

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205613Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205613
Priority or Standard	Standard
Submit Date(s)	November 15, 2013
Received Date(s)	
PDUFA Goal Date	September 15, 2014
Division / Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Zana H. Marks, MD, MPH
Review Completion Date	July 11, 2014
Established Name	Budesonide Rectal Foam
(Proposed) Trade Name	Uceris
Therapeutic Class	
Applicant	Salix Pharmaceuticals, Inc
Formulation(s)	Rectal Foam
Dosing Regimen	The recommended dosage is 1 metered dose administered twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks
Indication(s)	(budesonide) is a rectally administered glucocorticosteroid foam indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge [REDACTED] (b) (4)
Intended Population(s)	Adults

Template Version: March 6, 2009

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	9
1.1	Recommendation on Regulatory Action	9
1.2	Risk Benefit Assessment.....	9
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies ...	9
1.4	Recommendations for Postmarket Requirements and Commitments	9
2	INTRODUCTION AND REGULATORY BACKGROUND	9
2.1	Product Information	9
2.2	Tables of Currently Available Treatments for Proposed Indications	10
2.3	Availability of Proposed Active Ingredient in the United States	10
2.4	Important Safety Issues With Consideration to Related Drugs.....	11
2.5	Summary of Presubmission Regulatory Activity Related to Submission	11
2.6	Other Relevant Background Information	12
3	ETHICS AND GOOD CLINICAL PRACTICES.....	12
3.1	Submission Quality and Integrity	12
3.2	Compliance with Good Clinical Practices	12
3.3	Financial Disclosures.....	13
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	13
4.1	Chemistry Manufacturing and Controls	13
4.2	Clinical Microbiology.....	14
4.3	Preclinical Pharmacology/Toxicology	14
4.4	Clinical Pharmacology	14
4.4.1	Mechanism of Action.....	14
4.4.2	Pharmacodynamics.....	14
4.4.3	Pharmacokinetics.....	14
5	SOURCES OF CLINICAL DATA.....	16
5.1	Tables of Studies/Clinical Trials	16
5.2	Review Strategy	17
5.3	Discussion of Individual Studies/Clinical Trials.....	17
6	REVIEW OF EFFICACY	33
	Efficacy Summary.....	36
6.1	Indication.....	36
6.1.1	Methods	36
6.1.2	Demographics.....	37
6.1.3	Subject Disposition	40
6.1.4	Analysis of Primary Endpoint(s).....	40
6.1.5	Analysis of Secondary Endpoints(s).....	45
6.1.6	Other Endpoints	47

6.1.7	Subpopulations	47
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	48
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	48
6.1.10	Additional Efficacy Issues/Analyses	48
7	REVIEW OF SAFETY.....	50
	Safety Summary	50
7.1	Methods.....	50
7.1.1	Studies/Clinical Trials Used to Evaluate Safety	51
7.1.2	Categorization of Adverse Events.....	51
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	52
7.2	Adequacy of Safety Assessments	52
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	52
7.2.2	Explorations for Dose Response.....	53
7.2.3	Special Animal and/or In Vitro Testing	53
7.2.4	Routine Clinical Testing	53
7.2.5	Metabolic, Clearance, and Interaction Workup	53
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class ..	53
7.3	Major Safety Results	53
7.3.1	Deaths.....	53
7.3.2	Nonfatal Serious Adverse Events	54
7.3.3	Dropouts and/or Discontinuations	54
7.3.4	Significant Adverse Events	57
7.3.5	Submission Specific Primary Safety Concerns	58
7.4	Supportive Safety Results	58
7.4.1	Common Adverse Events	58
7.4.2	Laboratory Findings	59
7.4.3	Vital Signs	61
7.4.4	Electrocardiograms (ECGs)	62
7.4.5	Special Safety Studies/Clinical Trials	62
7.4.6	Immunogenicity	62
7.5	Other Safety Explorations.....	62
7.5.1	Dose Dependency for Adverse Events	62
7.5.2	Time Dependency for Adverse Events.....	62
7.5.3	Drug-Demographic Interactions	62
7.5.4	Drug-Disease Interactions.....	64
7.5.5	Drug-Drug Interactions.....	64
7.6	Additional Safety Evaluations	64
7.6.1	Human Carcinogenicity	64
7.6.2	Human Reproduction and Pregnancy Data.....	65
7.6.3	Pediatrics and Assessment of Effects on Growth	65
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	65
7.7	Additional Submissions / Safety Issues	66

8	POSTMARKET EXPERIENCE.....	66
9	APPENDICES	67
9.1	Literature Review/References	67
9.2	Labeling Recommendations	67
9.3	Advisory Committee Meeting.....	67

Table of Tables

Table 1: Phase 3 Clinical Efficacy and Safety Studies for the Treatment of Active UP and UPS.....	17
Table 2: Modified Mayo Disease Activity Index (MMDAI).....	24
Table 3: Subject Disposition (Randomized Subjects) Study BUCF 3001.....	29
Table 4 Analysis Population by Treatment Group (ITT Population) Study 3001.....	29
Table 5: Demographics Summary (ITT Population) Study BUCF 3001.....	30
Table 6 Baseline Characteristics Study BUCF 3001 (ITT Population).....	31
Table 7 Baseline Characteristics Continued Study BUCF 3001 (ITT Population).....	32
Table 8: Subject Disposition (Randomized Subjects) Study BUCF 3002.....	33
Table 9: Analysis Population by Treatment Group (ITT Population) Study 3002.....	33
Table 10: Demographics Summary (ITT Population) Study BUCF 3002.....	34
Table 11: Baseline Characteristics Study BUCF 3002 (ITT Population).....	35
Table 12: Baseline Characteristics Continued Study BUCF 3002 (ITT Population).....	36
Table 13: Demographic Summary- Pooled Analysis (ITT Population).....	37
Table 14: Baseline Characteristics Ulcerative Colitis History BUCF 3001 and 3002 (ITT Population).....	38
Table 15: Baseline Characteristics MMDAI Subscales BUCF 3001 and 3002 (ITT Population).....	39
Table 16: 5-ASA Use During the Studies- Pooled Analysis (ITT Population).....	40
Table 17: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (LOCF Analysis, ITT Population) Study BUCF 3001.....	41
Table 18: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (Worst Case Analysis, ITT Population) Study BUCF 3001.....	42
Table 19: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment.....	43
Table 20: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment.....	44
Table 21: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (Worst Case Analysis, ITT Population) Study BUCF 3002.....	44
Table 22 Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment.....	45
Table 23: Rectal Bleeding Responders by Study Week (LOCF Analysis, ITT Population).....	46
Table 24: Rectal Bleeding Responders by Study Week (LOCF Analysis, ITT Population).....	47
Table 25: Proportion of Responders for Post Hoc Exploratory Endpoints at the End of Treatment by Treatment Group Study BUCF 3001 (LOCF Analysis, ITT Population)...	49
Table 26: Proportion of Responders for Post Hoc Exploratory Endpoints at the End of Treatment by Treatment Group Study BUCF 3002 (LOCF Analysis, ITT Population)...	50
Table 27. Phase 3 Budesonide Studies Used for Safety Analysis.....	51
Table 28 Summary of Adverse Events Randomized Control Trial Safety Population (RCT).....	54
Table 29: TEAEs Leading to Study Drug Discontinuation (RCT Safety Population).....	55

Table 30: Serious TEAEs (RCT Safety Population)	58
Table 31: TEAEs Occurring in $\geq 2\%$ of Subjects Treated with Budesonide or Placebo (RCT Safety Population)	58
Table 32 PCS Laboratory Results (RCT Safety Population)	59
Table 33: Changes from Baseline in Cortisol Levels (RCT Safety Population)	60
Table 34: Changes from baseline in ACTH Challenge Results (RCT Safety Population)	60
Table 35: Proportion of Subjects with Cortisol Levels of $>5 \mu\text{g/dL}$ (138nmol/L) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge (RCT Safety Population)	61

Table of Figures

Figure 1 Analysis of Budenofalk Studies Using Primary Endpoint of Remission from the Salix Budesonide Foam Trials BUCF 3001/3002 (ITT Populations).....**Error! Bookmark not defined.**

Figure 2: Study Design BUCF 3001 and BUCF 3002 19

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of marketing approval for Budesonide Rectal Foam 2mg/25mL for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge ((b) (4)).

1.2 Risk Benefit Assessment

Currently approved rectal formulations such as mesalamine or glucocorticosteroids may provide adequate therapy to treat distal ulcerative colitis. However, the route of administration (i.e., enemas and suppositories) may prove uncomfortable to patients and result in decreased compliance. Foam preparations such as Uceris rectal foam deliver the therapeutic agent, budesonide, in a small volume that expands once it is administered. Retention efforts should be minimal and discomfort should be improved. There are other steroid rectal foams available; however, their use may be accompanied by unwanted glucocorticosteroid side effects. Budesonide exhibits a high ratio of topical to systemic activity, explained by extensive hepatic first-pass metabolism that results in limited systemic exposure.

Review of the current submission reveals that the benefit of Budesonide Rectal Foam for the induction of remission of active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge outweighs the risk of Budesonide Rectal Foam in the appropriate patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor submitted a partial pediatric waiver request for patients 0-4 years and a deferral request for patients 5-17 years on March 7, 2014. (b) (4)

The Pediatric Review Committee meeting to discuss these requests is scheduled for July 30, 2014. The Pediatric Review Committee recommendations will be added to the submission as an addendum in DARRTS.

2 Introduction and Regulatory Background

2.1 Product Information

Budesonide Rectal Foam is indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge. It is supplied as a topical synthetic

glucocorticosteroid in a formulation for rectal administration. The dosing regimen is 1 metered dose administered rectally twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

Budesonide Rectal Foam is formulated as an emulsion which is filled into an aluminum canister with an aerosol propellant. The rectal formulation was specifically designed to improve 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.

Budesonide is a non-halogenated glucocorticosteroid (16 α , 17 α -butylidene dioxy-11 β , 21-dihydroxy-1, 4-pregnadiene-3, 20-dione), which is structurally related to hydroxyprednisolone. Following topical administration, budesonide exhibits a high ratio of topical to systemic activity, explained by extensive hepatic first-pass metabolism that results in limited systemic exposure. Limiting systemic availability may result in less glucocorticoid related side effects.

2.2 Currently Available Treatments for Proposed Indications

The goals of treatment in the management of mild to moderate distal colitis are induction and maintenance of remission of symptoms to reduce the need for long term glucocorticoid steroid therapy, improve quality of life and minimize cancer risk. This may be best achieved by using oral aminosalicylates, topical mesalamine or topical steroids.¹ Oral aminosalicylates are effective in extensive mild-to-moderate disease, but in distal disease, the rates of remission are lower than those obtained with topical, rectally-administered mesalamine (5-ASA).² The rectally administered products that are FDA approved include hydrocortisone foam/enema and mesalamine rectal suspension enema/suppositories. While corticosteroids such as hydrocortisone have an important role in treating active flares of UC, the systemic effects associated with its use may prove limiting. Both mesalamine and hydrocortisone enemas are the only rectal products indicated for patients with disease extending above the rectum. Limitations of use exist with both enemas and suppositories. Rectal suppository treatment does not adequately reach the sigmoid colon and patients may experience difficulty with retention and leakage. Similarly, enemas may be poorly retained over the recommended retention period (~8 hours) due to the large volume and may be painful during an early flare of proctitis or proctosigmoiditis.

2.3 Availability of Proposed Active Ingredient in the United States

Budesonide is commercially available in both the United States and other countries. It is approved in the U.S. for indications including asthma (nebulized; Pulmicort®, metered inhalation Symbicort®), rhinitis (nasal spray; Rhinocort®), the treatment and maintenance of remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon for up to 3 months (delayed release capsule; Entocort EC®), and induction of remission in patients with active, mild to moderate UC (extended release tablets; Uceris®).

¹ Kornbluth A et al, Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee, Am J Gastroenterol 2010; 105:501-523.

² Cohen RD et al, A meta- analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol 2000 May; 95 (5):1263-76.

2.4 Important Safety Issues with Consideration to Related Drugs

Budesonide is a synthetic glucocorticosteroid. Side effects that may be associated with the use of systemic glucocorticosteroids include adrenal suppression, sleep and mood disturbance, acne, striae, hirsutism, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, bone loss, aseptic necrosis and reduced growth velocity.

These side effects are generally dependent on dose, duration of treatment, concomitant and previous glucocorticosteroid intake and individual sensitivity.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant Clinical Pre-submission Regulatory Background	
Date	Action
April 2009 Clinical	<p>30 April 2009 preIND meeting:</p> <ul style="list-style-type: none"> ➤ The Sponsor initially proposed a primary endpoint of remission defined as a Modified Mayo Disease Activity Index (MMDAI) endoscopy score of ≤ 1 with an MMDAI rectal bleeding score of 0. This endpoint was chosen as a clinically meaningful measure of the severity of ulcerative proctitis (UP) / ulcerative proctosigmoiditis (UPS) on the basis of discussions with clinicians who were experienced in the treatment of patients with these conditions. ➤ The Agency indicated that excluding stool frequency from the definition of remission could lead to the question of whether or not stool frequency worsened. ➤ In response to that discussion, the Sponsor revised the definition of the primary endpoint (i.e., remission) to the following: an endoscopy score of ≤ 1 (no friability observed), a rectal bleeding score of 0 (no bleeding observed), and improvement or no change from baseline in stool frequency subscales of the MMDAI at the end of 6 weeks. ➤ The sponsor proposed a placebo controlled trial of 6 weeks duration with budesonide foam compared to an equivalent volume/regimen of placebo foam administered over 6 weeks (2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks) ➤ The study population was subjects with a diagnosis of active, mild-to-moderate UP or UPS
April 2009 Non-Clinical	<p>30 April 2009 preIND meeting:</p> <ul style="list-style-type: none"> ➤ The Agency requested the Sponsor perform a 3-month, repeat-dose toxicology study of budesonide rectal foam in a non-rodent species.
July 2013 Clinical	<p>23 July 2013 preNDA meeting:</p> <ul style="list-style-type: none"> ➤ After preliminary review of a summary of primary endpoint results and other efficacy and safety data from the BUCF3001 and BUCF3002 studies, the FDA agreed that the results support an NDA submission. The Agency requested additional exploratory analyses that are discussed in Section 6.1.4 in this review. ➤ The Sponsor was asked to submit a rationale for not conducting a Thorough QT study
July 2013 Non-Clinical	<p>23 July 2013 preNDA meeting:</p> <ul style="list-style-type: none"> ➤ At this meeting, the Agency agreed that the nonclinical and toxicology studies support an NDA submission after review of results from the budesonide rectal foam toxicology program. The toxicology program included 6-week and 39-week toxicology studies in dogs that were completed in 2009 and 2012, respectively.
September 2013 Statistics	<p>29 September 2013 Information request</p> <ul style="list-style-type: none"> ➤ An information request from the Agency suggested additional statistical analyses of the primary efficacy endpoint and key secondary efficacy endpoints. These additional analyses are included in the BUCF3001/3002 study reports, the ISE,

Relevant Clinical Pre-submission Regulatory Background	
Date	Action
	and Modules 2.7.3 and 2.5.
November 2013	NDA 205613 was submitted.

2.6 Other Relevant Background Information

Information requests were sent pertaining to clinical and statistical issues. These information requests were requested to provide clarification for certain aspects of the application.

The sponsor was asked to explain differences in efficacy results for the treatment difference seen by subgroup and study between the US and Russia (January 28, 2014)

Further elucidation of 12 subjects who were reported to have “adrenal insufficiency” in the Integrated Summary of Safety was requested. This included demographic information such as age, gender, concomitant medications, co-morbidities, duration of therapy before the occurrence of adrenal insufficiency, severity classification and time to resolution. (January 28, 2014).

The Sponsor was asked to provide data for the Stool frequency subscore of the MMDAI at baseline and at timepoints during the trial to determine if stool frequency improved over time with therapy. The results were also presented by protocol defined extent of disease category (proctitis vs. proctosigmoiditis) (May 12, 2014).

3 Ethics and Good Clinical Practices

Per the sponsor, all studies were conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki, as well as described in the Code of Federal Regulations, Title 21, and Part 50 (21CFR50)

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was organized appropriately and easily navigable.

3.2 Compliance with Good Clinical Practices

According to the applicant, all studies were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human patients (21CFR 312). All studies were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs), which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization, and the Food and Drug Administration.

Sites for inspection were chosen on the basis of several factors including numbers enrolled at each site and the efficacy results at the sites. For Protocol BUCF3001 Site 857(Dr. Humberto I. Aguilar) had a high percentage of the subjects enrolled and with a positive outcome for product relative to other sites. The reported proportion of patients that met the primary endpoint at this site was 75% (6/8) in the budesonide

rectal foam group and 0% (0/7) in the placebo group. Site 520 (Dr. Wayne Schonfeld) also had a high percentage of the subjects enrolled and with a positive outcome for product in Study BUCF3001 relative to other sites. The reported proportion of patients that met the primary endpoint at this site was 40% (2/5) in the budesonide rectal foam group and 0% (0/5) in the placebo group.

For Protocol BUCF3002, Site 0198 (Dr. Ronald P. Fogel) had a high percentage of the subjects enrolled relative to other U.S. sites. The reported proportion of patients that met the primary endpoint at this site was 40% (2/5) in the budesonide rectal foam group and 0% (0/5) in the placebo group.

Initially for Study BUCF3002, Russian Site 0938 was selected for inspection because all 15 subjects randomized to product were responders and all 15 subjects randomized to placebo did not respond. Inspection of Russian Site 0938 was denied as the current political climate does not support travel to Eastern Europe. Further this site was inspected in 2009 by the Agency for NDA 22554 and had been No Action Indicated (NAI) at that time.

Based on the inspection results of these 3 sites, Dr. Susan Leibenhaut, Medical Officer in the Division of Good Clinical Practice Compliance/ Office of Scientific Investigations/ Office of Compliance/CDER, has determined the inspections of Drs. Aguilar and Fogel have the final classification of NAI. For the inspection of Dr. Schonfeld, the preliminary classification is NAI. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

Note: Observations above for Dr. Schonfeld's site are based on e-mail communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

3.3 Financial Disclosures

For studies BUCF3001 and BUCF3002 the Sponsor provided a signed copy of the FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21CFR part 54.2(d)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Budesonide is a non-halogenated glucocorticoid derived from 16 α -hydroxyprednisolone. It is a mixture of the two epimers (22S and 22R) differing in the orientation of an acetal chain. Both epimers are active glucocorticoids applied in a mixture of approximately 1:1. The molecular formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.53.

Relevant efficacy and safety CMC issues are discussed in Dr. Tarun Mehta's CMC review.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

There were no Pharmacology/Toxicology concerns in this application. See Pharmacology/Toxicology Review, Dr. Dinesh Gautam

4.4 Clinical Pharmacology

The Clinical Pharmacology Draft review or Final review was not available prior to the time of this reviewer's completion (July 11, 2014).

4.4.1 Mechanism of Action

Budesonide is a potent synthetic glucocorticoid that possesses anti-inflammatory, anti-allergy, anti-exudative, and anti-edematous properties. After oral dosing, budesonide undergoes extensive hepatic first pass metabolism via oxidative and reductive pathways, resulting in metabolites with little or no biologic activity. The rapid hepatic breakdown of budesonide in a non-cirrhotic liver reduces systemic bioavailability and the potential for corticosteroid-related side effects.

Budesonide is highly water soluble allowing for adequate intraluminal dissolution and its lipid solubility facilitates effective mucosal uptake and high local concentrations in the intestinal tissue. The rectal foam formulation was designed to improve the patient's ability to retain the drug in the rectum following administration.

4.4.2 Pharmacodynamics

Treatment with glucocorticosteroids, including budesonide rectal foam is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal axis function. These effects are measured by determination of plasma cortisol concentrations and responses to adrenocorticotropin challenge (i.e., ACTH stimulation test).

For further discussion of cortisol effects, please see the Safety section of this review and the Clinical Pharmacology review Dr. Dilara Jappar.

4.4.3 Pharmacokinetics

Colonic Spread

A scintigraphic investigation with technetium-labeled budesonide 2 mg rectal foam in patients with ulcerative colitis showed that the foam spreads to reach the sigmoid colon (mean: 25.4 cm; range of 11 to 40 cm). Maximal spread was achieved between 2 and 6 hours (mean 4 hours).

Absorption Healthy subjects

Systemic absorption of budesonide was evaluated after a single 2 mg dose and multiple 2 mg twice daily doses of budesonide rectal foam. Budesonide serum concentrations were low, and there was no evidence of significant accumulation of budesonide in serum following twice daily administration of budesonide for 4 days. Peak budesonide concentrations after 1 and 9 consecutive doses were 0.84 ng/mL and 0.90 ng/mL, respectively. AUC₀₋₁₂ estimates were 4.59 ng.h/mL and 4.30 ng.h/mL, respectively.

Distal Ulcerative Colitis

Pharmacokinetic sampling was performed for subjects in the two placebo-controlled efficacy trials patients. Population-based pharmacokinetic modeling demonstrated that there was not a significant difference in budesonide pharmacokinetics between distal ulcerative colitis patients and healthy subjects.

Distribution

Following intravenous administration, the volume of distribution (VSS) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range of 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is approximately 0.8.

Metabolism

Budesonide undergoes extensive biotransformation in the liver (approximately 90%) to metabolites of low glucocorticosteroid activity. The glucocorticosteroid activity of the major metabolites, 6β-hydroxybudesonide and 16α-hydroxyprednisolone, is less than 1% of that of budesonide.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [³H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6β-hydroxybudesonide and 16α-hydroxyprednisolone, are mainly renal excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine. The average elimination half-life of rectally administered budesonide is 4 hours.

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of UCERIS Rectal Foam have not been studied.

Renal Impairment

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renal excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function

Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of orally administered budesonide several-fold. Co-administration of ketoconazole results in an eight-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels. **The effect of CYP3A4 inhibitors and inducers on the pharmacokinetics of UCERIS Rectal Foam have not been studied.**

5 Sources of Clinical Data

In March 2008, the sponsor acquired the US licensing rights for Budenofalk rectal foam from Dr. Falk Pharma and started a clinical development program evaluating budesonide 2 mg rectal foam for the treatment of [REDACTED] (b) (4).

Studies BUCF3001 and BUCF3002 were replicate phase 3 randomized, double-blind, placebo-controlled, multicenter studies designed to assess the efficacy and safety of budesonide rectal foam (2 mg BID for 2 weeks, followed by 2 mg QD for 4 weeks) versus placebo in subjects with active mild to moderate UP or UPS. Protocol BFPS3073 is a currently ongoing phase 3, open-label, multicenter study designed to assess the safety and tolerability of budesonide foam after multiple doses in subjects with active UP or UPS.

The sponsor asserts that the drug product utilized in the Salix-sponsored studies for the current NDA, budesonide foam 2 mg (the proposed To Be Marketed Product (TBMP)), [REDACTED] (b) (4), Budenofalk 2 mg rectal foam, [REDACTED] (b) (4); however, there are formulation differences between the TBMP and the Budenofalk product which most likely will be discussed in one or more of the following reviews: CMC Review, Pharmacology/Toxicology Review, and/or Clinical Pharmacology Review. The sponsor also asserts that the subject population utilized for the Salix-sponsored studies was similar to the population in the Dr. Falk Pharma-sponsored studies, and therefore, efficacy data from studies BUF-5/UCA, BUF-6/UCA, and BUF-9/UCA should be considered supportive efficacy data for this NDA.

In the studies of the Budenofalk 2 mg foam product, the Clinical Activity Index (CAI) and the Disease Activity Index (DAI) were assessed in subjects with distal UC, based on the proportion of subjects who achieved clinical remission of distal UC (UP/UPS) at end of treatment. The CAI and DAI are disease activity indices that have been used to measure the signs and symptoms of distal UC (stool frequency, rectal bleeding, mucosal appearance). The DAI scoring system utilized in the Budenofalk studies is also referred to as the Mayo index. The MMDAI utilized in the primary studies was also based on the Mayo Index. The modification made to the original Mayo Index for the MMDAI was the deletion of "friability" from an endoscopy score of 1. See Appendix. The Budenofalk foam formulation was compared to the approved and marketed budesonide 2 mg enema formulation (Entocort®), and also to an approved and marketed hydrocortisone acetate 100 mg foam formulation (Colifoam®) in these studies; both of these products are approved outside the United States. The key findings from the studies of the Budenofalk 2 mg foam product are summarized in the Appendix (see Section 9.7).

5.1 Tables of Studies/Clinical Trials

An overview of the Salix phase 3 studies is provided in the table below.

Table 1: Salix Phase 3 Clinical Efficacy and Safety Studies for the Treatment of Active UP and UPS

Study Number/year completed	Study Design	Dosing Regimen and Duration	Subject Population
Salix BUCF3001/2013	Double-blind, randomized, placebo-controlled	Budesonide 2 mg rectal foam or placebo foam, BID for 2 weeks followed by QD for 4 weeks	Subjects with active distal UC (UP, UPS) Budesonide foam: 134 Placebo: 131
Salix BUCF3002/2013	Double-blind, randomized, placebo-controlled	Budesonide 2 mg rectal foam or placebo foam, BID for 2 weeks followed by QD for 4 weeks	Subjects with active distal UC (UP, UPS) Budesonide foam: 134 Placebo: 147
Salix BFPS3073/ongoing	Open-label, safety and tolerability evaluation	Budesonide 2 mg rectal foam, One cycle = BID for 2 weeks followed by QD for 4 weeks; subjects continued treatment cycles as needed	Subjects with active distal UC (UP, UPS) who completed BUCF3001/3002 Budesonide foam: 108

Source: Module 2 Clinical Overview 2.5.1.3.p.6

An overview of the phase 3 studies (Dr. Falk) is provided in the table below. See the summary of the key findings of these studies in the Appendix (Section 9.7):

Table 2: Dr. Falk Phase 3 Clinical Efficacy and Safety Studies for the Treatment of Active UP and UPS

Study Number/year completed	Study Design	Dosing Regimen and Duration	Subject Population
Dr. Falk BUF 6/UCA (10)/2000	Randomized, active-controlled, open-label, parallel group	Budesonide 2 mg rectal foam (Budenofalk foam) QD for 8 weeks Hydrocortisone acetate foam (Cortifoam) 100 mg QD for 8 weeks	Subjects with active distal UC (UP, UPS) Budesonide foam: 120 Hydrocortisone foam: 128
Dr. Falk BUF 9/UCA (11)	Randomized, active-controlled, double-blind, double-dummy, parallel group	Budesonide 2 mg rectal foam (Budenofalk foam) QD for 4 weeks Budesonide 2 mg rectal enema (Entocort enema) QD for 4 weeks	Subjects with active distal UC (UP, UPS) Budesonide foam: 265 Budesonide enema: 268

Abbreviations: BID = twice daily; QD = daily; UP = ulcerative proctitis; UPS = ulcerative proctosigmoiditis; UC = ulcerative colitis.

Source: Module 2 Clinical Overview 2.5.1.3.p.6

5.2 Review Strategy

In this application, the efficacy and safety for the drug were generated from two clinical efficacy and safety trials BUCF 3001 and BUCF 3002. These two clinical trials will be reviewed in section 5.3 and the comparative summary of efficacy and safety will be discussed in sections 6 and 7 respectively.

5.3 Discussion of Individual Studies/Clinical Trials

Efficacy and safety data from the two studies BUCF 3001 and BUCF 3002 were evaluated for the proposed indication of the induction of remission in patients with active mild to moderate distal ulcerative colitis (UC) extending up to 40 cm from the anal verge.

5.3.1 Study BUCF 3001 and Study BUCF 3002

Studies BUCF 3001 and BUCF 3002 are replicate phase 3, multicenter, randomized, double-blind, placebo-controlled studies designed to assess the efficacy and safety of budesonide 2 mg rectal foam (BID dosing for 2 weeks followed by QD dosing for 4 weeks) versus placebo in subjects with active mild to moderate UP or UPS.

Both studies were planned and conducted as identical trials. They shared the same protocol design, were conducted concurrently in the US and Russia, and utilized the same data acquisition tools.

5.3.2 Study Design and Objectives

The primary objective of the BUCF 3001 and BUCF 3002 studies was to establish the efficacy of rectally administered budesonide foam in subjects with UP or UPS. In these studies, budesonide foam was administered as 2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks, and compared to an equivalent volume of rectally administered placebo foam over the same dosing schedule.

The secondary objective for these studies was to confirm the safety profile for budesonide foam following 6 weeks of dosing in subjects with active mild-to-moderate UP or UPS. Salix also conducted an open label study (BFPS3073) to assess the long-term safety and tolerability of budesonide foam in patients with UP or UPS. This safety study was ongoing at the time of submission of this NDA.

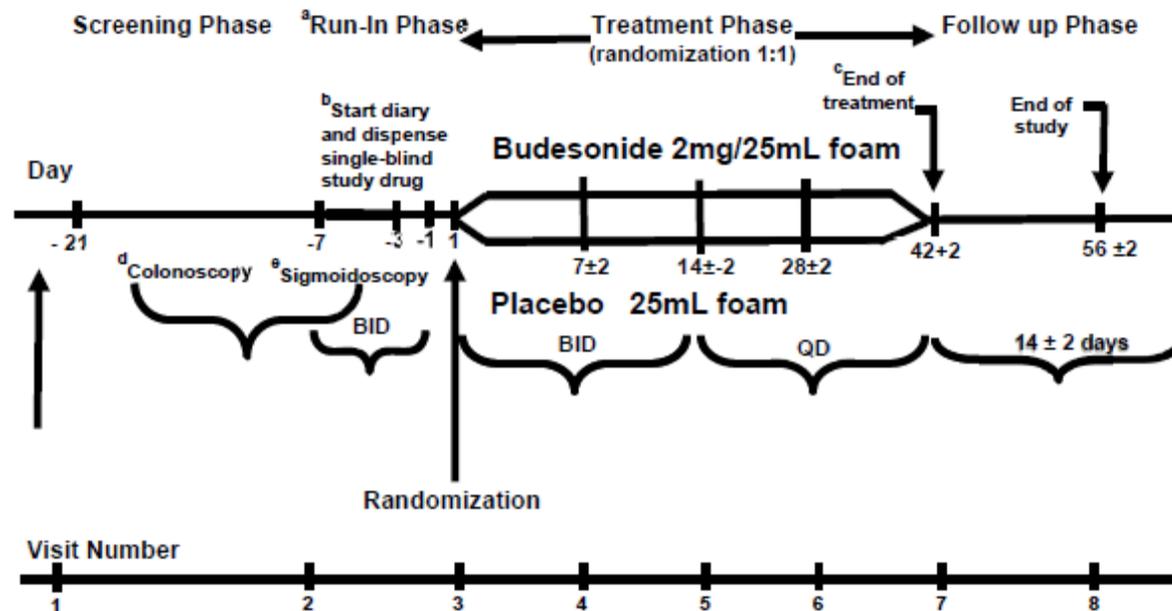
In both Studies BUCF 3001 and BUCF 3002, the subjects were randomized to receive study treatment in a 1:1 ratio.; either 2 mg budesonide foam BID for 2 weeks followed by 2 mg QD for 4 weeks, or placebo foam BID for 2 weeks followed by placebo foam QD for 4 weeks. Figure 2 presents an overview of the study design for both studies.

Both studies consisted of the following 4 phases:

- 1) Screening phase (Visit 1; Day-21 to Day-7): Subject eligibility was evaluated during this period.
- 2) Run-In/Stabilization (Visit 2; Days -7 to Day -1): The Run-In/Stabilization phase allowed subjects to become familiar with appropriate use of the single-blind medication (placebo foam), thus providing more experience with respect to administration as well as enhancing treatment compliance while in the study. This phase began the day of the Run-In visit, which was also the start of single-blind drug administration. Duration of the Run-In phase varied from a minimum of 4 days (Day -4 to Day -1) to a maximum of 7 days (Day -7 to Day -1).
- 3) Treatment phase (Visits 3-7; Days 1-42): defined as the 6-week study period starting with randomization and ending with completion of treatment.
- 4) Follow-up or End of Study (Visit 8; Day 56): Observation period of 14 ± 2 days, which occurred after treatment was completed.

The total duration for each study was approximately 11 weeks depending on the timing of study visits. Periodic safety monitoring including physical examinations, vitals, laboratory assessments, recording of adverse events and concomitant medications were performed during each study.

Figure 1: Study Design - BUCF 3001 and BUCF 3002



- a Run-In Visit scheduled 4-7 days prior to randomization.
- b Diary entries and single-blind BID study drug started no more than 7 days and no fewer than 4 days prior to randomization.
- c The last dose of study drug was administered in the evening occurring immediately prior to the End of Treatment visit (Week 6/Withdrawal: Visit 7).
- d Colonoscopy was required for new diagnosis or if diagnosis was not confirmed within 12 months of Screening visit and was performed no more than 10 days and no fewer than 4 days before Randomization. Histology results from baseline colonoscopy for newly-diagnosed subjects were required prior to Randomization. A pathology report identifying histological changes characteristic of UP/UPS was required to meet histological eligibility requirements for these subjects.
- e Sigmoidoscopy was scheduled between Days -7 and -4.

Source: Module 2 Summ Clin. Efficacy;2.7.3.1.4.1.1;p.29

5.3.3 Subject Population

In both studies BUCF 3001 and 3002, male and female subjects were at least 18 years of age with a confirmed diagnosis of active mild to moderate UP or UPS with disease extending at least 5 cm but no further than 40 cm from the anal verge. The following criteria were required for both trials:

- 1) Diagnosis was confirmed by endoscopy with easy passage of the endoscope to at least 10 cm above the proximal margin of the disease.
- 2) Subjects newly diagnosed with active, mild-to-moderate UP or UPS were required to have had symptoms (eg, rectal bleeding) for at least 45 days prior to screening and underwent colonoscopy to confirm diagnosis.
- 3) For initial diagnosis, a pathology report from a local pathologist identifying histological changes characteristic of distal UC (UP/UPS) was required to meet eligibility requirements.
- 4) Subjects had a baseline MMDAI score between 5 and 10, inclusive. Subjects scored ≥ 2 on the MMDAI rectal bleeding component and ≥ 2 on the MMDAI endoscopy or sigmoidoscopy component at Randomization (Visit 3) to be eligible.

A complete list of Inclusion/Exclusion criteria can be found in Appendix 1.

5.3.4 Dose Selection

The applicant conducted a review of the Dr. Falk Pharma GmbH program to determine the dose that minimized glucocorticoid side effects and optimized risk benefit ratio; the 2 mg BID dosing regimen for 2 weeks followed by 2 mg QD for the remaining 4 weeks of treatment was chosen based on the following information:

- Overall, the average time to clinical remission observed in the Falk studies was 5 to 9 days, based on both the Clinical Activity Index (CAI) and Disease Activity Index (DAI) scoring systems for primary endpoints.
- A pilot study (BUF-3/UCA) with a slightly different foam formulation used a 2 mg budesonide BID dosing regimen for 2 weeks followed by 2 weeks of 2 mg budesonide foam QD, as compared to 5 mg/100 mL betamethasone enema. Budesonide was well-tolerated in this study, and the greatest response with budesonide treatment occurred during the 2-week BID treatment period.
- Scintigraphy data from the BUF-4/BIO budesonide foam study demonstrated that ^{99m}Tc- labeled budesonide 2 mg foam is completely cleared within 6 hours. While a 4-times daily dosing regimen with a rectally administered topical formulation would be impractical to develop, an initial BID dosing regimen should allow significantly more topical drug exposure during the initial treatment phase than QD dosing, and thus enhance potential for a more immediate treatment response.
- There was a statistically significant positive treatment effect of budesonide foam 2 mg BID budesonide compared with placebo over 6 weeks of treatment in phase 2 study BUF-5/UCA
- In phase 3 study BUF-9/UCA, a CAI assessment taken at 2 weeks confirmed that the majority of subjects experienced an early treatment response, with the greatest change from baseline observed after the first 2 weeks of treatment. While a 2-week CAI or DAI assessment was not measured in BUF-6/UCA (i.e., first assessment at 4 weeks), subject diary information was collected in both studies, with mean weekly scores of stool number and rectal bleeding. These data also clearly demonstrate that the drug works quickly, with the greatest percent reduction in bowel frequency and blood in stools occurring after the first 2 weeks of treatment.

See also the Appendix (Section 9.7) for a summary of the key findings of the Dr. Falk studies.

5.3.5 Prior and Concomitant Therapy

Medications used to treat UP or UPS other than oral 5-ASA products were prohibited. Drugs that were in use but were not being used to treat UC, UP or UPS were recorded in the CRF starting 30 days prior to screening.

Medications that were permitted included:

- Tricyclic antidepressants and serotonin re-uptake inhibitors: permitted provided they were taken at stable doses for at least 6 weeks prior to Screening (Visit 1) and the subject agreed that the respective dose was to remain stable throughout duration of the study.
- Oral 5-ASA products at doses up to 4.8 g/day: allowed during the study, providing the following criteria were met:
 - A subject who had received a therapeutic dose of oral 5-ASA within the past 12 months, and who was receiving any oral 5-ASA dose at the time of the most recent UP/UPS relapse agreed to use the same product and stable therapeutic dose starting at the Screening visit (Visit 1), continuing throughout the duration of the study (Visit 7). Alternatively, use of oral 5-ASA could be discontinued at Run-In (Visit 2).
 - A subject who had not taken a therapeutic dose of oral 5-ASA within the past 12 months (including newly diagnosed) was required to receive a stable therapeutic dose for at least 30 days prior to Randomization (Visit 3), and agreed to use the same 5-ASA product and stable therapeutic dose each day throughout the duration of the study (Visit 7). Alternatively, use of oral 5-ASA could be discontinued at Run-In (Visit 2).

NOTE: A therapeutic 5-ASA dose was defined as ≥ 1.5 g /day mesalamine product.

- Subjects on stable treatment with a daily fiber supplementation or bulking agents (including stool softeners) could be enrolled provided that the administration schedule was intended to be maintained throughout the study and the subject had been on bulking therapy for at least 30 days prior to Screening (Visit 1); otherwise, these agents were prohibited in the study.
- Subjects receiving diuretics (without concomitant use of cardiac glycosides) were allowed, but a normal serum potassium level (within standard laboratory reference range) was required to have been confirmed prior to Randomization (Visit 3).

The following medications were prohibited during the study period:

- History of treatment with a cell-depleting therapy (eg, Adacolumn).
- Any type of vaccination (live and attenuated).
- Antipsychotics and anti-seizure medications.
- Concomitant use of diuretics with cardiac glycosides (eg, digoxin, digitoxin).
- Drugs used for the treatment of irritable bowel syndrome (eg, alosetron, lubiprostone).
- Inhaled corticosteroids. Subjects with asthma requiring use of intermittent inhaled steroids within the past 3 months were excluded.

NOTE: Use of intranasal corticosteroids [eg, fluticasone propionate, daily dose not greater than 200 μ g (two 50- μ g puffs per nostril) or equivalent] for seasonal allergic rhinitis was permitted.

- Immunosuppressants (eg, azathioprine, methotrexate, 6-mercaptopurine, cyclosporine)
- Anti-tumor necrosis factor alpha agents
- Anticoagulants (eg, warfarin, fractionated heparin, Factor Xa inhibitors).
- Systemic, rectal, topical, or oral corticosteroids (eg, prednisolone, methylprednisolone, prednisone, hydrocortisone). Includes oral, rectal, or inhaled budesonide (other than as investigative study drug for current study).

NOTE:

- Subjects receiving 2 or fewer days of corticosteroid treatment were immediately eligible for Screening, following discontinuation of the corticosteroid agent.
- While generally prohibited, if a topical steroid was required during study participation, treatment was permitted in some instances (eg, based on extent and duration of usage, including selection of agent); however, discussion with the study Sponsor on a case-per case basis was to have taken place prior to administration.

- Any investigational agents.
- Antibiotics (eg, metronidazole, ciprofloxacin).
- Antispasmodics and prokinetic drugs.
- Laxatives and enemas.

NOTE: Laxatives taken for endoscopy procedures were permitted.

- Narcotics (specifically opioid analgesics).

NOTE: Narcotics taken specifically for endoscopy procedures were permitted.

- Ketoconazole and other potent cytochrome P450 3A4 inhibitors (eg, itraconazole, indinavir, etc.).
- Rectally administered 5-ASA products/formulations were discontinued (at latest) on the day of the Run-In/Stabilization visit (Visit 2).
- Oral 5-ASA products at doses > 4.8 g/day.

NOTE: Subjects could have received up to 4.8 g/day of an oral 5-ASA product for the duration of the study. Alternatively, oral 5-ASA treatment could have been discontinued at the Run-In visit (Visit 2).

- Antidiarrheals (eg, loperamide and bismuth subsalicylate).
- Supplements or products specifically marked as probiotics. Examples of probiotics include, but were not limited to: Align® (*Bifidocaterium infantis*), Culturelle® (*Lactobacillus* GG), Cultura (*L casei* F19), Yakult® (*L casei* Shirota), and Vifit® (*L rhamnosus* ATCC53013).

NOTE: Standard food or yogurt products were allowed.

- Routine use of NSAIDs, with the exception of cardioprotective aspirin (≤ 162 mg/day). (Routine NSAID use was defined taking for ≥ 3 or more days over a 7-day period.)

If a subject failed to respond to study medication, prohibited medication such as rectal 5-ASA or corticosteroids could be used as rescue medication. However, subjects requiring rescue medication were discontinued from the study.

5.3.6 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint in BUCF3001 and BUCF3002 was the proportion of subjects who achieved remission with budesonide foam, as compared to an equivalent volume/regimen of placebo foam administered over 6 weeks (2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks) in subjects with a diagnosis of active, mild-to-moderate UP or UPS. Remission was defined as an endoscopy score of ≤ 1 (no friability observed), a rectal bleeding score of 0 (no bleeding observed), and improvement or no change from baseline in stool frequency subscales of the MMDAI at the end of 6 weeks.

Secondary Efficacy Endpoints

The key secondary endpoints were

1. Proportion of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment
2. Number of scheduled assessments with rectal bleeding responder classification
3. Proportion of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment

Other secondary efficacy endpoints included:

- 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.
- Proportion of subjects who achieved an MMDAI total score ≤ 3 with ≥ 2 points of improvement from baseline at the end of treatment.
- 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.
- 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.
- 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.
- Mean change from baseline to Week 6 visit in MMDAI total score and subscale scores.

The Agency requested post hoc exploratory efficacy endpoints at the preNDA meeting (July 23, 2013) that included the following:

Proportion of subjects who achieved each of the following responder criteria at the end of 6 weeks of treatment:

- Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency ≤ 1
- Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency = 1.
- Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency = 0.
- Endoscopy = 0, rectal bleeding = 0, and stool frequency = no change or improvement from baseline.
- Endoscopy ≤ 1 , rectal bleeding = 0, stool frequency = no change or improvement from baseline, and total MMDAI score ≤ 1 .

5.3.7 Efficacy Assessments

Daily Diary

The daily diaries were initiated during the Run-in/Stabilization period (Visit 2). Subjects were instructed to record symptom information on a daily basis (e.g., number of stools and whether the stools contained blood), starting with the day of the Run-In/Stabilization visit (Visit 2), and continuing until the End of Treatment (Week 6 or Withdrawal; Visit 7).

Colonoscopy

A colonoscopy was required if the diagnosis of UP/UPS had not been confirmed within the past 12 months. A biopsy was performed for newly diagnosed subjects. The colonoscopy was scheduled at the Screening visit (Visit 1) to take place no greater than 10 days and no less than 4 days prior to Randomization (Visit 3). Results defining extent of disease and mucosal appearance were reviewed and MMDAI scoring of the baseline endoscopy subscale occurred at Visit 2 (Run-In/Stabilization).

The colonoscopy was performed at least to a length of 40 cm from the anal verge and was at least 10 cm above the proximal extent of disease. During the procedure, mucosal appearance was rated on the MMDAI scale of 0 (normal/inactive disease) to 3 (severe disease). Every effort was made to use the same gastroenterologist for the procedure for a given subject.

Sigmoidoscopy

A scheduled sigmoidoscopy was performed at the Run-In/Stabilization Visit (Visit 2) and at End of Treatment Visit (Week 6 or Withdrawal; Visit 7). At these visits, the extent of disease and mucosal appearance were evaluated for the baseline MMDAI endoscopy/sigmoidoscopy subscale assessment. The baseline sigmoidoscopy procedure took place between 4 and 7 days prior to Randomization (i.e., between Days -7 and -4). A second sigmoidoscopy was scheduled at Visit 7. Additionally, unscheduled sigmoidoscopies could be performed as described. If a baseline colonoscopy was performed, a Run-in/Stabilization (Visit 2) sigmoidoscopy was not required.

The sigmoidoscopy was at least to a length of 40 cm from the anal verge and was at least 10 cm above the proximal extent of disease. During the sigmoidoscopy, mucosal appearance was rated on the MMDAI scale of 0 (normal/inactive disease) to 3 (severe disease). As with the colonoscopy assessment, every effort was made to ensure that the procedure was performed by the same gastroenterologist for a given subject.

Modified Mayo Disease Activity Index (MMDAI)

The MMDAI was used to assess the overall disease activity for each subject. The modification made to the original Mayo 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.

The MMDAI evaluates 4 indices each on a scale of 0 to 3 with a maximum total score of 12. In addition to the total score, individual indices were analyzed separately for comparisons between treatment groups. All 4 indices were scored at Randomization (Day 1; Visit 3) and at the End of Treatment (Week 6 or Withdrawal; Visit 7). In addition, 3 of the 4 indices (i.e., excluding the mucosal appearance; Abbreviated MMDAI) were scored at the Screening visit (Visit 1), and at Treatment Visits 4, 5, and 6 (Weeks 1, 2, and 4).

Table 3 summarizes the MMDAI subscales for scoring.

Table 3: Modified Mayo Disease Activity Index (MMDAI)

Modified Mayo Disease Activity Index (MMDAI)				
Index	Stool Frequency ^a	Rectal Bleeding ^b	Physicians 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 ^e) 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = severe disease (spontaneous bleeding, ulceration)

Source: NDA 205613 CSR Section 9.5.2.4.; p.53.

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.

5.3.8 Timing for Calculating MMDAI Assessments

At the screening visit (Visit 1) an abbreviated MMDAI that included rectal bleeding, bowel frequency, and PGA subscales was determined by subject interview and medical history review by the study investigator. Each subject served as their own control for bowel frequency. They established a reference point at the beginning of the study, the normal number of daily bowel movements routinely experienced prior to onset of the most recent flares of UP/UPS.

At the Run-In/Stabilization visit (Visit 2), no MMDAI calculations were made; however, review of the Baseline Abbreviated MMDAI plus the baseline endoscopy score took place to ensure continued subject eligibility prior to receiving single-blind study drug (Run-In/Stabilization phase).

For the Baseline MMDAI calculation (Randomization; Visit 3), bowel frequency and rectal bleeding subscales were calculated following the evaluation of subject diary information. The average for each subscale was obtained from all days of the Run-In treatment period.

The Run-In period varied for each subject (duration was 4 to 7 days, primarily dependent on the timing of the endoscopy procedure). Following review of the subject's daily diary questions and subject interview, the investigator graded the PGA subscale. A complete MMDAI (including all 4 subscale components) was taken at Baseline/Randomization (Visit 3).

For calculation of the MMDAI scores during the Treatment Period (Visits 4 through 7), bowel frequency and rectal bleeding subscales were calculated using data from the last 3 diary entries obtained prior to each respective visit. Following review of the subject's daily diary questions and subject interview, the investigator graded the PGA subscale.

5.3.9 Subscales

Endoscopy

Mucosal appearance was evaluated either by colonoscopy or sigmoidoscopy. To determine baseline mucosal scores, flexible sigmoidoscopy was used to assess mucosal appearance for all subjects at the End of Treatment (Week 6 or Withdrawal Visit; Visit 7). Mucosal appearance from unscheduled endoscopy procedures may also have been evaluated.

Physician's Global Assessment (PGA)

The PGA score was created by using endoscopic findings, review of subjects' diaries and personal interviews. PGA assessment takes into account the other 3 MMDAI criteria (i.e., rectal bleeding, stool frequency and endoscopic findings), the subject's daily record of abdominal discomfort and general sense of well-being (subject's functional assessment), as well as other findings, including physical condition and

the subject's performance status. This assessment was determined and recorded by the Investigator during each study visit. A summary of the PGA subscale grading is listed below.

0 = Normal. There are no symptoms of colitis, the patient feels well, and the flexible proctosigmoidoscopy score = 0. In addition, the stool frequency = 0, rectal bleeding = 0, and the subject's functional assessment = 0.

1 = Mild disease. Subject exhibits mild symptoms and proctoscopic findings that are mildly abnormal. Subscores should reflect mostly scores of 1: stool frequency = 0 or 1; rectal bleeding = 0 or 1; subject's functional assessment = 0 or 1; sigmoidoscopy findings = 0 or 1.

2 = Moderate disease. There are more serious abnormalities, with endoscopic and symptom scores of 1 to 2. Subscores should reflect mostly scores of 2: stool frequency = 1 or 2; rectal bleeding = 1 or 2; subject's functional assessment = 1 or 2; endoscopy findings = 1 or 2.

3 = Severe disease. The subject probably requires additional therapy and possibly hospitalization. Subscores should mostly reflect scores of 3: stool frequency = 2 or 3; rectal bleeding = 2 or 3; subject's functional assessment = 2 or 3; endoscopy findings = 2 or 3.

Note: The subject's functional assessment was not included directly in the 12-point index calculation, and was considered a measure of the subject's level of abdominal discomfort and general sense of well-being. Functional assessment was included as part of the PGA score, defined as follows: 0 = Generally well; 1 = Fair; 2 = Poor; 3 = Terrible.

Rectal Bleeding

Information from the daily diary and subject interview comprising the last 3 entries obtained prior to each study visit provided the basis for the bleeding subscale score during the treatment period. The grading was based on the most severe incidence of blood in the stool that was observed on each day of the scoring period.

Bowel Frequency

The number of bowel movements was considered the number of trips to the bathroom with evacuation. A bowel movement for the frequency calculation was defined as a trip to the bathroom where evacuation occurred. Stool, gas, blood, and mucus were all considered evacuations. In addition, for the bowel frequency calculation; a reference point of the normal number of daily bowel movements prior to onset of the most recent flare of UP/UPS was obtained per subject report. During the treatment period, an MMDAI bowel frequency grade of 0 to 3 was assigned at each study visit in the following manner:

- The average score was comprised of the last 3 bowel frequency entries obtained immediately prior to each respective study visit, and represents the overall MMDAI bowel frequency subscale score for an assessment period.

5.3.9 Histology Assessment

Subjects entering the study were required to have pathology consistent with UC more specifically ulcerative proctitis or ulcerative proctosigmoiditis (UPS). For subjects with UP/UPS disease previously diagnosed, histology results were not required prior to randomization (Visit 3). However, for subjects with newly diagnosed UP/UPS, confirmation from a local pathologist identifying histological changes characteristic of UP/UPS were required prior to randomization.

5.3.10 Pharmacokinetic Assessments

Blood samples were obtained for subjects enrolled at US centers to determine budesonide plasma concentrations at Baseline (Visit 3), each treatment visit (Visits 4, 5, and 6), and End of Treatment (Visit 7)

to assess the population pharmacokinetics of budesonide in UP/UPS patients. At each of these visits, date and time of last dose were recorded in the CRF.

5.3.11 Safety Endpoints

The following safety endpoints were assessed throughout the study for each treatment group:

- Incidence of TEAEs and SAEs, grouped by body system, relationship to study medication, and severity.
- Changes from baseline (Randomization; Visit 3) in clinical laboratory assessments: urinalysis, hematology, and clinical chemistry at Week 2 and Week 6 or withdrawal; and assessment of cortisol levels additionally at Week 1 and Week 4.
- Changes from baseline (Randomization; Visit 3) in vital sign assessments at Weeks 1, 2, 4, and 6 or withdrawal.
- Changes from baseline (Randomization) in physical examination findings at the end of 6 weeks of treatment or withdrawal.

5.3.12 Safety Assessments

Safety Assessments included the following:

- Adverse events both reported and observed.
- Physical examination findings.
- Vital sign measurements (blood pressure, pulse, and oral temperature).
- Routine hematology and blood chemistry tests (includes cortisol), calculated creatinine clearance, and urinalysis.

5.3.12.1 Adverse Events

Adverse events were collected from the Informed consent to End of Treatment (Week 6) or the Withdrawal Visit and the 14 day follow-up period. The investigator asked about AEs after the subjects spontaneously reported any problems experienced since the last visit. All AEs and SAEs were either followed until resolution, the condition stabilized or the subject was lost to follow-up.

For Studies BUCF 3001/3002, the sponsor asserts symptoms associated with UP/UPS such as abdominal discomfort, rectal bleeding and change in stool frequency were expected and were evaluated as efficacy endpoints for the study. Therefore they were not recorded as AEs unless they were considered more severe than expected based on the subjects baseline condition or they met the criteria for an SAE.

5.3.13 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory assessments were collected at Screening (Visit 1), Randomization (Visit 3), Treatment Week 2 (Visit 5), and End of Treatment visit (Week 6 or Withdrawal; Visit 7). Subjects fasted overnight prior to obtaining blood during each prescribed visit and every effort was made to obtain fasting hematology and chemistry, including serum cortisol assessments.

The clinical laboratory parameters evaluated were the following:

- **Hematology (fasting):** hemoglobin, hematocrit, red blood cell count, red cell mass measurements, white blood cell count with differential, and platelet count.
- **Blood Chemistry (fasting):** ALT, AST, alkaline phosphatase, total and direct bilirubin, blood urea nitrogen, creatinine, uric acid, electrolytes (Na⁺, K⁺, HCO₃⁻ and Cl⁻), lactate dehydrogenase, calcium, albumin, glucose, cholesterol, and triglycerides. Fasting serum cortisol levels were evaluated in addition to the standard chemistry panel, and were taken approximately 2 to 4 hours after waking.
- **Stool Cultures:** At screening, testing was performed to determine the presence of *Y. enterocolitica*, *C. jejuni*, *Salmonella*, *Shigella*, ovum and parasite, and *C. difficile* (Note: An

additional stool sample was not required if negative test was obtained within 14 days of randomization. Results of these tests were required for randomization.)

- **Urinalysis:** Routine urine analysis (pH, ketones, blood, glucose, and proteins).

5.3.14 ACTH Challenge or Stimulation Test for Subjects With Decreased Cortisol Levels

A fasting cortisol assessment was taken in the AM during the following study visits: Screening (Visit 1), Randomization (Visit 3), Treatment Week 1 (Visit 4), Treatment Week 2 (Visit 5), Treatment Week 4 (Visit 6), and End of Treatment (Week 6/Withdrawal; Visit 7). Subjects fasted overnight (~ 8 hours) prior to obtaining blood during each prescribed visit.

At Run-In (Visit 2) and End of Treatment (Week 6/Withdrawal; Visit 7), all subjects underwent an ACTH challenge test to assess changes in adrenal function. A 250 µg dose of cosyntropin was administered between 8 AM and 10 AM (or approximately 2-4 hours after waking) by intramuscular injection. Blood for serum cortisol assessments was drawn immediately prior to cosyntropin administration (Baseline), and at a 30-minute time point after the challenge. The peak value at 30 minutes was to have been an absolute value above 18 µg/dL (500 nmol/L). After the challenge, if the serum cortisol level was less than 18 µg/dL, the subject **was not eligible** for randomization. In addition, subjects with fasting cortisol values of < 5 µg/dL occurring at any time after being randomized in the study were scheduled to return immediately to the clinic to undergo an unscheduled ACTH challenge test. Prior to undergoing the test, the subject was temporarily discontinued from study drug for at least 24 hours or as close to 24 hours as possible, and the subject was required to continue to complete their daily diary assessments.

Subjects who did not meet the challenge criteria by producing peak cortisol levels of 18 µg/dL upon stimulation, were permanently discontinued from treatment, and underwent further evaluation for adrenal insufficiency per each site's standard institutional guidelines and/or recommendations. Those subjects producing sufficient cortisol levels following ACTH challenge resumed treatment in the study.

5.3.15 Urine or Serum Pregnancy Test

A urine pregnancy test was performed on all females of child-bearing potential at Randomization (before administration of any study drug). A serum pregnancy test was performed on all females of child-bearing potential during Screening (Visit 1) and the End of Treatment visit (Week 6 or Withdrawal; Visit 7).

5.3.16 12-Lead ECG

A single 12-lead ECG was obtained at Screening (Visit 1), using an ECG machine that automatically calculated the heart rate and measured PR, QRS, QT, and QTc intervals. The ECG was performed in the supine position after 5 minutes of rest.

Subjects with clinically significant ECG abnormalities (as defined by the institution's standard guidelines and investigator judgment) were excluded prior to Randomization (Visit 3).

5.3.17 Medical History

The following information was obtained as part of the medical history for Studies BUCF 3001/3002:

- Documented date of first diagnosis of UP or UPS (with endoscopy and any available pathology reports) and date/s of onset of symptoms.
- Prior treatment for UC, UP, or UPS.
- Normal number of daily stools per subject report.
- Current medications to treat UP or UPS.
- Documented physicals within the last year.
- Past medical history, including surgeries and any extra-colonic manifestations of the UP/UPS condition.
- Review of systems.

- Smoking history.
- History of alcohol ingestion.

5.3.18 Physical Examination

A physical examination was performed during the Screening visit (Visit 1) and at End of Treatment (Week 6 or Withdrawal; Visit 7). A symptom-directed physical examination was performed at the remaining visits (Visits 2-6) and as needed for unscheduled clinic visits.

5.3.19 Analysis Populations

The three analysis populations were defined as follows in the statistical analysis plan (SAP).

- Intent-to-treat (ITT) population included all randomized subjects. Efficacy analyses were performed on the ITT population by treatment group to which subjects were randomized.
- Safety population included all randomized subjects who were administered at least one dose of the study drug. All safety analyses used the Safety population. 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.
- Per-protocol (PP) population included all subjects in the ITT population who did not meet any of the following major protocol deviations:
 - Diagnosis of active, mild to moderate UP or UPS extending at least 5 cm but no further than 40 cm from the anal verge not confirmed
 - MMDAI score not between 5 and 10, and MMDAI rectal bleeding and/or endoscopy components < 2 at randomization
 - History or current diagnosis of Crohn's disease or indeterminate colitis
 - History of psychiatric disorders which are not controlled; history of psychoses
 - History of seizure disorder
 - Subject randomized in error or received incorrect randomized study drug.

5.3.20 Analysis of Primary and Secondary Efficacy Endpoints

Proportion of subjects who achieved remission with budesonide foam, as compared to an equivalent volume/regimen of placebo foam administered over 6 weeks (2 mg/25 mL BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks) in subjects with a diagnosis of active mild to moderate UP or UPS. 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 MMDAI at the end of 6 weeks of treatment.

Subjects were considered as not achieving remission if they received any rescue medication or any other therapy indicated for UP/UPS after randomization.

Statistical testing of the key secondary endpoints was conducted in a hierarchical fashion. See section 5.3.6. Significance testing was reported until a non-significant p-value was found ($p > 0.05$). Once a non-significant p-value occurred, all subsequent significance tests were considered exploratory in nature.

5.3.20 Study Subjects BUCF 3001

Disposition

In Study BUCF 3001, subjects were enrolled at 55 sites in the United States and Russia. A total of 265 subjects were randomized to 1 of 2 double-blind treatment groups and received at least 1 dose of study drug. Overall, 85% of subjects completed the study (budesonide 81% [108 of 133], placebo 88% [116 of 132]). 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%). See Table 4 below.

Table 4: Subject Disposition (Randomized Subjects) Study BUCF 3001

Category	Placebo n (%)	BUCF 2mg/25mL n (%)	Total n (%)
Randomized	132	133	265
Received at least 1 dose of BUCF	132 (100)	133 (100)	265 (100)
Completed study	116 (88)	108 (81)	224 (84)
Discontinued study early	16 (12)	25 (19)	41 (16)
Adverse event	7 (5)	13 (10)	20 (8)
Subject request	2 (2)	6 (5)	8 (3)
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 (2)	2 (0.8)
Lack of efficacy	6 (4)	2 (2)	8 (3)
Met exclusion criterion 3n prior to randomization ^b	1 (0.8)	0	1 (0.4)

Source: table 9 CSR NDA 205613; P.73.

^a Subject 0678-0014 in the placebo group had an ectopic pregnancy reported as a serious adverse event.

^b Exclusion criterion 3n was "Adrenal insufficiency, defined as a measurement of <18 µg/dL serum cortisol following adrenocorticotrophic hormone (ACTH) challenge."

Datasets Analyzed

The ITT/Safety population and the PP population were used for study analyses. These groups are summarized by treatment group in Table 5. One subject, Subject 0986-0002, was randomized to placebo but received both placebo and budesonide foam during the study. This subject is analyzed in the placebo group in all efficacy analyses and is summarized in the budesonide foam group in all safety analyses.

Table 5 Analysis Population by Treatment Group (ITT Population) Study 3001

Population Reason for Exclusion	Placebo n (%)	BUCF 2mg/25mL n (%)	Total n (%)
Intent to treat ^a	132	133	265
Safety ^b	131	134	265
Per protocol ^c	128 (97)	129 (97)	257 (97)
No confirmed UP/UPS	2 (2)	2 (2)	4 (2)
(-) qualified MMDAI criteria ^d	2 (2)	2 (2)	4 (2)
(+) Crohn's disease or Indeterminate colitis	0	0	0
History of psychiatric or seizure disorders	0	0	0
Incorrect randomization/receipt of study drug	0	0	0

Source: Table 10; NDA 205613; CSR; p.74

Abbreviations: ITT = intent to treat; MMDAI = Modified Mayo Disease Activity Index; UP = ulcerative proctitis; UPS = ulcerative proctosigmoiditis

^a Intent-to-treat population included all randomized subjects.

^b Safety population was all randomized subjects who were administered at least one dose of the study drug. ^c Per-protocol population excluded all randomized subjects who had violation of major entry criteria.

^d MMDAI total score not between 5 and 10, and MMDAI rectal bleeding and/or endoscopy subscale scores < 2 at randomization.

Note: Subject 0986-0002 was randomized to placebo, but received both placebo and budesonide foam during the study. This subject was analyzed in the placebo group in all efficacy analyses and is summarized in the budesonide foam group in all safety analyses.

Subject Demographics Study BUCF 3001

In Study 3001, most subjects were white females. The mean age of subjects overall was 42 years with ≥ 94% of subjects in each group < 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%). African Americans were represented (budesonide 11%, placebo 4%) and Hispanics and Latinos comprised 16% of the population studied. The 2 treatment groups were similar with respect to mean weight and body mass index (BMI). See Table 6.

Table 6: Demographics Summary (ITT Population) Study BUCF 3001

Characteristic Category or statistic	Placebo N = 132 n (%)	Budesonide Foam 2 mg/25 mL N = 133 n (%)	Total N = 265 n (%)
Age (years)			
Mean (SD)	41.4 (13.24)	43.2 (13.94)	42.4 (13.60)
Median (min, max)	40.0 (21, 76)	44.0 (18, 77)	41.0 (18, 77)
Age Group – n (%)			
< 65 years	127 (96.2)	125 (94.0)	252 (95.1)
≥ 65 years	5 (3.8)	8 (6.0)	13 (4.9)
Gender – n (%)			
Male	52 (39.4)	61 (45.9)	113 (42.6)
Female	80 (60.6)	72 (54.1)	152 (57.4)
Race – n (%)			
American Indian or Alaska Native	2 (1.5)	0	2 (0.8)
Asian	2 (1.5)	3 (2.3)	5 (1.9)
Black or African American	5 (3.8)	15 (11.3)	20 (7.5)
White	123 (93.2)	115 (86.5)	238 (89.8)
Race Group – n (%)			
White	123 (93.2)	115 (86.5)	238 (89.8)
Non-White	9 (6.8)	18 (13.5)	27 (10.2)
Ethnicity – n (%)			
Hispanic or Latino	22 (16.7)	20 (15.0)	42 (15.8)
Not Hispanic or Latino	110 (83.3)	113 (85.0)	223 (84.2)
Weight (kg)			
Mean (SD)	76.7 (18.32)	76.6 (18.46)	76.7 (18.35)
Median (min, max)	71.4 (46.3, 157.0)	72.5 (45.9, 153.6)	72.3 (45.9, 157.0)
BMI (kg/m²)			
Mean (SD)	26.8 (5.53)	26.7 (5.75)	26.7 (5.63)
Median (min, max)	25.7 (18.9, 54.1)	25.5 (18.4, 50.8)	25.6 (18.4, 54.1)

Source Table 11 NDA 205613 CSR p. 75.

Baseline Characteristics Study BUCF 3001

The treatment groups appeared comparable with respect to baseline characteristics. The mean normal number of stools per day when patients were asymptomatic for UP/UPS 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%). Notably, 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. These groups are summarized in Table 7.

Table 7 Baseline Characteristics Study BUCF 3001 (ITT Population)

	Placebo N = 132 n (%)	Budesonide Foam 2 mg/25 mL N = 133 n (%)	Total N = 265 n (%)
Baseline Disease Characteristics/ Statistic			
Normal Number of Stools Per Day^a			
Mean (SD)	1.4 (0.68)	1.3 (0.63)	1.3 (0.65)
Median (min, max)	1.0 (1, 5)	1.0 (1, 4)	1.0 (1, 5)
MMDAI Total Score			
Mean (SD)	7.9 (1.28)	7.8 (1.23)	7.9 (1.25)
Median (min, max)	8.0 (5, 10)	8.0 (4, 10)	8.0 (4, 10)
MMDAI Bowel Frequency Subscale – n (%)^b			
0	10 (7.6)	9 (6.8)	19 (7.2)
1	35 (26.5)	37 (27.8)	72 (27.2)
2	47 (35.6)	56 (42.1)	103 (38.9)
3	40 (30.3)	31 (23.3)	71 (26.8)
MMDAI Bleeding Subscale – n (%)^c			
0	0	1 (0.8)	1 (0.4)
1	2 (1.5)	1 (0.8)	3 (1.1)
2	113 (85.6)	116 (87.2)	229 (86.4)
3	17 (12.9)	15 (11.3)	32 (12.1)
MMDAI Physician Global Assessment Subscale – n (%)^d			
0	0	0	0
1	23 (17.4)	25 (18.8)	48 (18.1)
2	107 (81.1)	105 (78.9)	212 (80.0)
3	2 (1.5)	3 (2.3)	5 (1.9)
MMDAI Endoscopy/Sigmoidoscopy Finding Subscale – n (%)^e			
Normal or inactive	0	0	0
Mild	0	0	0
Moderate	120 (90.9)	120 (90.2)	240 (90.6)
Severe	12 (9.1)	13 (9.8)	25 (9.4)
Severity of Disease – n (%)			
Mild (MMDAI score 4 – 6)	22 (16.7)	15 (11.3)	37 (14.0)
Moderate (MMDAI score 7 – 10)	110 (83.3)	118 (88.7)	228 (86.0)
Severe (MMDAI score 11 – 12)	0	0	0
Type of Disease – n (%)			
Newly diagnosed	9 (6.8)	3 (2.3)	12 (4.5)
Established	123 (93.2)	130 (97.7)	253 (95.5)
Duration of Disease (years)			
Mean (SD)	5.0 (6.96)	4.5 (6.94)	4.7 (6.94)
Median (min, max)	2.4 (0.0, 37.1)	2.6 (0.0, 53.9)	2.4 (0.0, 53.9)
Extent of Disease – n (%)^f			
Proctitis	43 (32.6)	37 (27.8)	80 (31.2)
Proctosigmoiditis	88 (66.7)	95 (71.4)	183 (69.1)
Missing	1 (0.8)	1 (0.8)	2 (0.8)

Source: Table 12; NDA205613 CSR; p. 77.

Abbreviations: 5-ASA = 5-aminosalicylic acid; ITT = intent to treat; max = maximum; min = minimum; MMDAI = Modified Mayo Disease Activity Index; SD = standard deviation; UC = ulcerative colitis; UP = ulcerative proctitis; UPS = ulcerative proctosigmoiditis.

^a The question asked was "Think back to a time when you were not suffering from your most recent flare of Proctitis/Proctosigmoiditis. What was the normal number of bowel movements you had in a 24-hour period?" For the normal bowel movement calculation (ie, when no UP/UPS symptoms were present), a bowel movement represented when stool was passed.

^b Subscale scores were: 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.

^c Subscale scores were: 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.

^d Subscale scores were: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease.

^e Subscale scores were: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern), 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions), 3 = severe disease (spontaneous bleeding, ulceration). ^f Proctitis: disease limited to the rectum (up to ~15 cm); Proctosigmoiditis: disease limited to the rectum and sigmoid colon up to 40 cm

Most subjects were either former smokers (budesonide 26%, placebo 20%) or had never smoked (65%, 74%). The majority of subjects did not consume alcohol (62%, 61%).

The most common treatment for UP/UPS at the time of first dose of the study drug was 5-ASA (budesonide 59%, placebo 60%). One subject (0.8%) in the budesonide foam group used corticosteroids for UP/UPS at the time of first dose of study drug and 1 subject (0.8%) in the budesonide foam group used immunosuppressant therapy for UP /UPS at the time of first dose of study drug. No subjects used biologics at the time of the first dose of study drug.

Table 8 Baseline Characteristics Continued Study BUCF 3001(ITT Population)

Smoking History – n (%)			
Never smoked	97 (73.5)	87 (65.4)	184 (69.4)
Current smoker	9 (6.8)	11 (8.3)	20 (7.5)
Past smoker	26 (19.7)	35 (26.3)	61 (23.0)
Alcohol Ingestion – n (%)			
Non-drinker	81 (61.4)	82 (61.7)	163 (61.5)
Drinker	51 (38.6)	51 (38.2)	102 (38.5)
Continued			
Use of 5-ASA for UC/UP/UPS at time of first dose – n (%)	79 (59.8)	78 (58.6)	157 (59.2)
Use of corticosteroids for UC/UP/UPS at time of first dose – n (%)	0	1 (0.8)	1 (0.4)
Use of immunosuppressants for UC/UP/UPS at time of first dose – n (%)	0	1 (0.8)	1 (0.4)
Use of biologics for UC/UP/UPS at time of first dose – n (%)	0	0	0

Source: Table 12; NDA 205613 CSR Study BUCF 3001; p77.

5.3.21 Study Subjects BUCF 3002

Disposition

In Study BUCF 3001, subjects were enrolled at 59 sites in the United States and Russia. A total of 281 subjects were randomized to 1 of 2 double-blind treatment groups and received at least 1 dose of study drug. Overall, 85% of subjects completed the study (budesonide 86% [115 of 134], placebo 85% [125 of 147]). The most common reasons for early discontinuation from the study were AEs (budesonide 10%, placebo 4%), “other” (2%, 5%; of which lack of efficacy was the most common [0%, 3%]), and subject request (3%, 5%). See Table 9 below.

Table 9: Subject Disposition (Randomized Subjects) Study BUCF 3002

Category	Placebo n (%)	BUCF 2mg/25mL n (%)	Total n (%)
Randomized	147	134	281
Received at least 1 dose of BUCF	147 (100)	134 (100)	281 (100)
Completed study	125 (85)	115 (86)	240 (85)
Discontinued study early	22 (15)	19 (14)	41 (15)
Adverse event	6 (4)	13 (10)	19 (7)
Subject request	7 (5)	4 (3)	11 (4)
Lost to follow up	2(1)	0	2 (0.7)
Noncompliance	0	0	0
Pregnancy ^a	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)	0	5 (2)
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)

Datasets Analyzed

The ITT/Safety population and the PP population were used for study analyses. These groups are summarized by treatment group in Table 10. One subject, Subject 0035-0016, was randomized to the budesonide group but received a placebo kit at Week 1. This subject is analyzed in the budesonide group in all efficacy analyses.

Table 10: Analysis Population by Treatment Group (ITT Population) Study 3002

Population Reason for Exclusion	Placebo n (%)	BUCF 2mg/25mL n (%)	Total n (%)
Intent to treat ^a	147	134	281
Safety ^b	147	134	281
Per protocol ^c	146 (99)	127 (95)	273 (97)
No confirmed UP/UPS	0	2 (2)	2 (0.7)
(-) qualified MMDAI criteria ^d	1 (0.7)	5 (4)	6 (2)
(+) Crohn's disease or Indeterminate colitis	0	0	0
History of psychiatric or seizure disorders	0	0	0
Incorrect randomization/receipt of study drug	0	0	0

Source: Table 10; NDA 205613; CSR Study 3002; p.75.

Abbreviations: ITT = intent to treat; MMDAI = Modified Mayo Disease Activity Index; UP = ulcerative proctitis; UPS = ulcerative proctosigmoiditis

a Intent-to-treat population included all randomized subjects.

b Safety population was all randomized subjects who were administered at least one dose of the study drug. c Per-protocol population excluded all randomized subjects who had violation of major entry criteria.

d MMDAI total score not between 5 and 10 (inclusive), and MMDAI rectal bleeding and/or endoscopy subscale scores < 2 at randomization.

Note: Percentage calculated was based on the number of subjects randomized.

Note: Subject 0035-0016 was randomized to the budesonide group, but received a placebo kit at Week 1. This subject is counted in the budesonide group for all analyses.

Subject Demographics Study BUCF 3002

In Study 3002, most subjects were white females. The mean age of subjects overall was 43 years with ≥ 90% of subjects in each group < 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%). African Americans were not represented. Hispanics and Latinos comprised 11% of the population studied. The 2 treatment groups were similar with respect to mean weight and body mass index (BMI). See Table 11

Table 11: Demographics Summary (ITT Population) Study BUCF 3002

Characteristic Category or statistic	Placebo N = 147 n (%)	Budesonide Foam 2 mg/25 mL N = 134 n (%)	Total N = 281 n (%)
Age (years)			
Mean (SD)	41.9 (13.27)	44.3 (13.47)	43.0 (13.40)
Median (min, max)	40.0 (18, 80)	45.0 (19, 74)	42.0 (18, 80)
Age Group – n (%)			
< 65 years	138 (93.9)	121 (90.3)	259 (92.2)
≥ 65 years	9 (6.1)	13 (9.7)	22 (7.8)
Gender – n (%)			
Male	63 (42.9)	62 (46.3)	125 (44.5)
Female	84 (57.1)	72 (53.7)	156 (55.5)
Race – n (%)			
Asian	3 (2.0)	3 (2.2)	6 (2.1)
Black or African American	8 (5.4)	11 (8.2)	19 (6.8)
Native Hawaiian or other Pacific Islander	1 (0.7)	0	1 (0.4)
White	135 (91.8)	119 (88.8)	254 (90.4)
Other ^a	0	1 (0.7)	1 (0.4)
Race Group – n (%)			
White	135 (91.8)	119 (88.8)	254 (90.4)
Non-White	12 (8.2)	15 (11.2)	27 (9.6)
Ethnicity – n (%)			
Hispanic or Latino	17 (11.6)	15 (11.2)	32 (11.4)
Not Hispanic or Latino	130 (88.4)	119 (88.8)	249 (88.6)
Weight (kg)			
Mean (SD)	73.0 (16.31)	73.7 (18.37)	73.4 (17.30)
Median (min, max)	71.4 (42.6, 128.8)	71.0 (40.5, 138.6)	71.0 (40.5, 138.6)
BMI (kg/m²)			
Mean (SD)	25.4 (4.69)	25.7 (5.28)	25.6 (4.97)
Median (min, max)	25.0 (16.7, 43.7)	24.9 (15.9, 53.7)	25.0 (15.9, 53.7)

Table Source: Table 11; NDA 205613; CSR Study 3002; p.76.

Baseline Characteristics Study BUCF 3002

The treatment groups appeared comparable with respect to baseline characteristics. The mean normal number of stools per day when patients were asymptomatic for UP/UPS 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). The 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. These groups are summarized in Table 12.

Table 12: Baseline Characteristics Study BUCF 3002 (ITT Population)

Baseline Disease Characteristics/ Statistic	Placebo N = 147 n (%)	Budesonide Foam 2 mg/25 mL N = 134 n (%)	Total N = 281 n (%)
Normal Number of Stools per Day^a			
Mean (SD)	1.4 (0.63)	1.4 (0.77)	1.4 (0.70)
Median (min, max)	1.0 (1, 3)	1.0 (1, 7)	1.0 (1, 7)
MMDAI Total Score			
Mean (SD)	8.0 (1.17)	7.9 (1.25)	8.0 (1.21)
Median (min, max)	8.0 (5, 10)	8.0 (5, 12)	8.0 (5, 12)
MMDAI Bowel Frequency Subscale – n (%)^b			
0	9 (6.1)	13 (9.7)	22 (7.8)
1	49 (33.3)	44 (32.8)	93 (33.1)
2	53 (36.1)	44 (32.8)	97 (34.5)
3	36 (24.5)	33 (24.6)	69 (24.6)
MMDAI Bleeding Subscale – n (%)^c			
0	0	0	0
1	1 (0.7)	3 (2.2)	4 (1.4)
2	123 (83.7)	112 (83.6)	235 (83.6)
3	23 (15.6)	19 (14.2)	42 (14.9)
MMDAI Physician Global Assessment Subscale – n (%)^d			
0	0	0	0
1	10 (6.8)	7 (5.2)	17 (6.0)
2	133 (90.5)	125 (93.3)	258 (91.8)
3	4 (2.7)	2 (1.5)	6 (2.1)
MMDAI Endoscopy/Sigmoidoscopy Finding Subscale – n (%)^e			
Normal or inactive	0	0	0
Mild	0	0	0
Moderate	134 (91.2)	117 (87.3)	251 (89.3)
Severe	13 (8.8)	17 (12.7)	30 (10.7)
Severity of Disease – n (%)			
Mild (MMDAI score 4 – 6)	12 (8.2)	13 (9.7)	25 (8.9)
Moderate (MMDAI score 7 – 10)	135 (91.8)	119 (88.8)	254 (90.4)
Severe (MMDAI score 11 – 12)	0	2 (1.5)	2 (0.7)
Type of Disease – n (%)			
Newly diagnosed	11 (7.5)	6 (4.5)	17 (6.0)
Established	136 (92.5)	128 (95.5)	264 (94.0)
Duration of Disease (years)			
Mean (SD)	3.8 (4.82)	5.4 (6.25)	4.5 (5.60)
Median (min, max)	2.4 (0.0, 30.8)	2.8 (0.0, 27.7)	2.6 (0.0, 30.8)
Extent of Disease – n (%)^f			
Proctitis	38 (25.9)	35 (26.1)	73 (26.0)
Proctosigmoiditis	109 (74.1)	98 (73.1)	207 (73.7)
Missing	0	1 (0.7)	1 (0.4)

Source: Table 12; NDA 205613 CSR Study 3002; p.78.

Source: Table 14.1.4.

Abbreviations: 5-ASA = 5-aminosalicylic acid; ITT = intent to treat; max = maximum; min = minimum; MMDAI = Modified Mayo Disease Activity Index; SD = standard deviation; UC = ulcerative colitis; UP = ulcerative proctitis; UPS = ulcerative proctosigmoiditis.

^a The question asked was "Think back to a time when you were not suffering from your most recent flare of Proctitis/Proctosigmoiditis. What was the normal number of bowel movements you had in a 24-hour period?" For the normal bowel movement calculation (ie, when no UP/UPS symptoms were present), a bowel movement represented when stool was passed.

^b Subscale scores were: 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.

^c Subscale scores were: 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.

^d Subscale scores were: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease.

^e Subscale scores were: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern), 2 = moderate disease (marked erythema, absent vascular pattern, friability, and erosions), 3 = severe disease (spontaneous bleeding, ulceration).

^f Proctitis: disease limited to the rectum (up to ~15 cm); Proctosigmoiditis: disease limited to the rectum and sigmoid colon (up to ~40 cm).

Most subjects had never smoked (budesonide 78%, placebo 69%). The majority of subjects did not consume alcohol (67%, 63%).

The most common treatment for UP/UPS at the time of first dose of the study drug was 5-ASA (budesonide 52%, placebo 51%). One subject (0.7%) in the budesonide foam group used corticosteroids for UP/UPS at the time of first dose of study drug. No subjects used immunosuppressant therapy or biologics for UP/UPS.

Table 13: Baseline Characteristics Continued Study BUCF 3002 (ITT Population)

Smoking History – n (%)			
Never smoked	102 (69.4)	105 (78.4)	207 (73.7)
Current smoker	10 (6.8)	8 (6.0)	18 (6.4)
Past smoker	35 (23.8)	21 (15.7)	56 (19.9)
Alcohol Ingestion – n (%)			
Non-drinker	93 (63.3)	90 (67.2)	183 (65.1)
Drinker	54 (36.7)	44 (32.8)	98 (34.9)
Use of 5-ASA for UC/UP/UPS at time of first dose – n (%)	75 (51.0)	69 (51.5)	144 (51.2)
Use of corticosteroids for UC/UP/UPS at time of first dose – n (%)	0	1 (0.7)	1 (0.4)
Use of immunosuppressants for UC/UP/UPS at time of first dose – n (%)	0	0	0
Use of biologics for UC/UP/UPS at time of first dose – n (%)	0	0	0

Source: Table 12; NDA205613 CSR Study BUCF 3002; p78.

The efficacy results for the individual studies BUCF 3001 and BUCF 3002 will be included in the Review of Efficacy.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor has proposed the following indication:

Budesonide 2 mg rectal foam is indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

This indication is supported by the 2 pivotal studies BUCF 3001 and BUCF 3002 and the open-label study BFPS 3073 conducted under IND 104,725 in subjects with active mild to moderate UP or UPS.

6.1.1 Methods

Section 5.3 contains a discussion of the study protocols; Section 6 contains the study results in addition to a discussion of the efficacy issues that arose during the review of this application.

6.1.2 Demographics

The demographics for both studies BUCF 3001 and BUCF 3002 were discussed individually in Sections 5.3.20 and 5.3.21 respectively. In general, the demographic characteristics were similar across studies and treatment groups. See tables in referenced sections above.

Baseline demographics for the pooled analysis of the replicate studies, the mean age of subjects was 44 years in the budesonide foam group and 42 year in the placebo group. The demographics for the pooled data showed 90% of subjects in each group were < 65 years of age; both treatment groups had more whites and females. Table 14 summarizes the subject demographics for the pooled analysis of the BUCF3001 and BUCF 3002 studies.

Table 14: Demographic Summary- Pooled Analysis (ITT Population)

Characteristic	Placebo N=279	Budesonide Foam 2mg/25mL N=267
Age (years)		
Mean (SD)	42 (13)	44 (14)
Age Group n (%)		
<65 years	265 (95)	246 (92)
≥65 years	14 (4)	21 (8)
<45 years	170 (61)	134 (50)
≥45 years	109 (39)	133 (50)
Gender n (%)		
Male	115 (41)	123 (46)
Female	164 (59)	144 (54)
Race n (%)		
Am. Indian and Alaskan Native	2 (0.7)	0
Asian	5 (2)	6 (2)
African American	13 (5)	26 (10)
Native Hawaiian/Pacific Islander	1 (0.4)	0
White	258 (92)	234 (88)
Other ^a	0	1 (0.4)

Source Table 16. Summ Clin Eff. p. 69

^aIf >1 race was checked, the subject was included in the OTHER category.

Baseline Characteristics

MMDAI

The treatment groups in each study had comparable baseline characteristics. At baseline, the mean MMDAI total score was approximately 8 in each of the treatment groups for both studies BUCF 3001 and BUCF 3002. More than 80% of subjects in the treatment groups had disease described as moderate according to the MMDAI scale (7-10). Although the placebo group in BUCF 3001 had a higher percentage of subjects with mild disease activity per the MMDAI scale (4-6) the other treatment groups had 8-11% of subjects with “mild severity of disease.

Extent of Disease

The majority of subjects had diagnosed proctosigmoiditis in both studies: BUCF 3001 (budesonide 71 %, placebo 67%) and BUCF 3002 (budesonide 73%, placebo 74%). The other subjects had proctitis at baseline.

The mean duration of disease ranged from 4 to 5 years in the study treatment groups. The mean number of normal stools per day defined as stools occurring when asymptomatic ranged from 1.3 to 1.4 in the treatment study groups.

Table 15: Baseline Characteristics Ulcerative Colitis History BUCF 3001 and 3002 (ITT Population)

Baseline	BUCF 3001		BUCF 3002	
	Placebo N= 132	Budesonide Foam 2mg/mL N= 133	Placebo N= 147	Budesonide Foam 2mg/mL N= 134
Extent of Disease ^f				
Proctitis	43 (33)	37 (28)	38 (26)	35 (26)
Proctosigmoiditis	88 (67)	95 (71)	109 (74)	98 (73)
Missing	1 (0.8)	1 (0.8)	0	1 (0.7)
Type of Disease				
New Diagnosis	9 (7)	3 (2.3)	11 (8)	6 (4)
Established	123 (93)	130 (98)	136 (93)	128 (96)
Duration of Disease (years)				
Mean (SD)	5 (7)	5 (7)	4 (5)	5 (6)
Normal Number of Stools per Day ^a				
Mean (SD)	1.4 (0.7)	1.3 (0.6)	1.4 (0.6)	1.4 (0.8)

Source: Adapted from Table 17. NDA 205613 Summ Clin Eff. p.71

f. Proctitis: disease limited to rectum (up to ~15 cm); Proctosigmoiditis: disease limited to rectum and sigmoid colon (up to ~40 cm).

a. The question asked was "Think back to a time when you were not suffering from your most recent flare of Proctitis/Proctosigmoiditis. What was the normal number of bowel movements you had in a 24-hour period?" For the normal bowel movement calculation (ie, when no UP/UPS symptoms were present), a bowel movement represented when stool was passed.

MMDAI Subscales

Most subjects in the treatment groups in each study had a rectal bleeding score of 2 or 3 at baseline. The scores for bowel frequency were less uniform with subjects in each treatment group across the studies divided between 1, 2, or 3. Subjects in BUCF3001 appear to have had more severe scores for bowel frequency at baseline. Larger proportions of subjects began the study with a bowel frequency score of 0 or 1 in BUCF3002 (budesonide 43%, placebo 40%) compared with BUCF3001 (budesonide 36%, placebo 34%).

The majority of subjects had a PGA subscale score of 2 (BUCF3001: budesonide 79%, placebo 81%; BUCF3002: budesonide 93%, placebo 91%). Larger percentages of subjects in the BUCF3001 study (budesonide 19%, placebo 17%) had a PGA subscale score of 1 at baseline compared with subjects in the BUCF3002 study (budesonide 5%, placebo 7%). The majority of subjects in each treatment group across the studies had an endoscopy/sigmoidoscopy finding subscale rating of moderate at baseline (range: 87% to 91%).

Table 16: Baseline Characteristics MMDAI Subscales BUCF 3001 and 3002 (ITT Population)

Baseline Characteristic Category or statistic	BUCF3001		BUCF3002	
	Placebo N = 132	Budesonide Foam 2 mg/25 mL N = 133	Placebo N = 147	Budesonide Foam 2 mg/25 mL N = 134
MMDAI Total Score				
Mean (SD)	7.9 (1.28)	7.8 (1.23)	8.0 (1.17)	7.9 (1.25)
Median (min, max)	8.0 (5, 10)	8.0 (4, 10)	8.0 (5, 10)	8.0 (5, 12)
Bowel Frequency Subscale – n (%)^b				
0	10 (7.6)	9 (6.8)	9 (6.1)	13 (9.7)
1	35 (26.5)	37 (27.8)	49 (33.3)	44 (32.8)
2	47 (35.6)	56 (42.1)	53 (36.1)	44 (32.8)
3	40 (30.3)	31 (23.3)	36 (24.5)	33 (24.6)
Bleeding Subscale – n (%)^c				
0	0	1 (0.8)	0	0
1	2 (1.5)	1 (0.8)	1 (0.7)	3 (2.2)
2	113 (85.6)	116 (87.2)	123 (83.7)	112 (83.6)
3	17 (12.9)	15 (11.3)	23 (15.6)	19 (14.2)
PGA Subscale – n (%)^d				
0	0	0	0	0
1	23 (17.4)	25 (18.8)	10 (6.8)	7 (5.2)
2	107 (81.1)	105 (78.9)	133 (90.5)	125 (93.3)
3	2 (1.5)	3 (2.3)	4 (2.7)	2 (1.5)
Endoscopy/Sigmoidoscopy Finding Subscale – n (%)^e				
Normal or inactive	0	0	0	0
Mild	0	0	0	0
Moderate	120 (90.9)	120 (90.2)	134 (91.2)	117 (87.3)
Severe	12 (9.1)	13 (9.8)	13 (8.8)	17 (12.7)

Source: Table 17 NDA 205613 Summ of Clin Eff.p. 71.
passed.

b Subscale scores were: 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.

c Subscale scores were: 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.

d Subscale scores were: 0 = normal, 1 = mild disease, 2 = moderate disease, 3 = severe disease.

e Subscale scores were: 0 = normal or inactive disease, 1 = mild disease (erythema, decreased vascular pattern), 2 = moderate disease (marked erythema, absent vascular pattern, friability, and erosions), 3 = severe disease (spontaneous bleeding, ulceration).

f Proctitis: disease limited to rectum (up to ~15 cm); Proctosigmoiditis: disease limited to rectum and sigmoid colon (up to

Medication Use at Baseline

5-ASA was the most common treatment for UP/UPS at the time of first dose of study drug in each study. The use of 5-ASA at first dose was higher in BUCF3001 (budesonide 59%, placebo 60%) compared with BUCF3002 (budesonide 52%, placebo 51%). The use of concomitant 5-ASA during the study treatment period was also higher in BUCF3001 (budesonide 59%, placebo 61%) compared with BUCF3002 (budesonide 53%, placebo 51%).

In BUCF3001, 1 subject (budesonide group) was using corticosteroids and 1 subject (budesonide group) was using immunosuppressants for UP/UPS at the time of first dose. No subjects were using biologics at

the time of first dose. In BUCF3002, 1 subject (budesonide group) used corticosteroids and no subjects used immunosuppressants or biologics for UC at the time of the first dose.

Subjects were allowed to use up to 4.8g/day of an oral 5-ASA product throughout the studies. Table 17 summarizes 5-ASA use at baseline and during the study. More than half of the subjects were receiving 5-ASA therapy at the start of the study. Most subjects took 5-ASA between 35 and 50 days. Mesalamine and sulfasalazine were the most commonly used 5-ASA treatments in both groups.

Table 17: 5-ASA Use During the Studies- Pooled Analysis (ITT Population)

Characteristic	Placebo N= 279 n (%)	Budesonide Foam 2mg/mL N= 267 n (%)
5-ASA Use at Baseline ^a		
Yes	154 (55)	147 (55)
No	125 (45)	120 (45)
5-ASA During Treatment Period		
Yes	156 (56)	149 (56)
No	123 (44)	118 (44)
Number of Days Used 5-ASA During Treatment		
0 days	123 (44)	118 (44)
1 to 7 days	5 (2)	3 (1)
8 to 14 days	8 (3)	7 (3)
15 to 21 days	2 (0.7)	5 (2)
22 to 29 days	4 (1)	4 (2)
29 to 35 days	4 (1)	5 (2)
36 to 42 days	86 (31)	86 (32)
43 to 49 days	46 (16)	37 (14)
≥ 50 days	1 (0.4)	2 (0.7)
5-ASA Medications Used During Treatment		
Balsalazide	2 (0.7)	0
Balsalazide Sodium	4 (1)	2 (0.7)
Mesalazine	118 (42)	124 (46)
Olsalazine Sodium	0	1 (0.4)
Sulfasalazine	33 (12)	23 (9)

Source Table 19. NDA 205613 Summ Clin Eff. P. 75.
a Baseline refers to the time of the first dose

6.1.3 Subject Disposition

Subject disposition for both studies is discussed descriptively and in tabular form in Section 5.3.20 and 5.3.21.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint was the proportion of subjects who achieved remission with budesonide foam treatment, as compared to an equivalent volume/regimen of placebo foam administered over 6 weeks (2 mg/25 mL BID for 2 weeks followed by 2 mg/25 mL QD for 4 weeks) in subjects with a diagnosis of active mild to moderate UP or UPS. Remission was a combined assessment of clinical and endoscopic variables, 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 MMDAI at the end of 6 weeks of treatment. The rate of remission was higher in the budesonide foam group (38% compared to the placebo group 26%, p=0.0322).

STUDY BUCF 3001

Table 18: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (LOCF Analysis, ITT Population) Study BUCF 3001

Efficacy Endpoint	Placebo N=132 N (%)	Budesonide Foam 2mg/25mL N=133 N (%)
Achieved Remission^a		
Responder	34 (26)	51 (38)
Non-responder	98 (74)	82 (62)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	57 (43)	74 (56)
Non-responder	75 (57)	59 (44)
MMDAI Rectal Bleeding Score of 0		
Responder	37 (28)	62 (47)
Non-responder	95 (72)	71 (53)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	91 (69)	105 (79)
Non-responder	41 (31)	28 (21)

Source: Table 14 NDA 205613 CSR BUCF 3001 p. 80.

a. 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.

Sensitivity Analysis

Four sensitivity analyses were conducted to address the impact of insufficient data on the primary efficacy endpoint. Two were worst case analyses (one specified in the protocol and one post hoc requested by the Agency). The other two were an observed case analysis and a multiple imputation analysis. These analyses were conducted on data from both BUCF 3001 and BUCF 3002.

Worst Case Analysis. In the worst case analysis (WCA), subjects with insufficient data at a time point were considered treatment failures. The results of the WCA were almost identical to those from the primary efficacy analysis. The budesonide foam group achieved higher success rates than the placebo group for each remission component. A larger proportion of subjects in the budesonide group compared with placebo achieved an MMDAI rectal bleeding score of 0 (budesonide 45%, placebo 28%; $p=0.0045$), and achieved MMDAI endoscopy score of 0 or 1 (budesonide 57%, placebo 43%, $p=0.0488$). A numerically higher proportion achieved improvement or no change from baseline in the MMDAI bowel frequency score compared with the placebo group (budesonide 79%; placebo 69%); however, this did not reach statistical significance.

Table 19: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (Worst Case Analysis, ITT Population) Study BUCF 3001

Efficacy Endpoint	Placebo N=132 N (%)	Budesonide Foam 2mg/25mL N=133 N (%)
Achieved Remission^a		
Responder	34 (26)	51 (38)
Non-responder	98 (74)	82 (62)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	57 (43)	74 (56)
Non-responder	75 (57)	59 (44)
MMDAI Rectal Bleeding Score of 0		
Responder	37 (28)	60 (45)
Non-responder	95 (72)	73 (55)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	91 (69)	101 (79)
Non-responder	41 (31)	32 (24)

Source: Table 14.2.1c NDA 205613 CSR Section 14.2 Efficacy Data, p.8.

FDA-Requested Worst Case Analysis

This was a post-hoc analysis where subjects who received placebo with insufficient data at a time point under consideration were considered responders for that time point. Subjects receiving budesonide foam with insufficient data at a time point under consideration were considered non-responders for that time point.

The results of the Agency requested worst case analysis were similar to those of the primary efficacy analysis. The rate of remission was higher in the budesonide foam group (38%) compared to the placebo group (26%). The budesonide foam group achieved numerically higher success rates than the placebo group for each remission component. However, statistical significance was not reached. A significant proportion of subjects in the budesonide compared with the placebo group achieved an MMDAI rectal bleeding score of 0 (budesonide 45.1%, placebo 28.0%; $p = 0.0045$).

A numerically higher 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 44.7%); this difference trended toward statistical significance ($p = 0.0850$). A numerically larger proportion of subjects in the budesonide foam group (75.9%) achieved improvement or no change from baseline in the MMDAI bowel frequency score compared with the placebo group (68.9%); this difference did not reach statistical significance.

Table 20: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (FDA Requested Worst Case Analysis, ITT Population) Study BUCF 3001

Efficacy Endpoint	Placebo N=132 N (%)	Budesonide Foam 2mg/25mL N=133 N (%)
Achieved Remission		
Responder	35 (26)	51 (38)
Non-responder	97 (74)	82 (62)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	59 (45)	74 (56)
Non-responder	73 (55)	59 (44)
MMDAI Rectal Bleeding Score of 0		
Responder	37 (28)	60 (45)
Non-responder	95 (72)	73 (55)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	91 (69)	101 (76)
Non-responder	41 (31)	32 (24)

Source: Table 14.2.1d NDA 205613 BUCF 3001 CSR Section 14.2 Efficacy Data.p.8.

STUDY BUCF 3002

The rate of remission was significantly higher in the budesonide foam group (44%) compared with the placebo group (22%) p<0.0001.

The budesonide foam group achieved higher success rates than the placebo group for each remission component. 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 28.6%; p = 0.0001) and an MMDAI endoscopy score of 0 or 1 (budesonide 56.0%, placebo 36.7%; p = 0.0012). A larger proportion of subjects in the budesonide foam group (79.9%) achieved improvement or no change from baseline in the MMDAI bowel frequency score compared with the placebo group (72.8%); this difference did not reach statistical significance.

Table 21: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (LOCF Analysis, ITT Population) Study BUCF 3002

Efficacy Endpoint	Placebo N=147 N (%)	Budesonide Foam 2mg/25mL N=134 N (%)
Achieved Remission^a		
Responder	33 (22)	59 (44)
Non-responder	114 (78)	75 (56)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	54 (37)	75 (56)
Non-responder	93 (63)	59 (44)
MMDAI Rectal Bleeding Score of 0		
Responder	42 (29)	67 (50)
Non-responder	105 (71)	67 (50)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	107 (73)	107 (80)
Non-responder	40 (27)	27 (20)

Source table 14 NDA 205613 CSR BUCF 3002 p. 81 a. 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.

Sensitivity Analysis

Worst Case Analysis. In the worst case analysis (WCA), subjects with insufficient data at a time point were considered treatment failures. The results of the WCA were almost identical to those from the primary efficacy analysis. The rate of the combined clinical and endoscopic remission was significantly higher in the budesonide foam group (44%) compared with the placebo group (22%); $p < 0.0001$. The budesonide foam group achieved higher success rates than the placebo group for each remission component. Larger proportion of subjects in the budesonide group compared with the placebo group achieved an MMDAI rectal bleeding score of 0 (budesonide 50%, placebo 29%; $p=0.0002$); MMDAI endoscopy score of 0 or 1 (budesonide 57%, placebo 37%, $p=0.0008$); achieved improvement or no change from baseline in the MMDAI bowel frequency score compared with the placebo group 73%. This did not however reach statistical significance.

Table 22: Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (Worst Case Analysis, ITT Population) Study BUCF 3002

Efficacy Endpoint	Placebo N=147 N (%)	Budesonide Foam 2mg/25mL N=134 N (%)
Achieved Remission^a		
Responder	33 (22)	59 (44)
Non-responder	114 (78)	75 (56)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	54 (37)	76 (57)
Non-responder	93 (63)	58 (43)
MMDAI Rectal Bleeding Score of 0		
Responder	43 (29)	67 (50)
Non-responder	104 (71)	67 (50)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	107 (72)	107 (80)
Non-responder	40 (27)	27 (20)

Source Table 14.2.1c NDA 205613 CSR BUCF 3002 Section 14.2 Efficacy Data.p.8. a. 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.

FDA-Requested Worst Case Analysis

This was a post-hoc analysis where subjects who received placebo with insufficient data at a time point under consideration were considered responders for that time point. Subjects receiving budesonide foam with insufficient data at a time point under consideration were considered non-responders for that time point.

The results of the Agency requested worst case analysis were similar to those of the primary efficacy analysis. The rate of the combined clinical and endoscopic remission was higher in the budesonide foam group (44%) compared to the placebo group (25%). The budesonide foam group achieved higher success rates than the placebo group for each remission component. A significant proportion of subjects in the BFG compared with the placebo group achieved an MMDAI rectal bleeding score of 0 (budesonide 50%, placebo 31%; $p = 0.0006$).

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 57%, placebo 43%); A numerically larger proportion of subjects in the budesonide foam group (80%) achieved improvement or no change from baseline in the MMDAI bowel frequency score compared with the placebo group (74%); this difference did not reach statistical significance.

Table 23 Proportion of Subjects Who Achieved Remission at the End of 6 Weeks of Treatment (FDA Requested Worst Case Analysis, ITT Population) Study BUCF 3002

Efficacy Endpoint	Placebo N=147 N (%)	Budesonide Foam 2mg/25mL N=134 N (%)
Achieved Remission^a		
Responder	37 (25)	59 (44)
Non-responder	110 (74)	75 (56)
Components of Remission Score		
MMDAI Endoscopy Score of 0 or 1		
Responder	63 (43)	76 (57)
Non-responder	84 (57)	50 (43)
MMDAI Rectal Bleeding Score of 0		
Responder	45 (31)	67 (50)
Non-responder	102 (69)	67 (50)
Improvement or No Change from Baseline in MMDAI Bowel Frequency Score		
Responder	109 (74)	107 (80)
Non-responder	39 (26)	27 (20)

Source: Table 14.2.1d NDA 205613 BUCF 3002 CSR Section 14.2 Efficacy Data.p.9.

6.1.5 Analysis of Secondary Endpoints(s)

Multiplicity of the key secondary endpoints was handled statistically in a hierarchical fashion and the order was pre-specified in the protocol. The 3 key secondary endpoints were as follows:

- 1) Proportion of subjects who achieved a rectal bleeding MMDAI subscale score of 0 at the end of 6 weeks of treatment
- 2) Number of scheduled assessments with rectal bleeding responder classification
- 3) Proportion of subjects who achieved an endoscopy MMDAI subscale score of 0 or 1 at the end of 6 weeks of treatment.

Study BUCF 3001

Key Secondary Endpoint 1

In the ITT population the proportion of subjects who achieved a rectal bleeding score of 0 at the end of 6 weeks of treatment was significantly larger in the budesonide foam group (79%) as compared with the placebo group (69%). In the PP population the proportion of subjects who achieved a rectal bleeding score of 0 at the end of 6 weeks of treatment was significantly larger in the budesonide foam group (46%) as compared with the placebo group (28%).

Key Secondary Endpoint 2

A significantly larger proportion of subjects in the budesonide foam group compared with the placebo group achieved a rectal bleeding MMDAI subscale score of 0 (rectal bleeding responders) at Week 1, 2, 4, and 6 assessments. The main response to budesonide was within the first 2 weeks (29.3%), during BID dosing, and this was further improved at Week 4 (47.4%) and maintained at Week 6 (46.6%), during QD dosing.

Table 24: Rectal Bleeding Responders by Study Week (LOCF Analysis, ITT Population)

	Placebo ; N= 132	Budesonide Foam ; N = 133
Efficacy Endpoint		
Study Week (+) MMDAI Rectal Bleeding Score of 0		
Week 1 Responder	8(6)	18 (14)
Week 2 Responder	24 (18)	39 (29)
Week 4 Responder	35 (26)	63 (47)
Week 6 Responder	37 (28)	62 (47)

Source: Adapted from Table 15 NDA 205613 CSR BUCF 3001; p. 87

It should be noted that the key secondary endpoint 2 was defined in the statistical analysis plan (SAP) as the number of weeks subjects achieve a rectal bleeding MMDAI subscale score of 0 during the treatment phase. However, the applicant presented an analysis based on the number and proportion of subjects that had a rectal bleeding score of 0 at 0, 1, 2, 3, and 4 assessments. See the Statistical Review for additional discussion.

Key Secondary Endpoint 3

A significantly 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%; $p = 0.0488$) at the end of 6 weeks of treatment.

Study BUCF 3002

Key Secondary Endpoint 1

To evaluate the influence of lack of adherence to study procedures, the robustness of the key secondary efficacy analysis was examined using the PP population. The results were similar to the ITT population. In the ITT population the proportion of subjects who achieved a rectal bleeding score of 0 at the end of 6 weeks of treatment was significantly larger in the budesonide foam group (50%) as compared with the placebo group (29%). In the PP population the proportion of subjects who achieved a rectal bleeding score of 0 at the end of 6 weeks of treatment was significantly larger in the budesonide foam group (51%) as compared with the placebo group (29%); $p=0.0001$.

Key Secondary Endpoint 2

A significantly larger proportion of subjects in the budesonide foam group compared with the placebo group achieved a rectal bleeding MMDAI subscale score of 0 (rectal bleeding responders) at Week 1, 2,

4, and 6 assessments. The main response to budesonide was within the first 2 weeks (42%), during BID dosing, and this was further improved at Week 4 (49%) and maintained at Week 6 (50%), during QD dosing.

It should be noted that the key secondary endpoint 2 was defined in the statistical analysis plan (SAP) as the number of weeks subjects achieve a rectal bleeding MMDAI subscale score of 0 during the treatment phase. However, the applicant presented an analysis based on the number and proportion of subjects that had a rectal bleeding score of 0 at 0, 1, 2, 3, and 4 assessments. See the Statistical Review for additional discussion.

Table 25: Rectal Bleeding Responders by Study Week (LOCF Analysis, ITT Population)

	Placebo ; N= 132	Budesonide Foam ; N = 133
Efficacy Endpoint		
Study Week (+) MMDAI Rectal Bleeding Score of 0		
Week 1 Responder	11 (8)	26 (19)
Week 2 Responder	24 (16)	56 (42)
Week 4 Responder	45 (31)	65 (48)
Week 6 Responder	42 (27)	67 (50)

Source: Adapted from Table 15 NDA 205613 CSR BUCF 3002 p. 89

Key Secondary Endpoint 3

A significantly larger proportion of subjects in the budesonide foam group compared with the placebo group achieved an MMDAI endoscopy score of 0 or 1 (budesonide 56%, placebo 37%; $p = 0.0012$) at the end of 6 weeks of treatment.

6.1.6 Other Endpoints

The exploratory endpoints analyzed by the applicant are not proposed to support any labeling claims and are thus not presented in detail in this review.

6.1.7 Subpopulations

In the pooled data, the treatment effect of budesonide rectal foam resulted in a statistically significant effect compared with placebo in the primary endpoint scores across subgroups. The exception was subpopulations with limited number of subjects for analysis such as non-white subjects, newly diagnosed subjects and subjects with mild disease.

The budesonide treatment effect was consistent across subgroups. The treatment difference versus placebo was evident in males and females; subjects < 45 years and those ≥ 45 years; subjects with proctitis and those with proctosigmoiditis; subjects in the US and in Russia; subjects with moderate to severe UP/UPS.

The budesonide effect was also evident in subjects who were using 5-ASA at baseline and those who were not using 5-ASA at baseline. The proportion of budesonide-treated subjects who achieved remission (primary endpoint responders) was consistent in subjects using 5-ASA at baseline (42%) and in subjects not using 5-ASA at baseline (40%). In contrast, there was a marked difference in primary endpoint responders in the placebo group in subjects using 5-ASA at baseline (32%) versus those who were not (14%).

Reviewer comment: Subjects were allowed to use a stable dose of 5-ASA up to 4.8 g/day throughout the study. More than half of subjects used 5-ASA during treatment (56%). The fact

that there was a difference in primary endpoint responders in the placebo group between those that used 5-ASA and those that did not might suggest budesonide foam provides a treatment benefit irrespective of 5-ASA use.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The primary goal of dose selection for the phase 3 confirmatory studies was to identify a dose with a favorable efficacy profile while minimizing glucocorticoid-related side effects. The sponsor reviewed the data from the Dr. Falk Pharma program and the dose 2 mg BID dosing regimen for 2 weeks followed by a 2 mg QD regimen for the remaining 4 weeks of treatment was ultimately chosen for the confirmatory phase 3 BUCF3001 and BUCF3002 studies. The key findings from the studies of the Budesonide 2 mg foam product are summarized in the Appendix (see Section 9.7)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Budesonide Rectal Foam was used for a 6 week treatment interval. The open label long term study is ongoing. For the time administered improvement in symptoms such as rectal bleeding was observed in the analyses of rectal bleeding responders within the first 2 weeks and this was sustained until EOT (Week 6). Improvement in MMDAI subscales was observed early and this was sustained throughout the 6 week study period.

6.1.10 Additional Efficacy Issues/Analyses

In a pre-NDA meeting, July 23, 2013, the Agency requested analyses of post hoc exploratory efficacy endpoints. See Table 26 for Study BUCF 3001 and Table 27 for Study BUCF 3002.

Study BUCF 3001

The proportion of subjects who achieved endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency ≤ 1 at end of treatment was numerically higher in the budesonide group (35%) versus the placebo group (24%).

Responders for this endpoint include the subset of subjects who

1) had stool frequency = 0, endoscopy ≤ 1 , and rectal bleeding = 0 (budesonide: 17% versus placebo: 14.%)

2) The subset who had stool frequency = 1, endoscopy ≤ 1 , and rectal bleeding = 0 (budesonide: 17%, 3 versus placebo: 11%).

The proportion of subjects who achieved endoscopy = 0, rectal bleeding = 0, and stool frequency = no change or improvement from baseline was 11% in the budesonide group and 7% in the placebo group.

The proportion of subjects who achieved endoscopy ≤ 1 , rectal bleeding = 0, stool frequency = no change or improvement from baseline, and total MMDAI score ≤ 1 was 15% in the budesonide group and 11% in the placebo group.

The results of the observed case analysis and worst case analysis were similar to those in the primary analysis of these parameters for both studies BUCF 3001 and BUCF 3002

Table 26: Proportion of Responders for Post Hoc Exploratory Endpoints at the End of Treatment by Treatment Group Study BUCF 3001 (LOCF Analysis, ITT Population)

	Placebo N= 132	Budesonide Foam 2mg/mL N = 133
Responder Definition at End of Treatment		
Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency ≤ 1	32 (24)	46 (35)
Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency = 0	18 (14)	23 (17)
Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency = 1	14 (11)	23 (17)
Endoscopy = 0, rectal bleeding = 0, and stool frequency = no change or improvement from baseline	9(7)	15 (11)
Endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency = no change or improvement from baseline, total MMDAI score ≤ 1	14 (11)	20 (15)

Source: Table 19 NDA 205613 CSR BUCF 3001 p. 99

Study BUCF 3002

The proportion of subjects who achieved endoscopy ≤ 1 , rectal bleeding = 0, and stool frequency ≤ 1 at end of treatment was numerically higher in the budesonide group (44%) versus the placebo group (22%).

Responders for this endpoint include the subset of subjects who

- 1) had stool frequency = 0, endoscopy ≤ 1 , and rectal bleeding = 0 (budesonide: 30% versus placebo: 12.%)
- 2) the subset who had stool frequency = 1, endoscopy ≤ 1 , and rectal bleeding = 0 (budesonide: 14%, versus placebo: 10%).

The proportion of subjects who achieved endoscopy = 0, rectal bleeding = 0, and stool frequency = no change or improvement from baseline was 26% in the budesonide group and 12% in the placebo group.

The proportion of subjects who achieved endoscopy ≤ 1 , rectal bleeding = 0, stool frequency = no change or improvement from baseline, and total MMDAI score ≤ 1 was 26% in the budesonide group and 11% in the placebo group.

Table 27: Proportion of Responders for Post Hoc Exploratory Endpoints at the End of Treatment by Treatment Group Study BUCF 3002 (LOCF Analysis, ITT Population)

	Placebo N= 147	Budesonide Foam 2mg/mL N = 134
Responder Definition at End of Treatment		
Endoscopy ≤1, rectal bleeding = 0, and stool frequency ≤ 1	32 (22)	59 (44)
Endoscopy ≤1, rectal bleeding = 0, and stool frequency = 0	18 (12)	40 (30)
Endoscopy ≤1, rectal bleeding = 0, and stool frequency = 1	14 (10)	19 (14)
Endoscopy = 0, rectal bleeding = 0, and stool frequency = no change or improvement from baseline	17(12)	35 (26)
Endoscopy ≤1, rectal bleeding = 0, and stool frequency = no change or improvement from baseline, total MMDAI score ≤1	17 (12)	35 (26)

Source Table 19 NDA 205613 CSR BUCF 3002 p.101

7 Review of Safety

Safety Summary

7.1 Methods

Safety data were analyzed for the following integrated populations:

- **Randomized Controlled Trial (RCT) Population:** includes subjects who received at least 1 dose of study drug in studies BUCF3001 or BUCF3002. Data for the RCT Safety population were presented according to the double-blind study treatment that the subjects actually received. The treatment groups were presented in the tables as “Placebo” and “Budesonide Foam 2 mg/25 mL,” respectively.
- **All Budesonide Safety Population:** includes subjects who received at least 1 dose of budesonide foam in studies BUCF3001, BUCF3002, BUF-6/UCA, BUF-9/UCA, or BFPS3073. At the time of data cutoff for the NDA submission, BFPS3073 was ongoing. Data from the ongoing study are available for all subjects up to 01 April 2013 (clinical cutoff date). The experience of subjects while on placebo or non-budesonide comparator treatment during the randomized studies was not included in the All Budesonide Safety population analyses.
- **All Salix Budesonide Safety Population:** includes subjects who received at least 1 dose of budesonide foam in either of the Salix phase 3, double-blind studies BUCF3001 or BUCF3002, or in the open-label extension study BFPS3073. At the time of data cutoff for the NDA submission, BFPS3073 was ongoing. Data from the ongoing study are available for all subjects up to 01 April 2013 (clinical cutoff date). The experience of subjects while on placebo during the double-blind BUCF3001/3002 studies was not included in the All Salix Budesonide Safety population analyses.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety data analysis included integrated analyses of safety data pooled from Salix clinical studies BUCF3001, BUCF3002, and BFPS3073 (open label, ongoing)to assess the safety and tolerability of repeat cycles(based on flares of UP/UPS)of budesonide foam in subjects with UP/UPS., as well as Dr. Falk clinical studies BUF-6 /UCA and BUF-9/UCA. See the tables below.

Although the sponsor asserts that the drug product utilized in the Salix-sponsored studies for the current NDA, budesonide foam 2 mg (the proposed To Be Marketed Product (TBMP)), is (b) (4) Budenofalk 2 mg rectal foam, there are formulation differences between the TBMP and the Budenofalk product that most likely will be discussed in one or more of the following reviews: CMC Review, Pharmacology/Toxicology Review, and/or Clinical Pharmacology Review.

Table 28. Phase 3 Salix Budesonide Studies Used for Safety Analysis

Protocol/ Phase, Design	Subject Population	Treatment Group	Treatment	# of Subjects Treated ^a	Countries
BUCF3001/ Phase 3, DB placebo- controlled	Mild to moderate active UP or UPS	2 mg/25 mL budesonide rectal foam; placebo rectal foam 1:1 allocation	BID for 2 weeks followed by QD for 4 weeks	Total 265 Budesonide: 134 Placebo: 131	US, Russia
BUCF3002/ Phase 3, DB placebo- controlled	Mild to moderate active UP and UPS	2 mg/25 mL budesonide rectal foam; placebo rectal foam 1:1 allocation	BID for 2 weeks followed by QD for 4 weeks	Total 281 Budesonide: 134 Placebo: 147	US, Russia
BFPS3073/ Phase 3, OL (for continued active flare or recurrence of active flare)	Mild to moderate active UP and UPS	2 mg/25 mL budesonide rectal foam Open label	BID for 2 weeks followed by QD for 4 weeks	Budesonide: 108	US

Source: Table 5 Integrated Summ Safety; NDA 205613; p. 34.

Table 29. Phase 3 Dr. Falk Budesonide Studies Used for Safety Analysis

Protocol/ Phase, Design	Subject Population	Treatment Group	Treatment	# of Subjects Treated ^a	Countries
BUF-6/UCA/ Phase 3, OL active controlled	Proctitis and proctosigmoiditis	Group 1: Budenofalk rectal foam 2 mg Group 2: Hydrocortisone acetate rectal foam 100 mg	QD for 8 weeks	Total 248 Budesonide 2 mg: 120 Hydrocortisone acetate: 128	Germany, Israel, and Italy
BUF-9/UCA/ Phase 3, DB double dummy, active controlled	Active UP or UPS	Group 1: Budenofalk rectal foam and placebo enema Group 2: placebo rectal foam and budesonide enema	QD for 4 weeks	Total 535 Budesonide foam: 267 Budesonide enema: 268	Germany, Estonia, Hungary, Israel, Lithuania, Latvia, Netherlands

7.1.2 Categorization of Adverse Events

Adverse events were classified by the applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 13.0. Treatment-emergent AEs were defined as any AE with a start date occurring on or after treatment Day 1 or, if preexisting, worsening after treatment Day 1.

For the RCT Safety population, treatment Day 1 was the first dose date of the double-blind treatment. For the All Budesonide Safety and All Salix Budesonide Safety populations, treatment Day 1 was the first dose administration date of budesonide foam.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Adverse event incidence data were included from the Phase 3 studies. These studies included Salix studies BUCF 3001 and BUCF 3002 and the Budenofalk studies. See Section 7.1 for a description of how pooled data is presented.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry [including cortisol level and urinalysis]), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis population.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the RCT Safety population (studies BUCF3001 and BUCF3002 combined) the budesonide foam treatment group had 28.5 person-years of exposure and the placebo group had 29.8 years of exposure. The mean number of days of exposure to study drug was 38.8 in the budesonide foam group and 39 days in the placebo group.

Exposure durations of 29 to 44 days (4 to 6 weeks) were reported for 81% of subjects in the budesonide group and 83% of subjects in the placebo group. Although the protocol-specified treatment duration was 42 days, exposure durations of > 45 days were reported in both the placebo and treatment group because some subjects had Week 6 visits that were past the window of +2 days for the Day 42 (Week 6).

Table 30. Study Drug Exposure (RCT Safety Population)

Exposure Duration/Category	Placebo N = 278	Budesonide Foam 2 mg/25 mL N = 268
Total person-years of exposure ^a	29.8	28.5
Exposure duration (days)		
Mean (SD)	39.1 (9.15)	38.8 (9.92)
Median (minimum, maximum)	42.0 (1, 51)	42.0 (3, 58)
Exposure duration category – n (%)		
1 – 14 days	16 (5.8)	19 (7.1)
15 – 28 days	14 (4.0)	13 (4.9)
29 – 44 days	230 (82.7)	215 (81.2)
≥ 45 days	18 (6.5)	21 (7.8)

Source: ISS Table 5.1.1.

Abbreviation: ISS = Integrated Summary of Safety; RCT = randomized controlled trial; SD = standard deviation.

^a Total person years of exposure is calculated as (sum of all subject duration of exposure days ÷ 365.25).

Source: Page 76 of the Summary of Clinical Safety

Demographic characteristics were similar between treatment groups in the RCT Safety population. The mean ages of subjects in the budesonide and placebo groups were 44 and 42 years and all but 35 subjects were < 65 years old. Most of the subjects were White (budesonide 88%, placebo 92%) but the treatment groups were better balanced with respect to gender, males (budesonide 54%, placebo 59%) and females (budesonide 46%, placebo 41%).

7.2.2 Explorations for Dose Response

For dose selection, the primary goal was to identify a dose with a favorable efficacy profile, minimizing glucocorticoid-related side effects, and optimizing risk-benefit ratio. After a comprehensive review of the data from the Dr. Falk Pharma GmbH program, a 2 mg BID dosing regimen for 2 weeks followed by a 2 mg QD regimen for the remaining 4 weeks of treatment was ultimately chosen. Data to support use of the selected regimen included observations from a pilot study BUF-3/UCA, results from phase 2 dose ranging studies with foam (BUF-5/UCA) and enema (ENTOCORT®) budesonide formulations, and results of phase 3 studies of budesonide foam (Budenofalk foam).

7.2.3 Special Animal and/or In Vitro Testing

For more information, see the Pharmacology/Toxicology and Clinical Pharmacology Review

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

For information pertaining to the above, see the Clinical Pharmacology Review by Dr. Dilara Jappar.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The studies were adequately designed to evaluate safety analyses. The studies submitted monitored for potential adverse events that may be sequelae of corticosteroid use. This included monitoring morning cortisol concentrations, performing ACTH stimulation tests, and observing for overall glucocorticoid effects. The studies did not reveal any new safety signals.

7.3 Major Safety Results

7.3.1 Deaths

No subjects died during any of the primary safety studies sponsored by Salix or Dr. Falk Pharma.

7.3.2 Nonfatal Serious Adverse Events

In the RCT Safety population (studies BUCF3001 and BUCF3002), treatment emergent adverse events (TEAEs) were experienced by 46% (123 of 268) and 36% (101 of 278) of subjects in the budesonide foam group and placebo group, respectively.

The TEAEs were predominately mild or moderate in intensity; 8 subjects (3%) in the budesonide foam group and 4 subjects (1%) in the placebo group experienced severe TEAEs. Treatment emergent AEs considered by the investigator to be related to study drug were more frequent in the budesonide foam group (21%) compared with the placebo group (6%).

Table 31 Summary of Adverse Events Randomized Control Trial Safety Population (RCT)

	Placebo N = 278 n (%)	Budesonide Foam 2 mg/25 mL N = 268 n (%)
Subjects with TEAEs		
Any TEAE	101 (36.3)	123 (45.9)
Intensity of TEAEs^a		
Severe	4 (1.4)	8 (3.0)
Moderate	40 (14.4)	27 (10.1)
Mild	57 (20.5)	88 (32.8)
Treatment-emergent AEs related to study drug	16 (5.8)	56 (20.9)
Treatment-emergent SAEs	3 (1.1)	5 (1.9)
Treatment-emergent AEs leading to discontinuation from study	12 (4.3)	26 (9.7)
Deaths	0	0

Source: Table 54. NDA 205613 ISS page 103.

^a If a subject experienced more than 1 adverse event, the subject was counted only once for the maximum intensity

7.3.3 Dropouts and/or Discontinuations

In the RCT Safety population, 26 subjects in the budesonide group (10%) and 12 subjects in the placebo group (4%) had TEAEs that resulted in early withdrawal from the study. The following TEAEs resulted in early study withdrawal for more than 1 subject in either treatment group:

Blood cortisol decreased (budesonide 16 subjects [6%], placebo 1 subject [0.4%]), adrenal insufficiency (4 [2%], 1 [0.4%]), ulcerative proctitis (0, 4 [1%]). Most of these events were mild or moderate in intensity, with the exception of 1 severe event of proctalgia and 1 event of severe generalized exanthematous pustulosis in 1 budesonide treated subject each, and 1 severe event of ulcerative proctitis in a placebo-treated subject.

In general, the TEAEs resulting in study withdrawal resolved by the end of the study, with the exception of 1 case each of ulcerative proctitis, herpes zoster (placebo) and decreased blood cortisol (budesonide) and 2 cases of ulcerative colitis (placebo).

Individuals who did not meet the ACTH challenge criteria (i.e., those who did not produce peak cortisol levels of 18 µg/dL upon stimulation) were permanently discontinued from treatment, and were to have undergone further evaluation for adrenal insufficiency as outlined in each site's standard institutional guidelines.

Table 32: TEAEs Leading to Study Drug Discontinuation (RCT Safety Population)

Treatment Group	Subject Number	Date of Onset/End Date	Relative Start Day ^a	Preferred Term	Related to Drug?	Intensity	Outcome
Budesonide	3001-0156-0001	19 Apr 2010/ Ongoing	18	Blood cortisol decreased	Yes	Moderate	Not resolved ^c
Budesonide	3001-0186-0005	28 Dec 2010/ 10 Jan 2011	9	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-0561-0009	04 Jan 2013/ 16 Jan 2013	40	Hypersensitivity ^b (allergic reaction: mandarin oranges)	No	Moderate	Resolved with sequelae
Budesonide	3001-0857-0005	18 May 2010/ 01 Jun 2010	14	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-0889-0004	09 Nov 2011/ 23 Dec 2011	15	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-0956-0010	04 Mar 2011/ 08 Mar 2011	+1	ACTH stimulation test abnormal	Yes	Moderate	Resolved
Budesonide	3001-0991-0005	18 May 2011/ 01 Jun 2011	9	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-1381-0008	02 July 2012/ 26 July 2012	7	Blood cortisol decreased	No	Mild	Resolved
Budesonide	3001-1394-0004	19 Sep 2011/ 29 Sep 2011	29	Adrenal insufficiency	Yes	Mild	Resolved
Budesonide	3001-1399-0005	25 Oct 2011/ 07 Nov 2011	9	Adrenal insufficiency	Yes	Moderate	Resolved
Budesonide	3001-1399-0007	22 Nov 2011/ 28 Nov 2011	23	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-1399-0012	28 Nov 2011/ 08 Dec 2011	15	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3001-1399-0017	28 Feb 2012/ 06 Mar 2012	30	Blood cortisol decreased	Yes	Mild	Resolved

Treatment Group	Subject Number	Date of Onset/End Date	Relative Start Day ^a	Preferred Term	Related to Drug?	Intensity	Outcome
Budesonide	3002-0039-0003	13 Sep 2010/ 21 Sep 2010	29	Blood cortisol decreased	No	Mild	Resolved
Budesonide	3002-0050-0005	10 Jun 2011/ 12 Sep 2011	1	Blood cortisol decreased	No	Mild	Resolved
Budesonide	3002-0463-0023	31 Mar 2012/ 07 Apr 2012	38	Rash	Yes	Moderate	Resolved
Budesonide	3002-0547-0002	02 Jul 2010/ 09 Jul 2010	19	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3002-0933-0006	21 May 2012/ 13 Jun 2012	8	Blood cortisol decreased	No	Moderate	Resolved
Budesonide	3002-0938-0006	12 Sep 2011/ 20 Sep 2011	8	Adrenal insufficiency	Yes	Moderate	Resolved
Budesonide	3002-0961-0003	03 Apr 2010/ 28 Apr 2010	9	Acute generalized exanthematous pustulosis ^b	Yes	Severe	Resolved
Budesonide	3002-1301-0008	16 Apr 2010/ 17 Apr 2010	3	Proctalgia	Yes	Severe	Resolved
Budesonide	3002-1306-0011	09 Aug 2010/ 02 Sep 2010	8	Blood cortisol decreased	No	Mild	Resolved
Budesonide	3002-1375-0022	30 Apr 2012/ 25 May 2012	8	Adrenal insufficiency	Yes	Mild	Resolved
Budesonide	3002-1403-0001	17 May 2012/ 29 May 2012	8	Blood cortisol decreased	Yes	Mild	Resolved
Budesonide	3002-1405-0003	07 Dec 2011/ 04 Jan 2012	20	Hyperbilirubinemia	No	Mild	Resolved
Budesonide	3002-1405-0008	02 Mar 2012/ 07 Mar 2012	8	Blood cortisol decreased	No	Mild	Resolved
Placebo	3001-0520-0013	2012-07-11/ Ongoing	4	Proctitis ulcerative	No	Severe	Not resolved ^c
Placebo	3001-0834-0022	16 Apr 2012/ 16 May 2012	+1	Colitis ulcerative	No	Moderate	Resolved
Placebo	3001-0855-0003	07 Oct 2010/ 12 Oct 2010	14	Proctitis ulcerative	No	Moderate	Resolved
Placebo	3001-1123-0006	12 Sep 2010/ 20 Sep 2010	24	Proctitis ulcerative	No	Moderate	Resolved
Placebo	3001-1339-0001	30 Sep 2010/ 30 Oct 2010	9	Cellulitis	No	Moderate	Resolved
Placebo	3001-1394-0002	19 Sep 2011/ 29 Sep 2011	29	Adrenal insufficiency	Yes	Mild	Resolved
Placebo	3001-1471-0001	27 Dec 2012/ 31 Dec 2012	15	Application site pain	Yes	Mild	Resolved

Treatment Group	Subject Number	Date of Onset/End Date	Relative Start Day ^a	Preferred Term	Related to Drug?	Intensity	Outcome
Placebo	3002-0050-0004	03 Jul 2011/ 09 Jul 2011	+2	Proctitis ulcerative	No	Moderate	Resolved
Placebo	3002-0198-0002	25 Jan 2010/ Ongoing	+1	Colitis ulcerative	No	Moderate	Not resolved ^c
Placebo	3002-0939-0004	27 Nov 2011/ Ongoing	17	Colitis ulcerative	No	Moderate	Not resolved ^c
Placebo	3002-1384-0002	29 Jul 2011/ Ongoing	+2	Herpes zoster	No	Mild	Not resolved ^c
Placebo	3002-1403-0005	11 Oct 2011/ 18 Oct 2011	7	Blood cortisol decreased	Yes	Mild	Resolved

Source: Table 69 NDA 205613 ISS pages 119-121.

7.3.4 Significant Adverse Events

In the RCT safety population, 5 subjects experienced treatment emergent SAEs in the budesonide group (2%; one case each of abdominal pain, ulcerative colitis, hypersensitivity (food allergy, not related to study drug), acute generalized exanthematous pustulosis, and arteriothrombosis limb) and by 3 subjects in the placebo group (1%; one case each of anemia, colitis ulcerative, and ectopic pregnancy).

The SAE of acute generalized exanthematous pustulosis occurred in conjunction with a staphylococcal infection and was judged by the investigator to be drug-related; this subject was subsequently discontinued from the study.

The SAE of hypersensitivity (food allergy, not related to study drug) also resulted in the subject discontinuing early from the study. All SAEs were resolved by the end of the study.

Table 33: Serious TEAEs (RCT Safety Population)

Treatment Group	Subject Number	Date of Onset/End Date	Relative Start Day ^a	Preferred Term	Related to Drug?	Intensity	Outcome
Budesonide	3001-0561-0009	04 Jan 2013/ 16 Jan 2013	40	Hypersensitivity ^b (allergic reaction to mandarin oranges)	No	Moderate	Resolved with sequelae
Budesonide	3001-0855-0001	25 Jun 2010/ 29 Jun 2010	18	Arterial thrombosis limb	No	Severe	Resolved
Budesonide	3002-0039-0008	16 Oct 2011/ 22 Oct 2011	+8	Colitis ulcerative	No	Severe	Resolved
Budesonide	3002-0157-0005	17 Nov 2011/ 19 Nov 2011	+3	Abdominal pain	No	Severe	Resolved
Budesonide	3002-0961-0003	03 Apr 2010/ 28 Apr 2010	9	Acute generalized exanthematous pustulosis ^b	Yes	Severe	Resolved
Placebo	3001-0678-0014	13 Jun 2011/ 22 Jun 2011	35	Ectopic pregnancy	No	Moderate	Resolved with sequelae
Placebo	3001-1081-0005	11 Feb 2011/ 13 Feb 2011	+45	Anaemia	No	Severe	Resolved
Placebo	3001-1394-0002	05 Oct 2011/ 17 Oct 2011	+15	Colitis ulcerative	No	Moderate	Resolved

Source: Table 66. NDA 205613 ISS p. 116.
^b This event resulted in withdrawal from the study.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the RCT Safety population, the most frequently reported TEAEs by preferred term in $\geq 2\%$ of subjects in either group were decreased blood cortisol (budesonide 17%, placebo 2%), adrenal insufficiency (4%, 0.7%), and headache (2%, 3%).

Table 34: TEAEs Occurring in $\geq 2\%$ of Subjects Treated with Budesonide or Placebo (RCT Safety Population)

System Organ Class Preferred Term	Placebo N=278 n (%)	Budesonide Foam 2mg/25mL N=268 n (%)
Any system organ class	23 (8)	65 (24)
Endocrine disorders		
Adrenal Insufficiency	2 (0.7)	10 (4)
Gastrointestinal disorders		
Nausea	2 (0.7)	6 (2)
Ulcerative proctitis	6 (2)	0
Investigations		
Blood cortisol decreased	6 (2)	46 (17)
Nervous system disorders		
Headache	7 (2)	6 (2)

Source: Table 57. NDA 205613 ISS p. 106.

Glucocorticoid side effects such as moon face, striae rubrae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne, and hirsutism were rarely reported as TEAEs in these studies.

Among budesonide foam-treated subjects, 1 subject (0.4%) experienced insomnia (mild and not considered related to study drug), 1 subject experienced sleep disorder (severe and related), 1 subject experienced weight increased (mild and related), and 1 subject experienced acne (mild and related).

7.4.2 Laboratory Findings

In the RCT Safety population, the most frequently occurring laboratory results reported as TEAEs were blood cortisol decreased (budesonide 17%, placebo 2%) and adrenal insufficiency (4%, 0.7%). These TEAEs occurred in higher proportions of budesonide-treated subjects compared with placebo treated subjects.

Laboratory results that were considered potentially clinically significant (PCS) as defined in the protocol are presented in Table 32. The PCS results were primarily related to decreased cortisol levels and these decreased levels occurred in a greater proportion of budesonide treated subjects than placebo treated subjects.

Among subjects who had morning cortisol level < 5 µg/dL during the treatment period (budesonide 72 subjects; and placebo 19 subjects), there were increases in cortisol levels above the cut-off for a normal response post ACTH challenge (18 µg/dL [500 nmol/L]) for 68% (49 of 72 subjects) and 74% (14 of 19 subjects) in the budesonide and placebo groups, respectively.

There were no significant differences between treatment groups in the potentially clinically significant laboratory findings.

No subject met Hy's Law which is defined as an elevation of ≥ 3 x ULN in AST or ALT with an elevation of ≥ 2 x ULN in bilirubin.

Table 35 Potentially Clinically Significant Laboratory Results (RCT Safety Population)

	Placebo N = 278 n/N (%)	Budesonide Foam 2 mg/25 mL N = 268 n/N (%)
Parameter: PCS Criteria		
AM cortisol < 5 µg/dL (< 138 nmol/L) and ACTH challenge cortisol < 18 µg/dL (< 500 nmol/L) ^a	5/19 (26.3)	23/72 (31.9)
AM cortisol < 5 µg/dL	19/277 (6.9)	72/267 (27.0)
Cortisol < 18 µg/dL following ACTH challenge	17/265 (6.4)	56/259 (21.6)
Total bilirubin > 34.2 µmol/L	4/277 (1.4)	4/267 (1.5)
Alanine aminotransferase ≥ 3 × ULN (U/L)	3/277 (1.1)	1/267 (0.4)
Aspartate aminotransferase ≥ 3 × ULN (U/L)	2/277 (0.7)	1/267 (0.4)
Platelet < 25 or > 1000 × 10 ⁹ /L	1/277 (0.4)	1/267 (0.4)

Source: Table 82. NDA 205613 Summ Clin Safety p. 141.

^a The denominator is the number of subjects who had AM cortisol < 5 µg/dL (< 138 nmol/L) and the numerator is the number of these subjects who also had a total cortisol < 18 µg/dL (< 500 nmol/L) following ACTH challenge

Serum Cortisol Evaluation

Serum cortisol (AM cortisol) was collected at Baseline, and Weeks 1, 2, 4, and 6 in BUCF3001 and BUCF3002, the RCT safety population.

Data on ACTH challenge was collected in the Salix studies as follows: for double-blind studies BUCF3001 and BUCF3002 at Baseline and Week 6, and for the open-label study BFPS3073 at the Qualifying Visit for each cycle, then unscheduled ACTH tests were performed for subjects who had fasting AM serum cortisol levels < 5µg/dL during the treatment cycle.

Results from the RCT Safety population show initial decreases in mean serum cortisol levels at Weeks 1 and 2 in the budesonide group that gradually returned toward baseline levels by Week 6. At Week 6, mean (±SD) changes from baseline in total cortisol were -2.58 (± 182.060) nmol/L in the budesonide group and -2.30 (± 162.939) nmol/L in the placebo group. The total cortisol level had returned to approximately baseline levels in both treatment groups by Week 6.

The greater decreases in cortisol levels at Weeks 1 and 2, compared with Weeks 4 and 6, are likely due to BID dosing during the first 2 weeks and QD dosing during the subsequent 4 weeks.

Table 36: Changes from Baseline in Cortisol Levels (RCT Safety Population)

AM Cortisol Change from Baseline, nmol/L	Placebo N = 278	Budesonide Foam 2 mg/25 mL N = 268
Baseline	N = 278	N = 268
Mean (SD)	367.56 (136.108)	357.09 (143.926)
Week 1	N = 269	N = 252
Mean (SD)	367.97 (138.602)	308.06 (144.886)
Mean change from Baseline (SD)	3.12 (122.422)	-48.69 (160.186)
Week 2	N = 266	N = 250
Mean (SD)	362.98 (135.089)	297.18 (145.642)
Mean change from Baseline (SD)	-7.38 (126.757)	-58.39 (160.119)
Week 4	N = 249	N = 233
Mean (SD)	364.41 (141.278)	333.33 (140.551)
Mean change from Baseline (SD)	-4.64 (137.436)	-27.85 (148.246)
Week 6	N = 241	N = 221
Mean (SD)	368.91 (149.375)	362.78 (157.567)
Mean change from Baseline (SD)	-2.30 (162.939)	-2.58 (182.060)

Source: Table 87, NDA 205613 Summ Clin Safety, p. 145
Normal range: 5 µg/dL (138nmol/L) to 25 µg/dL (690 nmol/L)

Additionally, adrenal function was evaluated by the ACTH challenge test. Cortisol levels were measured in response to a cosyntropin challenge. Cosyntropin is synthetic ACTH. Greater decreases from baseline to Week 6 in cortisol levels following ACTH challenge were observed in the budesonide group compared with the placebo group.

Table 37: Changes from baseline in ACTH Challenge Results (RCT Safety Population)

Total Cortisol Levels Following ACTH Challenge, nmol/L	Placebo N = 278	Budesonide Foam 2 mg/25 mL N = 268
Baseline	N = 278	N = 266
Mean (SD)	732.57 (153.481)	713.28 (140.927)
Week 6	N = 235	N = 214
Mean (SD)	702.24 (146.913)	658.30 (170.803)
Mean change from Baseline (SD)	-24.52 (168.405)	-66.55 (182.214)

Source: Table 88, NDA 205613 Summ Clin Safety, p. 146.

The proportion of subjects with serum cortisol levels > 5µg/dL and the proportion of subjects with normal response to the ACTH was analyzed. Serum cortisol levels > 5 µg/dL(138 nmol/L) were maintained in approximately 84% of subjects in the budesonide and placebo treatment groups in the RCT Safety population at Weeks 1, 2, 4, and 6. The proportion of subjects who maintained serum cortisol levels > 5 µg/dL was lower in the budesonide group than in the placebo group at Weeks 1 and 2 which were the twice a day dosing phase.

During the once a day dosing phase, the difference between treatments was attenuated and the percentage of budesonide-treated and placebo-treated subjects who had serum cortisol levels > 5 µg/dL by Week 6 (94% and 97%,) were generally similar to those at baseline (97% and 99%,).

Reviewer comment: The increased effect of budesonide on serum cortisol levels during the twice a day treatment phase compared to the once a day treatment phase, measured by changes in the proportion of subjects with serum cortisol levels >5 µg/dL is consistent with the results presented in Table 33 where budesonide treatment resulted in serum cortisol decreases initially but a return to normal levels during Weeks 4-6.

To monitor for adrenal suppression, ACTH challenge (or stimulation) tests were performed at Baseline and the end of treatment (Week 6/Withdrawal). The normal response to ACTH challenge includes 3 criteria, as defined in the Cosyntropin® label: 1) morning serum cortisol > 5 µg/dL (138 nmol/L); 2) increase in serum cortisol from basal level (morning serum cortisol level prior to ACTH challenge) by ≥ 7 µg/dL (193 nmol/L) at 30 minutes following ACTH challenge; 3) serum cortisol > 18 µg/dL (500 nmol/L) at 30 minutes following ACTH challenge.

At baseline, 84% of subjects in the budesonide foam group had a normal response to the ACTH challenge and at Week 6, 69% of subjects had a normal response to the ACTH challenge; in the placebo group, these values were 86% and 77%, respectively.

Table 38: Proportion of Subjects with Cortisol Levels of >5 µg/dL (138nmol/L) During the Study and Proportion of Subjects with Normal Response to ACTH Challenge (RCT Safety Population)

Cortisol Parameter	Placebo N = 278 n (%)	Budesonide Foam 2 mg/25 mL N = 268 n (%)
Total cortisol > 5 µg/dL (138 nmol/L, lower limit of normal range)		
Baseline	275/278 (98.9)	259/268 (96.6)
Week 1	264/269 (98.1)	224/263 (85.2)
Week 2	263/266 (98.9)	216/257 (84.0)
Week 4	243/249 (97.6)	218/235 (92.8)
Week 6	234/241 (97.1)	211/224 (94.2)
Normal response to ACTH challenge^a		
Baseline	238/278 (85.6)	222/266 (83.5)
Week 6	180/235 (76.6)	148/216 (68.5)

Source: Table 89 NDA 205613, Summ Clin Safety, p. 147

^a The normal response to ACTH challenge includes 3 criteria, as defined in the cosyntropin label: 1) morning serum cortisol > 5 µg/dL (138 nmol/L); 2) increase in serum cortisol from basal level (morning serum cortisol level prior to ACTH challenge) by ≥ 7 µg/dL (193 nmol/L) at 30 minutes following ACTH challenge; 3) serum cortisol > 18 µg/dL (500 nmol/L) at 30 minutes following ACTH challenge.

7.4.3 Vital Signs

In the safety evaluation of vital signs, including pulse and blood pressure, obtained in each of the analysis groups, no findings of clinical importance were discerned with regard to values over time, individual patient changes, and individual clinically important abnormalities.

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms assessments were only performed at the screening visit. Notably, no subject experienced TEAEs in the cardiac disorders system organ class in the RCT Safety population.

7.4.5 Special Safety Studies/Clinical Trials

No specialty studies or clinical trials were submitted in support of this application.

7.4.6 Immunogenicity

The applicant did not provide any clinical or adverse event data pertaining to immunogenicity in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No explorations were conducted for dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

No explorations were conducted for time dependency of adverse events

7.5.3 Drug-Demographic Interactions

Age

Only a small numbers of subjects 65 years or older were studied in the RCT Safety population (budesonide N=21, placebo N=14) so no meaningful conclusions can be made with respect to age in this group. However, the All Budesonide Safety population (**includes** subjects who received at least 1 dose of budesonide foam in studies BUCF3001, BUCF3002, BUF-6/UCA, BUF-9/UCA, or BFPS3073) results are the following. The incidence of TEAEs in the budesonide foam group was 41% in subjects who were < 65 years of age and 31% in subjects who were ≥ 65.

The most frequently occurring (i.e., in ≥ 2% of subjects in the budesonide foam group) TEAEs for the overall population were reported in the following proportions of subjects who were < 65 years of age and in subjects who were ≥ 65 as follows: blood cortisol decreased (< 65 8%, ≥ 65 10%), headache (6%, 2%), nausea (3%, 2%), and abdominal pain (3%, 2%).

The incidence of SAEs was low; 6 subjects (0.6%) with SAEs in the budesonide foam group were < 65 years of age and 2 subjects (4%) were ≥ 65 years of age.

Gender

In the RCT Safety population, 123 budesonide subjects were male and 145 budesonide subjects were female. The incidence of TEAEs in the budesonide group was similar in males (47%) and females (45%).

The most frequently occurring (i.e., in $\geq 2\%$ of subjects in the budesonide foam group) TEAEs for the overall population were reported in the following proportions of males and females in the budesonide group: blood cortisol decreased (male 13%, female 21%), adrenal insufficiency (6%, 2%), headache (0.8%, 3%), and nausea (0.8%, 3%).

The incidence of SAEs was low overall with 4 subjects in the budesonide group having SAEs. (3 female, 1 male).

Race, Disease Severity, and Extent of Disease

There were no clinically relevant trends in the safety profile of budesonide between subjects based on race, disease severity or extent of disease.

A limited number of Blacks and Non-whites were included in the RCT Safety population: Blacks (budesonide N= 26, placebo N=13) and similarly Non-whites (budesonide N= 33, placebo N= 21)

With regards to disease severity, a small number of subjects with mild disease were included in the RCT Safety population (budesonide N=34 and placebo= 28). The incidence of TEAEs in the budesonide group was 39% in subjects with mild disease and 47% in subjects with moderate/severe disease.

TEAEs for the overall population were generally reported in lower proportions in subjects with mild disease than those with moderate/severe disease as follows: blood cortisol decreased (mild 14%, moderate/severe 18%), adrenal insufficiency (0, 4%), headache (0, 3%), and nausea (0.3%). The incidence of SAEs was also appropriately low with subjects experiencing SAEs in the budesonide group where the 5 subjects had moderate/severe disease.

Notably the majority of the subjects in the RCT Safety population presented with UPS and the TEAE occurring most frequently in the overall population was blood cortisol decrease (UP 14% and UPS 19%); adrenal insufficiency occurred at 4% in both UP and UPS.

Renal Impairment

There were no clinically relevant trends in the safety profile of budesonide between subjects with normal GFR versus those with mild/moderate or mild/moderate/severe decrease in GFR.

The majority of subjects in the RCT Safety population (Studies BUCF 3001 and BUCF 3002) had normal GFR (budesonide N = 214, placebo N = 226) and the remainder had a mild/moderate decrease in GFR (budesonide N = 54, placebo N = 52). The majority of subjects in the All Budesonide Safety population were < 65 years of age (budesonide foam N = 666, budesonide enema N = 242) and the remainder were ≥ 65 (foam N = 52, enema N = 26).

The most frequently occurring TEAEs (i.e., those that occurred in $\geq 2\%$ of subjects in the budesonide foam group) for the overall population were similar in subjects with normal GFR and those with mild/moderate decrease in GFR as follows: Blood cortisol decreased (normal GFR 17%, mild/mod GFR \downarrow 17%); adrenal insufficiency (both 4%); headache (3%, 0); nausea (2%, 4%).

The incidence of SAEs was low where all subjects with an SAE in the budesonide group had normal GFR (5 subjects = 2%).

Based on these findings, no dose modifications are recommended with respect to age, race, gender, disease severity or extent of disease or renal impairment.

7.5.4 Drug-Disease Interactions

No subgroup analyses were conducted in patients with concomitant illnesses or hepatic insufficiency. However, the following passages taken from the Uceris (budesonide) extended release tablets Prescribing Information/Package Insert pertain to renal and hepatic impairment subpopulations respectively:

“The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renal excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (<1/100).”

“In patients with liver cirrhosis, systemic availability of orally administered budesonide correlates with disease severity and is, on average, 2.5-fold higher compared with healthy controls. Patients with mild liver disease are minimally affected. Patients with severe liver dysfunction were not studied. Absorption parameters are not altered, and for the intravenous dose, no significant differences in CL or VSS are observed.”

7.5.5 Drug-Drug Interactions

No specific drug-drug interaction clinical studies were performed with the proposed budesonide TBMP. Budesonide is not a new chemical entity and is a well characterized corticosteroid metabolized through the cytochrome (CYP3A4) mixed function oxidase system in the liver, with known drug-drug interactions.

A number of known drug –drug interactions with budesonide are described in the recent Uceris (budesonide) extended release tablets Prescribing Information. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide by several-fold. Specifically, co-administration with ketoconazole results in an 8-fold increase in area under the concentration time curve (AUC) of budesonide, compared to budesonide alone. Treatment with other known inhibitors of the CYP3A4, such as itraconazole, ritonavir, indinavir, saquinavir, and erythromycin would be expected to have similar effects.

Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels.

Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (i.e., ethinyl estradiol).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not provide any clinical or adverse event data pertaining to human carcinogenicity in this application.

7.6.2 Human Reproduction and Pregnancy Data

No subjects using budesonide foam or enema in this development program became pregnant during the studies with the exception of 1 subject who had an ectopic pregnancy. The following subjects had positive pregnancy tests (ISS [120-day update])

- Subject 3001-0678-0014, a 29-year-old female in the placebo group, had a positive pregnancy test at Week 6 and was subsequently diagnosed with an ectopic pregnancy.
- Subject 3001-0857-0008, a 52-year-old postmenopausal female (BUCF3001) in the placebo group, had a positive pregnancy test at Week 6 (day after last dose of study drug), with an indeterminate pregnancy test approximately 1 week later.
- Subject 3001-3073-1123-0015, (BFPS3073open label study ongoing) a 54-year-old surgically sterile female using budesonide foam, had a positive pregnancy test at the Cycle 1 Qualifying Visit in BFPS3073; she continued in the study and had indeterminate pregnancy tests 7 days later and also at the Day 15 and 42 time points in that Cycle. She had indeterminate pregnancy test results at the Cycle 2 Qualifying Visit and a positive test on Cycle 2, Day 15.

Budesonide was teratogenic and embryocidal in rabbits and rats. There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

Children who are treated with corticosteroids by any route may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been in the absence of laboratory evidence of HPA axis suppression. The long-term effects of this reduction in growth velocity associated with corticosteroid treatment, including the impact on final adult height, are unknown.

The effects of budesonide rectal foam on pediatric populations were not studied in the budesonide rectal foam program, as the replicate studies BUCF 3001 and BUCF 3002 required participants to be at least 18 years of age. The safety and effectiveness of budesonide rectal foam has not been established in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Reports of acute toxicity and/or death following overdosage of glucocorticoids are rare. Treatment consists of supportive and symptomatic therapy. If glucocorticosteroids are used at excessive doses for prolonged periods, systemic glucocorticosteroid effects such as hypercorticism and adrenal suppression may occur.

Drug abuse with budesonide rectal foam is not expected given the route of administration. No cases of budesonide rectal foam abuse have been reported during the clinical studies for budesonide foam in the treatment of UP/UPS.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a response to an Information Request (March 5, 2014) requesting information about subjects who had treatment emergent adverse event of adrenal insufficiency. In Studies BUCF 3001 and BUCF 3002, adrenal insufficiency was defined as a cortisol level of < 18 µg/dL (< 500 nmol/L) at 30 minutes post challenge with ACTH. This protocol definition of adrenal insufficiency did not require overt clinical signs of adrenal insufficiency. Twelve subjects were identified as having adrenal insufficiency according to this definition.

Brief narratives for the 5 subjects who had treatment-emergent adverse events (TEAEs) of adrenal insufficiency and who subsequently withdrew from the studies are provided in Section 9.6. These events for all 12 subjects were recorded on the basis of laboratory data and did not include concurrent clinical signs of adrenal suppression.

8 Postmarket Experience

Dr. Falk Pharma completed the European Mutual Recognition Procedure in 2006 for marketing of Budenofalk 2 mg rectal foam for the acute treatment of UC that is limited to the rectum and sigmoid colon. As of 15 October 2012, Budenofalk 2 mg rectal foam has been granted authorization in 30 countries including the United Kingdom. (b) (4).

Patient exposures since approval is estimated as 109,958 patient treatment cycles (1 treatment cycle is 8 weeks of QD administration) based on (b) (4) distributed.

The periodic safety update report (PSUR) listing of reported postmarketing adverse events (AEs) since marketing approval in 2006 describes AEs for 12 patients. The source of these reports included spontaneous reports, clinical studies, literature, and other. Five of the 12 patients had SAEs including: pyrexia, dystonia, bloody diarrhea, drug ineffective, and pancreatitis.

No action was taken by the regulatory authorities or the marketing authorization holder, Dr. Falk Pharma, for safety reasons.

9 Appendices

9.1 Literature Review/References

- ¹ Kornbluth A et al, Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee, Am J Gastroenterol 2010; 105:501-523.
² Cohen RD et al, A meta- analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol 2000 May; 95(5):1263-76.

9.2 Labeling Recommendations

At the time of this review (July 9, 2014) labeling was not yet negotiated with the Sponsor.

9.3 Advisory Committee Meeting

No Advisory Committee meeting convened for this application.

9.4 Inclusion and Exclusion Criteria

Inclusion Criteria

A subject was eligible for inclusion in both studies BUCF 3001 and BUCF 3002 if he/she met all of the following criteria:

1. Subject understood the language of the ICF, and was capable and willing to sign the ICF.
2. Subject was \geq 18 years of age.
3. Subject was male or female.

Females of childbearing (reproductive) potential were required to have a negative serum pregnancy test at screening and agreed to use an acceptable method of contraception throughout their participation in the study. Acceptable methods of contraception included double barrier methods (condom with spermicide jelly or diaphragm with spermicide), hormonal methods (oral contraceptives, patches or medroxyprogesterone acetate), or an intrauterine device with a documented failure rate of less than 1% per year. Abstinence was considered an acceptable method of contraception at the discretion of the investigator.

NOTE: Females who had been surgically sterilized (eg, hysterectomy or bilateral tubal ligation) or who were postmenopausal (total cessation of menses for >1 year) were not considered "females of childbearing potential."

4. Subjects with confirmed diagnosis of active, mild to moderate UP or UPS, with disease extending at least 5 cm but no further than 40 cm from the anal verge. The following criteria were required to have been met:
 - Diagnosis was confirmed by endoscopy (ie, via colonoscopy or sigmoidoscopy, as described in Sections 9.5.2.2 and 9.5.2.3), with easy passage of the endoscope to at least 10 cm above the proximal margin of the disease.

NOTE: A subject was required to undergo colonoscopy at Baseline if a previous colonoscopy procedure had not been performed within 12 months of the screening date (Visit 1).

A standard of care endoscopy could be used as the qualifying baseline endoscopic procedure if performed within protocol specified time windows, provided that the procedure met study requirements.

– Subjects newly diagnosed with active, mild to moderate UP or UPS were required to have had symptoms (eg, rectal bleeding) for at least 45 days prior to screening and underwent colonoscopy to confirm diagnosis.

– For initial diagnosis, a pathological report from a local pathologist identifying histological changes characteristic of UP/UPS was required to meet eligibility requirements.

5. Subjects had a baseline MMDAI score between 5 and 10, inclusive. Subjects scored ≥ 2 on the MMDAI endoscopy or sigmoidoscopy component at Randomization (Visit 3) to be eligible

6. Subject was capable of understanding the requirements of the study, was willing to comply with all the study procedures including diary completion, and was willing to attend all study visits.

Exclusion Criteria

A subject was not eligible for inclusion in this study if she/he met any of the following criteria listed below. If a subject developed any of the exclusion criteria during the study, it may have been a basis for subject discontinuation

1. History or current diagnosis of Crohn's disease or indeterminate colitis.
2. Prior GI surgery except appendectomy and hernia (eg, inguinal, umbilical). NOTE: Prior hiatal hernia repair was not exclusionary. Prior cholecystectomy was not exclusionary if more than 1 year prior to Screening.
3. Diagnosis of 1 or more significant co-morbid condition(s), including:
 - a. Concomitant active GI disease, to include duodenal ulcer, gastric ulcer, erosive gastritis, or erosive esophagitis (Los Angeles Class B, C, or D).
 - b. History of sclerosing cholangitis, cirrhosis, or hepatic impairment, including chronic hepatitis of any etiology.
 - c. History of diverticulitis, collagenous colitis, celiac disease (sprue), recurrent pancreatitis, or known gallbladder disease.
 - d. Distortion of intestinal anatomy, such as small bowel, rectal, or colonic stricture.
 - e. Uncontrolled, previously diagnosed type 1 or 2 diabetes mellitus requiring medication, or fasting blood glucose ≥ 150 mg/dL taken at Screening (Visit 1). Undiagnosed type 1 or 2 diabetic subjects (confirmed new diabetes mellitus at Screening) were not eligible until they had achieved stabilization.
 - f. History of abnormal thyroid function not controlled by thyroid medications.

- g. Unstable significant cardiovascular (including, but not limited to, clinically significant electrocardiogram [ECG] abnormalities as noted by the investigator), endocrine, neurologic, or pulmonary disease. Subjects with hemoglobin levels < 7.5 g/dL were also excluded.
- h. Hepatic disease manifested by 1.5 times the upper limit of normal (ULN) for any of the following liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (Alk P), or total bilirubin (except in isolated elevation of unconjugated bilirubin due to Gilbert's Syndrome).
- i. Renal disease manifested by > 2.0 mg/dL serum creatinine.
- j. History of avascular necrosis of the hip.
- k. History of active tuberculosis or ocular herpes simplex or ocular varicella zoster.
- l. History of malignant disease with the following exceptions: basal cell carcinoma of the skin, or if female, in situ cervical carcinoma that had been surgically excised.
- m. History or diagnosis of human immunodeficiency virus, any other immunosuppressed condition, or hepatitis B or C.
- n. Adrenal insufficiency, defined as a measurement of <18 µg/dL serum cortisol following adrenocorticotrophic hormone (ACTH) challenge.
- o. Active systemic or cutaneous infection, including parasitic disease, at study entry.
- p. History of or current diagnosis of toxic megacolon, fistula, perforation, or abscess.
- q. Subject had history of psychiatric disorders that were not controlled (includes significant depression or suicidal ideation; "controlled" was based on the investigator's medical judgment); subjects with psychoses were excluded regardless of current therapy.
- r. Subject had history of seizure disorders.

s. Subjects with asthma requiring inhaled steroids within the past 3 months prior to Screening (Visit 1). NOTE: Only subjects with very mild, intermittent symptoms of asthma were to have been considered for this study.

t. Subject had current or recent history (within 12 months prior to Screening Visit) of drug or alcohol abuse.

u. Subject was pregnant or lactating.

4. Subject had a positive stool test for bacterial pathogens, *Clostridium difficile* toxin, or ovum and parasites.

NOTE: Stool sample was collected during the Screening phase. The test was repeated if the original assessment was not obtained within 14 days of Randomization. Results of these tests were confirmed as negative prior to Randomization.

5. History of receiving any type of vaccination (including live and attenuated virus vaccines) within the past 28 days prior to Randomization (Visit 3).

6. Subject had any condition or circumstance that could have caused noncompliance with treatment or visits.

7. Subject had known allergy to budesonide or to excipients and/or vehicles used in the formulation preparation.

8. Subject had participated in an investigational drug or device study within the 30 days prior to signing informed consent.

9. Subject was an employee of the site that was directly involved in the management, administration, or support of this study or was an immediate family member of the same.

10. The following medications (and/or medication history) were not permitted within the time points specified:

- History of treatment with a cell-depleting therapy (eg, Adacolumn).

- Any type of vaccination (live and attenuated) during the study.

- Anti-seizure and antipsychotic drugs (including those for manic depression).

NOTE: Tricyclic antidepressants and serotonin re-uptake inhibitors were allowed if the subject was at stable doses for at least 6 weeks prior to screening, and agreed to maintain the same (stable) dose for the respective medication throughout duration of the study.

- Concomitant use of diuretics with cardiac glycosides (eg, digoxin, digitoxin).

NOTE: Subjects receiving diuretics (eg, hydrochlorothiazide, furosemide) were allowed, but serum potassium levels within the normal laboratory reference range were required to be confirmed prior to Randomization.

- Within 6 months of Screening (Visit 1):

- Drugs used for the treatment of irritable bowel syndrome (eg, alosetron lubiprostone).

- Within 3 months of Screening (Visit 1):

- Inhaled corticosteroids: Subjects with asthma requiring use of intermittent inhaled steroids within the past 3 months were excluded.

NOTE: Use of intranasal corticosteroids [eg, fluticasone propionate, not to exceed a daily dose of 200 µg (two 50-µg puffs per nostril)] or equivalent for seasonal allergic rhinitis was permitted.

- Within 60 days of Screening (Visit 1):
 - Immunosuppressants (eg, azathioprine, methotrexate, 6-mercaptopurine, cyclosporine, anti-tumor necrosis factor alpha drug, inflixamab, certolizumab, or adalimumab).
 - Anticoagulants (eg, warfarin, fractionated heparin, Factor Xa inhibitors).
- Within 30 days of Screening (Visit 1):
 - Subject taking any investigational agents.
- Within 14 days of Screening (Visit 1):
 - Systemic, oral, topical or rectal corticosteroids (eg, prednisolone, methylprednisolone, prednisone, hydrocortisone), including budesonide (other than as investigative study drug for current study).

NOTE: Subjects receiving 2 or fewer days of corticosteroid treatment were immediately eligible for Screening, following discontinuation of the corticosteroid agent.

While generally prohibited, if a topical steroid was required during study participation, treatment was allowed in some instances (eg, based on extent and duration of usage, including selection of agent); however, discussion with the study Sponsor on a case-per-case basis was to have taken place prior to administration.

- Antibiotics.
- Antispasmodics and prokinetic drugs.
- Laxatives and enemas (other than 5-ASA enema products/formulations).
- Narcotics (specifically opioid analgesics).

NOTE: Subjects who were on stable treatment with a daily fiber supplementation or bulking agents (includes stool softeners) could be enrolled provided that the administration schedule was intended to be maintained throughout the study and the subject had been on bulking therapy for at least 30 days prior to Screening (Visit 1).

Laxatives and narcotics taken for endoscopic procedures were permitted.

- At the Screening visit (Visit 1):
 - Ketoconazole and other potent cytochrome P450 3A4 inhibitors (eg, itraconazole, indinavir, etc.).
- At the Run-In/Stabilization visit (Visit 2):
 - Rectal 5-ASA products. Use of rectal 5-ASA products/formulations was to have been discontinued no later than on the day of the Run-In visit (Visit 2).

- Oral 5-ASA products at doses > 4.8 g/day.

NOTE: Subjects were permitted to receive up to 4.8 g/day of an oral 5-ASA product for the duration of the study as specified in Section 9.4.7.2. Alternatively, oral 5-ASA treatment was discontinued at the Run-In visit (Visit 2).

- Antidiarrheals (eg, loperamide and bismuth subsalicylate).
- Subjects taking supplements or products specifically marketed as probiotics.

NOTE: Standard food or yogurt products were allowed. Routine use of non-steroidal anti-inflammatory drugs (NSAID), with the exception of cardioprotective aspirin (≤ 162 mg/day). Routine NSAID use was defined as taking for ≥ 3 or more days over a 7-day period.

9.5 Schedule of Assessments and Procedures for studies BUCF3001 and BUCF3002

Source: Table 6, NDA 205613 CSR BUCF 3001, p.46-49.

Assessments	SCREENING PHASE	RUN-IN PHASE	TREATMENT PHASE					FOLLOW-UP PHASE
	Screening (Visit 1) Days -21 to -7	Run-In (Visit 2) Days -7 to -4	Randomization (Visit 3) Day 1	Week 1 (Visit 4) Day 7 \pm 2	Week 2 (Visit 5) Day 14 \pm 2	Week 4 (Visit 6) Day 28 \pm 2	Week 6 (Visit 7) EoT Day 42 \pm 2	Week 8 (Visit 8) EoS 14 \pm 2 days following treatment
Informed consent	X							
Schedule colonoscopy, if applicable ^a	X							
Sigmoidoscopy		X ^b					X	
Assign subject identification number	X							
Medical history/Demographics ^c	X							
Assess and confirm eligibility	X	X	X					
Vital signs (temperature, blood pressure, pulse, weight, height ^d)	X	X	X	X	X	X	X	
Physical exam	X	X ^e	X ^e	X ^e	X ^e	X ^e	X	X ^e
12-lead ECG	X							
Serum pregnancy test ^f	X						X	
Urine pregnancy test ^g			X					
Fasting blood chemistry (includes cortisol), hematology, and urinalysis ^h	X	X	X	X ⁱ	X	X ⁱ	X	
Collect blood samples for budesonide plasma concentration analysis ^j			X	X	X	X	X	
ACTH challenge		X					X	
Collect stool sample ^k	X	X ^m						
Review diary completed in IVR/IWR system ⁿ		X	X	X	X	X	X	

Assessments	SCREENING PHASE	RUN-IN PHASE	TREATMENT PHASE				FOLLOW-UP PHASE	
	Screening (Visit 1) Days -21 to -7	Run-In (Visit 2) Days -7 to -4	Randomization (Visit 3) Day 1	Week 1 (Visit 4) Day 7±2	Week 2 (Visit 5) Day 14±2	Week 4 (Visit 6) Day 28±2	Week 6 (Visit 7) EoT Day 42±2	Week 8 (Visit 8) EoS 14±2 days following treatment
Randomize/ Assign Treatment from IVR/IWR			X					
Review / Record concomitant medications	X	X	X	X	X	X	X	X
Record AEs/study-emergent events ^o		X	X	X	X	X	X	X
Dispense single-blind placebo drug and instruct on proper administration		X ^o						
Dispense double-blind study drug and instruct on proper administration			X	X	X	X ^a		
Collect study drug and count unused applicators				X	X	X	X	
Calculate MMDAI score	X ^r	X ^a	X ^t	X ^u	X ^u	X ^u	X ^t	
Collect single-blind drug container and assess compliance			X					

Abbreviations: ACTH = adrenocorticotropic hormone; AE = adverse event; AM = morning; BID = twice daily; CRF = case report form; EDTA = ethylenediaminetetraacetic acid; EoS = end of study; EoT = end of treatment; HR = heart rate; ID = identification; IVR = interactive voice response; IWR=interactive web response; MMDAI = Modified Mayo Disease Activity Index; PM = evening; UP/UPS = ulcerative proctitis/ulcerative proctosigmoiditis

- a If no colonoscopy documenting UP/UPS diagnosis was performed within the past 12 months, a colonoscopy was scheduled at the Screening visit and performed between Days -10 and -4. Biopsy was obtained for newly diagnosed subjects, and histology results from newly diagnosed subjects confirming UP/UPS disease status were required prior to Randomization. A local pathology lab was used to confirm initial diagnosis. Biopsy from subjects previously diagnosed with UP/UPS was not required; however, investigator was required to reasonably ensure no significant changes to initial UP/UPS diagnosis had occurred before a subject was randomized. Extent of proximal disease was not greater than 40 cm from anal verge. Note: A standard-of-care endoscopy could be used as the qualifying baseline endoscopic procedure if performed within protocol-specified time windows, provided that the procedure met study requirements as defined in Section 9.3.1.
- b If the UP/UPS diagnosis was confirmed by colonoscopy within the past year (12 months), a sigmoidoscopy was performed instead of a colonoscopy prior to Randomization (Visit 3). The sigmoidoscopy was recommended to take place at Visit 2, between Days -7 and -4, and was performed no later than Day -4. Biopsy was not required; however, investigator needed to reasonably ensure that no significant changes to initial UP/UPS diagnosis had occurred before a subject was randomized. Extent of proximal disease was not to exceed 40 cm from anal verge.
- c Medical history included dates of diagnosis and onset of UP/UPS symptoms.
- d Height was obtained only at the Screening visit.
- e Symptom-directed physical exam, if applicable.
- f Serum pregnancy test performed for all childbearing females; negative test results were available before first study drug dosing.
- g Urine pregnancy test performed for all childbearing females; negative test results were available before first double-blind study drug dosing.
- h All blood samples collected during scheduled visits were taken after overnight fasting (~ 8 hours).
- i Reviewed laboratory assessments taken at Screening. Repeated clinically significant tests (hematology, blood chemistry, and urinalysis) as needed to determine eligibility.
- j A fasting cortisol blood sample was collected as part of the chemistry laboratory panel at Screening (Visit 1), Randomization (Visit 3), and Study Treatment Week 2 (Visit 5). At Run-In/Stabilization (Visit 2) and at Study Treatment Week 6 (End of Treatment; Visit 7), fasting cortisol assessments were collected during the ACTH challenge only.
- k A fasting cortisol blood sample was the only scheduled laboratory assessment taken at Week 1 (Visit 4) and Week 4 (Visit 6).
- l Collected stool sample for assessment of culture (*Yersinia enterocolitica*, *Campylobacter jejuni*, *Salmonella*, *Shigella*), ovum and parasite and/or *Clostridium difficile*.
- m If results were available at this visit, confirmed that the stool sample to assess bacteria, ovum and parasite, and *C difficile* toxin assay which was taken during the Screening phase was negative. If positive, obtained another sample during Visit 2 for analysis, and ensured data were available prior to Randomization. (If original sample was obtained > 14 days prior to Randomization, another sample was required.)
- n Instructed subjects regarding diary entry (daily symptoms) for the period prior to Randomization. Study diary and single-blind drug administration initiated on the day of the Run-In visit. First dose of single-blind study drug was administered in the AM at the clinic. Diaries and single-blind medication could be started up to 7 days prior to Randomization (Days -7 to -1), but they were required to have been started no later than on Day -4 (administered Days -4 to -1). Single-blind drug was not administered after Day -1.
- o Study-emergent events were recorded after the subject had signed informed consent and prior to Randomization to study treatment.
- p Subjects administered the single-blind foam BID on the day of the Run-In visit: first dose in the clinic in the AM and then ~12 hours later in the PM. Twice daily administration continued up to Day -1 of the study, the day immediately prior to Randomization.
- q Double-blind study drug was not administered on the day of the End of Treatment visit (Week 6 or Withdrawal; Visit 7). The last dose of study drug was administered in the evening of the day immediately prior to the visit.

- r A bowel movement for the stool frequency calculation was defined as a trip to the bathroom where evacuation occurred (eg, stool, blood, gas, mucus, etc.). The baseline normal number of daily bowel movements experienced by the subject prior to onset of the most recent flare of UP/UPS was obtained. Based on current knowledge of subject's disease status during the subject interview at the Screening visit, calculated individual MMDAI components for stool frequency, rectal bleeding, and physician's rating subscales (Abbreviated MMDAI). Progressed to next visit if subject's score fell within the range allowed for enrollment in the study, and if subject continued to meet all other eligibility criteria.
- s No calculation was made for MMDAI at the Run-In visit. At this visit, to ensure subject was eligible to receive single-blind study drug, used the baseline endoscopy findings (ie, mucosal or endoscopy score prior to Randomization) to evaluate mucosal appearance. Used the MMDAI scores obtained from the Screening visit (Visit 1) for the remaining 3 subscales (stool frequency, rectal bleeding, and physician's global rating; Abbreviated MMDAI).
- t For Baseline/Randomization (Visit 3) and Week 6/Withdrawal visit (Visit 7), calculated and recorded MMDAI score for all 4 subscales: stool frequency, rectal bleeding, mucosal appearance, and physician's global rating. To grade stool frequency and rectal bleeding scores for the Baseline/Randomization (Visit 3) calculation, the average from all days of the single-blind drug administration period (Run-In/Stabilization period), which ended immediately prior to the day of Randomization, was taken. To grade stool frequency and rectal bleeding components for Week 6/Withdrawal visit (Visit 7), the average from the 3 previous days of diary entries prior to the day of the visit (See Section 9.5.2.4 for specific scoring details) was taken.
- u To grade stool frequency and rectal bleeding components for Treatment Weeks 1, 2, and 4 (Visits 4, 5, and 6), the average from the 3 previous days of diary entries prior to the day of the visit (See Section 9.5.2.4 for specific scoring details) was taken.
- v Pharmacokinetic assessments were collected only for subjects enrolled at US study centers. Blood samples (~4 mL) were collected in vacutainers with dipotassium EDTA to determine budesonide plasma concentration. This blood sample was taken during collection of other laboratory assessments. At each visit, date and time of last dose was recorded in the source/CRF.

9.6 Narratives of subjects who had treatment emergent adverse events (TEAEs) who withdrew from the studies.

Subject Number / Country: 1394-0002 / Russia
Study Number: BUCF3001; Treatment: Placebo

Subject 1394-0002 was a 57-year-old Caucasian female. The subject had a prior history of hypertension. No ongoing co-morbid conditions were reported at study start. No prior medications were reported. Concomitant medication was sulfasalazine (1 g 3 times daily).

On 22 Aug 2011, the subject began treatment with placebo. The last dose of study drug was on 20 September 2011. The total duration of exposure to study drug (placebo) was 30 days. The subject withdrew from the study due to the event of adrenal insufficiency.

19 Sep 2011 was the date of onset of adrenal insufficiency. The **duration of treatment prior to event onset was 29 days.**

Event description: At the **Week 4** assessment on 19 Sep 2011, the subject's AM cortisol result, 115 nmol/L, was low (normal range: 138-690 nmol/L). **At an unscheduled visit** on 22 Sep 2011 (2 days after the last dose of study drug), the AM cortisol result, 116 nmol/L, was low, and the cortisol result at 30 minutes post ACTH challenge, 469 nmol/L, was below normal (normal range: \geq 500 nmol/L). **At the next scheduled assessment (Week 6)** on 29 Sep 2011 (9 days after last dose of study drug), the AM cortisol result, **555 nmol/L**, and the cortisol level in response to ACTH challenge, **872 nmol/L, were normal.** The date of event resolution was 29 Sep 2011; event duration was 11 days. The severity classification was **mild.**

Subject Number / Country: 0938-0006 / Russia
Study Number: BUCF3002; Treatment: Budesonide

Subject 0938-0006 was a 24-year-old Caucasian male. The subject reported a prior history of gastroduodenitis and reflux esophagitis, but no ongoing co-morbid conditions were reported at study start. Prior medications were sulfasalazine 500 mg 4 times daily, ciprofloxacin 500 mg twice daily, **prednisolone 90 mg once daily intravenously or 15 mg twice daily orally**, and mesalazine 500 mg 3 times daily or twice daily. No concomitant medications were reported.

On 05 September 2011, the subject began treatment with budesonide. The date of last dose of study drug (budesonide) was 14 September 2011; **the total duration of exposure was 10 days.** The subject withdrew from the study due to the event of adrenal insufficiency.

12 September 2011 was the date of onset of adrenal insufficiency. **The duration of treatment prior to event onset was 8 days.**

Event description: At the **Week 1 assessment** on 12 September 2011, the **subject's AM cortisol result, < 28 nmol/L, was low (normal range: 138-690 nmol/L).** At an **unscheduled assessment** on 16 September 2011 (2 days after last dose of study drug), the **AM cortisol result, 32 nmol/L was low and the cortisol level at 30 minutes post ACTH challenge, 263 nmol/L, was also low (normal range: \geq 500 nmol/L).** On 20 September 2011 (6 days after the last dose of study drug), **the AM cortisol result, 430 nmol/L, and cortisol level at 30 minutes post ACTH challenge, 546 nmol/L, were normal.**

The date of event resolution was 20 September 2011; **event duration was 9 days. The severity classification was moderate.**

Subject Number / Country: 1375-0022/ Russia

Study Number: BUCF3002; Treatment: Budesonide

Subject 1375-0022 was a 68-year-old Caucasian male. The subject reported no prior medical history. There were multiple ongoing co-morbid conditions including anxiety, post-traumatic stress disorder, gastroesophageal reflux disease, diverticulum, hemorrhoids, colonic polyp, **prostatomegaly**, hypothyroidism and **asthma**. Prior medications were docusate sodium (250 mg once daily) and hydrocortisone (25 mg as needed).

Concomitant medications were omeprazole (20 mg as needed), tamsulosin (0.4 mg once daily), ipratropium bromide (1 spray as needed), levothyroxine (50 µg once daily), **finasteride** (5 mg once daily), fish oil (1 tablet once daily), calcium (333 mg once daily), vitamin C (500 mg once daily), colecalciferol (1000 IU once daily), multivitamins (1 capsule as needed), vitamin Bcomplex (1 tablet once daily), loratadine (10 mg as needed), and acetylsalicylic acid (81 mg once daily).

On 23 April 2012, the subject began treatment with budesonide. The date of last dose of study drug (budesonide) was 02 May 2012; **the total duration of exposure was 10 days**. The subject withdrew from the study due to the event of adrenal insufficiency.

30 April 2012 was the date of onset of adrenal insufficiency. **The duration of treatment prior to event onset was 8 days.**

Event description: At the **Week 1 assessment** on 30 April 2012, the subject's **AM cortisol result, 113 nmol/L was low (normal range: 138-690 nmol/L)**. At an **unscheduled assessment** on 03 May 2012 (1 day after last dose of study drug), **the AM cortisol level, 237 nmol/L, was normal; however, the cortisol level at 30 minutes post ACTH challenge, 420 nmol/L, was low (normal range: ≥ 500 nmol/L)**. On 07 May 2012 (5 days after the last dose of study drug), **the AM cortisol result, 282 nmol/L, was normal**. At another **unscheduled assessment** on 25 May 2012 (23 days after last dose of study drug), **the AM cortisol result, 284 nmol/L, and the cortisol level at 30 minutes post ACTH challenge, 511 nmol/L, were normal**.

The date of event resolution was 25 May 2012; **event duration was 26 days**. The severity classification was **mild**.

Subject Number / Country: 1394-0004 / Russia
Study Number: BUCF3001; Treatment: Budesonide

Subject 1394-0004 was a 29-year-old Caucasian male. The subject reported a prior history of gastritis, but no ongoing co-morbid conditions were reported at study start.

Concomitant medication was mesalazine (1 g 3 times daily).

On 22 August 2011, the subject began treatment with budesonide. The date of last dose of study drug (budesonide) was 20 September 2011; **the total duration of exposure was 30 days**. The subject withdrew from the study due to the event of adrenal insufficiency.

19 September 2011 was the date of onset of adrenal insufficiency. **The duration of treatment prior to event onset was 29 days.**

Event description: At the **Week 4 assessment** on 19 September 2011, the **subject's AM cortisol result, 135 nmol/L was low (normal range: 138-690 nmol/L)**. At an **unscheduled visit** on 22 September 2011 (2 days after last dose of study drug), **the AM cortisol level, 94 nmol/L, was low and the cortisol result at 30 minutes post ACTH challenge, 455 nmol/L, was also low (normal range: ≥ 500 nmol/L)**. At the **Week 6 end-of-study assessment** on 29 September 2011 (9 days after last dose of study drug), **the AM cortisol result, 203 nmol/L, and the cortisol level in response to ACTH challenge, 676 nmol/L, were normal**.

The date of event resolution was 29 September 2011; **event duration was 11 days. The severity classification was mild.**

Subject Number / Country: 1399-0005 / Russia
Study Number: BUCF3001; Treatment: Budesonide

Subject 1399-0005 was a 48-year-old Caucasian female. No prior conditions and no ongoing co-morbid conditions were reported at study start. No prior medication was reported. Concomitant medication was sulfasalazine (1 g twice daily).

On 17 Oct 2011, the subject began treatment with budesonide. The date of last dose of study drug (budesonide) was 27 October 2011; **the total duration of exposure was 11 days.** The subject withdrew from the study due to the event of adrenal insufficiency.

25 October 2011 was the date of onset of adrenal insufficiency. **The duration of treatment prior to event onset was 9 days.**

Event description: At the **Week 1 assessment** on 25 October 2011, the subject's AM cortisol result, < 28 nmol/L was low (normal range: 138-690 nmol/L). At **an unscheduled assessment** on 28 October 2011 (1 day after last dose of study drug), the cortisol result, 326 nmol/L, was normal. At **another unscheduled visit** on 01 November 2011 (5 days after last dose of study drug), **the AM cortisol level, < 28 nmol/L, was low and the cortisol level at 30 minutes post ACTH challenge, 411 nmol/L, was also low (normal range: \geq 500 nmol/L).** At a **third unscheduled visit** on 07 November 2011, **the AM cortisol level, 284 nmol/L, was normal and the cortisol result at 30 minutes post ACTH challenge, 574 nmol/L, was also normal.**

The date of event resolution was 07 November 2011; event duration was 11 days. The severity classification was **moderate.**

Reviewer Comment: It is unclear why Subject 1394-0002 who received the placebo would have a decrease in cortisol. No history of prior or concurrent use of steroids was presented. At the time of submission of this review an IR was being generated to address this finding. Notably all of the TEAEs of adrenal insufficiency resolved, including those subjects who did not withdraw from the study.

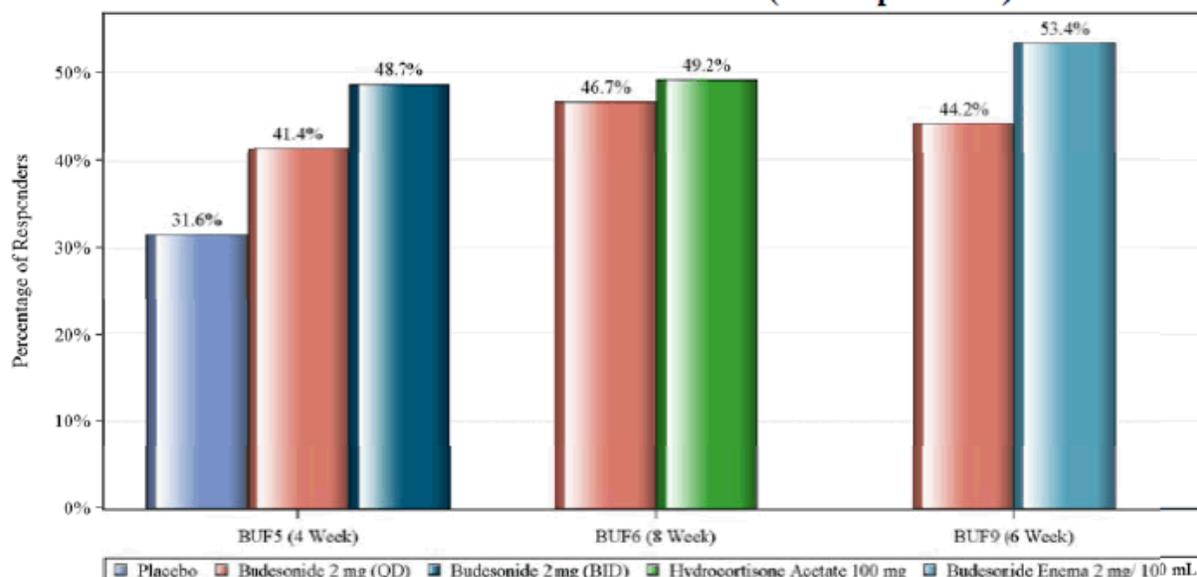
9.7 Summary of Key Findings from Budenofalk Rectal Foam Studies

- 1) In BUF-6/UCA, 55% of subjects in the budesonide 2 mg foam QD group and 51% of subjects in the hydrocortisone acetate 100 mg foam QD group were in clinical remission (defined as DAI score \leq 3 at the end of 8 weeks of treatment) (see DAI scoring system in Appendix 9.8). The difference in responders was 4% (95% CI: -10.6%, 18.6%) between budesonide foam and the approved hydrocortisone acetate 100 mg foam product in the treatment of UP/UPS.
- 2) In BUF-9/UCA, a comparative trial versus budesonide enema, the clinical remission rates based on the CAI (where clinical remission was defined as CAI score > 4 at the end of 4 weeks of treatment). (see CAI scoring system in Appendix 9.8)) in the PP population analysis set were 60% for budesonide 2 mg foam and 66% for budesonide 2 mg enema.
- 3) In the phase 2 BUF-5/UCA study, analyses were conducted with the following definitions for remission: (1) CAI score \leq 1 at week 6; or (2) DAI score \leq 1 at week 6. The analyses demonstrated a statistically significant difference between budesonide subjects in the 2 mg BID group and placebo subjects in the proportion who achieved a CAI score \leq 1 at week 6 (budesonide 40%, placebo 24%;

p=0.0363) and a DAI score ≤1 at week 6 (budesonide 39%, placebo 22%; p=0.0268). Statistical trends were also seen in favor of budesonide 2 mg BID versus placebo in the proportion of subjects with a CAI score ≤1 at week 6 with normal stool frequency and no rectal bleeding (37% vs 24%; p=0.0775), and in the proportion of subjects with a DAI score ≤1 at week 6 with normal stool frequency and no rectal bleeding (33% vs 19%; p=0.0507).

In general, the efficacy results from the Dr. Falk studies were similar to findings observed in the Salix clinical development program for budesonide foam 2 mg. In exploratory post hoc analyses (conducted by the applicant), the remission endpoint for BUCF 3001/3002 was applied to the results from the Dr. Falk studies and a consistent treatment effect was observed in the budesonide foam groups. See Figure 1 below.

Figure 2 Post Hoc Exploratory Analysis of Budenofalk Studies Using Primary Endpoint of Remission from the Salix Budesonide Foam Trials BUCF 3001/3002 (ITT Populations)



Note: 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 (see Section 6.2.2 of the ISE)

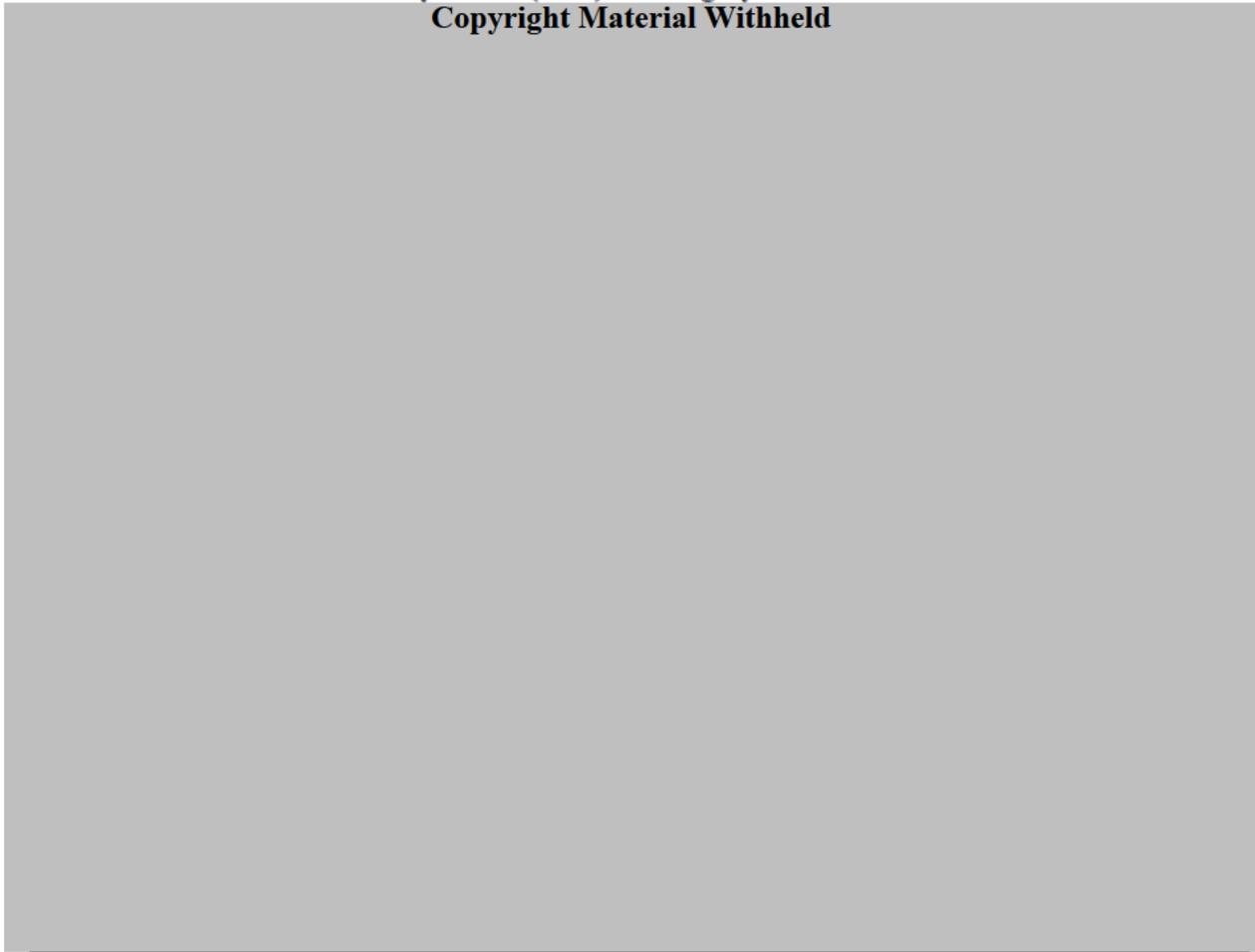
Figure1 was electronically reproduced from Module 2 Clinical Overview page 27

Although there were differences in the study design, budesonide dose, duration of treatment, and more stringent criteria for endoscopy score in the Salix studies, the observed treatment effect in the exploratory analyses of Budenofalk foam was similar to that observed in the Salix studies.

The applicant selected the initial 2-week BID regimen that was used in the Salix budesonide foam development program (for Studies BUCF 3001 and BUCF 3002) because of the effect of treatment observed with the BID regimen in BUF-5/UCA.

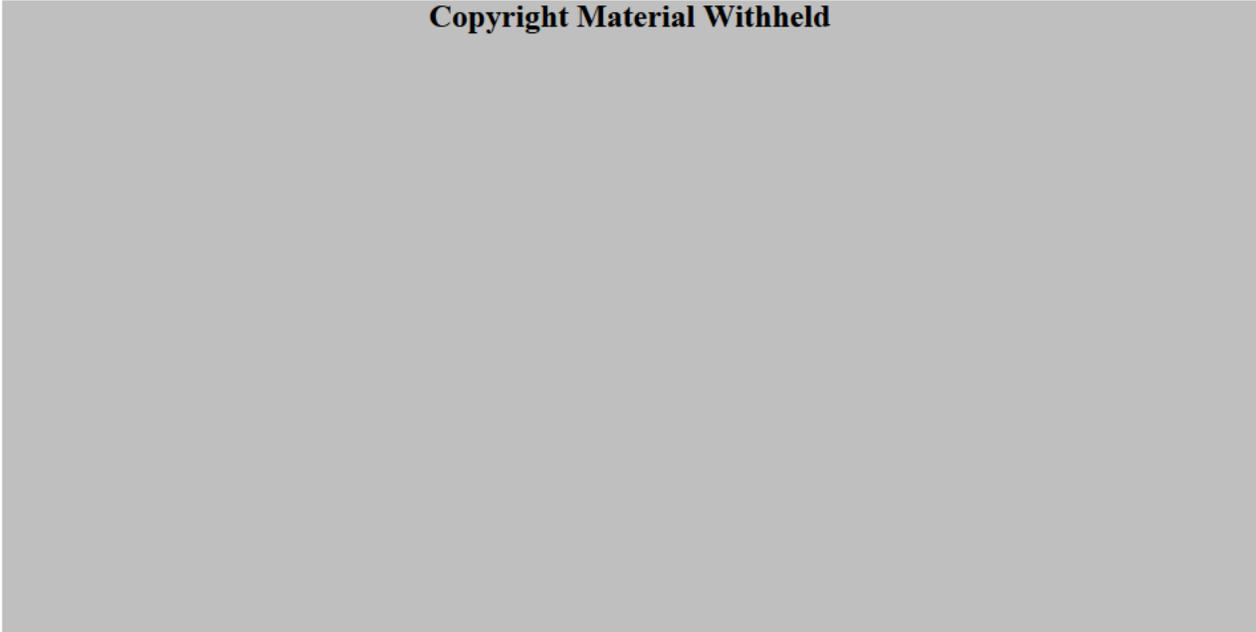
9.8 Summary of the CAI and DAI Scoring Systems

Table 7: Clinical Activity Index (CAI) Scoring System
Copyright Material Withheld



Source: [Rachmilewitz 1989 \(28;29\)](#)
Source: Electronically reproduced from NDA 205613 Summ Clin Effi page 46

Table 8: Disease Activity Index (DAI) Scoring System
Copyright Material Withheld



Source: [Sutherland 1987 \(28;29\)](#)

Source: Electronically reproduced from NDA 205613 Summ of Clin Eff. Page 47.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ZANA H MARKS
08/04/2014

ANIL K RAJPAL
08/04/2014
I concur with Dr. Marks.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

**NDA/BLA Number: NDA 205613 Applicant: Salix
Pharmaceuticals, Inc.**

Stamp Date: Nov 15, 2013

Drug Name: Budesonide Foam NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			PLR format and consistent with requirements in 21 CFR 201.56(d) and 201.57
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Summarized in Clinical Overview (2.5)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: A randomised, double-blind, placebo-controlled Phase IIb dose-finding study of the efficacy and safety of two doses of Budenofalk® foam formulation in the treatment of proctitis and proctosigmoiditis Sample Size: n=223 Arms: 2 mg BID (n=76); 2 mg QD (n=71); placebo (n=76) Duration of Tx: 6 wks	X			proposed dosing regimen for the label: • 2 mg BID X 2 wks; • followed by 2 mg QD X 4wks

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Location in submission: 5.3.5.1 Additional rationale for the proposed dosing regimen for the label [i.e., 2 mg BID X 2 wks; followed by 2 mg QD X 4wks (instead of 2 mg BID X 6 wks)] was provided in the BUCF3001 and BUCF3002 study reports (Section 9.4.4 of each study report)				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: BUCF3001 Indication: "...for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge." Pivotal Study #2: BUCF3002 Indication: "... for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge."	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		The Applicant has provided rationale for not conducting a TQT study; the QT-IRT will be consulted to review this rationale.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	Intended to be used for 6 wks only.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			However, the applicant has proposed waiver for < ^(b) / ₍₄₎ yrs and deferral for ≥ ^(b) / ₍₄₎ yrs. At the July 23, 2013 Meeting, the Division advised the sponsor that typically in this population a waiver is granted for <5 yrs and deferral for ≥5 yrs.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	reasonable review of the patient data?				
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___ Yes ___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

N/A

Reviewing Medical Officer

Date

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KLAUS T GOTTLIEB
12/16/2013

ANIL K RAJPAL
12/16/2013