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*APPLICATION NUMBER:*

**205613Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	September 15, 2014
<b>From</b>	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/ BLA Supplement #</b>	NDA 205613
<b>Applicant</b>	Salix Pharmaceuticals, Inc.
<b>Date of Submission</b>	November 15, 2013
<b>PDUFA Goal Date</b>	September 15, 2014
<b>Proprietary Name / Established (USAN) names</b>	Uceris Rectal Foam / budesonide
<b>Dosage forms / Strength</b>	emulsion (aerosol foam) / 2 mg budesonide per metered dose
<b>Proposed Indication</b>	Induction of remission in patients with mild to moderate distal UC (extending up to 40 cm from the anal verge)
<b>Recommended Action:</b>	Tentative Approval

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## 1. Introduction

This submission, received November 15, 2013, is the initial New Drug Application (NDA) for Uceris (budesonide) Rectal Foam, a synthetic corticosteroid with glucocorticosteroid activity. It is formulated as an emulsion which is filled into an aluminum canister with an aerosol propellant. The Applicant is Salix Pharmaceuticals, Inc.

The Applicant proposes the following 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.”

The proposed product is available in one dosage strength:

- 2 mg budesonide per metered dose.

The proposed dose is:

- 1 metered dose administered rectally twice daily for 2 weeks; followed by
- 1 metered dose administered rectally once daily for 4 weeks.

This is a 505(b)(2) application. Entocort EC (NDA 21324) and Uceris (NDA 203634) are the reference drugs; it should be noted that NDA 203634 (Uceris) (owned by Salix) was a 505(b)(2) application that relied upon NDA 21324 (Entocort EC).

## 2. Background

### 2.1 Distal Ulcerative Colitis

Ulcerative colitis (UC) affects up to 15 people per 100,000, with peak incidence occurring between the ages of 15 and 25 years.<sup>1</sup> Ulcerative colitis confined to the rectum is characterized as ulcerative proctitis (UP) and reported rates range from 25% to 55% of all UC cases at initial diagnosis.<sup>2</sup> Although the precise incidence is not known, ulcerative proctosigmoiditis (UPS) has been estimated to represent 25% to 75% of new UC cases.<sup>1</sup> The Sponsor defined proctitis as disease limited to the rectum (up to ~15 cm); and proctosigmoiditis as disease limited to the rectum and sigmoid colon (up to ~40 cm).<sup>3</sup>

### 2.2 Current Treatments (UP and/or UPS)

Currently approved rectally administered drugs for the treatment of UP and/or UPS (including year of approval and the indication) are summarized in the table below.

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<sup>1</sup> Reguiero MD, Diagnosis and Treatment of Ulcerative Proctitis. J Clin Gastroenterol 2004;38:733–740) 2004.

<sup>2</sup> Meucci G, Vecchi M, Astegiano M, Beretta L, Cesari P, Dizioli P, et al. The natural history of ulcerative proctitis: a multicenter, retrospective study. Gruppo di Studio per le Malattie Infiammatorie Intestinali (GSMII). Am J Gastroenterol 2000 Feb;95(2):469-73.

<sup>3</sup> Study Reports of BUCF3001 and BUCF3002

**Table 1. Rectally Administered Drugs for the Treatment of UP and/or UPS**

Product <sup>1</sup>	Active Ingredient(s) / Dose	Formulation	Company	Approval	Indication
Cortifoam	Hydrocortisone 80 mg	Rectal Foam	Meda	1982	Adjunctive therapy in the topical treatment of ulcerative proctitis of the distal portion of the rectum in patients who cannot retain hydrocortisone or other corticosteroid enemas.
Cortenema	Hydrocortisone 100 mg / 60 mL	Enema	original RLD filed by Solvay	1966	Adjunctive therapy in the treatment of ulcerative colitis, especially distal forms, including ulcerative proctitis, ulcerative proctosigmoiditis, and left-sided ulcerative colitis. It has proved useful also in some cases involving the transverse and ascending colons.
Canasa	Mesalamine 1000 mg	Suppository	Axcan Scandi- pharm	2001	Treatment of mild to moderately active ulcerative proctitis. The safety and effectiveness of Canasa beyond 6 weeks have not been established.
Rowasa	Mesalamine 4.0 g / 60 mL	Enema	Meda	1987	Treatment of active mild to moderate distal ulcerative colitis, proctosigmoiditis or proctitis

Table above is taken from Page 17 of the Pre-NDA Meeting Package.

## 2.3 Regulatory History - Uceris Rectal Foam

The table below provides an overview of the regulatory activity of Uceris Rectal Foam.

**Table 2. Pertinent Regulatory History of Uceris Rectal Foam (NDA 205613)\***

Date	Event
April 30, 2009	Pre-IND / Pre-Phase 3 Meeting
July 23, 2013	Pre-NDA Meeting <sup>#</sup>
November 15, 2013	NDA Submission received

\*IND 104,725

<sup>#</sup>Responses to Statistics questions were sent to the Sponsor in an Advice Letter dated September 29, 2013

Key comments communicated to the sponsor during the meetings and review of the IND submission included the following:

### (1) Pre-IND / Pre-Phase 3 Meeting (April 30, 2009):

- Modified Mayo Disease Activity Index: The Division agreed with the Sponsor's proposal to use the Modified Mayo Disease Activity Index (MMDAI) in which the endoscopy component is modified as follows: mucosal friability is classified as an endoscopy subscore of 2 instead of 1. See Section 7.2 and Appendix 1 of this CDTL Review.
- Primary Endpoint Definition: The Sponsor had originally proposed a primary endpoint that was based on endoscopy and rectal bleeding subscores only. In response to the Division's concern that not including the stool frequency subscore in the primary endpoint definition would not allow an assessment of whether stool frequency worsened,



The relevant review disciplines have all written review documents. The primary review documents relied upon were the following:

- (1) Clinical Review by Zana Marks, dated August 4, 2014
- (2) Statistics Review by Shahla Farr, dated August 5, 2014
- (3) Clinical Pharmacology Review by Dilara Jappar, dated August 18, 2014, and Addendum dated September 8, 2014
- (4) Pharmacology/Toxicology Review by Dinesh Gautam, dated August 25, 2014, and Addendum dated September 3, 2014
- (5) Quality Review by Tarun Mehta, dated September 4, 2014
- (6) Quality Microbiology Review by Vinayak Pawar, dated December 3, 2013
- (7) OSI Clinical Inspection Summary by Susan Leibenhaut, dated July 3, 2014
- (8) QT Interdisciplinary Review Team (QT-IRT) Consult Review by Jiang Liu, dated April 9, 2014
- (9) Pediatric and Maternal Health Staff (PMHS) Review by Erica Radden, dated September 3, 2014
- (10) CDRH Consult Reviews:
  - (a) CDRH Office of Device Evaluation Consult Review by Branden Reid dated August 12, 2014
  - (b) CDRH Office of Compliance Consult Review by Bleta Vuniqi dated July 14, 2014
  - (c) CDRH Human Factors Consult Review by QuynhNhu Nguyen dated June 19, 2014
- (11) Labeling Reviews:
  - (a) Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review by Matthew Barlow, dated April 9, 2014
  - (b) Division of Medication Error Prevention and Analysis (DMEPA) Labeling Review by Matthew Barlow dated June 24, 2014
  - (c) Office of Prescription Drug Promotion (OPDP) Labeling Review by Meeta Patel dated August 13, 2014
  - (d) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Morgan Walker dated August 14, 2014

The reviews should be consulted for more specific details of the current application.

### **3. CMC**

The reader is referred to the Quality Review (dated September 4, 2014) by Tarun Mehta and the Quality Microbiology Review (dated December 3, 2013) by Vinayak Pawar, for complete information.

#### **3.1 Drug Substance (DS)**

The Quality Reviewer noted the following regarding the drug substance (DS):

- The drug substance budesonide is a compendial (USP) material.
- It has been used as an active drug substance in previously approved prescription drug

products. The DMF (b) (4) for the drug substance was reviewed and found adequate.

- Based on available stability data, a retest period of (b) (4) months for budesonide drug substance is granted, when stored as follows:  
“Protect from humidity and light. Store tightly sealed at 15°C to 30°C”.
- The retest period may be extended when additional real-time stability data are available.

## 3.2 Drug Product (DP)

### 3.2.1 Overview

- The proposed formulation is a non-sterile emulsion consisting of budesonide as an active ingredient.
- The emulsion is pressurized using a propellant mixture to deliver it as a foam.
- Each multi-dose canister delivers fourteen (14) 1.35-mL doses (equivalent to 2 mg budesonide per dose).
- (b) (4)
- The drug substance, excipients, and propellant gases (n-butane, iso-butane and propane) used in the formulation are compendial (USP) grade.

### 3.2.2 Manufacturing Process

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

### 3.2.3 Drug Product Specification

- The proposed regulatory specification is deemed adequate to assure the drug product quality at release and on stability.
- Physical attributes are controlled using compendial monograph (USP <601>) for “Aerosols metered dose products” monograph.
- Foam characterization and property were tested using validated in-house method.
- Potency and impurities of the active ingredient are monitored using validated chromatographic methods.
- The impurity specification is based on the compendial (USP) monograph for the budesonide.
- Delivered dose uniformity testing when samples were prepared according to label instructions (using five canisters and 10 actuations per canister) showed a low mean assay value ( (b) (4) %); the minimum assay value was (b) (4) % but excluding that value, the range was (b) (4) % to (b) (4) % (see Pages 45-50 of the Quality Review). Repeat delivered dose uniformity testing of five additional canisters and 10 actuations per canister showed improvement (range of (b) (4) % to (b) (4) %). Also, 10 additional canisters and three actuations per canister 24 hours apart showed consistent recovery (range (b) (4) % to (b) (4) %). In a meeting that included the Quality Reviewers and Clinical Reviewers to discuss the concern of inconsistent dosing, it was

decided that because the second and third sets of results showed improvement over the first set of results, and because the same drug product was used in the clinical trials and efficacy and safety had been demonstrated, no further action was required to explain the inconsistency of the first set of results.

### 3.2.4 Container Closure System

- The primary container closure system for the drug product is a (b) (4) aluminum canister (b) (4).
- The canister is filled with the emulsion and propellant mixture.
- Canister is fitted with 1-inch metering valve which houses 1.35 mL of metering head.
- The size of valve housing and metering valve determines the amount of emulsion and expansion of the foam with each actuation.
- The Quality Reviewer noted the following regarding the applicator: "CDRH has expressed some concern about potential leachables from the applicator, however, not only because there will be very short duration of exposure for the applicator to the drug while the drug is being administered, but also each applicator is for single use, we did not find the leachable studies for the applicator necessary. There are 14 single use applicators supplied with the product, each of which is coated with compendial grades (NF) (b) (4) Paraffin."

### 3.2.5 Stability

- The registration batches demonstrate the chemical, physical, and microbiological stability of Budesonide 2 mg Rectal Foam stored through 12 months at 25°C/60% RH and 6 months at 40°C/75% RH.
- All results met the proposed acceptance criteria under both storage conditions.
- Stability samples were stored in horizontal and vertical orientations.
- The supporting stability batches demonstrate up to 36 months of stability at the long term condition.
- Based on the adequate stability data, the proposed expiration dating period of 24 months for Budesonide 2 mg Rectal Foam is granted, when stored as follows: "Store at 20–25°C (68–77°F) [see USP Controlled Room Temperature]; excursions permitted to 15–30°C".

## 3.3 Product Microbiology

The Quality Microbiology Reviewer noted that all of the NDA registration batches of Budesonide 2 mg Rectal Foam met USP requirements for microbial limits at all time points tested under both storage conditions and orientations; and concluded that the microbiological quality of the drug product is controlled via a suitable testing protocol.

## 3.4 Recommendation

Quality:

The Quality Reviewer recommended approval based on the following:

- The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.
- The label/labeling issues are fully resolved.
- The Office of Compliance has issued an overall “Acceptable” recommendation for the facilities involved in this application.

The Quality Reviewer noted that the applicant has agreed (via an amendment 0046 dated August 20, 2014) to complete the following Extractables and Leachables studies, and submit the data in the first annual report.

(1) To perform forced extraction studies as follows:

- Typical Sample preparation: 5g test article/ 200mL extraction solvent
- Expose cut or crushed pieces of the valve Housing and Stem using 57% propylene glycol, 30% alcohol at elevated temperature (55<sup>0</sup>C) for longer exposure times (such as 2-3 days).
- Reflux cut or crushed pieces of the valve Housing and Stem for 30 minutes in n-heptane.

(2) To list the specific composition of the Housing and Stem components and report the extraction profiles (qualitative and quantitative).

(3) To provide leachable data for the drug product stored in the proposed container closure for expiry period at the long term storage condition.

It should be noted that the above is not a postmarketing commitment; rather, it is an agreement from the applicant.

#### Quality Microbiology:

An Approval Action is the recommendation by the Quality Microbiology discipline.

## **4. Nonclinical Pharmacology/Toxicology**

The reader is referred to the Nonclinical Pharmacology/Toxicology Review (dated August 25, 2014) by Dinesh Gautam, for complete information.

### **4.1 Issues**

The Nonclinical Reviewer noted that the applicant provided the following data:

- Published literature on the pharmacology, pharmacokinetics, mutagenicity, carcinogenicity and reproductive toxicology studies of budesonide.
- Study reports of single- and repeated-dose toxicity studies in rats, mice and dogs.

The Nonclinical Reviewer noted the following key nonclinical findings:

- Budesonide is a non-halogenated glucocorticosteroid, which is structurally related to hydroxyprednisolone.
- *In vitro* pharmacology studies showed that it has a high glucocorticoid receptor affinity compared to other corticosteroids (hydrocortisone, prednisolone, and dexamethasone).

Following topical administration, budesonide exhibits a high ratio of topical to systemic activity.

- Budesonide has a pronounced anti-inflammatory effect after both subcutaneous and topical administration in animals.
  - In an *in vitro* hERG assay at concentrations of 4.5, 15, 45 and 150  $\mu\text{M}$  budesonide produced 4, 14, 31 and 58% inhibition of hERG potassium ion current, respectively, with an  $\text{IC}_{50}$  value of 106  $\mu\text{M}$ .
- Safety pharmacology studies of budesonide were conducted in mice, rats, guinea pigs, cats and dogs.
  - These studies showed no pronounced action on the central nervous system, respiratory system, circulatory system, or the autonomic nervous system at doses up to 10.0 mg/kg.
  - No action on the neuromuscular junction or the blood clotting system was observed.
  - Extremely mild acceleration of urinary electrolyte excretion was observed in the rat kidneys at 0.01, 0.1, 1.0, and 10.0 mg/kg budesonide.

The Nonclinical Reviewer noted that in published reports, the absorption, distribution and excretion of budesonide were evaluated in mice, rats and dogs following intravenous, subcutaneous, oral, colonic, inhalation and rectal administrations. The Nonclinical Reviewer summarized the results as follows:

- Budesonide has moderate to high clearance and a high volume of distribution in all species following intravenous administration.
- Low systemic bioavailability of budesonide was observed following oral and rectal administration, which can be attributable to a high first pass effect.
- Following repeated rectal administration of budesonide in the dog in a chronic study, it was rapidly absorbed into the systemic circulation.

The Nonclinical Reviewer noted that acute and repeated dose toxicology studies of budesonide have been conducted in mice, rats, dogs, and monkeys after oral, intravenous, intraperitoneal, subcutaneous and intrarectal administration. The Nonclinical Reviewer summarized the results as follows:

- In acute toxicity study, deaths occurred mostly in the 2nd week after treatment.
- In the chronic toxicity studies, budesonide at high doses showed glucocorticoid related activities such as atrophy of the thymus, adrenals and lymph nodes, gastric ulcerations, decreases in white blood cell counts, depression of the hypothalamic pituitary adrenal (HPA) axis, increased liver glycogen, and gastrointestinal hemorrhage.
- Twice daily rectal administration of budesonide foam in dogs was well tolerated at doses up to 4 mg/day in 6- and 39-week studies.

The Nonclinical Reviewer noted the following results of genotoxicity testing:

- Budesonide was not genotoxic in the Ames test, the mouse lymphoma cell forward gene mutation ( $\text{TK}^{+/-}$ ) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test and the mouse micronucleus test.

The Nonclinical Reviewer noted that carcinogenicity studies with budesonide were conducted in rats and mice, and summarized the results as follows:

- In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 µg/kg. In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 µg/kg and above. No tumorigenicity was seen in female rats at oral doses up to 50 µg/kg.
- In an additional two-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 µg/kg. However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 µg/kg.
- In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 µg/kg.

The Nonclinical Reviewer noted the following results from studies of fertility and early embryonic development, embryonic fetal development, and prenatal and postnatal development:

- Budesonide was teratogenic and embryocidal in rabbits and rats.
- Budesonide had no effect on fertility in rats at subcutaneous doses up to 100 µg/kg.
- Budesonide caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at a subcutaneous dose of 20 µg/kg. No such effects were noted at 5 µg/kg.

The Nonclinical Reviewer noted the following results of special toxicology studies:

- Topical administration of budesonide in guinea pigs showed no phototoxicity and had no photoallergic effects.
- Budesonide has no ocular toxicity in rabbits.

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the NDA. The Nonclinical Reviewer additionally recommends that the proposed labeling be revised to include the following:

#### Section 8.1 of Label (Pregnancy)

Wording in the Pregnancy section should be revised to:

##### **"8.1 Pregnancy**

##### *Pregnancy Category C*

##### *Risk Summary*

There are no adequate and well controlled studies with UCERIS in pregnant women. Animal reproduction studies using subcutaneous administration of budesonide were conducted in rats and rabbits. Skeletal abnormalities, fetal loss and decreased pup weight were observed in these studies. UCERIS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies, regardless of drug exposure, have a background rate of 2 to 4 percent for major malformations, and 15 to 20 percent for pregnancy loss.

### *Animal Data*

Budesonide is teratogenic and embryocidal in rabbits and rats. In a subcutaneous embryofetal development studies, fetal loss, decreased pup weights, and skeletal abnormalities were observed at a subcutaneous dose of 25 mcg/kg in rabbits (approximately 0.12 times the recommended human intrarectal dose of 4 mg/day, based on the body surface area) and 500 µg/kg in rats (approximately 1.2 times the recommended human intrarectal dose of 4 mg/day, based on the body surface area)."

### Section 13 of Label (Nonclinical Toxicology)

Wording in the Nonclinical Toxicology section should be revised to:

## **"13. NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### *Carcinogenicity*

Carcinogenicity studies with budesonide were conducted in rats and mice. In a 2-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 µg/kg (approximately 0.12 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area). In addition, there were increased incidences of primary hepatocellular tumors in male rats at 25 µg/kg (approximately 0.06 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area) and above. No tumorigenicity was seen in female rats at oral doses up to 50 µg/kg (approximately 0.12 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area). In an additional 2-year study in male Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 µg/kg (approximately 0.12 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area). However, it caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 µg/kg (approximately 0.12 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area). The concurrent reference glucocorticosteroids (prednisolone and triamcinolone acetonide) showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 µg/kg (approximately 0.24 times the recommended intrarectal dose of 4 mg/day in humans, based on the body surface area).

#### *Mutagenesis*

Budesonide showed no evidence of mutagenic potential in the Ames test, the mouse lymphoma cell forward gene mutation (TK+/-) test, the human lymphocyte chromosome aberration test, the *Drosophila melanogaster* sex-linked recessive lethality test, the rat hepatocyte UDS test or the mouse micronucleus test.

### *Impairment of Fertility*

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 µg/kg (approximately 0.20 times recommended intrarectal dose of 4 mg/day in humans, based on a body surface area basis). However, it caused a decrease in prenatal viability and viability in pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 µg/kg (approximately 0.05 times recommended intrarectal dose of 4 mg/day in humans, based on a body surface area basis) and above. No such effects were noted at 5 µg/kg.

## **4.2 Recommendation**

An Approval Action is the recommendation by the Nonclinical Pharmacology/Toxicology discipline provided the labeling revisions described above are made.

## **5. Clinical Pharmacology/Biopharmaceutics**

### **5.1 Clinical Pharmacology**

The reader is referred to the Clinical Pharmacology Review by Dilara Jappar, dated August 18, 2014, for complete information. The following is summarized from the Clinical Pharmacology Review.

#### **A. Dose Selection Rationale:**

The proposed dosing regimen is 2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks. The sponsor had conducted a phase 2b dose finding study (BUF-5/UCA) where 2 mg BID dosing regimen of budesonide rectal foam yielded more favorable treatment effect compared to that of placebo and 2 mg QD dosing (4 mg/day (BID) > 2 mg/day(QD) > placebo). Supportive phase 3 studies (BUF-9/UCA and BUF-6/UCA) have shown that majority of subjects experienced maximum treatment response after the first 2 weeks of treatment. Thus, the sponsor considers it reasonable to have a dosing regimen of 2 mg BID for the first 2 weeks followed by a reduced dose of 2 mg QD for 4 weeks.

#### **B. Single-Dose and Multiple-Dose PK:**

Both single dose and multiple doses PK of budesonide 2 mg rectal foam were evaluated in healthy subjects in this application (study BUF-7/BIO). However, since the stability of budesonide in the serum PK samples under the storage conditions was not properly established in this study, it is difficult to interpret the result of this PK study. Therefore, the PK parameters from this study will not be reflected in the label.

#### **C. Population PK Analysis:**

The sponsor had collected sparse PK samples in two phase 3 studies (study BUCF 3001 and 3002) and conducted population PK analysis. Following administration of budesonide rectal foam 2 mg BID, mean budesonide AUC<sub>0-12h</sub> in the target patient population was estimated to be 4.31 ng\*hr/mL with a CV of 64%.

#### **D. Hypothalamic pituitary adrenal (HPA) axis suppression:**

Adrenocorticotrophic hormone (ACTH) stimulation test was performed in two Phase 3 trials where budesonide rectal foam was administered for 6 weeks. The normal response to ACTH challenge included 3 criteria, as defined in the cosyntropin label: (1) morning cortisol level > 5 µg/dL; (2) increase in cortisol level by ≥ 7 µg/dL above the morning (pre-challenge) level following ACTH challenge; and (3) cortisol level of > 18 µg/dL following ACTH challenge.

The percentages of patients with normal response to ACTH challenge by treatment group (combined data from the two trials) were as follows:

- Budesonide group: Baseline: 83.5%; Wk 6: 68.5%; Difference (Baseline to Wk 6): 15.0%
- Placebo group: Baseline: 85.6%; Wk 6: 76.6% ; Difference (Baseline to Wk 6): 9.0%

If one takes into account subjects who were discontinued prior to Week 6 due to reasons related to HPA axis suppression, a larger difference was seen between the two treatment groups; the percentages were as follows:

- Budesonide group: Baseline: 83.5%; Wk 6: 62.7%; Difference (Baseline to Wk 6): 20.8%
- Placebo group: Baseline: 85.6%; Wk 6: 75.9% ; Difference (Baseline to Wk 6): 9.7%

#### **E. Assessment of drug interaction potential: In vitro evaluation of Cytochrome P450 and transporters:**

The sponsor has conducted several in vitro studies to assess the drug interaction potential for budesonide rectal foam. Aside from the known interaction with CYP3A inhibitors, the new data did not reveal any potential for significant metabolism or transporter-mediated drug-drug interactions in vivo.

Based on in vitro results showing IC<sub>50</sub> >1130 ng/mL, budesonide rectal foam at therapeutic concentration is not expected to inhibit CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4/5 in vivo. No data is available for CYP2C8 and CYP2C19. Based on in vitro results showing little or no effect of budesonide concentration up to 9000 nM (3875 ng/mL) on the activity or messenger RNA (mRNA) expression of CYP1A2, CYP2B6, CYP2C9, and CYP3A4, budesonide rectal foam at therapeutic concentration is not expected to induce CYP enzymes in vivo.

In vitro studies showed that budesonide is not a substrate of BCRP and a weak substrate of P-gp. Budesonide was a weak inhibitor of P-glycoprotein (IC<sub>50</sub> 9.78 µM or 4.21 µg/mL) and BCRP (IC<sub>50</sub> 43.1 µM or 18.6 µg/mL). Based on these IC<sub>50</sub> values, budesonide foam is not expected to inhibit these transporters in clinical use.

In vitro studies showed that budesonide is not a substrate of OATP1B3. The results were inconclusive for OATP1B1 and suggested that budesonide is either not a substrate of OATP1B1 or a weak substrate of OATP1B1. Budesonide at concentrations up to 300 nM did not inhibit OATP1B1 or OATP1B3. Budesonide foam is not expected to inhibit these transporters in clinical use.

## 5.2 Biopharmaceutics

The reader is referred to the Biopharmaceutics Review for complete information. The following is summarized from the Biopharmaceutics Review:

There was no Biopharmaceutics-related information included in original submission of this NDA. However, Information Requests (IR's) were sent to the applicant.

IR #1: the following IR was sent (January 17, 2014):

- We suggest that you propose an in vitro release acceptance criterion (range) based on a developed in vitro release test (IVRT) methodology for your product at release and during stability as a quality control parameter. Your proposed acceptance criterion should be based on generated data on the final to be marketed batches.

Response to IR #1: The Applicant submitted the following response (February 14, 2014):

- Salix agrees to develop and validate an in vitro release rate testing procedure for Budesonide 2 mg Rectal Foam with anticipated completion of that activity in June 2014. Salix will use the validated procedure to test three process validation batches currently scheduled for production immediately after approval of the marketing application. Those batches represent the first to be marketed batches. As those data will not be available until after approval of the NDA and since they represent a limited population of drug product batches, Salix proposes to submit acceptance criterion for the new in vitro release test approximately two months after the first anniversary of the approval of the NDA. At that time, Salix will have collected release data from drug product manufactured during the first twelve months of commercial production along with approximately 12 months of stability data for the first three commercial batches of drug product. Those data will better represent batch-to-batch variability of drug product manufactured with the validated manufacturing process while also providing information on drug release performance during storage of the drug product under long-term storage conditions, data that does not currently exist at this time.

IR#2: The following additional IR was sent (May 12, 2014):

- We acknowledge your agreement to develop and validate an in vitro release test (IVRT) procedure, with an anticipated completion date of June 2014. We also acknowledge your proposal to develop acceptance criterion based on IVRT data generated for the final to-be-marketed batches post-approval of the NDA. The IVRT method development report and validation reports should be submitted to the Agency for review.
- The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:

a.  (b) (4)

- b.  (b) (4)
- c.
- d.
- e.

- The IVRT method validation report should contain (but is not limited to) the following validation components:

- a.  (b) (4)
- b.
- c.
- d.
- e.
- f.
- g.
- h.

Response to IR #2: The Applicant submitted the following response (July 8, 2014):

- An in vitro release rate testing (IVRT) procedure for Budesonide 2 mg Rectal Foam has been developed and fully validated. Salix document METH-VALRPT-184 describes the activities surrounding the development of the procedure and the results of the validation of the method. The method presented therein will be implemented at  (b) (4) and used for the testing of drug product process validation and future commercial batches of drug product. This method will also be added to ongoing and future stability studies for the drug product. Salix will submit acceptance criterion for the new in vitro release test approximately two months after the anniversary of the approval of the NDA. At that time, Salix will have collected release data from drug product manufactured during the first twelve months of commercial production along with approximately 12 months of stability data for the first three commercial batches of drug product. Those data will better represent batch-to-batch variability of drug product manufactured with the validated manufacturing process while also providing information on drug release performance during storage of the drug product under long-term storage conditions, data that does not currently exist at this time.

Conclusion: The Biopharmaceutics Reviewer noted that the Biopharmaceutics review is focused on the evaluation of the proposed IVRT method, but the review of the proposed IVRT method and acceptance criteria is ongoing. The Biopharmaceutics Reviewer concluded that there are no approvability issues for NDA 205613 from a Biopharmaceutics perspective.

### **5.3 Recommendation**

Clinical Pharmacology: An Approval Action is the recommendation by the Clinical Pharmacology discipline.

Biopharmaceutics: An Approval Action is the recommendation by the Biopharmaceutics discipline.

## **6. Clinical Microbiology**

Clinical Microbiology considerations do not apply to this application because Uceris is not an antimicrobial agent.

## **7. Clinical/Statistical - Efficacy**

The reader is referred to the Clinical Review by Zana Marks and the Statistics Review by Shahla Farr for complete information.

### **7.1 Overview**

#### **Proposed Indication:**

The Applicant proposed the following 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."

#### **Overview of Phase 3 Trials:**

An overview of the two key Phase 3 trials is shown in the table below. The design is described in more detail in Section 7.2 of this CDTL Review.

**Table 3. Key Phase 3 Trials**

Study	Design/ Population	Treatment Arms
BUCF-3001	<ul style="list-style-type: none"> <li>▪ R, DB, PC</li> <li>▪ active mild/moderate distal UC*</li> </ul>	<ul style="list-style-type: none"> <li>▪ Uceris Rectal Foam 2 mg BID X 2 wks; then, 2 mg QD X 4 wks (n=134)</li> <li>▪ Placebo (n=131)</li> </ul>
BUCF-3002	<ul style="list-style-type: none"> <li>▪ R, DB, PC</li> <li>▪ active mild/moderate distal UC*</li> </ul>	<ul style="list-style-type: none"> <li>▪ Uceris Rectal Foam 2 mg BID X 2 wks; then, 2 mg QD X 4 wks (n=134)</li> <li>▪ Placebo (n=147)</li> </ul>

R: Randomized; DB: Double-blind; PC: Placebo-controlled

\* MMDAI Total Score = 5-10; Endoscopy subscore  $\geq 2$ ; Rectal Bleeding subscore  $\geq 2$ ; disease extending at least 5 cm but no further than 40 cm from the anal verge (see Section 7.2 and Appendix 1 of this CDTL Review).

Table above modified from the Clinical Review by Zana Marks.

It should be noted that there is also an open label single-arm ongoing safety and tolerability study (Study BFPS3073) that has enrolled a total of 108 patients (who completed either of the above trials and were experiencing symptoms of active UP/UPS); patients received the same dosing regimen (2 mg BID for 2 weeks, followed by 2 mg QD for 4 weeks) and continued treatment cycles as needed (see Section 8.1 and Appendix 7 of this CDTL Review; and see Clinical Review).

In addition, it should be noted that a number of studies were conducted using a different formulation (Budenofalk; Dr. Falk)(see Appendix 2 of this CDTL Review).

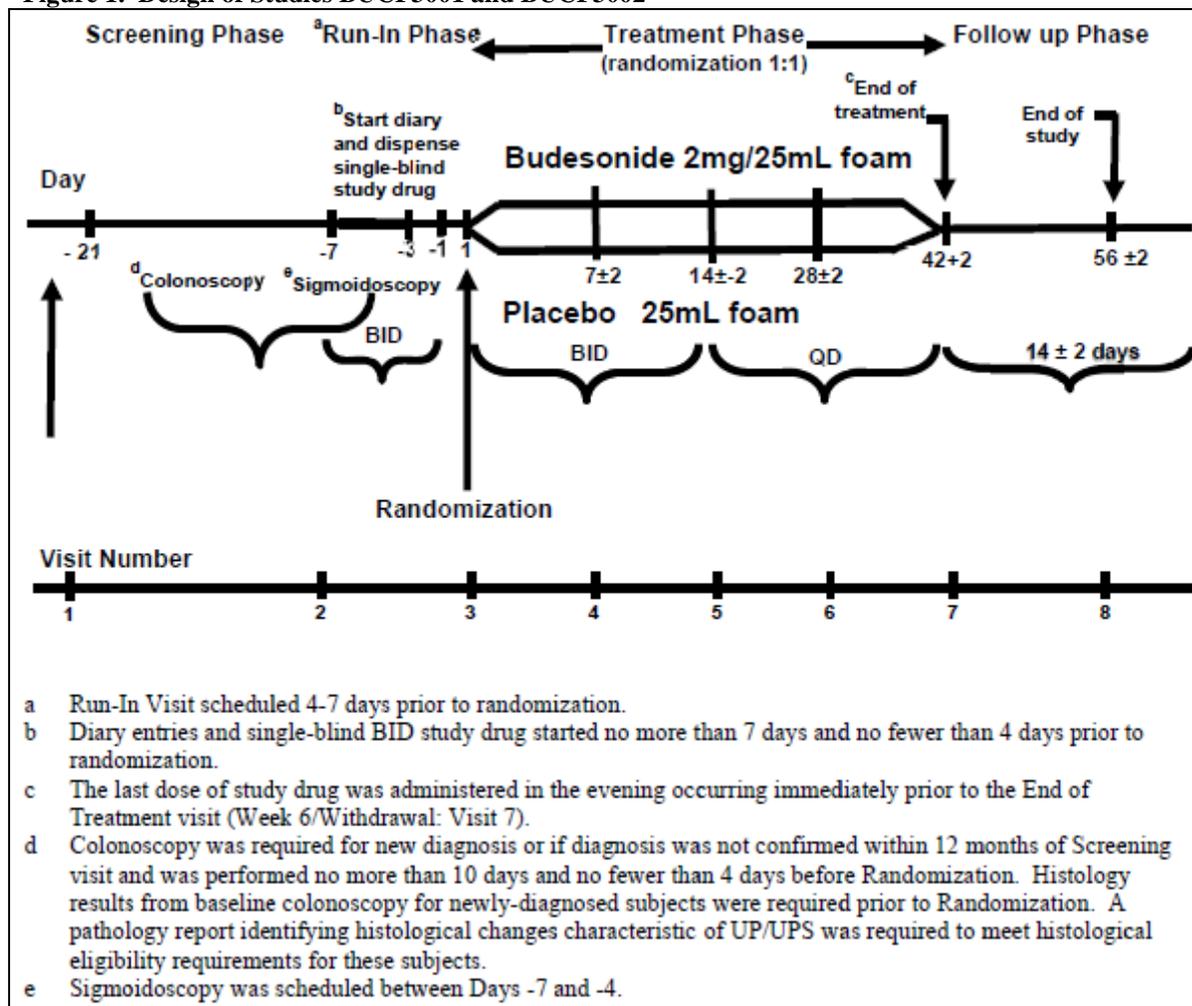
## 7.2 Design Features of Key Phase 3 Trials (Studies BUCF3001 and BUCF3002)

Studies BUCF3001 and BUCF3002 were replicate trials. The features of the trials are summarized below.

### Design:

The design of Studies BUCF3001 and BUCF3002 is summarized in the figure below.

**Figure 1. Design of Studies BUCF3001 and BUCF3002**



The figure above is taken from the Clinical Review. Source: Summary of Clinical Efficacy page 29

## **Key Entry Criteria:**

Key inclusion criteria were the following:

- A confirmed diagnosis of active, mild to moderate UP or UPS, with disease extending  $\geq 5$  cm but  $\leq 40$  cm from the anal verge<sup>4</sup>, where the following criteria apply:
  - Confirmed diagnosis by endoscopy (via colonoscopy or sigmoidoscopy, as defined in Appendix 3 of this CDTL Review) with easy passage of the endoscope to at least 10 cm above the proximal margin of the disease.
  - A subject must undergo colonoscopy at Baseline if a previous colonoscopy procedure has not been performed within 12 months of the screening date (Visit 1).
  - Newly diagnosed subjects must have had symptoms associated with UP/UPS for at least 45 days (e.g., rectal bleeding) prior to Screening (Visit 1).
  - For initial diagnosis, a pathological report from a local pathologist identifying histological changes characteristic of UP/UPS will be required to meet eligibility requirements.
- Baseline MMDAI score between 5 and 10, inclusive. Subjects must score  $\geq 2$  on the MMDAI rectal bleeding component and  $\geq 2$  on the MMDAI endoscopy or sigmoidoscopy component. (See Appendix 1 of this CDTL Review for the MMDAI scoring system.)

Key exclusion criteria were the following:

- Use of immunosuppressants (e.g., azathioprine, methotrexate, 6-mercaptopurine, Cyclosporine) or TNF $\alpha$ -antagonists (e.g., infliximab, certolizumab or adalimumab) within 60 days of screening.
- Use of corticosteroids (systemic, oral, topical or rectal) including budesonide within 14 days of screening with the following exceptions: (a) Subjects receiving  $\leq 2$  days of corticosteroid treatment will be immediately eligible for Screening. (b) While generally prohibited, if a topical steroid is required during study participation, treatment may be allowed in some instances (e.g., based on extent and duration of usage, including selection of agent); however, discussion with the study Sponsor on a case-per-case basis should take place prior to administration.
- Rectal 5-ASA products must be discontinued no later than the day of the Run-In Visit (Visit 2)
- Oral 5-ASA products at doses  $> 4.8$  grams/day. (Note that subjects may receive up to 4.8g/day of an oral 5-ASA product for the duration of the study. See Concomitant and Rescue Therapy section below.)

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<sup>4</sup> In the original protocol, disease extent was limited to 30 cm from the anal verge. The sponsor provided the following rationale for changing 30 cm to 40 cm (in the latest Amendment to the Protocol; January 26, 2011): "A thorough assessment of the histological and mucosal data reported from Phase 3 studies, along with data from a Phase 1 scintigraphy study with a similar product (Budenofalk), prompted proximal extension to 40cm in this protocol. In the Phase 1 scintigraphy study, maximal spread of the foam reached between 20 and 40cm from the anal verge. Additionally, radioactivity was detected in the proximal half of the sigmoid and the distal third of the descending colon in nine and six patients, respectively, and in the middle third of the descending colon and the proximal third of the descending colon in three patients and one patient, respectively. Therefore, the scintigraphy data further support the evaluation of UP/UPS disease to 40-cm in the current study."

**Randomization and Stratification:**

Randomization: Patients in Studies BUCF3001 and BUCF3002 were randomized 1:1 to placebo or budesonide rectal foam (2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks).

Stratification: Patients were stratified by study center.

**Concomitant and Rescue Therapy:**

Concomitant Therapy: Oral 5-ASA products at doses at up to 4.8 g/day were allowed during the study, providing:

- A subject who has received a therapeutic dose of oral 5-ASA within the past 12 months, and who may be receiving any oral 5-ASA dose at the time of the most recent UP/UPS relapse, must agree to use the same product and stable therapeutic dose starting at the Screening Visit (Visit 1), continuing throughout duration of the study (EoT; Visit 7). Alternatively, use of oral 5-ASA can be discontinued at Run-In (Visit 2).
- A subject who has not taken a therapeutic dose of oral 5-ASA within the past 12 months (includes newly diagnosed) must receive a stable therapeutic dose for at least 30 days prior to Randomization (Visit 3), and must agree to use the same 5-ASA product and stable therapeutic dose each day throughout duration of the study (EoT; Visit 7). Alternatively, use of oral 5-ASA can be discontinued at Run-In (Visit 2).

Rescue Therapy: In the event that a subject has failed to respond to study medication, prohibited medications (e.g., rectal 5-ASA, corticosteroids) may be used. However, subjects who require rescue medication will be discontinued from the study.

**Endpoints:**

The primary and secondary endpoints of Studies BUCF3001 and BUCF3002 are shown in the table below.

**Table 4. Primary and Secondary Endpoints of Studies BUCF3001 and BUCF3002**

Endpoint	Definition
Primary:	Proportion of subjects who achieve remission defined as an endoscopy score of $\leq 1$ , a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency sub scales of the Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks of treatment or withdrawal.
1st Ranked Secondary:	Proportion of subjects with a rectal bleeding MMDAI subscale score of 0 at the end of six weeks of treatment or withdrawal.
2nd Ranked Secondary:	Number of weeks subjects achieve a rectal bleeding MMDAI sub scale score of 0 during the treatment phase (Weeks 1 through 6).
3rd Ranked Secondary:	Proportion of subjects who achieve an endoscopy MMDAI subscale score of 0 or 1 at the end of six weeks of treatment or withdrawal.

### 7.3 Results of Key Phase 3 Trials (Studies BUCF3001 and BUCF3002)

#### **Demographics:**

The two arms of each study were similar with regard to sex, age, race, ethnicity, and BMI. The mean age in each study was 42 years and 43 years (5% and 8% were  $\geq 65$  years of age), 57% and 56% were female, 90% and 90% were Caucasian, and 16% and 11% were Hispanic or Latino in Studies BUCF3001 and BUCF3002, respectively. See table below.

**Table 5. Demographics (Studies BUCF3001 and BUCF 3002)**

Characteristic Category or statistic	BUCF3001		BUCF3002	
	Placebo N = 132 n (%)	Budesonide Foam 2 mg/25 mL N = 133 n (%)	Placebo N = 147 n (%)	Budesonide Foam 2 mg/25 mL N = 134 n (%)
<b>Age (years)</b>				
Mean (SD)	41.4 (13.24)	43.2 (13.94)	41.9 (13.27)	44.3 (13.47)
Median (min, max)	40.0 (21, 76)	44.0 (18, 77)	40.0 (18, 80)	45.0 (19, 74)
<b>Age Group – n (%)</b>				
< 65 years	127 (96.2)	125 (94.0)	138 (93.9)	121 (90.3)
$\geq 65$ years	5 (3.8)	8 (6.0)	9 (6.1)	13 (9.7)
<b>Gender – n (%)</b>				
Male	52 (39.4)	61 (45.9)	63 (42.9)	62 (46.3)
Female	80 (60.6)	72 (54.1)	84 (57.1)	72 (53.7)
<b>Race – n (%)</b>				
American Indian or Alaska Native	2 (1.5)	0	0	0
Asian	2 (1.5)	3 (2.3)	3 (2.0)	3 (2.2)
Black or African American	5 (3.8)	15 (11.3)	8 (5.4)	11 (8.2)
Native Hawaiian or other Pacific Islander	0	0	1 (0.7)	0
White	123 (93.2)	115 (86.5)	135 (91.8)	119 (88.8)
Other <sup>a</sup>	0	0	0	1 (0.7)
<b>Ethnicity – n (%)</b>				
Hispanic or Latino	22 (16.7)	20 (15.0)	17 (11.6)	15 (11.2)
Not Hispanic or Latino	110 (83.3)	113 (85.0)	130 (88.4)	119 (88.8)
<b>BMI (kg/m<sup>2</sup>)</b>				
Mean (SD)	26.8 (5.53)	26.7 (5.75)	25.4 (4.69)	25.7 (5.28)
Median (min, max)	25.7 (18.9, 54.1)	25.5 (18.4, 50.8)	25.0 (16.7, 43.7)	24.9 (15.9, 53.7)

Table above is modified from Page 68 of the Summary of Clinical Efficacy.

#### **Baseline Disease Characteristics:**

The two arms of each study were similar with regard to baseline disease characteristics:

**MMDAI Total Score and Subscores:** The distribution of MMDAI total score and each of the subscores was similar in the two arms of each study (BUCF3001 and BUCF3002). See the table below.

**Table 6. MMDAI Total Score and Subscores**

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
<b>MMDAI Total Score</b>				
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)
<b>Bowel Frequency Subscale – n (%)<sup>b</sup></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)
<b>Bleeding Subscale – n (%)<sup>c</sup></b>				
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)
<b>PGA Subscale – n (%)<sup>d</sup></b>				
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)
<b>Endoscopy/Sigmoidoscopy Finding Subscale – n (%)<sup>e</sup></b>				
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)

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).

Table above is modified from Page 71 of the Summary of Clinical Efficacy.

**Concomitant Oral 5-ASA Use at Baseline:** Concomitant oral 5-ASA use at baseline was similar in both treatment groups in both studies: 59% in the UCERIS Rectal Foam group and 60% in the placebo group in Study BUCF3001 and 51% in both treatment groups in Study BUCF3002. See the table below.

**Table 7. Concomitant Oral 5-ASA Use at Baseline**

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
Use of 5-ASA for UC/UP/UPS at time of first dose – n (%)	79 (59.8)	78 (58.6)	75 (51.0)	69 (51.5)

Table above is modified from Page 72 of the Summary of Clinical Efficacy.

**Other Baseline Disease Characteristics:** Other baseline disease characteristics [extent of disease, normal number of stools per day (based on the question asked as part of the MMDAI assessment), type of disease (newly diagnosed vs. established), and duration of disease] were similar between the two arms of each of the two studies (see table below).

**Table 8. Other Baseline Disease Characteristics**

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
<b>Extent of Disease – n (%)<sup>f</sup></b>				
Proctitis	43 (32.6)	37 (27.8)	38 (25.9)	35 (26.1)
Proctosigmoiditis	88 (66.7)	95 (71.4)	109 (74.1)	98 (73.1)
Missing	1 (0.8)	1 (0.8)	0	1 (0.7)
<b>Normal Number of Stools per Day<sup>a</sup></b>				
Mean (SD)	1.4 (0.68)	1.3 (0.63)	1.4 (0.63)	1.4 (0.77)
Median (min, max)	1.0 (1, 5)	1.0 (1, 4)	1.0 (1, 3)	1.0 (1, 7)
<b>Type of Disease – n (%)</b>				
Newly diagnosed	9 (6.8)	3 (2.3)	11 (7.5)	6 (4.5)
Established	123 (93.2)	130 (97.7)	136 (92.5)	128 (95.5)
<b>Duration of Disease (years)</b>				
Mean (SD)	5.0 (6.96)	4.5 (6.94)	3.8 (4.82)	5.4 (6.25)
Median (min, max)	2.4 (0.0, 37.1)	2.6 (0.0, 53.9)	2.4 (0.0, 30.8)	2.8 (0.0, 27.7)

<sup>f</sup> Proctitis: disease limited to rectum (up to ~15 cm); Proctosigmoiditis: disease limited to rectum and sigmoid colon (up to ~40 cm)

<sup>a</sup> 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.

Table above is modified from Page 72 of the Summary of Clinical Efficacy.

## **Disposition:**

The two arms of each study were similar with regard to percentage of patients that completed the studies (see table below); 85% of subjects completed each of the studies (BUCF3001 and BUCF3002).

In both studies, rates of discontinuation due to AE's were higher in the Budesonide Rectal Foam group (10% in each study) compared to the placebo group (5% in Study BUCF3001 and 4% in Study BUCF3002).

**Table 9. Patient Disposition, Studies BUCF3001 and BUCF3002 (ITT Population)**

Category	Study BUCF3001		Study BUCF3002	
	Placebo n (%)	Budesonide Foam n (%)	Placebo n (%)	Budesonide Foam n (%)
Randomized	132	133	147	134
Received at least 1 dose of BUCF	132 (100)	133 (100)	147 (100)	134 (100)
Completed study	116 (87.9)	108 (81.2)	125 (85.0)	115 (85.8)
Discontinued study early	16 (12.1)	25 (18.8)	22 (15.0)	19 (14.2)
Adverse event	7 (5.3)	13 (9.8)	6 (4.1)	13 (9.7)
Subject request	2 (1.5)	6 (4.5)	7 (4.8)	4 (3.0)
Lost to follow up	0	1 (0.8)	2(1.4)	0
Noncompliance	0	1 (0.8)	0	0
Pregnancy <sup>a</sup>	0	0	0	0
Other	7 (5.3)	4 (3.0)	7 (4.8)	2 (1.5)
Low cortisol	0	2 (1.5)	1 (0.7)	0
Lack of efficacy	6 (4.5)	2 (1.5)	5 (3.4)	0
Met exclusion criterion 3n prior to randomization <sup>b</sup>	1 (0.8)	0	0	0
Disease extent 70 cm	0	0	0	1 (0.7)
Personal conflict	0	0	0	1 (0.7)
Unknown	0	0	1 (0.7)	0

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."

Table above modified from tables in the Clinical Review. Source: BUCF3001 Study Report Page 73; BUCF3002 Study Report Page 73.

### **Primary Endpoint:**

There was a statistically significant difference for the Budesonide Rectal Foam group versus placebo for the primary endpoint in Studies BUCF3001 and BUCF3002 (see table below). The Statistics Reviewer noted that the Statistical Analysis Plan (SAP) of each of the protocols stated that primary endpoint analyses would be based on both the logistic regression model as well as the Cochran-Mantel-Haenszel (CMH) test, adjusted for analysis center; note that both of these are presented below.

**Table 10. Primary Endpoint: Remission\* (Studies BUCF3001 and BUCF3002) (ITT Populations; LOCF Analysis)**

Efficacy Endpoint	Study BUCF3001				Study BUCF3002			
	Placebo N=132 n (%)	Budesonide Foam N=133 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>	Placebo N=147 n (%)	Budesonide Foam N=134 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>
Achieved Remission*								
Responder	34 (25.8)	51 (38.3)	0.0324	0.0322	33 (22.4)	59 (44.0)	<0.0001	<0.0001
Non-responder	98 (74.2)	82 (61.7)			114 (77.6)	75 (56.0)		

\*Remission defined as an endoscopy score of  $\leq 1$ , a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency sub scales of the Modified Mayo Disease Activity Index (MMDAI) at the end of 6 weeks of treatment or withdrawal.

ITT = intent to treat; LOCF = last observation carried forward.

a. p-values obtained from a logistic regression model with fixed effects: treatment arm and country.

b. p-values obtained from the Cochran-Mantel-Haenszel (CMH) test adjusting for country.

Table above modified from tables in the Clinical Review. Source: Summary of Clinical Efficacy Page 79.

The Statistics Reviewer performed a sensitivity analysis which assigned treatment failure to subjects who terminated early; the results of this analysis (see Statistics Review) showed 4 additional budesonide treatment failures resulting in a reduction of treatment effect from 12.6% to 9.6%. The Statistics Reviewer noted that additional sensitivity analyses performed by the Sponsor were generally consistent with the primary analysis based on Last Observation Carried Forward (LOCF) shown above.

## **Secondary Endpoints:**

### **First Secondary Endpoint:**

In each trial, a higher proportion of patients in the budesonide rectal foam group than in the placebo group had a rectal bleeding subscore of zero at Week 6 (see the table below).

**Table 11. Rectal Bleeding Subscore of Zero at Week 6 (ITT Populations; LOCF Analysis)**

Efficacy Endpoint	Study BUCF3001				Study BUCF3002			
	Placebo N=132 n (%)	Budesonide Foam N=133 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>	Placebo N=147 n (%)	Budesonide Foam N=134 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>
Rectal Bleeding Subscore of 0 at Wk 6								
Responder	37 (28.0)	62 (46.6)	0.0022	0.0020	42 (28.6)	67 (50.0)	0.0002	0.0001
Non-responder	95 (72.0)	71 (53.4)			105 (71.4)	67 (50.0)		

ITT = intent to treat; LOCF = last observation carried forward.

a. p-values obtained from a logistic regression model with fixed effects: treatment arm and country.

b. p-values obtained from the Cochran-Mantel-Haenszel (CMH) test adjusting for country.

Table above modified from tables in the Clinical Review. Source: Summary of Clinical Efficacy Page 79.

### **Second Secondary Endpoint:**

The Statistics Reviewer noted that the sponsor did not analyze this secondary endpoint as pre-specified; and that instead, two additional endpoints were presented in the study report: (1) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments and (2) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at study weeks 1 to 6. The results of these analyses are provided in Appendix 4 of this CDTL Review. The Statistics Reviewer noted that neither of these endpoints can be considered pre-specified and neither would be suitable for statistical testing or labeling. In an Information Request, the sponsor was requested to perform an analysis of the pre-specified endpoint; however, these results were similar to those for the endpoints already in the CSR and further clarification was not provided. Thus, the results for this secondary endpoint were not included in the labeling (see Section 12.3 of this CDTL Review).

### **Third Secondary Endpoint:**

In each trial, a higher proportion of patients in the budesonide rectal foam group than in the placebo group had an endoscopy subscore of zero or one at Week 6 (see the table below). It should be noted that the results for this secondary endpoint were presented descriptively in the labeling (see Section 12.3 of this CDTL Review) because the second secondary endpoint was not met (see above).

**Table 12. Endoscopy Subscore of Zero or One at Week 6 (ITT Populations; LOCF Analysis)**

Efficacy Endpoint	Study BUCF3001				Study BUCF3002			
	Placebo N=132 n (%)	Budesonide Foam N=133 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>	Placebo N=147 n (%)	Budesonide Foam N=134 n (%)	p- value <sup>a</sup>	p- value <sup>b</sup>
Endoscopy subscore of 0 or 1 at Wk 6								
Responder	57 (43.2)	74 (55.6)	0.0486	0.0488	54 (36.7)	75 (56.0)	0.0013	0.0012
Non-responder	75 (56.8)	59 (44.4)			93 (63.3)	59 (44.0)		

ITT = intent to treat; LOCF = last observation carried forward.

a. p-values obtained from a logistic regression model with fixed effects: treatment arm and country.

b. p-values obtained from the Cochran-Mantel-Haenszel (CMH) test adjusting for country.

Table above modified from tables in the Clinical Review. Source: Summary of Clinical Efficacy Page 79.

## **Post Hoc Analyses:**

### **Post-Hoc Analyses using Varying Responder Definitions:**

Results of post hoc analyses (using varying responder definitions) requested at the Pre-NDA Meeting are shown below (see table below). Each of the post-hoc analyses showed a numerically higher proportion meeting each of the responder definitions in the budesonide rectal foam group compared to the placebo group.

**Table 13. Post-Hoc Analyses using Varying Responder Definitions (Studies BUCF3001 and BUCF3002)**

	Study BUCF3001		Study BUCF3002	
	Placebo N= 132	Budesonide Foam N = 133	Placebo N= 147	Budesonide Foam N = 134
Responder Definition at End of Treatment				
Endo $\leq$ 1, RB = 0, and SF $\leq$ 1	32 (24)	46 (35)	32 (22)	59 (44)
Endo $\leq$ 1, RB = 0, and SF = 0	18 (14)	23 (17)	18 (12)	40 (30)
Endo $\leq$ 1, RB = 0, and SF = 1	14 (11)	23 (17)	14 (10)	19 (14)
Endo = 0, RB = 0, and SF = decrease or no change	9 (7)	15 (11)	17 (12)	35 (26)
Endo $\leq$ 1, RB = 0, SF = decrease or no change, and total MMDAI score $\leq$ 1	14 (11)	20 (15)	17 (12)	35 (26)

Endo: Endoscopy subscore; RB: Rectal Bleeding subscore; SF: Stool Frequency subscore

Table above is modified from tables in the Clinical Review. Source: BUCF3001 Study Report Page 99 and BUCF3002 Study Report Page 101

### **Stool Frequency:**

Because the primary endpoint (as defined) could be met even if the stool frequency subscore did not decrease, the change in stool frequency subscore from Baseline to Week 6 by treatment group in patients that met the primary endpoint, and in patients that did not meet the primary endpoint were reviewed. The results suggested that in each study there was a numerically higher decrease in stool frequency subscore (from Baseline to Week 6) in patients that met the primary endpoint vs. patients that did not; however, the decrease in stool frequency subscore was similar

for budesonide rectal foam and placebo in both the subgroup of patients that met the primary endpoint and the subgroup of patients who did not (see Appendix 5 of this CDTL Review).

The mean (SD) decrease in stool frequency subscores (in patients that met the primary endpoint of remission) were included in Section 14 of the label (see Section 12.3 of this CDTL Review) and are also shown below:

- Study BUCF3001: 1.2 (0.9) (budesonide rectal foam) vs. 1.2 (0.8) (placebo)
- Study BUCF3002: 1.3 (0.8) (budesonide rectal foam) vs. 1.1 (0.9) (placebo).

### **Subgroup Analyses:**

**Gender, Age, Race:** The Statistics Reviewer noted that both female and male subjects showed response rates that were numerically greater in favor of the study drug, that both age groups (>42 years old, ≤ 42 years old) showed higher response rates in favor of the study drug, and that all three race groups (White, Black, Asian) showed numerically higher response rates in favor of the study drug. See Statistics Review.

**Country:** The Statistics Reviewer noted the following regarding Russian sites vs. US sites (see table below):

- For Study BUCF3001, the budesonide treatment effect is 6% for the Russian sites and 15% for the U.S. sites.
- For Study BUCF3002, the treatment effect appears to be larger for the Russian sites (30% vs. 16%).

**Table 14. Analysis of the Primary Endpoint by Country**

Study	Country	Budesonide n/N (%)	Placebo n/N (%)	Difference (Budesonide-Placebo) (95% CI)
Study 3001	Russia	23/51 (45.1)	18/47 (38.3)	6% (-13.1%, 26.0%)
	US	28/82 (34.2)	16/85 (18.8)	15% (2.0%, 29.1%)
Study 3002	Russia	36/49 (73.5)	22/51 (43.1)	30.3% (12.0%, 48.7%)
	US	23/85 (27.1)	11/96 (11.5)	15.6% (4.2%, 27.0%)

Table above is modified from the Statistical Review.

The Statistics Reviewer concluded that the larger effect for the Russian sites in Study 3002 seems to be due to the 100% vs 0% response rates observed for the budesonide and placebo arms respectively for Site 938. The Statistics Reviewer performed an analysis of Study BUCF3002 where site 938 was excluded (see table below).

**Table 15. Primary Efficacy Endpoint BUCF3002 (ITT and ITT with site 938 excluded)**

Population	Budesonide Foam n/N (%)	Placebo n/N (%)	P-Value	Difference Budesonide – Placebo (95% CI)
ITT	59/134 (44.0)	33/147 (22.5)	<0.001	21.6% (10.8%, 32.4%)
ITT (w/o site 938)	44/119 (37.0)	33/132 (25.0)	0.04	12% (0.6%, 23.4%)

Table above is modified from the Statistics Review.

Disease Severity (Mild vs. Moderate): The Statistics Reviewer noted that in each of the two disease severity categories (mild and moderate) (where mild was defined as MMDAI Score 4-6 and moderate was defined as MMDAI Score 7-10), higher response rates were seen in favor of the study drug. See Statistics Review.

Region of Disease (Proctitis vs. Proctosigmoiditis): The Statistics Reviewer noted that in each of the two regions of disease (proctitis and proctosigmoiditis), higher response rates were seen in favor of the study drug. See Statistics Review.

The sponsor's presentations of subgroup analyses are provided in Appendix 6 (by study).

## 7.4 Recommendation

An Approval Action is the final recommendation from a Clinical/Statistical standpoint.

## 8. Safety

The reader is referred to the Clinical Review by Zana Marks, for complete information.

### 8.1 Overview of Data Evaluated for Safety

#### Analysis Populations

Three primary analysis sets were used for the review of safety:

- (1) Randomized Controlled Trial (RCT) Population: Studies BUCF3001 and BUCF3002.
- (2) All Salix Budesonide Safety Population: Studies BUCF3001, BUCF3002, and BFPS3073
- (3) All Budesonide Safety Population: Studies BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA

#### Disposition

Of the 268 patients that were randomized to budesonide foam in the RCT Studies (BUCF3001 and BUCF3002), 83.6% completed the study.<sup>5</sup>

In the Open Label Study (BFPS3073), of the 108 patients that received budesonide foam, 65.7% are ongoing; 100% entered Cycle 1, 50% entered Cycle 2, 28% entered Cycle 3, 14% entered Cycle 4, 4% entered Cycle 5, and 2% entered Cycle 6.<sup>6</sup> (See Appendix 7 of this CDTL Review for an overview of the BFPS3073 study.)

See also Appendix 8 of this CDTL Review for disposition of subjects (primary safety trials).

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<sup>5</sup> Source: Page 73 of the Summary of Clinical Safety.

<sup>6</sup> Source: Page 74 of the Summary of Clinical Safety.

## 8.2 Exposure

### **RCT Population (Studies BUCF3001 and BUCF3002):**

The exposure in person years was 29.8 person-years on Placebo, and 28.5 person-years on budesonide foam. See the table below.

**Table 16. Duration of Exposure (RCT Population) (BUCF3001 and BUCF3002)**

<b>Exposure Duration/Category</b>	<b>Placebo N = 278</b>	<b>Budesonide Foam 2 mg/25 mL N = 268</b>
Total person-years of exposure <sup>a</sup>	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)

Table modified from Clinical Review. Source is Summary of Clinical Safety p. 76.

### **All Salix Budesonide Safety Population (Studies BUCF3001, BUCF3002, and BFPS3073):**

The exposure in person-years was 49.1 person-years (see the table below).

In the open label study (BFPS3073), the mean ( $\pm$  SD) duration of exposure was 73.9 (52.65) days, with a minimum of 10 days and a maximum of 258 days (approximately 9 months; interim data).<sup>7</sup> Mean exposure durations for individual cycles ranged from 36.5 days to 44.8 days. See the table below.

<sup>7</sup> Data cutoff date of April 1, 2013

**Table 17. Duration of Exposure (All Salix Budesonide Safety Population) (Studies BUCF3001, BUCF3002, and BFPS3073)**

<b>Exposure Duration</b>	<b>Budesonide Foam 2 mg/25 mL N = 331</b>
Total person-years of exposure <sup>a</sup>	49.1
Overall (days)	N = 325
Mean (SD)	55.2 (40.09)
Median (minimum, maximum)	42.0 (3, 258)
Double-Blind Studies	N = 268
Mean (SD)	38.8 (9.92)
Median (minimum, maximum)	42.0 (3, 58)
Open-Label Study Cycle 1	N = 101
Mean (SD)	39.1 (9.79)
Median (minimum, maximum)	42.0 (10, 91)
Open-Label Study Cycle 2	N = 45
Mean (SD)	41.5 (5.83)
Median (minimum, maximum)	42.0 (22, 58)
Open-Label Study Cycle 3	N = 27
Mean (SD)	39.1 (8.38)
Median (minimum, maximum)	42.0 (6, 46)
Open-Label Study Cycle 4	N = 10
Mean (SD)	41.7 (1.89)
Median (minimum, maximum)	41.5 (39, 45)
Open-Label Study Cycle 5	N = 4
Mean (SD)	44.8 (3.86)
Median (minimum, maximum)	44.5 (41, 49)
Open-Label Study Cycle 6	N = 2
Mean (SD)	36.5 (10.61)
Median (minimum, maximum)	36.5 (29, 44)

Source: Page 78 of the Summary of Clinical Safety.

**All Budesonide Safety Population (Studies BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA):**

The exposure in person-years was 83.7 person-years in the budesonide foam group and 20.4 person-years in the placebo group (see the table below).

**Table 18. Duration of Exposure (All Budesonide Safety Population) (Studies BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA)**

<b>Exposure Duration</b>	<b>Budesonide Foam 2 mg/25 mL N = 718</b>	<b>Budesonide Enema 2 mg/100 mL N = 268</b>
Total person-years of exposure <sup>a</sup>	83.7	20.4
Overall (days)	N = 712	N = 268
Mean (SD)	42.9 (31.03)	27.8 (5.38)
Median (minimum, maximum)	36.0 (3, 258)	28.0 (6, 39)
Randomized Studies	N = 655	N = 268
Mean (SD)	35.1 (12.72)	27.8 (5.38)
Median (minimum, maximum)	34.0 (3, 76)	28.0 (6, 39)

Source: Page 77 of the Summary of Clinical Safety.

## 8.3 Safety Findings

### A. Deaths:

No deaths were reported in any of the primary safety studies (BUCF3001, BUCF3002, BFPS3073, BUF-6/UCA, and BUF-9/UCA).

### B. Serious Adverse Events:

Serious adverse events (SAEs) are summarized below for the RCT Population, All Salix Budesonide Safety Population, and All Budesonide Safety Population.

#### RCT Population:

The following SAEs were reported by treatment group:<sup>8</sup>

- **Budesonide Foam: 5 subjects (2%);** one case each of the following:
  - Abdominal pain
  - Ulcerative colitis
  - Hypersensitivity - food allergy
  - Acute generalized exanthematous pustulosis
  - Limb arterial thrombosis
- **Placebo: 3 subjects (1%);** one case each of the following:
  - Anemia
  - Ulcerative colitis
  - Ectopic pregnancy

Of all the SAE's above, only Acute generalized exanthematous pustulosis (AGEP) was considered to be related to the study drug.<sup>9</sup>

This case occurred in a 65 year old male. At Day 3 (three days after starting study drug), a pustule in the crease of the patient's finger broke and exfoliated into an open sore. At Day 9, the patient presented with a mild rash on the forearms. At Day 12, the rash was present on the arms, legs, back, buttocks, and torso; study drug was discontinued at that time. The patient received prednisone, triamcinolone cream, and sulfamethoxazole/trimethoprim. Wound culture results were positive for methicillin-resistant staphylococcus aureus (MRSA); a consulted dermatologist cited a diagnosis of infectious eczematoid dermatitis. The investigator assessed the infectious eczematoid dermatitis as the result of the patient scratching the AGEP and spreading the pustulous fluid. By Day 25, the event resolved. The investigator suspected that the event was a drug-induced or allergic reaction to the study drug, and stated that AGEP is associated with drug-induced bullous disorders.

The hypersensitivity (food allergy) SAE was not considered to be related to study drug; the case was likely due to a food allergy to mandarin oranges.

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<sup>8</sup> Pages 105-106 of the Summary of Clinical Safety

<sup>9</sup> Page 145 of the BUCF3002 Study Report

All SAE's resolved by the end of the study.

**All Salix Population:**

No additional SAE's were reported other than those described above in the RCT Population.

**All Budesonide Population:**

The following SAE's were reported by treatment group:

- **Budesonide Foam: 8 subjects (1%)**; in addition to the SAE's described above in the Budesonide Foam group of the RCT Population, the following additional SAE's were reported (one case each of the following):
  - Diarrhea
  - Unstable angina
  - Ulcerative colitis
- **Budesonide Enema: 4 subjects (2%)**; one case each of the following (except where indicated):
  - Ulcerative colitis
  - Ulcerative colitis
  - Renal colic
  - Pneumonia and Cerebrovascular accident (one subject experienced both these SAE's)

None of these SAE's was considered to be related to the study drug.

All SAEs were resolved by the end of the study except for 1 case of ulcerative colitis in the budesonide foam group that was considered to be resolving at the last assessment.

**C. Dropouts and/or Discontinuations:**

Dropouts and/or discontinuations are summarized below for the RCT Population, All Salix Budesonide Safety Population, and All Budesonide Safety Population.

**RCT and All Salix Populations:**

**RCT Population**: Total AE's leading to discontinuation and AE's leading to discontinuation in > 1 subject are shown in the table below for the RCT Population.

**Table 19. RCT Population: Total AE's leading to Discontinuation and AE's Leading to Discontinuation in > 1 Subject**

AE Leading to Discontinuation	Placebo N=268 n (%)	Budesonide Foam N=278 n (%)
<b>Total [n (%)]</b>	<b>12 (4%)</b>	<b>26 (10%)</b>
AE's Leading to Discontinuation in ≥ 1 Subject:		
Blood cortisol decreased*	1 (0.4%)	16 (6%)
Adrenal insufficiency#	1 (0.4%)	4 (2%)
Ulcerative proctitis	4 (1.5%)	0
Ulcerative colitis	3 (1.1%)	0

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Numbers of AEs in the table above are taken from Pages 108-111 of the Summary of Clinical Safety.

All Salix Population: Total AE's leading to discontinuation and AE's leading to discontinuation in > 1 subject are shown in the table below for the All Salix Population.

**Table 20. All Salix Population: Total AE's leading to Discontinuation and AE's Leading to Discontinuation in > 1 Subject**

AE Leading to Discontinuation	Budesonide Foam N=331 n (%)
<b>Total [n (%)]</b>	<b>39 (12%)</b>
AE's Leading to Discontinuation in ≥ 1 Subject:	
Blood cortisol decreased*	20 (6%)
Adrenal insufficiency#	7 (2%)
Rash	2 (0.6%)

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Numbers of AE's in the table above are taken from Pages 115-118 of the Summary of Clinical Safety.

Blood cortisol decreased and Adrenal insufficiency accounted for most of the AE's leading to discontinuation. It should be noted that both of these AE's were defined according to laboratory criteria (as shown in the footnotes of the tables above), and that the criteria for each of these AE's differed from the criteria for a normal ACTH Stimulation test (see Section 5.1 of this CDTL Review). (See also the next section "D. Potential Glucocorticoid-related Effects.")

**All Budesonide Population:**

Total AE's leading to discontinuation and AE's leading to discontinuation in > 1 subject are shown in the table below for the All Budesonide Population.

**Table 21. All Budesonide Population: Total AE's leading to Discontinuation and AE's Leading to Discontinuation in > 1 Subject**

AE Leading to Discontinuation	Budesonide Foam N=718 n (%)	Budesonide Enema N=268 n (%)
<b>Total [n (%)]</b>	<b>54 (8%)</b>	<b>7 (3%)</b>
AE's Leading to Discontinuation in > 1 Subject:		
Blood cortisol decreased*	20 (3%)	0
Adrenal insufficiency <sup>#</sup>	7 (1%)	0
Ulcerative colitis	3 (0.4%)	2 (0.7%)
Diarrhea	3 (0.4%)	0
Abdominal pain	2 (0.6%)	0
Nausea	2 (0.6%)	0
Rash	2 (0.6%)	0

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Numbers of AE's in the table above are taken from Pages 111-115 of the Summary of Clinical Safety.

Comparison of the table above (All Budesonide Population) to the previous table (Salix Population) shows that there were no cases of Blood cortisol decreased or Adrenal insufficiency leading to discontinuation in the Budenofalk studies (see the next section "D. Potential Glucocorticoid-related Effects").

**D. Potential Glucocorticoid-related Effects:**

Potential glucocorticoid-related effects are summarized below for the RCT Population, the All Salix Budesonide Safety Population, and the All Budesonide Safety Population.

**RCT Population:****Potential Glucocorticoid Related Adverse Events**

The table below summarizes the percentages of patients reporting potential glucocorticoid related AEs in the RCT Population.

**Table 22. RCT Population: Potential Glucocorticoid Related Adverse Events**

Adverse Event	Placebo N = 278 n (%)	Budesonide Foam N = 268 n (%)
<b>Overall</b>	<b>10 (3.6%)</b>	<b>60 (22.4%)</b>
Blood cortisol decreased*	6 (2.2%)	46 (17.2%)
Adrenal insufficiency <sup>#</sup>	2 (0.7%)	10 (3.7%)
Insomnia	1 (0.4%)	1 (0.4%)
Sleep disorder	0	1 (0.4%)
Acne	0	1 (0.4%)
Depression	1 (0.4%)	1 (0.4%)
Hyperglycemia	0	1 (0.4%)

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

<sup>#</sup> Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Source: Response to Information Request received August 22, 2014

Blood cortisol decreased and Adrenal insufficiency were the most common individual potential glucocorticoid-related AEs. It should be noted that both of these AE's were defined according to laboratory criteria (as shown in the footnotes of the tables above). Of the 46 Budesonide Foam treated patients with Blood cortisol decreased (as defined above), none had Adrenal insufficiency (as defined above). All cases of Adrenal insufficiency resolved.

**Changes in Cortisol Levels and ACTH Challenge Results**

**Cortisol Levels:** Initial decreases in mean serum cortisol levels at Weeks 1 and 2 in the budesonide group gradually returned toward baseline levels by Week 6. See the table below and the figure below. The Clinical Reviewer noted that this finding is likely due to more frequent (BID) dosing during the first 2 weeks and less frequent (QD) dosing during the subsequent 4 weeks.

**Table 23. 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
<b>Baseline</b>	N = 278	N = 268
Mean (SD)	367.56 (136.108)	357.09 (143.926)
<b>Week 1</b>	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)
<b>Week 2</b>	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)
<b>Week 4</b>	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)
<b>Week 6</b>	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)

Serum cortisol (AM cortisol) was collected at Baseline, and Weeks 1, 2, 4, and 6 in the RCT safety population. Normal range: 5 µg/dL (138nmol/L) to 25 µg/dL (690 nmol/L)  
The table above is taken from the Clinical Review. Source: Summary of Clinical Safety, p. 145

**Table 24. Mean ± SD cortisol values by visit and treatment group (RCT Safety Population)**

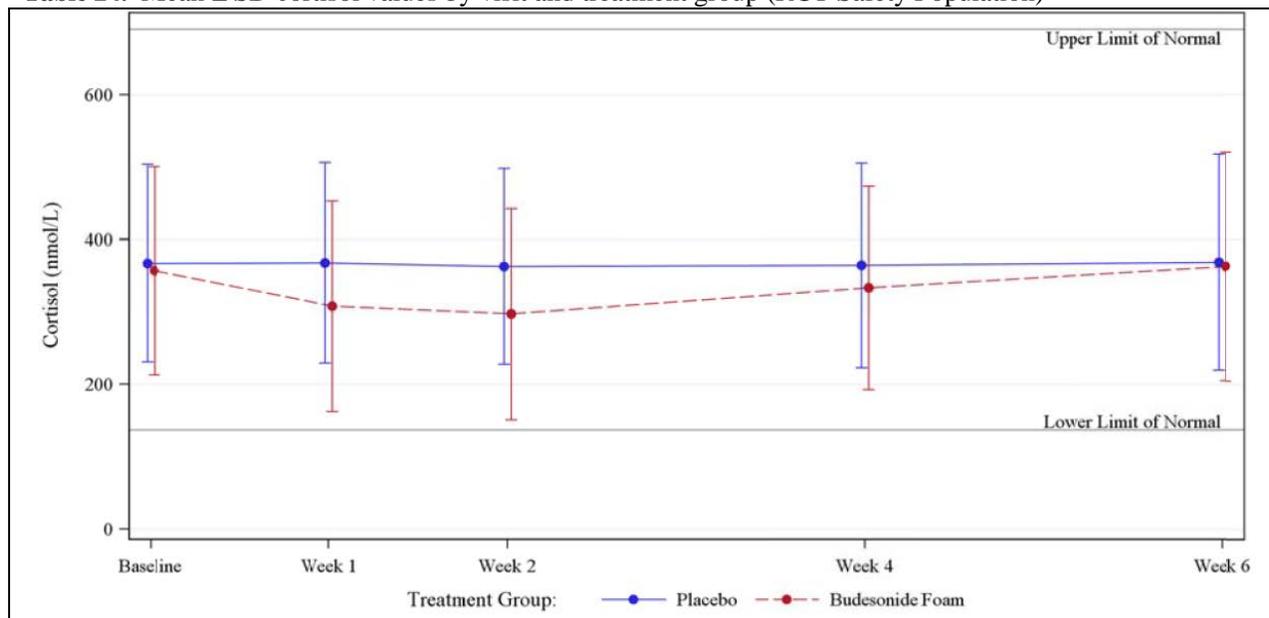


Figure above is taken from Page 145 of the Summary of Clinical Safety.

Note: Gray lines denote normal range, which was 5 µg/dL (138nmol/L) to 25 µg/dL (690 nmol/L)

Proportion of Subjects with Cortisol Levels > 5 µg/dL: Normal morning serum cortisol levels (> 5 µg/dL) were maintained in 85% and 84% of UCERIS Rectal Foam treated subjects during Weeks 1 and 2 (twice daily treatment) and 93% and 94% during Weeks 4 and 6 (once daily treatment), respectively. See the table below. The Clinical Reviewer noted that during the QD 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%).

**Table 25. Proportion of Subjects with Cortisol Levels of >5 µg/dL (RCT Safety Population)**

Cortisol Parameter	Placebo N = 278 n (%)	Budesonide Foam 2 mg/25 mL N = 268 n (%)
<b>Total cortisol &gt; 5 µg/dL (138 nmol/L, lower limit of normal range)</b>		
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)

The table above is modified from the Clinical Review. Source: Summary of Clinical Safety, p. 147

**Cortisol Levels Following ACTH Challenge:** A greater decrease from Baseline to Week 6 in mean cortisol level following ACTH challenge was observed in the budesonide group than with the placebo group. See the table below.

**Table 26. Cortisol Levels Following ACTH Challenge (RCT Safety Population)**

Total Cortisol Levels Following ACTH Challenge, nmol/L	Placebo N = 278	Budesonide Foam 2 mg/25 mL N = 268
<b>Baseline</b>	N = 278	N = 266
Mean (SD)	732.57 (153.481)	713.28 (140.927)
<b>Week 6</b>	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)

The table above is taken from the Clinical Review. Source: Summary of Clinical Safety, p. 146.

**Proportion of Subjects with Normal ACTH Challenge Test Results:** At baseline, 83.5% of subjects in the budesonide foam group had a normal response to the ACTH challenge and at Week 6, 62.7% of subjects had a normal response to the ACTH challenge; in the placebo group, these values were 85.6% and 75.9%, respectively. See the table below.

**Table 27. Proportion of Subjects with Normal Response to ACTH Challenge (RCT Safety Population)**

Normal response to ACTH challenge <sup>a</sup>	Placebo N=278 n (%)	Budesonide Foam N=268 n (%)
Baseline	238/278 (85.6)	222/266 (83.5)
Week 6 <sup>b</sup>	180/237 (75.9)	148/236 (62.7)

<sup>a</sup> 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.

<sup>b</sup> Includes 20 subjects in the UCERIS Rectal Foam arm and 2 subjects in the placebo arm who discontinued prior to week 6 due to adverse events related to low cortisol or abnormal response to ACTH challenge.

The table above is modified from the Clinical Pharmacology Review.

See also discussion of results of the ACTH Challenge Test in Section 5.1 of this CDTL Review.

**All Salix and All Budesonide Populations:**

**All Salix Population:** The table below summarizes the percentages of patients reporting potential glucocorticoid related effects in the All Salix Population.

**Table 28. All Salix Population: Potential Glucocorticoid Related Effects**

Adverse Event	Budesonide Foam N = 331 n (%)
Overall	75 (22.7%)
Blood cortisol decreased*	57 (17.2%)
Adrenal insufficiency <sup>#</sup>	13 (3.9%)
Depression	3 (0.9%)
Acne	2 (0.6%)
Insomnia	2 (0.6%)
Agitation	1 (0.3%)
Sleep disorder	1 (0.3%)

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Numbers of AE's in the table above are taken from Pages 119-120 of the Summary of Clinical Safety.

**All Budesonide Population:** The table below summarizes the percentages of patients reporting potential glucocorticoid related effects in the All Budesonide Population. The much higher number of "Blood cortisol decreased" and "Adrenal insufficiency" events in the Salix studies compared to the Budenofalk studies is mainly attributable to differences in instructions provided to the investigators regarding how to record AE's related to laboratory results. In the Budenofalk studies, abnormal laboratory results were recorded only if the patient was discontinued or hospitalized, or if the result was considered an AE by the investigator. In the Salix studies, abnormal laboratory results were recorded as AE's even if they were of unknown clinical significance. Another reason for the higher number of "Blood cortisol decreased" and "Adrenal insufficiency" events in the Salix studies compared to the Budenofalk studies is that ACTH challenge tests were done in the Salix studies but not the Budenofalk studies; abnormal laboratory results from these tests were recorded as AE's.

**Table 29. All Budesonide Population: Potential Glucocorticoid Related Effects**

Adverse Event	Budesonide Foam N=718 n (%)	Budesonide Enema N=268 n (%)
Overall	79 (11.0%)	1 (0.4%)
Blood cortisol decreased*	58 (8.1%)	0
Adrenal insufficiency <sup>#</sup>	13 (1.8%)	0
Depression	3 (0.4%)	0
Acne	4 (0.6%)	0
Insomnia	3 (0.4%)	0
Agitation	1 (0.1%)	0
Sleep disorder	1 (0.1%)	1 (0.4%)

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Numbers of AE's in the table above are taken from Pages 119-120 of the Summary of Clinical Safety.

### **E. Common Adverse Events:**

Common adverse events (AEs) are summarized below for the RCT Population, the All Salix Budesonide Safety Population, and the All Budesonide Safety Population.

#### **RCT Population**

In the RCT Population, AE's were experienced by 36.3% (101/278) of patients in the Placebo group and 45.9% (123/268) of patients in the Budesonide Foam group. The most common AE's ( $\geq 2\%$  of the Budesonide Foam group or Placebo group and at higher frequency in the Budesonide Foam group) were Blood cortisol decreased, Adrenal insufficiency, and Nausea. See the table below. (See additional discussion about the AE's of Blood cortisol decreased and Adrenal insufficiency in the previous section "D. Potential Glucocorticoid-related Effects.")

**Table 30. AE's Occurring in  $\geq 2\%$  of the Budesonide Foam Group or Placebo Group and at Higher Frequency in the Budesonide Foam Group (RCT Population)**

Adverse Event System Organ Class Preferred Term	Placebo N = 278 n (%)	Budesonide Foam N = 268 n (%)
Investigations		
Blood cortisol decreased*	6 (2.2%)	46 (17.2%)
Endocrine disorders		
Adrenal insufficiency <sup>#</sup>	2 (0.7%)	10 (3.7%)
Gastrointestinal disorders		
Nausea	2 (0.7%)	6 (2.2%)

\* Decreased blood cortisol was defined as a morning cortisol level of < 5 mcg/dL.

# Adrenal insufficiency was defined as a cortisol level of < 18 mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Table above is modified from Page 96 of the Summary of Clinical Safety.

**All Salix Population:**

In the All Salix Population, AE's were experienced by 50% (166/331) of patients. The most common AE's (occurring in  $\geq 2\%$  of patients) were Blood cortisol decreased, Adrenal insufficiency, Headache, Nausea, Abdominal pain, and Nasopharyngitis. See the table below.

**Table 31. AE's Occurring in  $\geq 2\%$  of Patients (All Salix Population)**

Adverse Event System Organ Class Preferred Term	Budesonide Foam N = 331 n (%)
Investigations	
Blood cortisol decreased*	57 (17.2%)
Endocrine disorders	
Adrenal insufficiency <sup>#</sup>	13 (3.9%)
Nervous system disorders	
Headache	11 (3.3%)
Gastrointestinal disorders	
Nausea	10 (3.0%)
Abdominal pain	9 (2.7%)
Infections and Infestations	
Nasopharyngitis	7 (2.1%)

\* Decreased blood cortisol was defined as a morning cortisol level of  $< 5$  mcg/dL.

<sup>#</sup> Adrenal insufficiency was defined as a cortisol level of  $< 18$  mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Table above is modified from Page 98 of the Summary of Clinical Safety.

**All Budesonide Population:**

In the All Budesonide Population, AE's were experienced by 40% (288/718) of patients in the Budesonide Foam group and 32% (86/286) in the Budesonide Enema group. The most common AE's (occurring in  $\geq 2\%$  of patients treated with Budesonide Foam or Budesonide Enema) were Blood cortisol decreased, Headache, Abdominal pain, Nausea, and Ulcerative colitis. See the table below. (See also the previous section "D. Potential Glucocorticoid-related Effects".)

**Table 32. AE's Occurring in  $\geq 2\%$  of Patients (All Budesonide Population)**

Adverse Event System Organ Class Preferred Term	Budesonide Foam N = 718 n (%)	Budesonide Enema N = 268 n (%)
Investigations		
Blood cortisol decreased*	58 (8.1%)	0
Nervous system disorders		
Headache	42 (5.8%)	29 (10.8%)
Gastrointestinal disorders		
Abdominal pain	22 (3.1%)	6 (2.2%)
Nausea	18 (2.5%)	2 (0.7%)
Ulcerative colitis	7 (1.0%)	9 (3.4%)

\* Decreased blood cortisol was defined as a morning cortisol level of  $< 5$  mcg/dL.

<sup>#</sup> Adrenal insufficiency was defined as a cortisol level of  $< 18$  mcg/dL at 30 minutes post challenge with adrenocorticotrophic hormone (ACTH).

Table above is modified from Page 97 of the Summary of Clinical Safety.

## 8.4 Recommendation

An Approval Action is the final recommendation from a Safety standpoint.

## 9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

## 10. Pediatrics

PREA does not apply to the adult indication as the pediatric indication has orphan status (designation date of May 6, 2013<sup>10</sup>). Thus, this NDA was not presented to the Pediatric Research Committee (PeRC). (b) (4)

A PMC to conduct a pediatric study is recommended. See Section 13.6.

## 11. Other Relevant Regulatory Issues

### 11.1 QT Evaluation

The reader is referred to the QT-IRT Consult Review by Jiang Liu dated April 9, 2014 for complete information.

The QT-IRT Reviewer concluded that a TQT study is not needed for the following reasons:

- Review of the safety data for pivotal phase 3 studies BUCF3001 and BUCF3002, as well as nonclinical safety assessment of studies BUSA0300 and BUSA0301 does not indicate the presence of a cardiovascular safety signal associated with budesonide foam at therapeutic and suprathreshold doses. There is also no history of QT prolongation associated with budesonide use in currently marketed products (Uceris Summary Basis of Approval), and similar or lower systemic exposures have been observed with budesonide foam as compared with these products.
- There were no TEAEs that may signal proarrhythmic effects, as defined in the E14 guidance on clinical evaluation QT/QTc interval prolongation and proarrhythmic potential, including torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter,

<sup>10</sup>[http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD\\_Results\\_2.cfm?Index\\_Number=394613](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=394613) (accessed August 25, 2014)

<sup>11</sup>E-mail from Erica Radden (PMHS Reviewer) dated July 25, 2014.

syncope, and seizures.<sup>12</sup> Electrocardiogram assessments were performed at the Screening visit only.

- In the 6-week (BUSA0300) and 39-week (BUSA0301) repeat-dose dog toxicology studies, animals received budesonide foam by rectal administration at dose levels up to 2 mg BID. All animals received electrocardiographic examinations prior to the initiation of dosing; and predose, and 1 to 2 hours postdose on Day 1 and again during the last week of dosing. A Board-certified Veterinary Cardiologist conducted a qualitative and quantitative review of the electrocardiograms. There was no effect of the rectal administration of budesonide on qualitative or quantitative electrocardiogram parameters.
- In addition, in vitro hERG (human ether-à-go-go-related gene) potency data demonstrate a > 18,000-fold separation between the IC<sub>50</sub> for hERG inhibition and the highest plasma concentration associated with budesonide foam use in healthy subjects or UP/UPS patients (BUIV0101). In addition, corticosteroids as a class are not associated with QT prolongation.
- Given these supportive data, the low systemic exposure of budesonide following budesonide foam administration in healthy subjects and UP/UPS patients (similar to or lower than systemic exposure reported for currently marketed budesonide dosage forms), the absence of a cardiac safety concerns in over 30 years of budesonide use in over 30 countries (including the US) in clinical practice, and the current concerns around the utility of the thorough QT (TQT) study,<sup>13</sup> Salix proposes that a TQT study not be required for NDA approval of budesonide foam.

## 11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary by Susan Leibenhaut for complete information.

For Study BUCF3001, Sites 857 and 520 were selected because each had a high percentage of the subjects in Study BUCF3001 relative to other sites. In Site 857, the reported proportion of patients that met the primary endpoint was 75% (6/8) in the budesonide rectal foam group and 0% (0/7) in the placebo group. In Site 520, the reported proportion of patients that met the primary endpoint was 40% (2/5) in the budesonide rectal foam group and 0% (0/5) in the placebo group.

For Study BUCF3002, Site 0938 (in Russia) was initially selected because it had a high percentage of the subjects in Study BUCF3001 relative to other sites. In Site 0938, the reported proportion of patients that met the primary endpoint was 100% (15/15) in the budesonide rectal foam group and 0% (0/15) in the placebo group. The inspection of Site 0938 (in Russia) was denied. It should be noted that Site 0938 (in Russia) was inspected in 2009 by the Agency for another NDA (NDA 22554) and had been given a classification of No Action Indicated (NAI) at that time. Another site (site 0198) in Study BUCF3002 was selected (see table below).

<sup>12</sup> ICH E14 Step 5. The clinical evaluation of QT/QT<sub>c</sub> interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Federal Register. 70, 61134-61135. 2005.

<sup>13</sup> Stockbridge N. "Can the thorough QT study be replaced?" Cardiac Safety Research Consortium Annual Meeting, Washington DC, December 10, 2012. 2012.

Overview of Inspections and Final Classifications:

An overview of the three sites inspected and final classifications are presented in the table below.

**Table 33. Overview of Sites Inspected and Final Classifications**

Investigator / Location / Site No.	Study	No. Pts*	Final Classification
Humberto Aguilar Shreveport, LA / 857	BUCF3001	15	NAI
Wayne Schonfeld Hollywood, FL / 520	BUCF3001	10	NAI
Ronald Fogel Chesterfield, MI / 0198	BUCF3002	10	NAI

Inspector's Key Findings:

The Inspector's key findings are summarized below for each of the three site inspections (by Clinical Investigator (CI).

Ronald Fogel:

- The Modified Mayo scores were calculated on a worksheet using the diary scores transcribed from the website. Some of the scores were not transcribed correctly by study staff and were changed following queries from the sponsor after reviewing the diaries. The worksheets were not always changed. The study coordinator was able to print out the data audit trail to show the query and his changes to the eCRF and the reason for the change.
- Subjects 0001 and 0002 had deviation reports in their files, saying the subjects had signed an earlier version of the informed consent document (ICD). On December 23, 2009, they signed an ICD with the version date of October 19, 2009, although a new version had been approved by the IRB on December 7, 2009. Deviation Reports were sent to the IRB in 2012 when the study closed. The Study Coordinator was able to find a letter issuing the new ICF version that had a date-stamp in January 2010. Therefore, they had not received the updated ICFs and the deviation reports were wrong. A new monitor from the sponsor did the closeout audit and asked them to file the deviations.

The OSI Reviewer concluded that the discussion item noted above is considered an isolated occurrence and does not impact data reliability or subject safety; and that the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indications.

Humberto Aguilar:

No significant regulatory violations were noted and no Form FDA 483 was issued. . A discussion item was that Subject 0857-004, randomized to active arm should have potentially been excluded because colonoscopy done at visit 2 failed to note the extent of the disease, which is an inclusion/ exclusion criteria. This was noted in the protocol deviations line listings submitted to FDA. There was no evidence of underreporting of AE's. The OSI Reviewer concluded that the data generated by this site appear acceptable in support of the respective indication.

Wayne Schonfeld:

No significant regulatory violations were noted and no Form FDA 483 was issued. All data points provided corresponded with source documents, except for protocol deviations. The electronic data capture system did not capture Protocol Deviations under a specific tab. Therefore, all deviations that were encountered were sent to the sponsor directly, and reported to the IRB if applicable. The site properly reported their deviations, and none were egregious. There was no evidence of underreporting of AE's. The OSI Reviewer concluded that the data generated by each of these sites appear acceptable in support of the respective indication.

Final Conclusion:

OSI concluded that the studies appear to have been conducted adequately, and the data generated by each of the three sites may be used in support of the respective indications.

### 11.3 Device Issues and CDRH Reviews

For complete information, see CDRH Office of Device Evaluation Consult Review by Branden Reid, CDRH Office of Compliance Consult Review by Bleta Vuniqui, and CDRH Human Factors Consult Review by QuynhNhu Nguyen.

#### 11.3.1 Combination Product Description (Device Constituents)

The combination product description (device constituents) is summarized below (taken from the CDRH Office of Compliance Consult Review):

- Budesonide foam is supplied in a canister containing a minimum of fourteen 2-mg doses of budesonide. Each canister contains budesonide active ingredient as well as the following inactive ingredients: cetyl alcohol, citric acid monohydrate, edetate disodium, emulsifying wax, (b) (4) stearyl ether, propylene glycol, and purified water. A propellant mixture of n-butane, isobutane, and propane is used.
- The primary container closure system for the drug product is comprised of a 54-mL, white, aluminum (b) (4) canister (b) (4), fitted with a 1-inch metering valve consisting of a (b) (4) valve body and stem affixed with a 1.35 mL metering head.
- A plastic safety tab that prevents accidental actuation is attached to a foam shield and must be removed prior to use.
- The canister only delivers a dose when it is held inverted. Once activated, the valve opens and the metering head dome fills with a single dose of the drug product emulsion and propellant mixture.
- The foam is expelled once the metering head is released.
- The canister is packed in a carton containing fourteen single-use applicators pre-lubricated (b) (4).

#### 11.3.2 CDRH Office of Device Evaluation Consult Review



IR Item #5: The submission does not include a systematic evaluation of use-related risk, a determination of the necessity of human factors (HF) validation and, if necessary, how you would undertake the human factors validation. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. This risk analysis of user tasks should include a comprehensive evaluation of all the steps involved in using your device (e.g., based on a task analysis), a description of pertinent characteristics of the intended population of users, the potential errors that users might commit including critical tasks they might fail to perform, and the harm that would result. You should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. Provide a comprehensive analysis of use-related risks and a justification for whether an HF/usability validation study is necessary for the proposed product. In addition, provide a discussion on how you have addressed potential difficulty that the user may experience when administering the product in a specific position.

The CDRH ODE Reviewer noted that the responses to IR Item #1, IR Item #2, and IR Item #3 were adequate, and that the remaining items were not from that Reviewer; this is documented in the Quality Review. The sponsor proposed addressing IR Item #4 and IR Item #5 by a modified instructions for use (see DMPP Patient Labeling Review) and a systematic evaluation of use-related risk (see discussion in Section 11.3.3 below).

Item 2 from the CDRH ODE Review was communicated to the Applicant in an IR dated August 18, 2014 (see below) (numbering from the IR):

IR Item #1: According to the FDA Blue Book Memorandum #G95-1, entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.", your rectal applicator is considered limited surface contacting. We recommend cytotoxicity, sensitization, and irritation / intracutaneous reactivity tests per FDA's recognized standards to 2-117: AAMI / ANSI / ISO 10993-3:2003/(R) 2009.

A response to this IR was received from the Applicant on August 23, 2014; the CDRH Reviewer concluded that the Applicant's response to this IR addressed their concerns.<sup>14</sup> See Section 3.2.4 of this CDTL Review for discussion of the Quality Reviewer's conclusion regarding leachable studies for the applicator.

### 11.3.3 CDRH Human Factors Consult Review

The CDRH Human Factors Premarket Evaluation Team (HFPMET) was consulted primarily to provide a comprehensive analysis of use-related risks and a justification for whether an HF/usability validation study is necessary for the proposed product. The Consult Reviewer concluded that review of a human factors validation study for this submission by the CDRH HFPMET is not needed, and noted the following:

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<sup>14</sup>E-mails from Regulatory Project Manager (Kelly Richards) and CDRH ODE Reviewer (Branden Reid) dated September 2, 2014.

- The Sponsor provided a systematic evaluation of use-related risk for budesonide 2 mg rectal foam in accordance with the 2011 draft guidance, Applying Human Factors and Usability Engineering to Optimize Medical Device Design. A task prioritization chart, showing the potential clinical consequence and risk prioritization for each task involved with delivering the drug
- The risk analysis did not identify any use errors or major or serious risks that could lead to negative clinical consequence while using the canister to administer budesonide 2 mg rectal foam. The Sponsor concluded that taken into consideration the risk analysis and the additional data generated during two pivotal Phase 3 clinical studies in which the drug was delivered with this device in accordance with the instructions for use, a human factors validation study is not necessary.
- The Sponsor has performed a use-related risk analysis and did not identify any safety concerns associated with users not holding the device in place for 10 seconds before withdrawing the canister. The Consult Reviewer commented that the issues associated with product performance would be addressed through engineering and CMC review.

### 11.3.4 CDRH Office of Compliance Consult Review

The CDRH Office of Compliance was consulted from the CDER Office of Compliance to evaluate this NDA covering the medical device constituents of the combination product, and to determine if an inspection of the manufacturing facilities is warranted. The CDRH Office of Compliance recommended approval of Budesonide 2mg Rectal Foam be deferred until the time when a satisfactory preapproval inspection has been conducted at [REDACTED] (b) (4)

[REDACTED] Based on the EES Establishment Evaluation Request Summary Report, an overall acceptable decision was recommended (September 4, 2014)(including acceptable decision for [REDACTED] (b) (4)); this is documented in the Quality Review.

## 11.4 505 (b)(2) Application Issues

On August 15, 2014, at the Agency's request, the Applicant amended this NDA from a 505(b)(1) application to a 505(b)(2) application in order to reference portions of the Agency's previous finding of safety for Entocort EC (NDA 21324) and Uceris (NDA 203634). It should be noted that NDA 203634 (Uceris) was a 505(b)(2) application that referenced NDA 21324 (Entocort EC).

### 11.4.1 Scientific Justification for 505 (b)(2) Application to Utilize Findings in Entocort EC NDA / Uceris NDA / Published Literature

On August 26, 2014, the Applicant submitted a scientific justification for this 505(b)(2) application to utilize the findings in Entocort capsules, Uceris tablets, and available published literature.

The Nonclinical Reviewer noted the following regarding the Applicant's scientific justification:

- "...the Applicant submitted a scientific justification for the 505(b)(2) application cross-referencing Entocort capsules, Uceris tablets, publically available safety data for budesonide, available published literature, and the nonclinical studies submitted in the application."

- "... the Applicant provided adequate information to scientifically justify the bridging of the nonclinical PK, toxicity, genotoxicity, carcinogenicity and reproductive toxicity information for the current NDA to the publicly available information and/ or published literature. The Applicant's approach to bridge publicly available information and published nonclinical data to the Uceris Rectal Foam application (NDA 205-613) appears to be adequate and is acceptable."

The Clinical Pharmacology Reviewer noted the following regarding the Applicant's scientific justification:

- "The sponsor claims that the data referenced in support of the Uceris Rectal foam application are scientifically relevant due to the comparable or greater systemic exposures in studies cited to describe clinical pharmacology section of the Entocort or Uceris tablet label as compared to doses and exposures for Uceris Rectal foam."
- "... we disagree with the sponsor that [REDACTED] (b) (4)

[REDACTED] However, the data showed that the systemic exposure for these dosage forms are most likely to be in the same order of magnitude and the information in the proposed label for Uceris rectal foam that relies on Entocort label such as metabolism, distribution, excretion, use in specific populations and drug-drug interaction is appropriate."

#### **11.4.2 505(b)(2) Coordinating Committee Meeting**

This application was discussed at the 505(b)(2) Coordinating Committee Meeting on September 2, 2014. The outcome of that meeting was as follows:<sup>15</sup>

"This application is ~ cleared for a Tentative Approval (TA) action at best ~ from a 505(b)(2) perspective. The clearance for a TA action at best is because the applicant has submitted proof that NDA holder/patent owner were notified of the paragraph IV certification on August 18, 2014 and the NDA holder and/or patent owner have a window of 45 days in which to file a lawsuit. That window will close on October 2, 2014 which is after the PDUFA date."

See language for Tentative Approval Letter in Section 13.1 of this CDTL Review.

## **12. Labeling**

### **12.1 Proprietary Name**

For complete information, see the DMEPA Proprietary Name Review by Matthew Barlow.

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<sup>15</sup> E-mail from Mary Ann Holovac dated September 3, 2014

DMEPA concluded in the review, that the proprietary name of “Uceris” was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated April 10, 2014.

## 12.2 Office of Prescription Drug Promotion (OPDP) Comments

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name (Uceris) is acceptable from a promotional perspective. This is documented in the Proprietary Name Review by Matthew Barlow.

## 12.3 Physician Labeling / Medication Guide / Carton and Container Labeling

The main revisions to the Applicant’s proposed Physician Labeling are summarized below:

- Dosage and Administration (Section 2 of Label): A sub-section "Administration Instructions" was added with key instructions for patients, most notably the instruction to "Warm the canister in the hands while shaking it vigorously for 10 to 15 seconds prior to use."
- Warnings and Precautions (Section 5 of Label): A warning and precaution about the flammability of the contents was revised to include a statement that patients should discontinue use before initiation of bowel preparation for colonoscopy.
- Adverse Reactions (Section 6 of Label): The following key revisions were made:
  - The Clinical Trials Experience sub-section was revised to include a separate summary table of potential glucocorticoid-related adverse reactions and discussion of those data..
  - The Post-Marketing Experience sub-section was revised to include adverse reactions reported from oral formulations of budesonide.
- Use in Specific Populations (Section 8 of Label): The following key revisions were made:
  - The Pregnancy sub-section was revised as recommended by the Nonclinical Pharmacology/Toxicology Reviewer (see Section 4.1 of this CDTL Review); in addition, a statement about possible hypoadrenalism in neonates exposed to glucocorticosteroids in utero was added (as recommended by the PMHS Maternal Health Reviewer).
  - The Nursing Mothers and Pediatric Use sub-sections were revised (as recommended by the PMHS Maternal Health Reviewer).
  - The Hepatic Impairment sub-section was revised to include the Child-Pugh Class corresponding to the severity of hepatic impairment; also, a statement was added that dosage adjustment is not needed for mild (Child-Pugh Class A) hepatic impairment.
- Nonclinical Toxicology (Section 13 of Label): This section was revised as recommended by the Nonclinical Pharmacology/Toxicology Reviewer (see Section 4.1 of this CDTL Review).
- Clinical Studies (Section 14 of Label): The following revisions were made:
  - All results were presented separately for each study [REDACTED] (b) (4)
  - The results for the second secondary endpoint were not included because the sponsor did not conduct the analysis of this endpoint as pre-specified in the Statistical Analysis Plan (see Section 7.3 of this CDTL Review).

- The results for the third secondary endpoint were presented descriptively because the second secondary endpoint was not met (see Section 7.3 of this CDTL Review).
- Stool frequency data were presented for patients that met the primary endpoint because the primary endpoint (as defined) could be met even if the stool frequency subscore did not decrease.

In addition to these revisions, additional revisions were negotiated with the Applicant. Many of these revisions are based on recommendations from the DMPP Patient Labeling Review, the OPDP Labeling Review, and the OPDP Patient Labeling Review. The reader is referred to each of these reviews for complete information.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. They made a number of recommendations that were communicated to the Applicant on July 18, 2014 (see DMEPA Label and Labeling Review).

## **13. Recommendations/Risk Benefit Assessment**

### **13.1 Recommended Regulatory Action**

All of the review disciplines recommended an Approval action. This Reviewer concurs with the recommendations from each of the disciplines. However, this application is cleared for a Tentative Approval at best from a 505(b)(2) perspective (see Section 11.4 of this CDTL Review) with the following language for the Tentative Approval Letter:

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, text for the patient package insert, carton and immediate container labels). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application (“Paragraph IV certifications”).

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an

action is brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of 45 days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

However, because the 45-day period described in section 505(c)(3)(C) of the Act has not yet expired, final approval cannot be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent(s) or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as “REQUEST FOR FINAL APPROVAL”. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

## **13.2 Risk Benefit Assessment**

The benefit of Uceris Rectal Foam in mild to moderate distal UC (extending up to 40 cm from the anal verge) has been established in the clinical trials. The safety profile was acceptable based on what was found in the clinical trials. There are known risks associated with this class of product (corticosteroids) that are adequately described in the label.

## **13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategy Requirements (REMS)**

No special postmarketing risk management activities are recommended for this Application.

## **13.4 Recommendation for Postmarketing Required Pediatric Studies**

No postmarketing required pediatric studies are recommended; PREA does not apply to the adult indication as the pediatric indication has orphan status. However, a PMC to conduct a pediatric study is recommended. See PMC in Section 13.6.

### **13.5 Recommendation for other Postmarketing Study Requirements (PMRs)**

None of the primary review disciplines had recommendations for additional postmarketing requirements.

### **13.6 Recommendation for Postmarketing Study Commitments (PMCs)**

The following postmarketing commitment is recommended:

A 6-week randomized, double blind, placebo-controlled trial in children 5 to 17 years of age with active, mild to moderate distal ulcerative colitis (extending up to 40 cm from the anal verge). The trial will evaluate pharmacokinetics (PK), efficacy for induction of remission, and safety of at least 2 doses of Uceris (budesonide) Rectal Foam. The effects of 6 weeks of Uceris (budesonide) Rectal Foam on the hypothalamic-pituitary-adrenal (HPA) axis will be assessed.

Final Protocol Submission: 4/2015

Trial Completion: 1/2018

Final Report Submission: 4/2018

### **13.7 Recommended Comments to Applicant**

None.

## APPENDIX 1: Modified Mayo Disease Activity Index (MMDAI)

**Table 34. Modified Mayo Disease Activity Index**

Index	Stool frequency <sup>a</sup>	Rectal Bleeding <sup>b</sup>	Physician's Global Assessment <sup>c</sup>	Endoscopy/Sigmoidoscopy Findings
MMDAI or Ulcerative Colitis Symptom Score (UCSS) <sup>d</sup>	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 <sup>d</sup> ) 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3 = severe disease (spontaneous bleeding, ulceration)

a. Each patient served as his or her own control to establish the degree of abnormality of the stool frequency.

b. The daily bleeding score represented the most severe bleeding of the day.

c. The physician's global assessment acknowledged the 3 other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

d. The modification made to the Mayo Index was the deletion of "friability" from an endoscopy score equal to 1. With this modification, the presence of friability was indicative of an endoscopy score of 2 or 3.

(The table above is taken modified from the Clinical Review by Zana Marks. Source is Page 53 of the BUCF 3001 Study Report.)

## APPENDIX 2: Phase 3 Studies with Budenofalk (Dr. Falk) Formulation

**Table 35: Phase 3 Studies with Budenofalk (Dr. Falk) Formulation**

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.

Table above is taken from the Clinical Review by Zana Marks. Source: Module 2 Clinical Overview 2.5.1.3.p.6

### APPENDIX 3: Confirmation of Diagnosis of UP or UPS by Endoscopy

The following instructions are summarized from the protocol of each of the Studies (BUCF3001 and BUCF3002)(Section 6.1.1 of each of the protocols):

- Confirm subject has had a colonoscopy within the past year [12 months from Screening (Visit 1)] for UP or UPS. Subjects must either undergo a colonoscopy or sigmoidoscopy procedure prior to Randomization (Visit 3), as shown in the table below:

**Table 36. Requirements for Confirmation of Diagnosis of UP or UPS by Various Situations**

Situation	Requirements for Confirmation of Diagnosis of UP or UPS
<ul style="list-style-type: none"> <li>• A subject has not undergone a colonoscopy within the previous year [12 months from Screening (Visit 1)], but</li> <li>• a diagnosis of UP/UPS has been previously confirmed.</li> </ul>	<ul style="list-style-type: none"> <li>• A colonoscopy procedure will be performed.</li> <li>• Histological confirmation via concurrent biopsy during the procedure will not be required prior to Randomization (Visit 3), but the investigator must be able to reasonably ensure no significant changes to the initial diagnosis have occurred before a subject is randomized.</li> </ul>
<ul style="list-style-type: none"> <li>• A subject has undergone a colonoscopy within the previous year [12 months from Screening (Visit 1)], and</li> <li>• a diagnosis of UP/UPS has been previously confirmed</li> </ul>	<ul style="list-style-type: none"> <li>• A sigmoidoscopy procedure will be performed instead of a colonoscopy.</li> <li>• Histological confirmation via concurrent biopsy during the procedure will not be required prior to Randomization (Visit 3); however, the investigator must be able to reasonably ensure no significant changes to the initial UP/UPS diagnosis have occurred before a subject is randomized.</li> </ul>
<ul style="list-style-type: none"> <li>• A diagnosis of UP or UPS has not been previously confirmed (i.e., newly diagnosed)</li> </ul>	<ul style="list-style-type: none"> <li>• Colonoscopy with biopsy will be performed.</li> <li>• Histological confirmation of disease characteristic of UP or UPS from a local pathologist will be required prior to Randomization (Visit 3).</li> <li>• Newly diagnosed subjects must have had symptoms associated with UP/UPS for at least 45 days (e.g., rectal bleeding) prior to Screening (Visit 1).</li> </ul>

- Based on subject's medical history (as defined above), schedule a colonoscopy (or a colonoscopy with biopsy for newly-diagnosed subjects) prior to the Run-In Visit (Visit 2), or a sigmoidoscopy for the day of the Run-In Visit, as shown in the table below:

**Table 37. Scheduling of Endoscopy (relative to Run-In Visit and Randomization)**

Procedure	Scheduling
<ul style="list-style-type: none"> <li>• Colonoscopy</li> </ul>	<ul style="list-style-type: none"> <li>• <math>\leq 10</math> days or <math>\geq 4</math> days prior to Randomization (Visit 3)</li> </ul>
<ul style="list-style-type: none"> <li>• Sigmoidoscopy</li> </ul>	<ul style="list-style-type: none"> <li>• at Visit 2, which occurs between Days -7 and -4</li> <li>• NOTE: At the investigator's discretion, this procedure can be performed earlier than Visit 2</li> </ul>

- Results from the sigmoidoscopy or colonoscopy for identification of the mucosal grading MMDAI sub-score should be available for review at the Run-In/Stabilization Visit (Visit 2), to enable a decision regarding a subject's progression into the single-blind Run-In/Stabilization study phase.

## APPENDIX 4: Additional Analyses Conducted by the Sponsor in Lieu of the Pre-Specified Second Secondary Endpoint Analysis

In lieu of the pre-specified second secondary endpoint analysis, analyses of two additional endpoints were presented in the study report: (1) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at 0, 1, 2, 3 or 4 scheduled assessments and (2) the numbers of subjects who achieved an MMDAI rectal bleeding subscale score of 0 at study weeks 1 to 6. The results for these analyses are presented below.

**Table 38. Number of Assessments with Rectal Bleeding Responder Classification in BUCF3001 and BUCF3002 (LOCF Analysis, ITT Population)**

Efficacy Endpoint/ Time or Time Point	BUCF3001				BUCF3002			
	Placebo (N = 132) n (%)	Budesonide Foam 2mg/25mL (N = 133) n (%)	p-value	p-value	Placebo (N = 147) n (%)	Budesonide Foam 2mg/25mL (N = 134) n (%)	p-value	p-value
<b>Number of Scheduled Assessments Achieving an MMDAI Rectal Bleeding Score of 0<sup>a</sup></b>								
No response (0 assessments)	80 (60.6)	56 (42.1)	0.0004 <sup>b</sup>	0.0004 <sup>c</sup>	81 (55.1)	54 (40.3)	< 0.0001 <sup>b</sup>	< 0.0001 <sup>c</sup>
Responder at 1 assessment	18 (13.6)	16 (12.0)			27 (18.4)	11 (8.2)		
Responder at 2 assessments	18 (13.6)	25 (18.8)			25 (17.0)	22 (16.4)		
Responder at 3 assessments	14 (10.6)	28 (21.1)			11 (7.5)	29 (21.6)		
Responder at 4 assessments	2 (1.5)	8 (6.0)			3 (2.0)	18 (13.4)		
<b>Study Week in Which Subject Achieved an MMDAI Rectal Bleeding Score of 0</b>								
Week 1 responder	8 (6.1)	18 (13.5)	0.0438 <sup>d</sup>	0.0394 <sup>e</sup>	11 (7.5)	26 (19.4)	0.0043 <sup>d</sup>	0.0033 <sup>e</sup>
Week 2 responder	24 (18.2)	39 (29.3)	0.0349 <sup>d</sup>	0.0342 <sup>e</sup>	24 (16.3)	56 (41.8)	< 0.0001 <sup>d</sup>	< 0.0001 <sup>e</sup>
Week 4 responder	35 (26.5)	63 (47.4)	0.0006 <sup>d</sup>	0.0005 <sup>e</sup>	45 (30.6)	65 (48.5)	0.0020 <sup>d</sup>	0.0019 <sup>e</sup>
Week 6 responder	37 (28.0)	62 (46.6)	0.0022 <sup>d</sup>	0.0020 <sup>e</sup>	42 (28.6)	67 (50.0)	0.0002 <sup>d</sup>	0.0001 <sup>e</sup>

Abbreviations: ITT = intent to treat; LOCF = last observation carried forward; MMDAI = Modified Mayo Disease Activity Index.

a Number of time points/weeks a subject achieved a rectal bleeding MMDAI subscale score of 0 at weeks when the MMDAI was calculated (Weeks 1, 2, 4, and 6).

b p-value obtained using the proportional odds model for ordinal outcome with fixed effects: treatment arm and country.

c p-value obtained from the van Elteren's test adjusting for country.

d p-values obtained from the logistic regression model with fixed effects: treatment arm and country.

e p-values obtained from the Cochran-Mantel-Haenszel test adjusting for country.

## APPENDIX 5: Change from Baseline in Stool Frequency Subscore

Change from baseline to Week 6 in stool frequency subscore is shown below (by study) for patients that met the primary endpoint, patients that did not meet the primary endpoint, and overall.

### Study BUCF3001:

**Table 39. Change from Baseline to Week 6 Stool Frequency Subscore (Study BUCF3001) (Patients that Met the Primary Endpoint, Patients that Did Not Meet the Primary Endpoint, and Overall)**

Assessment Time Statistic	Achieved Remission		Did not Achieved Remission		Overall	
	Placebo (N = 34)	Budesonide Foam 2mg/25mL (N = 51)	Placebo (N = 98)	Budesonide Foam 2mg/25mL (N = 82)	Placebo (N = 132)	Budesonide Foam 2mg/25mL (N = 133)
Change from Baseline to Week 6						
n	34	51	98	82	132	133
Mean	-1.2	-1.2	-0.2	-0.4	-0.5	-0.7
SD	0.76	0.87	0.75	0.91	0.85	0.98
Median	-1.0	-1.0	0.0	0.0	0.0	-1.0
Min	-3	-3	-2	-3	-3	-3
Max	0	0	2	2	2	2

(Table above is taken from Page 6 of the Response to Information Request received July 15, 2014.)

### Study BUCF3002:

**Table 40. Change from Baseline to Week 6 Stool Frequency Subscore (Study BUCF3002) (Patients that Met the Primary Endpoint, Patients that Did Not Meet the Primary Endpoint, and Overall)**

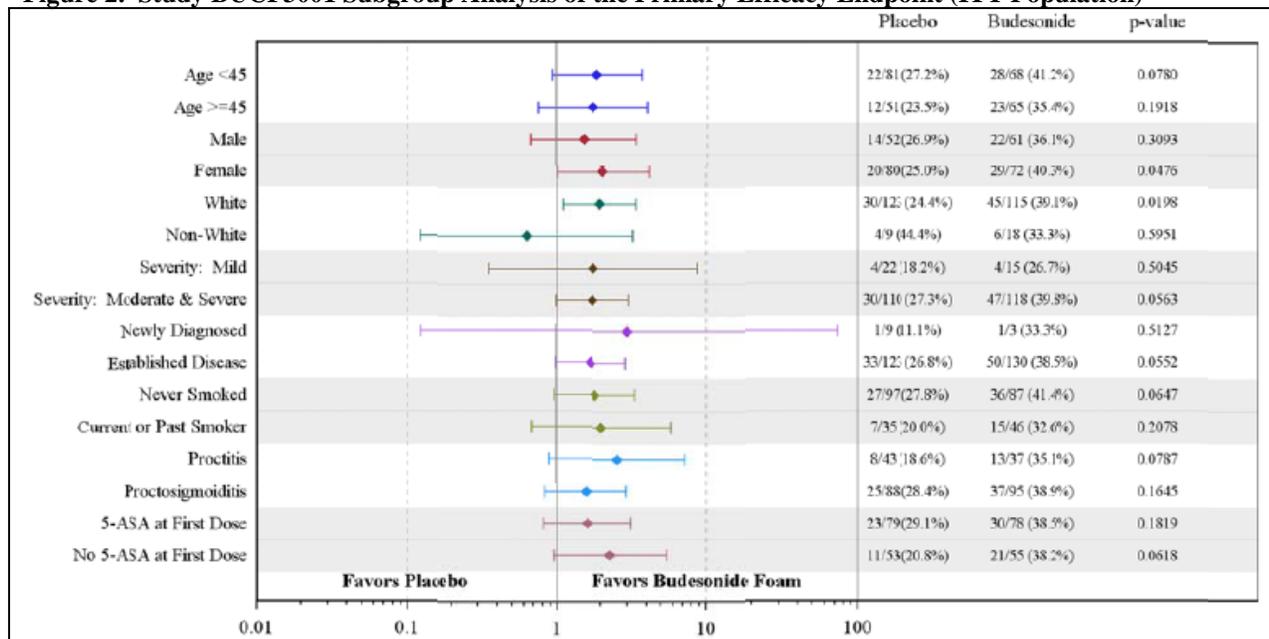
Assessment Time Statistic	Achieved Remission		Did not Achieved Remission		Overall	
	Placebo (N = 33)	Budesonide Foam 2mg/25mL (N = 59)	Placebo (N = 114)	Budesonide Foam 2mg/25mL (N = 75)	Placebo (N = 147)	Budesonide Foam 2mg/25mL (N = 134)
Change from Baseline to Week 6						
n	33	59	114	74	147	133
Mean	-1.1	-1.3	-0.4	-0.3	-0.5	-0.8
SD	0.93	0.84	0.85	0.84	0.92	0.99
Median	-1.0	-1.0	0.0	0.0	0.0	-1.0
Min	-3	-3	-3	-2	-3	-3
Max	0	0	1	2	1	2

(Table above is taken from Page 11 of the Response to Information Request received July 15, 2014.)

## APPENDIX 6: Sponsor's Presentations of Subgroup Analyses (by Study)

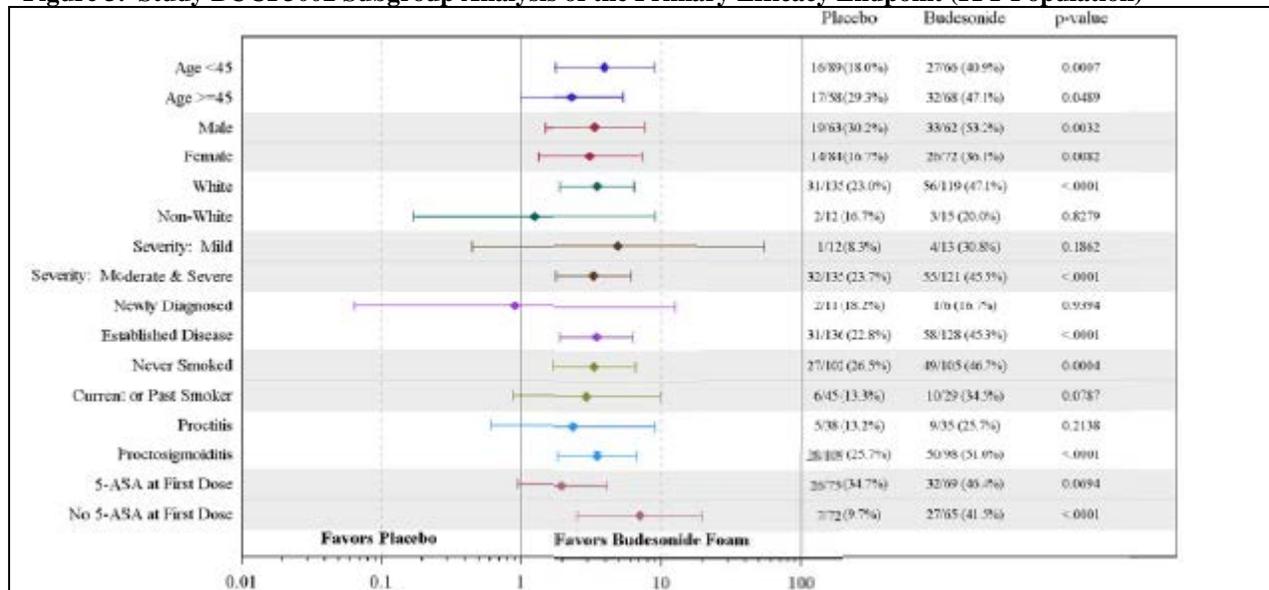
The sponsor's presentations of subgroup analyses are provided in the figures below (by study).

**Figure 2. Study BUCF3001 Subgroup Analysis of the Primary Efficacy Endpoint (ITT Population)**



The figure above is taken from page 101 of the BUCF3001 Study Report.

**Figure 3. Study BUCF3002 Subgroup Analysis of the Primary Efficacy Endpoint (ITT Population)**



The figure above is taken from page 103 of the BUCF3001 Study Report.

## APPENDIX 7: Overview of Study BFPS3073 Design

The following is summarized from the Protocol for Study BFPS3073:

As subjects complete participation in BUCF3001 or BUCF3002, eligible subjects currently experiencing active UP/UPS symptoms (inclusive of those subjects that may have withdrawn due to worsening of UP/UPS symptoms) may directly enroll into Study BFPS3073 and those subjects in remission will be provided information on how to enroll at a later time in the event that symptoms of UP/UPS recur.

The 6-week Treatment Cycle Phase of Study BFPS3073 will consist of subjects assigned to receive budesonide foam administered initially as 2mg/25mL BID for 2 weeks followed by 2mg/25mL QD for 4 weeks.

Approximately 7 days following Visit 4 of a cycle, a cycle termination phone call will be performed. The call is not required if a subject starts a new cycle within the 7 day follow up period. At the conclusion of a cycle, it must be determined if a subject will go into a subsequent cycle or into a 7-day follow-up phase. Additional 6-week treatment cycles with budesonide will be implemented for eligible subjects who experience active UP/UPS symptoms, until regulatory approval of budesonide occurs, or the sponsor decides to terminate the study. See the figure below.

**Figure 4. BFPS3073 Study Design: Schematic**

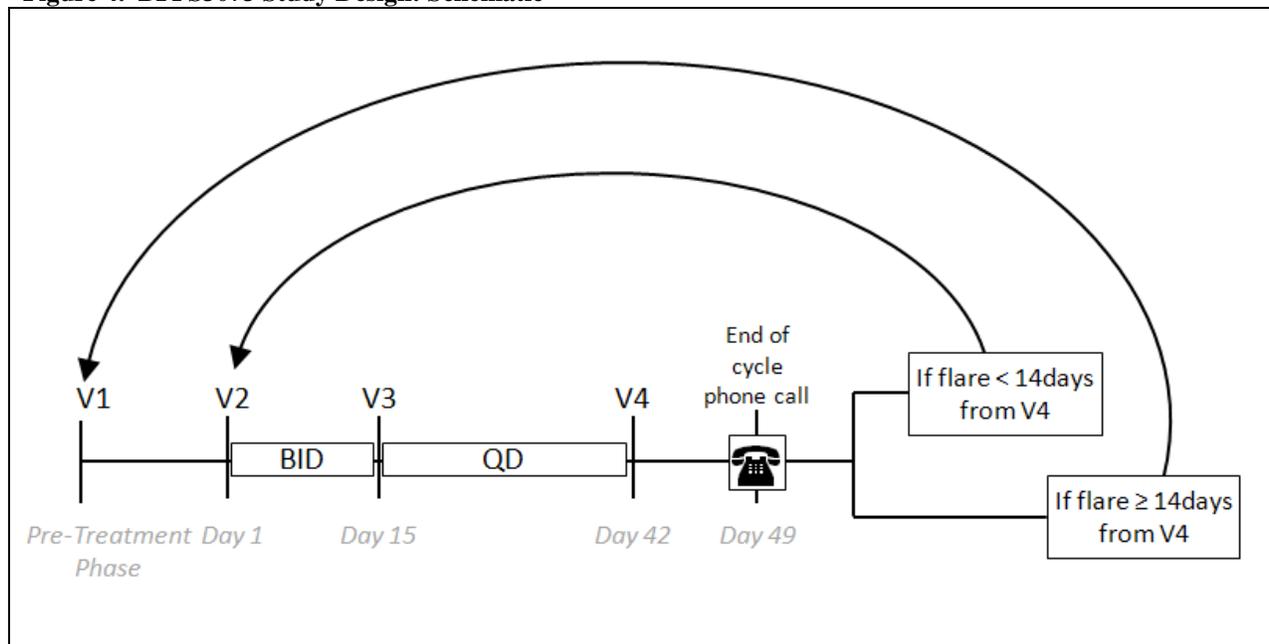
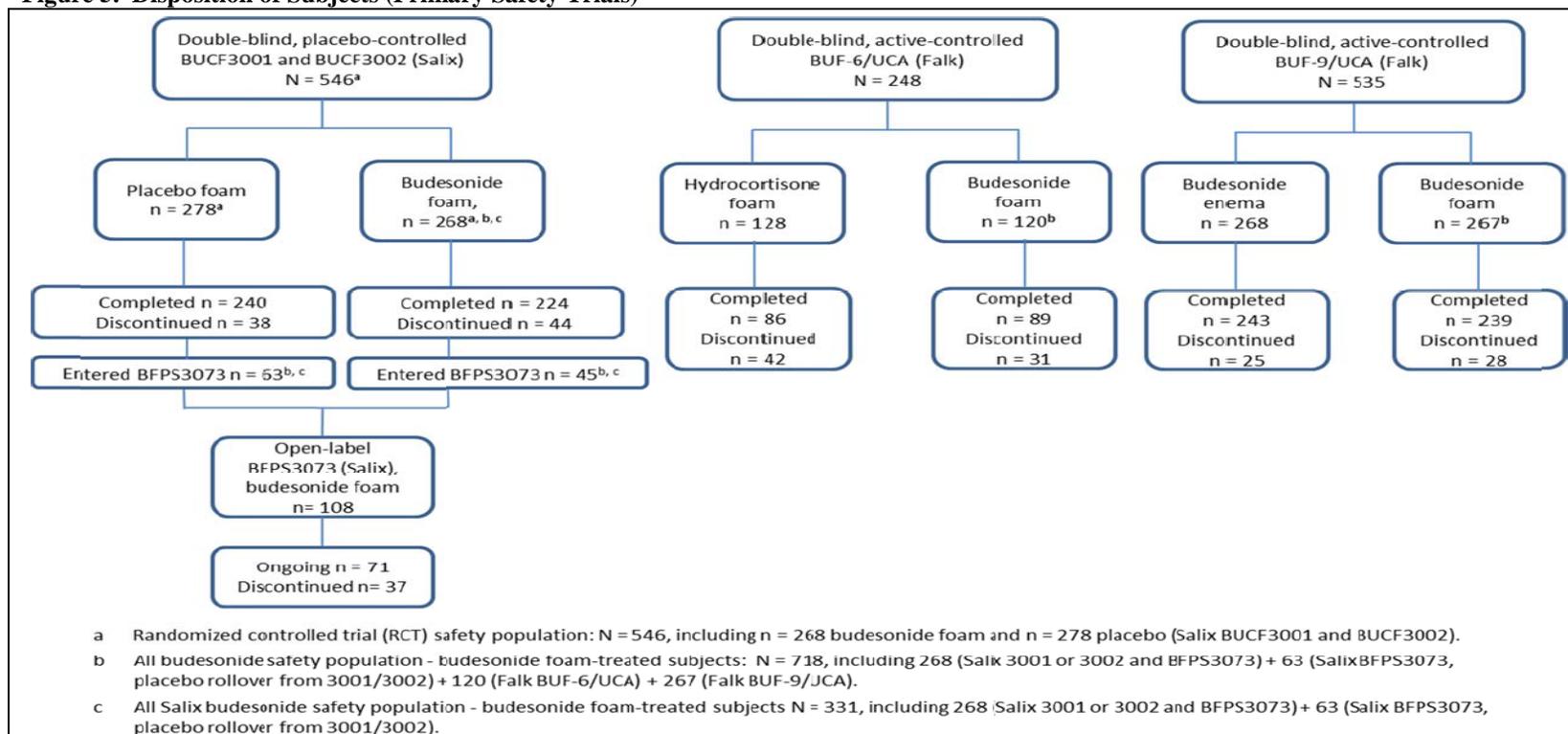


Figure above is taken from Page 26 of the Protocol for Study BFPS3073

## APPENDIX 8: Disposition of Subjects (Primary Safety Trials)

Figure 5. Disposition of Subjects (Primary Safety Trials)



The figure above is taken from Page 72 of the Summary of Clinical Safety.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANIL K RAJPAL  
09/15/2014