SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: ACCOLATE™

ACTIVE INGREDIENT: zafirlukast (ZD9188)

Trial title (number): Randomized, Double-blind, Placebo-controlled, Crossover Trial of the Effect of ACCOLATE™ on Upper- and Lower-airway Symptoms and Markers of Inflammation Following Exposure to Cat Allergen (9188US/0019)

Clinical phase: IV

First subject recruited: 28 January 1998
Last subject completed: 14 May 1998
Zeneca approval date: 26 January 1999

Publications: J Corren, S Spector, L Fuller, G Rachelsfsky, S Siegel, H Shanker, and M Minkwitz. Effect of Zafirlukast (Accolate®) on Pulmonary Responses to Natural Cat Allergen Exposure. Allergy Research Foundation, Los Angeles, California and Zeneca Pharmaceuticals, Wilmington, Delaware

OBJECTIVES: The primary objectives of this trial were to evaluate the efficacy of multiple doses of ACCOLATE (steady-state conditions) on reducing upper- and lower-airway symptoms and response (immediate and late phase) including markers of inflammation, following exposure to cat allergen.

METHODS

Design: single-center, randomized, double-blind, placebo-controlled, 2-period crossover trial, involving approximately 18 completed subjects.

Population: approximately 25 subjects were expected to be exposed to trial medication and procedures to achieve at least 18 completed and evaluable subjects; evaluable subjects were those subjects who completed both periods of the trial.

Key inclusion criteria: men or women aged 12 to 65 years, personal history of cat-induced asthma and rhinitis, treated with short-acting β_2-agonist only

Key exclusion criteria: history of unstable asthma or chronic lung disease other than asthma, any history of illness that might confound the results of the trial or place the subject at undue risk; any use of disallowed concomitant medications within a specified time period before screening

Dosage: Zeneca Pharmaceuticals supplied the following trial medications (formulation number followed by lot numbers): 20-mg zafirlukast, F7157, N53212D, and matching placebo tablets F7173, N53020A. Subjects received 20-mg zafirlukast bid or matching placebo bid during trial Period 1 and the alternative treatment during trial Period 2.

Key assessments: maximum drop in FEV_1 as a percentage change from prechallenge baseline for a fixed allergen exposure time; maximum composite upper and lower airway-symptom scores for a fixed allergen exposure time; eosinophil count and percent in nasal lavage and induced sputum after cat challenge; nasal lavage and induced sputum eosinophilic cationic protein (ECP) levels

Demography: Twenty-three subjects (13 men and 10 women) aged 18 through 49 years entered the trial. Eighteen subjects completed the trial. Eleven subjects were randomized to the treatment sequence for trial Period 1 and 12 subjects were randomized to the treatment sequence for Period 2. All 5 subjects withdrawn were from Period 2 of the trial; however, subjects were replaced in both treatment sequences during the trial. The final number of subjects in each treatment sequence was 11 and 7 in Periods 1 and 2, respectively.

RESULTS

Efficacy: FEV_1 results for spirometry performed immediately before and after cat-room allergen-challenge exposure, showed a significant treatment effect favoring zafirlukast-treated subjects. These results were also duplicated at the end-of-challenge FEV_1 as a % of predicted, the maximum percent change in FEV_1, and the end-of-challenge PEFR. There was also a trend toward improved PEFR at baseline for zafirlukast-treated subjects but the difference between treatments was not statistically significant.

Statistical significance was not achieved in the comparison of treatment groups for upper-airway symptoms scores; however, significance favoring the zafirlukast-treated group was achieved across all measures of lower-airway symptoms. In all cases, zafirlukast-treated subjects showed fewer symptoms. No significant treatment differences associated with eosinophils or ECP levels were found in nasal lavage cells or for induced sputum testing. There was an indication that subjects had a reduction in nasal lavage cells after treatment with zafirlukast, but not for the primary cell type of interest, eosinophils.

Little or no association was found between the level of *fel d* 1 antigen exposure and the level of efficacy variables examined (ie, upper- and lower-airway symptoms, total cells, differentiated cells, and ECP levels).

In summary, the results of cat-allergen challenge, which simulates a natural exposure to cats, demonstrated a consistent attenuation of the lower-airway symptoms and the drop in pulmonary function associated with this exposure but did not significantly alter nasal responses.

Safety: No subjects died during the trial and none had serious adverse events. The rate of adverse events varied little between treatment groups and no nonserious adverse events were considered as related to treatment. The most common adverse event occurring during the trial was pharyngitis, which occurred in 3 (15.8%) of subjects during placebo treatment and no subjects during zafirlukast treatment. No significant changes in vital signs occurred during trial treatment. Treatment with 20-mg zafirlukast bid was comparable with placebo-treatment and was safe and well tolerated.