies. The 5mg dose of Accolate is approaching significance in Study 0079 for FEV₁ assessment, but with two different effectiveness measures for this PFT measurement, with the FEV₁ change rather than the change in percent predicted FEV₁ used to determine sample size, no claim is substantiated. [The nominal p-value for this comparison, however, is very close to significance (p=0.0502).] Moreover, the 10mg dose has not demonstrated efficacy in either study, for either of these FEV₁ parameters. The evidence of effectiveness for the 10mg dose using PEFr assessments in Study 0139 is weakened by the failure of the 20 and 40 mg doses to show effectiveness with the observed large drop in mean change from baseline for these two doses.

The sample size of the study may not have been adequate to demonstrate efficacy for FEV₁, in that the sample size was chosen to detect a difference of 0.20 liters between placebo and a treatment group. The observed difference was about half the expected difference.

This reviewer was able to duplicate the sponsor's results from the CANDA.

Overall Comments

These two dose response studies are suggestive of efficacy in that the mean changes from baseline of the Accolate groups are almost always numerically larger (more negative) than the mean changes from baseline of the placebo group. However, considering the results of both studies, no dose level has adequately demonstrated efficacy.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson

/S/

8/27/99

Dr. Nevius

/S/

9-13-99

This review contains 8 pages of text.

cc:
Orig NDA 20-547/SE1-007
HFD-570