U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

sNDA/Serial Number:	NDA 20-829/S-059 (eCTD 137), 20-830/S-061 (eCTD 138), and 21-409/SD-036 (eCTD 135)
Drug Name:	SINGULAIR™ Tablets (NDA 20-829/S059), SINGULAIR™ Chewable Tablets (NDA21-409/S036), and SINGULAIR™ Oral Granules (NDA21-409/S036).
Indication(s):	EIB
Applicant:	Merck
Date(s):	Received 5/26/11
Review Priority:	10
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Keywords: NDA labeling

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Merck submitted this labeling supplement on May 26, 2011, to modify the product labeling for Singulair line of products, in response to a request from FDA dated April 28, 2011, in which FDA requested that information from the pediatric exercise-induced bronchoconstriction (EIB) study - protocol 377-00 be added to the labeling for Singulair so as to furnish adequate information for the safe and effective use of the drug.

The applicant submitted the study (protocol 377-00) results and data (b) (4) to provide additional information for the prevention of exercise-induced bronchoconstriction (EIB) in patients 6 to 14 years of age in order to fulfill the Pediatric Research Equity Act commitment. The applicant seeks to extend their indication which is currently in patients aged 15 years and above to include patients from 6 to 14 years of age. I reviewed the study report and performed statistical analyses on their primary endpoint; my analyses confirmed the applicant study results. Based on my statistical review of the application, the changes made to the package insert and patient package insert are reasonable.

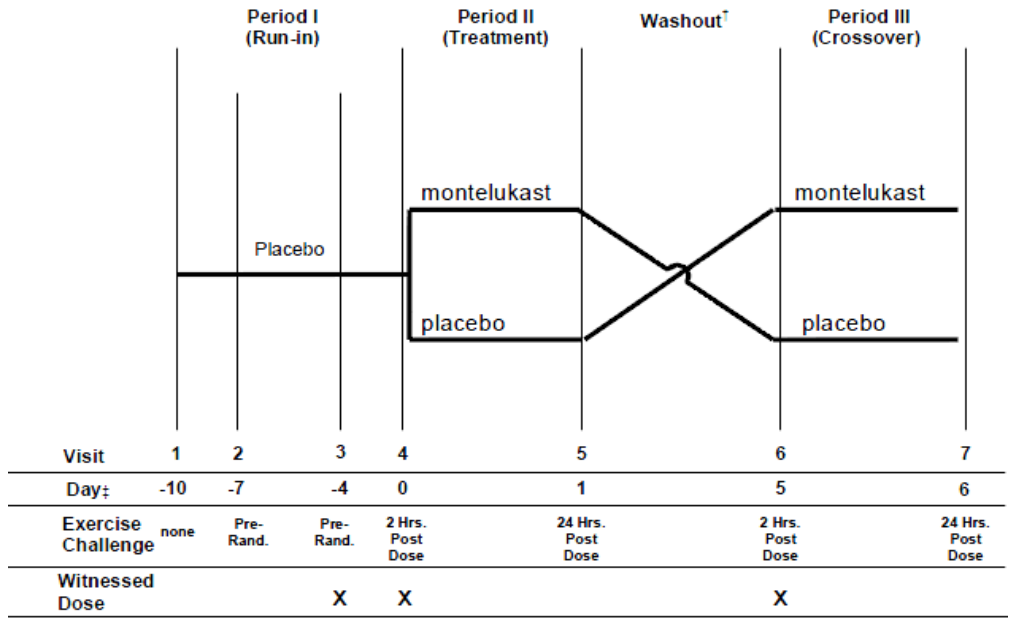
1.2 Brief Overview of Clinical Studies

Protocol 377-00 was a double-blind, placebo-controlled, multicenter, crossover study to evaluate the effects of a single oral dose of Singulair (4 mg or 5 mg), compared with placebo, on EIB in pediatric patients aged 4 to 14 years old. The study was conduced in 12 centers in Colombia (2), Costa Rice (1), Estonia (1), and United States (8) during the years of 2008 to 2010. The primary objective of this study was to determine the effect of a single oral dose of Singulair, compared with placebo, on EIB as measured by the maximal percent fall in FEV_1 (post-exercise change from pre-exercise baseline) after exercise challenge performed 2 hours post-dose.

A summary of the study design is as follows and shown in Figure 1:

> The study included three periods. During period I, at Visit 1 and Visit 2, no study medication was to be taken. During Visit 3, patients received a single witnessed dose of the matching-image placebo for Singulair in a single-blind manner. This study drug was administered 2 hours before the Visit 3 exercise challenge. During periods II and III, according to the allocated treatment sequence: 1) Singulair followed by placebo; 2) placebo followed by Singulair), each patient received a single witnessed dose of oral study drug in a double-blind fashion during Periods II (Visit 4) and III (visit 6).
>
> Exercise challenges were performed at Visits 2, 3, 4, 5, 6, and 7. The 2-hour exercise challenges occurred 2 hours after the witnessed dose of study medication at Visits 3, 4, and 6. The 24-hour exercise challenges (Visits 5, and 7) occurred 20 to 24 hours after the witnessed dose of study medication given at Visits 4 and 6.

Figure 1: Study Schematic



† Period II and Period III will be separated by 3 to 7 days, unless the patient develops an upper respiratory infection, in which case the interval between the two periods may be up to 14 days.

Source: Study report p377.pdf (NDA 20-829/s036 [eCTD 128])

Of the 66 patients randomized into the study, 63 patients completed the study. Of note, patients ages 6 to 14 years received a 5 mg tablet; the 4 mg dose was not dispensed as no 4 to 5 years olds were randomized.

For all exercise challenge endpoints, the baseline for the challenge was the FEV_1 measurement obtained 5 minutes before exercise and was specific to each exercise challenge.

Maximum Percent Fall in FEV_1 after exercise challenge at 2 hours post-dose was the primary endpoint. Maximum Percent Fall in FEV_1 was defined as the percent change from pre-exercise baseline FEV_1 (FEV_1 value measured 5 minutes before exercise) to the lowest FEV_1 within 60 minutes after exercise and was calculated using the following formula:

$$\text{Maximum Percent Fall in } FEV_1 = \left[\frac{\text{Pre-Exercise } FEV_1 \text{ (L)} - \text{Lowest } FEV_1 \text{ After Exercise (L)}}{\text{Pre-Exercise } FEV_1 \text{ (L)}}\right] * 100$$

The analysis of efficacy data was carried out using a completer's analysis population (63) which was defined as all randomized patients who received the witnessed dose of study drug in both active treatment periods and had at least one post-exercise FEV_1 measurement in both active treatment periods. The primary endpoint was analyzed using an Analysis of Variance (ANOVA) model with factors for patient, treatment, and period effects. Treatment comparison was performed using adequate contrast within the ANOVA model. In addition, least-squares (LS)

means and corresponding 95% confidence intervals (CIs) were computed for each treatment, as well as the difference in LS means and the corresponding 95% CIs. Of note, the applicant included the Maximum Percent Fall in FEV_1 after exercise challenge at 24 hours post-dose in the label, which was one of the secondary endpoints.

1.3 Statistical Issues and Findings

During my review of the study, I found that the results generated by the applicant and by me are similar.

The major efficacy findings are as follows:

- The treatment effect of Singulair in EIB was measured by the Maximum Percent Fall in FEV_1. A single dose of Singulair significantly reduced the Maximum Percent Fall in FEV_1 (p=0.021) after exercise challenge performed at 2 hours post-dose, compared with placebo. The LS mean for Maximum Percent Fall in FEV_1 was 15% on Singulair and 20% on placebo. The effect size was -5%, with a 95%CI of (-9%, -1%). A single dose of Singulair significantly reduced the Maximum Percent Fall in FEV_1 (p= 0.005) after exercise challenge performed at 24 hours post-dose, compared with placebo. The LS mean treatment difference was -4% with a 95% CI of (-7, -1). Results are shown in Table 1.

Table 1: Analysis of Maximum Percent-Fall in FEV_1 after Exercise Challenge at 2 and 24 hrs Post-dose (Completers Analysis Population)

Time of exercise challenge following medication administration	**Mean maximum percent fall in FEV_1***		**Treatment difference % for Singulair versus Placebo (95%CI)***
	Singulair	Placebo	
2 hours	15	20	-5 (-9, -1)
24 hours	13	17	-4 (-7, -1)

* Estimated from the ANOVA model with factors for patient, treatment, and period effects.

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/s/

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02/15/2012

JOAN K BUENCONSEJO
02/15/2012
I concur with Ms. Zhou's review.