CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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 #:	205613
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Indication(s):	Treatment of Mild to Moderate Ulcerative [redacted] (b) (4)
Applicant:	Salix Pharmaceutical, Inc.
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1 EXECUTIVE SUMMARY

Salix Pharmaceutical, Inc. has submitted the results of two, similar phase 3, randomized, parallel-group, double-blind, placebo-controlled, multicenter studies to assess the efficacy and safety of budesonide foam (2 mg/25 ml bid for two weeks, followed by 2 mg/25 ml qd for four weeks) versus placebo foam in approximately 280 subjects with active mild to moderate distal UC (ulcerative proctitis or proctosigmoiditis). The primary endpoint was the proportion of subjects who achieved remission. Remission was defined as having achieved an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency subscales of the MMDAI at the end of 6 weeks of treatment or at withdrawal. Both studies were designed to show the superiority of budesonide foam to placebo.

Study BUCF3001 showed budesonide foam to be superior to placebo with respect to the primary endpoint of remission. For the ITT population, 38% (51/133) achieved remission in the budesonide arm, and 25.8% (34/132) achieved remission in the placebo arm (p=0.03). The difference in treatment arms and the 95% CI for the difference was: 12.6% (1.5%, 23.7%). These results were consistent with analyses based on the Per Protocol population. The reviewer's sensitivity analysis considered subjects who did not complete the study, as non-responders The result of this analysis showed 4 additional budesonide foam treatment failures resulting in a reduction of treatment effect to: 9.6% (-1.5%, 20.6%). The sponsor's sensitivity analyses were consistent with their primary analysis results.

The sponsor proposed three key secondary endpoints: (1) the proportion of subjects who had no rectal bleeding at end of study; (2) numbers of weeks subjects had no rectal bleeding; and (3) the proportion of subjects with endoscopy score of 0 or 1 at end of study. Instead of endpoint #2 the sponsor analyzed numbers of subjects with no rectal bleeding at each "scheduled assessment." Because of the hierarchical nature of the testing and the post hoc nature of key endpoint #2, only the first key secondary endpoint was formally testable. The results for secondary endpoint #1 showed 46.6% vs 28% response in the budesonide and placebo arms respectively (p=0.002). The 95% CI of the difference was (7%, 30%).

Study BUCF3002 also showed budesonide foam to be superior to placebo with respect to the primary endpoint of remission. In the ITT analysis, 44% (59/134) achieved remission in the budesonide foam arm, and 22.4% (33/147) achieved remission in the placebo arm (p<0.001). The difference in treatment arms and the 95% CI for the difference was: 21.6% (10.8%, 32.4%). These results were consistent with analyses based on the Per Protocol population. The reviewer's sensitivity analysis considered subjects who did not complete the study, as non-responders. The results of this analysis showed 2 additional treatment group non-responders, and the results as well as the sponsor's sensitivity analyses were consistent with the primary analysis. The larger treatment effect observed for this study can be attributed to disproportionate results that favored budesonide observed for one of the Russian sites.

As discussed for Study BUCF3001, the only key secondary endpoint that was testable was the proportion of subjects who had no rectal bleeding at end of study. The results for this secondary endpoint showed 50% vs 28% response in the budesonide and placebo arms respectively (p<0.001).. The 95% CI of the difference was (10%, 33%).

From a statistical perspective, the data from two adequate and well-controlled studies have shown efficacy of budesonide foam compared to placebo in subjects with active mild to moderate ulcerative proctitis or proctosigmoiditis.

2 INTRODUCTION

Budesonide has been approved for human use in over 30 countries, including the US, since 1982. First developed for treatment of bronchial asthma and allergic rhinitis, budesonide has since been developed for the treatment of inflammatory bowel diseases. Budesonide foam is, also, approved in Europe for the treatment of ulcerative proctitis (UP) and ulcerative proctosigmoiditis (UPS).

The sponsor claims that the rectal foam formulation was specifically designed to improve both the patient's ability to retain the drug in the rectum following administration as well as distribution of the active drug to the rectum and sigmoid colon. Therefore, they have submitted two identical clinical trials for the approval of their formulation.

2.1 Overview

The studies included in this NDA were conducted under the IND # 104,725. The sponsor has submitted the results of two phase 3 clinical trials (Study BUCF3001 and Study BUCF3002). The two studies are identical in design, endpoints, sample size, and statistical methodology.

The table below shows a brief description of these two studies.

Table 1: A Brief Description of the Two Pivotal Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design/Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	BUCF3001 (Salix)	5.3.5.1.4	Evaluation of the efficacy and safety of budesonide 2 mg rectal foam compared to placebo foam	Randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 study	Budesonide 2 mg rectal form or placebo foam twice daily for 2 weeks followed by once daily for 4 weeks	265	Mild to moderate active ulcerative proctitis or proctosigmoiditis	6 weeks	Complete; Full
Safety and efficacy	BUCF3002 (Salix)	5.3.5.1.5	Evaluation of the efficacy and safety of budesonide 2 mg rectal foam compared to placebo foam	Randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 study	Budesonide 2 mg rectal form or placebo foam twice daily for 2 weeks followed by once daily for 4 weeks	281	Mild to moderate active ulcerative proctitis or proctosigmoiditis	6 weeks	Complete; Full

Source: Sponsor's Study Report

Both studies are randomized, double-blind, parallel-group, placebo-controlled, multicenter studies to assess the efficacy and safety of Budesonide foam (2mg/25ml bid for 2 weeks, followed by 2mg/25ml qd for 4 weeks) versus placebo foam in approximately 280 subjects with active mild to moderate ulcerative proctitis or proctosigmoiditis.

2.2 Data Sources

All data were supplied electronically by the applicant as SAS transport files and located in the CDER electronic document room (EDR):
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3 STATISTICAL EVALUATION

3.1 Study Objectives (Studies BUCF3001 and BUCF3002)

The primary objective of the two studies was to establish the efficacy profile of rectally administered budesonide foam administered as 2 mg/25 mL BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks, as compared to an equivalent volume of rectally administered placebo foam over the same dosing schedule, in subjects who presented with a diagnosis of active mild to moderate ulcerative proctitis (UP) or ulcerative proctosigmoiditis (UPS).

The secondary objective of the studies was to confirm the safety of budesonide foam following 6 weeks of dosing in subjects with active mild to moderate UP or UPS.

3.2 Study Design and Endpoints (Studies BUCF3001 and BUCF3002)

Eligible subjects were to be randomized in a 1:1 ratio to either active budesonide (the study drug) or placebo. The studies were comprised of four study phases defined as follows:

1. Screening (Visit, 1; Day -21 to Day -7)
2. Run-In/Stabilization (Visit 2; Days -7 to Day -1)
3. Treatment (Visit 3 Randomization; Visits 4-6 Treatment, and Visit 7 [End of Treatment /Week 6 or Withdrawal]). Days 1-42
4. Follow-up or End of Study (Visit 8; Day 56)

During the Run-In/Stabilization phase, single-blind (patient-blinded) placebo medication was administered. On the day of the Run-In visit (Visit 2), subjects were instructed on its proper administration and they administered placebo foam BID, with the first dose in the clinic in the morning and then approximately 12 hours later in the evening. The BID dosing continued up to Day -1 of the study, the day immediately prior to randomization. Subjects were instructed not to administer the medication on the day of randomization (Visit 3).

Primary and Secondary Endpoints
The primary efficacy endpoint objective was to compare the proportions of subjects in remission in each study group. Remission was defined as an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency subscales of the Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks of treatment or withdrawal.

The key secondary efficacy endpoint objectives were to compare:

1. The proportions of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of treatment or withdrawal.

2. The number of weeks subjects achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase (Weeks 1 through 6).
3. The proportions of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of six weeks of treatment or withdrawal.

It is noted that the secondary endpoint # 2 was not analyzed in the CSR; instead the sponsor analyzed the "number of scheduled assessments" subjects achieved a rectal bleeding MMDAI subscale score of 0.

Other secondary efficacy endpoints included:

1. The proportion of subjects who achieved a score of 0 for rectal bleeding subscale and a combined score of ≤ 2 for bowel frequency and physician's global assessment (PGA) in the MMDAI subscales at the end of 6 weeks of treatment.

2. The proportion of subjects who achieved an MMDAI total score ≤ 3 with ≥ 2 points of improvement from baseline at the end of treatment.

3. The proportion of subjects who achieved improvement of ≥ 1 point from baseline in the MMDAI endoscopy subscale score at the end of 6 weeks of treatment.

4. The proportion of subjects who achieved improvement of ≥ 1 point from baseline in the MMDAI rectal bleeding subscale score at the end of 6 weeks of treatment.

5. The proportion of subjects who achieved ≥ 3 point improvement from baseline in the MMDAI total score, including improvement of ≥ 1 point from baseline in the rectal bleeding subscale and improvement of ≥ 1 point from baseline in endoscopy subscale of the MMDAI, at the end of 6 weeks of treatment.

6. Mean change from baseline to Week 6 visit in MMDAI total score and subscale scores.

These additional secondary endpoints will not be included in the label; therefore, we do not discuss them in this review.

MMDAI

The Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks of treatment) was used to assess the overall disease activity for each subject. The MMDAI rates four indices each on a scale of 0 to 3 with a maximum total score of 12. These indices, as shown in Table 2, are based on stool frequency, rectal bleeding, physician's global assessment, and endoscopy findings. The modification made to the original Mayo Disease Activity Index was the deletion of "friability" from an endoscopy score of 1. With this modification, the presence of friability reflects an endoscopy score of 2 or 3; see Table 2.

All four indices were scored at randomization (Day 1; Visit 3) and at the end of treatment (Week 6 or Withdrawal; Visit 7). In addition, an abbreviated MMDAI based on 3 indices (excluding endoscopy) was scored at the screening visit (Visit 1), and at Treatment Visits 4, 5, and 6 (Weeks 1, 2, and 4).

Subjects were to possess a baseline MMDAI score between 5 and 10, inclusive. Subjects must have scored ≥2 on the MMDAI rectal bleeding component and ≥2 on the MMDAI endoscopy or sigmoidoscopy component at Randomization to be eligible.

For subjects who discontinued prior to Week 6, a sigmoidoscopy, UP/UPS assessments, and safety assessments were to have been performed at the time of withdrawal.

Table 2: Modified Mayo Disease Activity Index (MMDAI)

Index	Stool frequency [a]	Rectal Bleeding [b]	Physician's Global Assessment [c]	Endoscopy/Sigmoidoscopy Findings
MMDAI or Ulcerative Colitis Symptom Score (UCSS) [d]	0 = Normal number of stools per day for this patient 1 = 1 to 2 more stools than normal 2 = 3 to 4 more stools than normal 3 = 5 or more stools than normal	0 = no blood seen 1 = streaks of blood with stool less than half the time 2 = obvious blood with stool most of the time 3 = blood alone passed	0 = normal 1 = mild disease 2 = moderate disease 3 = severe disease	0 = normal or inactive disease 1 = mild disease (erythema, decreased vascular pattern[d]) 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = severe disease (spontaneous bleeding, ulceration)

a. Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.
b. The daily bleeding score represented the most severe bleeding of the day.
c. The physician's global assessment acknowledged the 3 other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.
d. The modification made to the Mayo Index was the deletion of "friability" from an endoscopy score equal to 1. With this modification, the presence of friability was indicative of an endoscopy score of 2 or 3.
Source: Sponsor CSR

Analysis Populations
TheIntent-to-treat (ITT) population included all randomized subjects. Efficacy analyses were performed on the ITT population by treatment group to which subjects were randomized.

The safety population included all randomized subjects who were administered at least one dose of the study drug. If a subject received both placebo and budesonide foam during the study, he/she was counted in the budesonide foam group in all safety analyses, but was counted in the randomized treatment group in all efficacy analyses.

The per-protocol (PP) population included all subjects in the ITT population who did not have major protocol deviations.

3.3 Statistical Methods (Studies BUCF3001 and BUCF3002)

For the primary efficacy analysis, the sponsor stated in their protocol that they planned to summarize the number and proportion of subjects who have achieved remission at Week 6/Withdrawal Visit by treatment arm and utilize logistic regression to test for a statistically significant difference in the proportions between the two treatment arms after adjusting for the analysis center effect. They planned to form the analysis centers in such a way that there would be sufficient subjects per pooled analysis center for the assessment of center effects. The null hypothesis of no difference between

treatment arms would be rejected if the resulting p-value was less than 0.05. If it was evident that the proportion of subjects achieving remission at Week 6/Withdrawal Visit was confounded by the influence of background variables, then the primary efficacy analysis would be conducted adjusting for the effects of the background variables using logistic regression. They would note the differences between this adjusted analysis and the unadjusted analysis, and the impact of such differences would be discussed.

However, in the review of the protocol at the IND stage, the reviewer had conveyed to the sponsor that the use of logistic regression methods were inappropriate and that a Cochran-Mantel-Haenszel (CMH) test (with stratification) should be used for the primary efficacy analysis. In addition, adjusting a logistic regression model for the effects of the background variables selected after the results of the study had been revealed was an inappropriate strategy.

The sponsor did not revise their protocol based on our recommendations; but noted in their SAP that primary endpoint analyses would be based on both the logistic regression model as well as the CMH test, adjusted for analysis center. In this review, we consider the use of the CMH test as the principle analysis method and present analyses using the CMH and Pearson chi-square tests, where appropriate.

Power and Sample Size Considerations
For the sample size calculations, the sponsor assumed a 40% remission rate for budesonide foam and a 23% remission rate for placebo. These assumptions were based on previous conducted budesonide foam trials. Based on these assumptions and a significance level of 5%, 133 subjects in each treatment arm was estimated to enable the test for the primary efficacy hypothesis to achieve a power of 85%. These studies planned to enroll approximately 140 subjects in each of the 2 treatment arms.

Multiple Comparison/Multiplicity
The study had three key secondary endpoints as well as multiple secondary efficacy variables collected at numerous time points. Study-wise type I error was to be controlled by testing the primary endpoint, then the secondary endpoints as listed in Section 3.2 above in a hierarchical fashion.

Randomization
Subjects were randomized in a 1:1 allocation to the two treatment arms. Each center randomized subjects to treatment arms using a randomization code generated by the interactive voice response system (IVRS) that was independent of the randomization code of any other center in the study.

Handling of Dropouts or Missing Data
In the final version of the protocol, the sponsor stated that for subjects who discontinue prematurely, missing values would be imputed using the last completed post-baseline assessment.

In the SAP, the sponsor specified that missing MMDAI subscale scores would be imputed as follows:

- The bowel frequency and rectal bleeding subscale scores were determined by the investigator at screening; randomization; and Weeks 1, 2, 4, and 6/EOT. If the post-baseline subscale scores were missing, but could be calculated from subjects' diary entries, then the calculated scores from subjects' diary entries were to be used for the missing subscale scores. Otherwise, the last non-missing post-baseline subscale scores were to be carried forward to impute missing scores.

- The PGA subscale score was determined by the investigator at screening; randomization; and Weeks 1, 2, 4, and 6/EOT. A missing post-baseline PGA subscale score was to be imputed by the last non-missing post-baseline subscale score.

- The endoscopy/sigmoidoscopy subscale score was determined by the investigator at randomization and Week 6/EOT. The last non missing Endoscopy/Sigmoidoscopy score (including the baseline score) was to be carried forward to impute the missing Week 6/EOT endoscopy/sigmoidoscopy subscale score.

Sensitivity Analyses
The SAP specified that two sensitivity analyses were to be performed**:**

- Worse case analysis: Subjects with missing bowel frequency, rectal bleeding or endoscopy sub-scale scores at a time point under consideration would be considered as treatment failure.

- Observed case analysis: Subjects with missing subscale scores at a time point under consideration would be excluded from the analysis.

3.4 Study Results

3.4.1 Study BUCF3001

Patient Disposition, Demographic and Baseline Characteristics
A total of 265 subjects were randomized and received at least 1 dose of study drug: 133 budesonide subjects and 132 placebo subjects. See Table 3. Overall, 85% of subjects completed the study (budesonide 81% and placebo 88%). The most common reasons for early discontinuation from the study were AEs (budesonide 10%, placebo 5%), "other" (3%, 5%; of which lack of efficacy was the most common [2%, 5%]), and subject request (5%, 2%).

Subjects were enrolled at 55 sites in the United States and Russia. With respect to disposition by country, 167 subjects (63%) were enrolled in the U.S. (budesonide 62%, placebo 64%) and 98 subjects (37%) were enrolled in Russia (budesonide 38%, placebo 36%). A larger proportion of subjects from the U.S. (18%) compared with subjects from Russia (11%) discontinued early from the study; the reasons for early discontinuation were relatively similar among subjects from the 2 countries.

Table 3: Disposition of Subjects (Randomized Population) - Study BUCF3001

Category	Placebo n (%)	Budesonide Foam 2 mg/25 mL n (%)	Total n (%)
Subjects randomized	132	133	265
Subjects randomized and received at least 1 dose of study drug	132 (100)	133 (100)	265 (100)
Subjects completed study	116 (87.9)	108 (81.2)	224 (84.5)
Subjects discontinued study early	16 (12.1)	25 (18.8)	41 (15.5)
Adverse event	7 (5.3)	13 (9.8)	20 (7.5)
Subject request	2 (1.5)	6 (4.5)	8 (3.0)
Lost to follow up	0	1 (0.8)	1 (0.4)
Noncompliance	0	1 (0.8)	1 (0.4)
Pregnancy[a]	0	0	0
Other	7 (5.3)	4 (3.0)	11 (4.2)
Low cortisol	0	2 (1.5)	2 (0.8)
Lack of efficacy	6 (4.5)	2 (1.5)	8 (3.0)
Meeting exclusion criterion 3n prior to randomization	1 (0.8)	0	1 (0.4)

Source: Sponsor's Study Report
a: Subject 0678-0014 in the placebo group had an ectopic pregnancy reported as a serious adverse event.
Note: Percentage calculated is based on the number of subjects randomized.

The mean age of subjects overall was 42 years with 94% of subjects in each group less than 65 years of age. While both treatment groups had more female subjects than male subjects, the difference in these proportions was larger in the placebo group (39% males, 61% females) than in the budesonide group (46%, 54%). Most subjects were White (budesonide 87%, placebo 93%) or Black/African American (11%, 4%), and 16% overall were Hispanic or Latino.

The treatment groups were comparable with respect to baseline characteristics. The mean normal number of stools per day (i.e., when no UP/UPS symptoms were present) was 1.3 in the budesonide group and 1.4 in the placebo group and the mean MMDAI total score was 8 in each group. Most subjects in each treatment group had MMDAI bowel frequency subscale scores of 1, 2, or 3 overall 27%, 39%, 27%, respectively) and bleeding subscale scores of 2 (86% overall). The majority of subjects had MMDAI PGA subscale scores of 2 (budesonide 79%, placebo 81%), moderate MMDAI endoscopy/sigmoidoscopy finding subscale scores (90%, 91%), and moderate severity of disease (89%, 83%). Over 90% of subjects in each group had established disease (budesonide 98%, placebo 93%). More subjects had UPS (budesonide 71%, placebo 67%) than UP (28%, 33%). The mean duration of disease was approximately 5 years in both treatment groups. Most subjects had never smoked (budesonide 65%, placebo 74%) or were past smokers (26%, 20%) and most were non-drinkers (budesonide 62%, placebo 61%). The two treatment groups were similar with respect to mean weight and body mass index (BMI).

Analysis of the Primary Efficacy Endpoint

In the SAP, the sponsor indicated that they would use a logistic regression method for the primary efficacy analyses as well as the CMH test stratified by analysis center. Table 4 shows the sponsor's analysis of the primary endpoint (adjusted for country), including individual components of the remissions score. These results show the rate of remission was significantly higher in the budesonide foam 2 mg/ 25 mL group (38.3%) compared with the placebo group (25.8%)

The sponsor's primary analysis is based on LOCF, that is, for subject who discontinued early, missing values were imputed using the last completed post-baseline assessment. Table 4 also shows

the three components of the remission score; the first two components of the remission score are, respectively, the third and first key secondary endpoints. The third component score was not a pre-specified secondary endpoint.

Table 4: Sponsor's Analysis of Primary Efficacy Endpoint (Study BUCF3001)

Efficacy Endpoint/ Category	Placebo N = 132 n (%)	Budesonide Foam 2 mg/25 mL N = 133 n (%)	P-value[a]	P-value[b]
Achieved Remission[c]			0.0324	0.0322
Responder	34 (25.8)	51 (38.3)		
Non-responder	98 (74.2)	82 (61.7)		
Components of Remission Score				
Achieved MMDAI Endoscopy Score of 0 or 1			0.0486	0.0488
Responder	57 (43.2)	74 (55.6)		
Non-responder	75 (56.8)	59 (44.4)		
Achieved MMDAI Rectal Bleeding Score of 0			0.0022	0.0020
Responder	37 (28.0)	62 (46.6)		
Non-responder	95 (72.0)	71 (53.4)		
Achieved Improvement or No Change from Baseline in MMDAI Bowel Frequency Score			0.0734	0.0731
Responder	91 (68.9)	105 (78.9)		
Non-responder	41 (31.1)	28 (21.1)		

Source: Table 14.2.1a.
Abbreviations: ITT = intent to treat; LOCF = last observation carried forward; MMDAI = Modified Mayo Disease Activity Index.
a P-value was obtained from a logistic regression model with fixed effects: treatment arm and country.
b P-values were obtained from the Cochran-Mantel-Haenszel (CMH) test adjusting for country.
c Remission was defined as an endoscopy score of 0 or 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency subscales of the MMDAI at the end of 6 weeks of treatment.

Table 5 shows the reviewer's results of the primary endpoint analysis of the proportion of subjects who achieved remission for the ITT and PP analysis populations. The reviewer utilized the CMH test, adjusting for country; and the sponsor's ITT data set with LOCF imputation. The results for the ITT and PP populations are identical to the sponsor's assessments.

Table 5: Reviewers Analysis of Primary Efficacy Endpoint – Study BUCF3001

Population	Budesonide Foam n/N (%)	Placebo n/N (%)	P-Value	Difference Budesonide – Placebo (95% CI)
ITT	51/133 (38.4)	34/132 (25.8)	0.03	12.6% (1.5%, 23.7%)
PP	49/129 (38.0)	33/128 (25.8)	0.04	12.2% (1.0%, 23.5%)
ITT*	47/133 (35.3)	34/132 (25.8)	0.09	9.6% (-1.5%, 20.6%)

* Sensitivity analysis; (drop-outs = no remission)
Source: Reviewer

The reviewer also performed a sensitivity analysis which assigned treatment failure to subjects who terminated early. The results of this analysis (Table 5) showed 4 additional budesonide treatment failures resulting in a reduction of treatment effect.

The sponsor also performed additional sensitivity analyses, and these, in general, were consistent with the primary analysis based on the use of LOCF.

Key Secondary Endpoints:
Key secondary endpoints are listed below:

1. The Proportion of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment.
2. The number of weeks subjects achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase (Weeks 1 through 6).
3. Proportion of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment.

The sponsor did not analyze the key secondary endpoint #2 as pre-specified. Instead, two additional endpoints were presented in the study report: (1) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments and (2) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at study weeks 1 to 6. Neither of these endpoints can be considered pre-specified and neither would be suitable for statistical testing or labeling. In an IR, the sponsor was requested to perform an analysis of the pre-specified endpoint; however, these results were similar to those for the endpoints already in the CSR and further clarification not provided.

Several other secondary efficacy endpoints were introduced by the sponsor; however, since these endpoints will not be included in the label, we do not report them in this review.

The results of the key secondary variables listed above for study BUCF3001 are shown in Table 6. Note that because of the hierarchical nature of the testing and the post hoc nature of key endpoint #2, only the first key secondary endpoint can be formally tested. The results for key endpoints #1 and #3 are also shown in Table 4.

Table 6: Analysis of Key Secondary Endpoints – Study BUCF3001

Population	Budesonide Foam n/N (%)	Placebo n/N (%)	P-Value	Difference Budesonide – Placebo (95% CI)
Key Secondary # 1[1]	62/133 (46.6)	37/132 (28.0)	0.002	18.6% (7.2%, 30.0%)
Key Secondary # 2[2]			--[4]	
Responders at:				
0 Assessment (no resp.)	56/133 (42)	80/132 (61)		
1 Assessment	16/133 (12)	18/132 (14)		
2 Assessments	25/133 (19)	18/132 (14)		
3 Assessments	28/133 (21)	14/132 (11)		
4 Assessments	8/133 (6)	2/132 (2)		
Key Secondary # 3[3]	74/133 (55.6)	57/132 (43.2)	--[4]	12.5% (0.5%, 24.4%)

1. Subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment
2. Subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments
3. Subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment
4. Results not testable

Source: Reviewer

These results indicate that significantly larger proportions of subjects in the budesonide foam group compared with the placebo group achieved an MMDAI rectal bleeding score of 0 (budesonide 46.6%, placebo 28.0%) at the end of 6 weeks of treatment (key secondary endpoint #1).

The numbers of subjects who achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase were greater in the budesonide group for those who responded at 2, 3 and 4 scheduled assessments. (Key Secondary Endpoint #2).

A larger proportion of subjects in the budesonide foam group compared with the placebo group achieved an MMDAI endoscopy score of 0 or 1 (budesonide 55.6%, placebo 43.2%) at the end of 6 weeks of treatment (key secondary endpoint #3).

3.4.2 Study BUCF3002

Patient Disposition, Demographic and Baseline Characteristics

A total of 281 subjects were randomized: 134 subjects to budesonide and 147 subjects to placebo. See Table 7. All of these subjects received at least 1 dose of study drug. Overall, 85% of subjects completed the study (budesonide 86%, placebo 85%). The most common reasons for early discontinuation from the study were AEs (budesonide 10%, placebo 4%), subject request (3%, 5%), and "other" (2%, 5%), of which lack of efficacy was the most common (0, 3%).

Subjects were enrolled at 59 sites in the United States and Russia. With respect to disposition by country, 181 subjects (64%) were enrolled in the U.S. (budesonide 63%, placebo 65%) and 100 subjects (36%) were enrolled in Russia (budesonide 37%, placebo 35%). A larger proportion of subjects from the U.S. (17%) compared with subjects from Russia (10%) discontinued early from the study; the reasons for early discontinuation were similar among subjects from the 2 countries.

Table7: Disposition of Subjects (Randomized Population) - Study BUCF3002

Category	Placebo n (%)	Budesonide Foam 2 mg/25 mL n (%)	Total n (%)
Subjects randomized	147	134	281
Subjects randomized and received at least 1 dose of study drug	147 (100)	134 (100)	281 (100)
Subjects completed study	125 (85.0)	115 (85.8)	240 (85.4)
Subjects discontinued study early	22 (15.0)	19 (14.2)	41 (14.6)
Adverse event	6 (4.1)	13 (9.7)	19 (6.8)
Subject request	7 (4.8)	4 (3.0)	11 (3.9)
Lost to follow up	2 (1.4)	0	2 (0.7)
Noncompliance	0	0	0
Pregnancy	0	0	0
Other	7 (4.8)	2 (1.5)	9 (3.2)
Low cortisol	1 (0.7)	0	1 (0.4)
Lack of efficacy	5 (3.4)	0	5 (1.8)
Disease extent 70 cm	0	1 (0.7)	1 (0.4)
Personal conflict	0	1 (0.7)	1 (0.4)
Unknown	1 (0.7)	0	1 (0.4)

Source: Sponsor's Study Report
Percentage calculated is based on the number of subjects randomized

The mean age of subjects overall was 43 years with 90% of subjects in each group less than 65 years of age. While both treatment groups had more female subjects than male subjects, the difference in these proportions was larger in the placebo group (43% males, 57% females) than in the budesonide group (46%, 54%). Most subjects were White (budesonide 89%, placebo 92%) and 11% overall were Hispanic or Latino. The 2 treatment groups were similar with respect to mean weight and BMI.

The treatment groups were comparable with respect to baseline characteristics. The mean normal number of stools per day (i.e., when no UP/UPS symptoms were present) was 1.4 in each group and the mean MMDAI total score was 8 in each group. Most subjects in each treatment group had MMDAI bowel frequency subscale scores of 1, 2, or 3 (overall 33%, 35%, 25%, respectively) and bleeding subscale scores of 2 (84% in each group and overall). The large majority of subjects had MMDAI PGA subscale scores of 2 (budesonide 93%, placebo 91%), moderate MMDAI endoscopy/sigmoidoscopy finding subscale scores (87%, 91%), and moderate severity of disease (89%, 92%). Most subjects had established disease (budesonide 96%, placebo 93%): about three quarters of the study population had UPS (73%, 74%) and about one quarter had UP (26% each group). The mean duration of disease was 5.4 years in the budesonide foam group and 3.8 years in the placebo group. Most subjects had never smoked (budesonide 78%, placebo 69%) and most were non-drinkers (budesonide 67%, placebo 63%). The most common treatment for UC, UP, or UPS at the time of first dose was 5-ASA (budesonide 52%, placebo 51%). One subject (0.7%) in the budesonide foam group had used corticosteroids for UC, UP, or UPS. No subjects had used immune-suppressants or biologics for UC, UP, or UPS.

Analysis of the Primary Efficacy Endpoint:
Table 8 shows the sponsor's analysis of the primary endpoint (adjusted for country), including individual components of the remissions score. These results show the rate of remission was significantly higher in the budesonide foam 2 mg/ 25 mL group (44.0%) compared with the placebo group (22.4%).

The sponsor's primary analysis is based on LOCF, that is, for subjects who discontinued early, missing values were imputed using the last completed post-baseline assessment. Table 8 also shows the three components of the remission score; the first two components of the remission score are, respectively, the third and first key secondary endpoints. The third component score was not a pre-specified secondary endpoint.

Table 8: Sponsor's Analysis of Primary Efficacy Endpoint (Study BUCF3002)

Efficacy Endpoint/ Category	Placebo N = 147 n (%)	Budesonide Foam 2 mg/25 mL N = 134 n (%)	P-value[a]	P-value[b]
Achieved Remission[c]			< 0.0001	< 0.0001
Responder	33 (22.4)	59 (44.0)		
Non-responder	114 (77.6)	75 (56.0)		
Components of Remission Score				
Achieved MMDAI Endoscopy Score of 0 or 1			0.0013	0.0012
Responder	54 (36.7)	75 (56.0)		
Non-responder	93 (63.3)	59 (44.0)		
Achieved MMDAI Rectal Bleeding Score of 0			0.0002	0.0001
Responder	42 (28.6)	67 (50.0)		
Non-responder	105 (71.4)	67 (50.0)		
Achieved Improvement or No Change from Baseline in MMDAI Bowel Frequency Score			0.1784	0.1786
Responder	107 (72.8)	107 (79.9)		
Non-responder	40 (27.2)	27 (20.1)		

Source: Table 14.2.1a.
Abbreviations: ITT = intent to treat; LOCF = last observation carried forward; MMDAI = Modified Mayo Disease Activity Index.
a P-value was obtained from a logistic regression model with fixed effects: treatment arm and country.
b P-values were obtained from the Cochran-Mantel-Haenszel (CMH) test adjusting for country.
c Remission was defined as an endoscopy score of 0 or 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency subscales of the MMDAI at the end of 6 weeks of treatment.

Table 9 shows the reviewer's results of the primary endpoint analysis of the proportion of subjects who achieved remission for the ITT and PP analysis populations. The reviewer utilized the CMH test, adjusting for country; and the sponsor's ITT data set with LOCF imputation. The results for the ITT and PP populations are identical to the sponsor's assessments

One of the sites (Russian Site 938) was identified as having a disproportionate number of responders: all 15 subjects in the budesonide foam arm were responders, and all 15 the subjects in the placebo arm were non-responders. For this reason, I have repeated the evaluation of the results by eliminating this site from the analyses of efficacy. By removing this site, the estimated treatment remains significant but the treatment effect estimate changed from 22% to 12%.

An IR was issued to the sponsor requesting they provide an explanation for the unusual response rates at Site 938 and provide assurance that data integrity was maintained for that site. The sponsor replied that a routine audit was conducted during the study and no discrepancies were found; however, they did not provide any rationale for the observed response rates.

The reviewer also performed a sensitivity analysis which assigned treatment failure to subjects who terminated early. The results of this analysis showed 2 additional budesonide treatment failures resulting in a slight reduction (1.6%) of treatment effect compared to the primary analysis.

The sponsor also performed additional sensitivity analyses, and these, in general, were consistent with the primary analysis based on the use of LOCF.

Table 9: Reviewer's Analysis of Primary Efficacy Endpoint – Study BUCF3002

Population	Budesonide Foam n/N (%)	Placebo n/N (%)	P-Value	Difference Budesonide – Placebo (95% CI)
ITT	59/134 (44.0)	33/147 (22.5)	<0.001	21.6% (10.8%, 32.4%)
ITT (w/o site 938)	44/119 (37.0)	33/132 (25.0)	0.04	12% (0.6%, 23.4%)
PP	57/127 (44.9)	33/146 (22.6)	<0.001	22.3% (11.3%, 33.3%)
ITT*	57/134 (42.5)	33/147 (22.5)	<0.001	20.0% (9.3%, 30.8%)

* Sensitivity analysis; (drop-outs = no remission)
Source: Reviewer

Table 9 shows that in ITT population Budesonide Foam (44%) was statistically superior to Placebo (23%) and for the PP populations Budesonide Foam (45%) was statistically superior to Placebo (23%), as well. For the sensitivity analysis, we considered subjects who did not complete the study, as non-responders. The results of these analyses also showed statistical significance.

Key Secondary Endpoints:
Key secondary endpoints are listed below:

1. The Proportion of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment.
2. The number of weeks subjects achieve a rectal bleeding MMDAI subscale score of 0 during the treatment phase (Weeks 1 through 6).
3. Proportion of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment.

As discussed in Section 3.4.1, instead of endpoint #2 the sponsor analyzed the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments. The results of the key secondary variables are shown in table 10.

Table 10: Analysis of Key Secondary Endpoints – Study BUCF3002

Population	Budesonide Foam n/N (%)	Placebo n/N (%)	P-Value	Difference Budesonide – Placebo (95% CI)
Key Secondary # 1[1]	67/134 (50.0)	42/147 (28.6)	<0.001	21.4% (10.3%, 32.6%)
Key Secondary # 2[2] Responders at:			--[4]	
0 Assessment (no resp.)	54/134 (40)	81/147 (55)		
1 Assessment	11/134 (8)	27/147 (18)		
2 Assessments	22/134 (16)	25/147 (17)		
3 Assessments	29/134 (22)	11/147 (7)		
4 Assessments	18/134 (13)	3/147 (2)		
Key Secondary # 3[3]	75/134 (56.0)	54/147 (36.7)	--[4]	19.2% (7.8%, 30.7%)

1. Subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment
2. Subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments
3. Subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment
4. Results not testable

Source: Reviewer

Significantly larger proportions of subjects in the budesonide foam group compared with the placebo group achieved an MMDAI rectal bleeding score of 0 (budesonide 50.0%, placebo 28.60%) at the end of 6 weeks of treatment (key secondary endpoint #1).

The numbers of subjects who achieved a rectal bleeding MMDAI subscale score of 0 during the treatment phase were greater in the budesonide group for those who responded at 2, 3 and 4 scheduled assessments. (key secondary endpoint #2).

Larger proportions of subjects in the budesonide foam group compared with the placebo group achieved an MMDAI endoscopy score of 0 or 1 (budesonide 56.0%, placebo 36.7%) at the end of 6 weeks of treatment (key secondary endpoint #3).

3.5 Safety

For safety evaluation, refer to the Medical Officer's review.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The tables below show efficacy results by gender, race, age (<42 years of age vs 42 and over) and geographic region (U.S. vs Russia). Since the two submitted studies were identical in terms of the study design and primary efficacy endpoints, I combined the studies to conduct the subgroup analyses, in addition to showing the results within study.

4.1 Gender, Race, Age, and Geographic Region

Table 11: Analysis of the Primary Endpoint by Gender

		Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Female	29/72 (40.3)	20/80 (25.0)	15.3% (1%, 30%)
	Male	22/61 (36.1)	14/52 (26.9)	9.1% (-8%, 26.2%)
Study 3002	Female	26/72 (36.1)	14/84 (16.7)	19.4% (5.8%, 33.1%)
	Male	33/62 (53.2)	19/63 (30.2)	23.1% (6.3%, 39.9%)
Combined Studies	Female	55/144 (38.2)	34/164 (20.7)	17.5% (7.4%, 27.5%)
	Male	55/123 (44.7)	33/115 (28.7)	16% (4.0%, 28.1%)

Source: Reviewer

In each of the two studies, as shown in Table 11, both female and male subjects showed response rates that were numerically greater in favor of the study drug. Based on the combined data, the difference between the treatment arms and the 95% CI for the difference were 17.5% (7.4%, 27.5%) for Females and 16% (4.0%, 28.1%) for male subjects.

Table 12: Analysis of the Primary Endpoint by Race

Study	Race	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Asian	1/3 (33.3)	1/2 (50.0)	-16.7% (-1.0%, 71%)
	Black	5/15 (33.3)	1/5 (20.0)	13.3% (-2.9.1%, 55.7%)
	White	45/115 (39.1)	30/123 (24.4)	14.7% (3.0%, 26.5%)
Study 3002	Asian	1/3 (33.3)	0	33.3% (-20.0%, 86.7%)
	Black	2/11 (18.2)	1/8 (12.5)	5.9% (26.6%, 38.0%)
	White	56/119 (47.1)	31/135 (23.0)	24.1% (12.7%, 35.5%)
Combined Studies	Asian	2/6 (33.3)	1/5 (20.0)	13% (-38.2%, 64.8%)
	Black	7/29 (26.9)	2/13 (15.4)	11.5% (-14.5%, 37.5%)
	White	101/234 (43.2)	61/258 (23.6)	19.5% (11.3%, 27.7%)

Source: Reviewer

Based on the combining the data from the two studies, as it is shown in Table 12, all three race groups showed numerically higher response rates in favor of the study drug. The difference between the treatment arms and the 95% CI for the difference were 13% (-38.2%, 64.8%) for Asians, 11.5% (-14.5%, 37.5%) for Blacks and 19.5% (11.3%, 27.7%) for the White subjects.

Table 13: Analysis of the Primary Endpoint by Age Category

Study	Age Category	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	≤ 42	26/65 (40.0)	20/74 (27.0)	13.0% (-2.7%, 28.6%)
	>42	25/68 (36.8)	14/58 (24.1)	12.6% (-3.3%, 28.5%)
Study 3002	≤ 42	22/60 (36.7)	16/87 (18.4)	18.3% (3.6%, 32.9%)
	>42	37/74 (50.0)	17/60 (28.3)	21.7% (5.6%, 37.8%)
Combined Studies	≤ 42	48/125 (38.4)	36/161 (22.4)	16.0% (5.4%, 26.7%)
	>42	62/142 (43.7)	31/118 (26.7)	17.4% (6.0%, 28.8%)

Source: Reviewer

The median age for study subjects, 42 years, was used to define the age category. In each of the two studies, shown in Table 13, both age groups showed higher response rates in favor of the study drug. For the combined studies, the difference between the treatment arms and the 95% CI for the difference were 16.0% (5.4%, 26.7%) for subjects <=42 and 17.4% (6.0%, 28.8%) for age category >42.

Table 14: Analysis of the Primary Endpoint by Country

Study	Country	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Russia	23/51 (45.1)	18/47 (38.3)	6% (-13.1%, 26.0%)
	US	28/82 (34.2)	16/85 (18.8)	15% (2.0%, 29.1%)
Study 3002	Russia	36/49 (73.5)	22/51 (43.1)	30.3% (12.0%, 48.7%)
	US	23/85 (27.1)	11/96 (11.5)	15.6% (4.2%, 27.0%)
Combined Studies	Russia	44/85 (51.8)	40/83 (48.2)	3.6% (-11.5%, 18.7%)
	US	51/167 (30.5)	27/181 (14.9)	15.6% (6.9%, 24.3%)

Source: Reviewer

Table 14 shows that for Study 3001, the budesonide treatment effect is 6% for the Russian sites and 15% for the U.S. sites. For Study 3002, the treatment effect appears to be larger for the Russian sites (30% vs. 16%). The larger effect for the Russian sites in Study 3002 seems to be due to the 100% vs 0% response rates observed for the budesonide and placebo arms respectively for Site 938. (See Table 9.) For the combined studies, both countries showed efficacy in favor of the study drug. However, the results for Russia were not as strong as those observed for the U.S. The difference between the treatment arms and the 95% CI for the difference were 3.6% (-11.5%, 18.7%) for Russia and 15.6% (6.9%, 24.3%) for the U.S.

Table 15: Analysis of the Primary Endpoint by Disease Severity

Study	Disease Severity	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Mild (MMDAI Score 4-6)	4/15 (26.7)	4/22 (18.2)	8.5% (-19.1%, 36.1%)
	Moderate (MMDAI Score 7-10)	47/118 (39.8)	30/110 (27.3)	12.6% (0.4%, 24.7%)
Study 3002	Mild (MMDAI Score 4-6)	4/13 (30.8)	1/12 (8.3%)	22.4% (-7.1%, 52.0%)
	Moderate (MMDAI Score 7-10)	54/119 (45.4)	32/135 (23.7%)	21.7% (10.2%, 33.1%)
Combined Studies	Mild (MMDAI Score 4-6)	8/28 (28.6)	5/34 (14.7)	13.9% (-6.7%, 34.4%)
	Moderate (MMDAI Score 7-10)	101/237 (42.6)	62/245 (25.3)	17.3% (9.0%, 25.6%)

Source: Reviewer

For the combined studies, as shown in Table 15, the two disease severity categories showed higher response rates in favor of the study drug. The difference between the treatment arms and the 95% CI for the difference were 13.9% (-6.7%, 34.4%) for the Mild category and 17.3% (9.0%, 25.6%) for the Moderate category. There was not adequate numbers of subjects in the Severe category for a meaningful comparison.

Table 16: Analysis of the Primary Endpoint by Disease Type

Study	UP vs. UPS	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Proctitis	13/37 (35.1)	8/43 (18.6)	16.5% (-2.8%, 35.8%)
	Proctosigmoiditis	37/95 (39.0)	25/88 (28.4)	10.5% (-3.1%, 24.1%)
Study 3002	Proctitis	9/35 (25.7)	5/38 (13.2)	12.6% (-5.5%, 30.6%)
	Proctosigmoiditis	50/98 (51.0)	28/109 (25.7)	25.3% (12.5%, 38.2%)
Combined Studies	Proctitis	22/72 (30.6)	13/81 (16.1)	14.5% (1.2%, 27.8%)
	Proctosigmoiditis	87/193 (45.1)	53/197 (26.9)	18.2% (8.8%, 27.5%)

Source: Reviewer

Based on the combined data from the two studies, as shown in Table 16, the two disease types showed higher response rates in favor of the study drug. The difference between the treatment arms and the 95% CI for the difference were 14.5% (1.2%, 27.8%) for Proctitis and 18.2% (8.8%, 27.5%) for the Proctosigmoiditis group.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

Study BUCF3001 showed budesonide foam to be superior to placebo with respect to the primary endpoint of remission. There was a 38% (51/133) remission rate in the budesonide foam arm and a 25.8% (34/132) remission rate in the placebo arm for the primary analysis of the ITT population (p=0.03). The difference in treatment arms and the 95% CI for the difference was: 12.6% (1.5%, 23.7%). These results were consistent with analyses based on the Per Protocol population. The reviewer's sensitivity analysis considered subjects who did not complete the study, as non-responders The results of this analysis showed 4 additional budesonide foam treatment failures resulting in a reduction of treatment effect to: 9.6% (-1.5%, 20.6%). The sponsor's sensitivity analyses were consistent with their primary analysis.

The sponsor proposed three key secondary endpoints: the proportion of subjects who had no rectal bleeding at end of study; numbers of weeks subjects had no rectal bleeding; and the proportion of subjects with endoscopy score of 0 or 1 at end of study. Instead of endpoint #2 the sponsor analyzed numbers of subjects with no rectal bleeding at each "scheduled assessment." Because of the hierarchical nature of the testing and the post hoc nature of key endpoint #2, only the first key secondary endpoint was formally testable. The results for secondary endpoint #1 showed 46.6% vs 28% responders in the budesonide and placebo arms respectively (p=0.002).. The 95% CI of the difference was (7%, 30%).

Study BUCF3002 also showed budesonide foam to be superior to placebo with respect to the primary endpoint of remission. There was a 44% (59/134) remission rate in the budesonide foam arm and a 22.4% (33/147) remission rate in the placebo arm for the primary analysis of the ITT population (p<0.001). The difference in treatment arms and the 95% CI for the difference was: 21.6% (10.8%, 32.4%). These results were consistent with analyses based on the Per Protocol population. The reviewer's sensitivity analysis considered subjects who did not complete the study,

as non-responders. The results of this analysis showed 2 additional treatment group non-responders, and the results as well as the sponsor's sensitivity analyses were consistent with their primary results. The larger treatment effect observed for Study 3002 can be attributed to disproportionate results observed for one of the Russian sites.

From a statistical perspective, based on the data from two adequate and well-controlled studies, the efficacy of budesonide foam was shown.

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/s/

SHAHLA S FARR
08/05/2014

MICHAEL E WELCH
08/05/2014

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number:	Applicant:	Stamp Date:
205613	Salix Pharmaceutical, Inc.	November 15, 2013

Drug Name:	NDA Type:	Indication:
Budesonide Foam 2mg	Standard	Distal Ulcerative Colitis (UC)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X*			This is a review issue.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

*The Sponsor did not follow the statistical reviewer's advice in terms of statistical methodology (more details below under Reviewer's Comments)

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Brief Summary of Controlled Clinical Trials:
The studies included in this NDA were conducted under the IND # 104,725. The sponsor has submitted the results of two phase 3 clinical trials (Study BUCF3001 and Study BUCF3002). The two studies are identical in design, endpoints, sample size, statistical methodology, and duration.

This NDA was submitted electronically and is located at:
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Table below gives a brief description of the two studies.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design/Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety and efficacy	BUCF3001 (Salix)	5.3.5.1.4	Evaluation of the efficacy and safety of budesonide 2 mg rectal foam compared to placebo foam	Randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 study	Budesonide 2 mg rectal form or placebo foam twice daily for 2 weeks followed by once daily for 4 weeks	265	Mild to moderate active ulcerative proctitis or proctosigmoiditis	6 weeks	Complete; Full
Safety and efficacy	BUCF3002 (Salix)	5.3.5.1.5	Evaluation of the efficacy and safety of budesonide 2 mg rectal foam compared to placebo foam	Randomized, double-blind, placebo-controlled, parallel group, multicenter, phase 3 study	Budesonide 2 mg rectal form or placebo foam twice daily for 2 weeks followed by once daily for 4 weeks	281	Mild to moderate active ulcerative proctitis or proctosigmoiditis	6 weeks	Complete; Full

The two phase 3, randomized, double-blind, placebo-controlled, multicenter studies were to assess the efficacy and safety of Budesonide foam (2 mg/25 ml bid [twice a day] for two weeks, followed by 2 mg/25 ml qd [once a day] for four weeks) versus placebo foam in approximately 280 subjects with active mild to moderate distal UC (i.e., ulcerative proctitis or proctosigmoiditis [UP or UPS]).

Eligible subjects were to be randomized in a 1:1 ratio to either active budesonide (the study drug) or placebo. Both studies included four study phases defined as follows:

- Screening (Visit, 1; Day -21 to Day -7).
- Run-In/Stabilization (Visit 2; Days -7 to Day -1).
- Treatment (Visit 3 Randomization; Visits 4-6 Treatment, and Visit 7 [End of treatment/Week 6 or Withdrawal]). Days 1-42,
- Follow-up or End of Study (Visit 8; Day 56).

Total duration of the study was up to 11 weeks, depending on the timing of study visits.

The primary efficacy endpoint of the two trials was the proportion of subjects who have achieved remission at Week 6/Withdrawal visit. A logistic regression model was utilized to test for the treatment effect difference in the proportions between the two treatment arms after adjusting for center effect.

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Reviewer's Comments:

- Although the data sets are not completely in CDISC format, but they are easy to access and manipulate. Hence, the data sets submitted are adequate for conducting statistical review.

- In a communication dated December of 2009, the statistical reviewer of the IND # 104,725 had recommended that for the primary analysis of the primary efficacy endpoint, a Fisher's exact test and/or chi-square test (without stratification) and a Cochran Mantel Haenszel (CMH) (with stratification) instead of the proposed Logistic Regression Model would be more appropriate statistical methods for the analysis of binary data in the clinical studies. However, the sponsor did not incorporate this recommendation in the statistical analysis plan.

Comments to be conveyed to the Sponsor:

- Your submitted SAS programs contain macro that is difficult to comprehend. Please re-submit the SAS programs without macro codes, if feasible.

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/s/

SHAHLA S FARR
01/08/2014

FREDA COONER
01/08/2014