CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-301

STATISTICAL REVIEW(S)

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

NDA/Serial Number:	22-301
Drug Name:	Encapsulated Mesalamine Granules, 0.375 g (eMG) (5-aminosalicylic acid or 5-ASA)
Indication(s):	Maintenance of Remission of Ulcerative Colitis
Applicant:	Salix Pharmaceuticals
Date(s):	Stamp: December 21, 2007; PDUFA October 31, 2008
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
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Keywords: NDA Review, Clinical studies, Multiple Comparisons, Hierarchical Analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on data from two randomized and controlled studies, Encapsulated Mesalamine Granules, 0.375 g (eMG) (5-aminosalicylic acid or 5-ASA) taken once a day for six months appear to be efficacious for maintenance of remission of Ulcerative Colitis, as assessed by relapse-free rate, the primary endpoint. The results from Study MCUP3003 provided clearer evidence of efficacy compared to StudyMCUP 3004. Both studies failed to show consistent secondary endpoint efficacy. For Study MCUP3004, the trial completed at approximately the same time the protocol was amended to reduce the sample size; thus interpretation of even the primary result is problematic, and, at best, that study should be considered as showing marginal efficacy in support of the first trial.

1.2 Brief Overview of Clinical Studies

The sponsor has submitted results from two, Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trials to investigate the efficacy and safety of Encapsulated Mesalamine (5-aminosalicylic acid or 5-ASA), Granules (eMG) for maintenance of remission of Ulcerative Colitis (UC). The studies were conducted in males and non-pregnant females ages 18 years and older, with mildly to moderately active UC who had previously demonstrated remission of UC. Study MPUC3003 enrolled 160 U.S. subjects and 145 in Russia; Study MPUC3004 enrolled 103 in the U.S. and 154 in Russia.

The primary efficacy analysis endpoint was the proportion of subjects who were relapse-free after six months of treatment. Relapse or treatment failure was defined as a rectal bleeding score of 1 or more and a mucosal appearance score of 2 or more as described in the revised Sutherland Disease Activity Index (DAI). In addition, subjects who experienced a UC flare or initiated medication used previously to treat UC were also considered treatment failures. Subjects were randomized 2:1 to receive the test product (eMG) or placebo. Secondary endpoints included rectal bleeding score, mucosal appearance score, physicians' rating of disease activity, and individual components of the Sutherland DAI.

1.3 Statistical Issues and Findings

For Study MPUC3003, the primary efficacy comparison shows a highly statistically significant difference between Mesalamine and placebo ($p < .001$). For Study MPUC3004, the primary efficacy results were also statistically significant ($p = .029$).

The sponsor's imputation strategy assigned treatment failures to subjects who terminated the study early but only if the reason for drop-out was related to lack of efficacy or a UC-related adverse event. This approach to handling drop-outs was changed in late-stage protocol amendments after study completion; the original plan was to consider all subjects who terminated early as treatment failures. The results from this more conservative analysis do not change the efficacy conclusions for the first study; however, the efficacy results for Study MPUC3004 are marginal ($p = .046$).

To control for experiment-wise type I error, the sponsor planned a hierarchical testing strategy for the secondary endpoints, although the order of testing was specified in a protocol amendment after completion of studies but prior to unblinding. For Study MPUC3003, only the first secondary endpoint (change from baseline in rectal bleeding score) showed a statistically significant improvement from baseline. None of the secondary endpoints were statistically significant in Study MPUC3004.

The planned sample size for Study MPUC3004 was reduced in a late-stage protocol amendment. A total of 257 patients instead of the planned 300 were analyzed. This could be interpreted as an unplanned or early stopping of the study. Even though the decision appears to have been made prior to breaking the blind, the study completion date precedes the protocol amendment date. A sensitivity analysis shows that if the additional 43 subjects were enrolled and had a 68% treatment success rate for both treatment groups (consistent with the observed placebo rate) then the primary ITT analysis would have failed ($p = .06$). This may suggest that the study was terminated early to avert possible failure of the primary endpoint.

The reviewer performed several subgroup analyses using the combined study data. These results suggest a smaller effect size for the Russian and males subpopulations but can be attributed to higher placebo response rates. Efficacy results are consistent across baseline disease severity as well as time on remission.

2 INTRODUCTION

2.1 Overview

Encapsulated mesalamine (5-aminosalicylic acid or 5-ASA) granule is a capsule oral dosage form of mesalamine developed by Salix Pharmaceuticals, Inc., as a once daily (QD) dosing regimen in the maintenance of remission of ulcerative colitis (UC). The proposed dosage and administration is four 0.375 g eMG capsules (1.5 g/day) administered QD ——— for subjects in remission of UC. Several mesalamine-containing dosage forms have been approved in the United States for use in UC over the last twenty years. However, there is, currently, no marketed mesalamine product in the US with QD dosing for the maintenance or remission of UC.

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Disease activity in the two trials MPUC3003 and MPUC 3004 was measured using the revised Sutherland DAI. The Sutherland DAI was selected because it represents a historical standard for assessing the symptoms of UC (rectal bleeding, mucosal appearance, physician's rating, and stool frequency). No standard scoring system for measuring UC disease activity has been validated for clinical use. At the request of the agency and to clarify the diagnosis of UC remission, two changes were made to the Sutherland definition of mucosal appearance for protocols MPUC3003 and MPUC 3004 before the studies were started. For these studies, the term "mild friability" was removed from the mucosal appearance score of 1, and the term "moderate friability" was removed from the mucosal appearance score of 2 as defined in Sutherland, et al., 1987. (See end-of-phase 2 meeting minutes dated October 6, 2004.)

The sponsor conducted two similar, Phase 3, double-blind, randomized, parallel-group, placebo-controlled, multi-center trials to investigate the efficacy and safety of Encapsulated Mesalamine

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