CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205613Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	September 15, 2014
From	Andrew E. Mulberg, MD, FAAP, CPI
Subject	Division Deputy Director Summary Review
NDA/BLA # Supplement #	205613
Applicant Name	Salix Pharmaceuticals
Date of Submission	November 15, 2013
PDUFA Goal Date	September 15, 2014
Proprietary Name / Established (USAN) Name	Uceris
Dosage Forms / Strength	emulsion (aerosol foam) / 2 mg budesonide per metered dose
Proposed Indication(s)	induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge (b) (4)
Action/Recommended Action for NME:	**Tentative Approval**

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Zana Marks, MD
CDTL Reviews	Anil Rajpal, MD
Clinical Pharmacology Review	Dilara Jappar, Ph.D. Sue Chih-Lee, Ph.D.
CMC	Tarun Mehta, Ph.D., Marie Kowblansky, Ph.D.
Quality Micro	Vinayak Pawar
CDRH Reviews	Branden Reid Bleta Vuniqi QuynhNhu Nguyen
OSI	Susan Liebenhaut, MD
Nonclinical (DGIEP)	Dinesh Gautam, Ph.D.
QT Review Team	Jiang Liu
Labeling Reviews	Matthew Barlow Meeta Patel Morgan Walker
Statistical Reviewer	Shahla Farrar, Ph.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

Salix has proposed the following indication for Uceris (budesonide) 2 mg rectal foam:

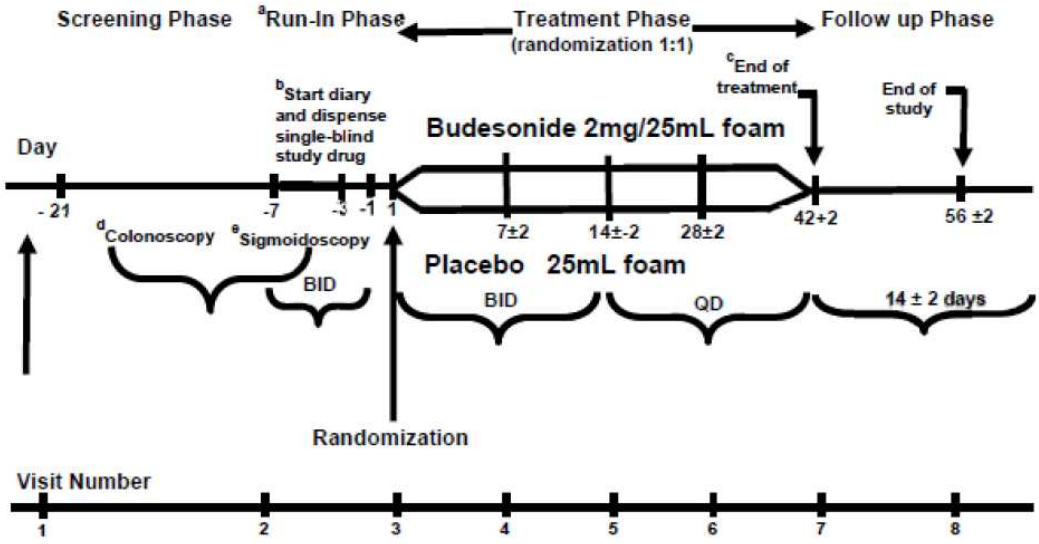
> 1) Budesonide 2 mg rectal foam is indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge

Budesonide 2 mg rectal foam (Uceris) contains a synthetic corticosteroid with topical anti-inflammatory properties, weak mineralocorticoid activity, and undergoes substantial first-pass elimination. This extensive first-pass metabolism by the liver may ensure little systemic availability, which may result in less glucocorticoid (GCS)-related side effects compared to conventional systemically available steroids. The rectal formulation is provided as an emulsion which is filled into an aluminum can with an aerosol propellant. In this New Drug Application (NDA), the Applicant pursues the approval of budesonide with labeling for "…the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge." This is a 505(b)(2) application based onThis 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).

Studies used to support registration have included BUCF 3001 and BUCF 3002 are replicate phase 3, multicenter, randomized ,double-blind, placebo-controlled studies designed to assess the efficacy and safety of budesonide 2 mg rectal foam (BID dosing for 2 weeks followed by QD dosing for 4 weeks) versus placebo in subjects with active mild to moderate UP or UPS. Both studies were planned and conducted as identical trials. They shared the same protocol design, were conducted concurrently in the US and Russia, and utilized the same data acquisition tools. In both Studies BUCF 3001 and BUCF 3002, the subjects were randomized to receive study treatment in a 1:1 ratio.; either 2 mg budesonide foam BID for 2 weeks followed by 2 mg QD for 4 weeks, or placebo foam BID for 2 weeks followed by placebo foam QD for 4 weeks.

Figure 1 presents an overview of the study design for both studies:

Figure 1: Study Flowchart for Pivotal trials



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

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

Other studies used to support the registration of Uceris 2 mg recal foam are illustrated below in Table 1, Completed Studies:

Table 1: Completed Studies

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

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

This Summary review will discuss the sufficiency of evidence of clinical benefit supported by the data in this application to establish that Uceris 2 mg rectal foam is effective and safe for the treatment for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge. My review will focus on the salient issues related to this risk/benefit assessment.

2. Background

Ulcerative proctitis (UP) is defined as a chronic inflammatory process limited to the rectum. The diagnosis of UP has been defined endoscopically as rectal mucosal inflammation extending up to, but not beyond, 15 cm proximal to the dentate line, normal-appearing mucosa proximal to the edge of inflammation, and histology compatible with idiopathic proctitis, including distorted crypt architecture or other features of chronicity, lamina propria

inflammation, crypt abscess, and neutrophils in the surface epithelium. The presence of a granuloma on rectal biopsy or perianal disease such as fissure or tags would suggest Crohn's disease and exclude a diagnosis of ulcerative proctitis. Appropriate stool cultures exclude identifiable enteric pathogens as a cause of symptoms. Grossly and histologically normal mucosa proximal to 15 cm from the dentate line is used to confirm a diagnosis of ulcerative proctitis as documented by flexible sigmoidoscopy or colonoscopy and biopsy.[1]

It is generally considered to represent one clinical variant of ulcerative colitis, and in studies of adults constitutes ≈20-35% of newly diagnosed cases of ulcerative colitis[1]. In contrast to more extensive ulcerative colitis, ulcerative proctitis is thought to follow a more benign course with less severe symptoms and a decreased propensity to develop cancer. Hyams has further noted that initially diagnosed UP often extends proximally and involves more medication as time progresses. This observation has been reported in studies of adults in that proximal extension with more significant colonic involvement may occur in 10-30% of subjects, and may occur either early or late after diagnosis. Topical medication with rectally administered 5-aminosalicylic acid (5-ASA) and corticosteroid suppositories or enemas are considered effective treatment for most UP patients. The combination of topical 5-ASA and oral 5-ASA or topical steroids is considered for escalation of treatment. 5-ASA suppositories are suggested as first-line maintenance therapy if accepted by patients, although oral 5-ASA as maintenance therapy might prevent proximal extension of the disease. After re-assessment, chronically active patients refractory or intolerant to 5-ASAs and corticosteroids may require immunomodulators or biological therapy. Exceptional cases may require a proctocolectomy.

The pathophysiology of UP is believed to be the same in adults and pediatric patients. The mechanism of action of products including mesalamines and steroids in UP is local and does not require systemic metabolism.

The Modified Mayo Disease Activity Index used in these clinical trials referred to as the MMDAI is unique in several aspects of disease activity scores but does have the components characterized in the formal Mayo Score as well as variant forms like the Sutherland discussed below. These include endoscopic subscore, rectal bleeding, stool frequency and Physician Global assessment (PGA)-see Table 2 below. 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. In contrast to the UCDAI, for example, also referred to as the Sutherland Index, the UCDAI developed by Sutherland is a series of qualifiers about the symptoms of ulcerative colitis including stool frequency, rectal bleeding, the appearance of the lining of the colon, and a physician rating of disease activity[2]. Each of these items is given a number from 0 to 3, with 3 being the highest rating for disease activity. In

[1] *Hyams J, Davis P, Lerer T et al . Clinical Outcome of Ulcerative Proctitis in Children.* J Pediatr Gastroenterol *N*utr;1997;25:149-152

[2] Sutherland LR, Martin F, Greer S et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987 Jun;92(6):1894-8.

clinical trials in adults, remission is often defined as a UCDAI score of 1 or less, and improvement is a reduction of 3 or more points from the score at the beginning of the trial.[3]

In the MMDAI it is very likely that the presence of friability in a higher subscore of endoscopy mandates a higher subscore for minimal disease. This issue will be discussed below.

Table 2: Modified Mayo Disease Activity Index (MMDAI)

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

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

3. CMC

The reader is referred to the CMC review of Tarun Mehta, Ph.D dated September 5, 2014 for complete information. The CMC Review noted certain issues that required clarification, specifically related to the Valve and Metering Head Materials of Construction, and Duration of Contact with Drug Product. 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, the CMC reviewer did not find the leachable studies for the applicator necessary.

Other issues related to the formulation content uniformity as the Delivered Dose Uniformity for Budesonide 2 mg Rectal Foam Lot Prepared as Directed in QCTP-278 (b) (4) As noted by

[3] http://ibdcrohns.about.com/od/Glossary/g/Ulcerative-Colitis-Disease-Activity-Index-Ucdai htm

Dr. Mehta, "The samples analyzed using in house method (QCTP 278) at (b) (4), show the consistent results for all actuations except one outlier and meet the specification and USP <601> criteria. However, when the samples were analyzed using patient label instruction (USP <601>); the results were inconsistent and the mean assay value was law (b) (4)%), overall results did not meet the USP <601> requirement. These results were discussed within the review team for this application. Based on the discussion it was concluded that the applicant has to provide more data to (1) negate the doubt of inconsistent dosing when used by patients in real life and (2) the priming of the canister is needed or not because the first actuation result for 4 out of 5 canister showed the failure.) A meeting to discuss the conflicting results from the extra five canisters and consistent lower % label claim for the first actuation was discussed with the clinical team to provide their concern of efficacy and safety risk of the drug product due to inconsistent dosing (range from (b) (4)% to (b) (4)%). After the discussion it was decided that the same drug product was used in the clinical setting and had proven efficacious and safe. Therefore, no further action required to explain these data."

The CMC Reviewer recommends approval.

4. Nonclinical Pharmacology/Toxicology

There are no new nonclinical issues raised with this application reviewed by Dinesh Gautam, Ph.D. The reviewers recommended changes to the Section 8.1 (Pregnancy) to conform to the format of the Proposed Pregnancy and Lactation Labeling Rule (PLLR) and to Section 13 Carcinogenicity. Please see Dr. Rajpal's memorandum.

5. Clinical Pharmacology

Dose ranging studies were performed to justify the current proposed dosing regimen of Budesonide 2 mg BID for 2 weeks followed by 2 mg QD for 4 weeks. Support for these recommendations is derived from appropriately performed Phase 2b and current Phase 3 Studies. Briefly, the Phase 2b dose finding study (BUF-5/UCA) in which 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. Further details are discussed in Clinical Pharmacology review summary of Dr. Jippar.

In terms of suppression of the hypothalamic-pituitary axis, commonly observed with Uceris 9 mg capsules and other steroid formulations, the issue is somewhat different for this Uceris formulation under review. As noted in Dr. Rajpal's review, the percentages of patients with normal response to ACTH challenge by treatment group (combined data from the two trials) were as follows:

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%

These data support that Uceris 2 mg rectal formulation is also associated with short-term HPA suppression. The Clinical Pharmacology reviewer recommended Approval.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this supplemental application because the product is not an antimicrobial product.

7. Clinical/Statistical-Efficacy

The reader is referred to the Clinical review of Dr. Marks and the CDTL memorandum of Dr. Rajpal for further details. I will focus on specific issues relevant to the approval of this NDA.

a. Assessment of Disease activity in Ulcerative proctitis and Ulcerative proctosigmoiditis and Definition of Remission:

There are a number of different UC disease activity indices that have been approved for labeling of products for the management of UC including the Mayo Score of Disease activity, Sutherland Index and variant forms of each. In this NDA the clinical endpoint definition is described by the use of the Modified Mayo Disease Activity Index (MMDAI). The components of this score are delineated above in **Table 2**. Inclusion criteria for subjects in both pivotal trials, BUCF3001 and 3002 included baseline MMDAI score between 5 and 10, inclusive. Subjects must score ≥2 on the MMDAI rectal bleeding component and ≥2 on the MMDAI endoscopy or sigmoidoscopy component. The most important clinical characteristics in these presentations of Ulcerative colitis focus on rectal bleeding and endoscopic disease activity. Diarrhea is a prominent clinical sign as well in this disease. The remission definition for both trials included components of an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in stool frequency sub scales of the MMDAI at the end of 6 weeks of treatment or withdrawal. These are further described below in **Table 3**:

Table 3: Primary and Secondary Endpoints of Studies BUCF3001 and BUCF3002

Endpoint	Definition
Primary:	Proportion of subjects who achieve remission defined as an endoscopy score of ≤ 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 achieves a rectal bleeding MMD AI sub scale score of 0 during the treatment phase (Weeks 1 through 6).
3rd Ranked Secondary:	Proportion of subjects who achieve an endoscopy MMD AI subscale score of 0 or 1 at the end of six weeks of treatment or withdrawal.

Table 4 below reflects the results of the clinical trials noting several important features of remission characteristics and results. It is clear that there is benefit in the responder groups who achieved clinical remission but a very large percentage of patients were nonresponders (74% and 62% in placebo and Budesonide Foam treatment groups). This lack of clinical remission was manifested in all three parameters of the remission definition with the lack of

Table 4: Primary Endpoint: Remission* (Studies BUCF3001 and BUCF3002) (ITT Populations; LOCF Analysis)

*Remission defined as an endoscopy score of ≤ 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.

	Study BUCF3001				Study BUCF3002			
Efficacy Endpoint	Placebo N=132 n (%)	Budesonide Foam N=133 n (%)	p-value[a]	p-value[b]	Placebo N=147 n (%)	Budesonide Foam N=134 n (%)	p-value[a]	p-value[b]
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)		

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.

achievement of a MMDAI Endoscopy score of 0 or 1, MMDAI Rectal Bleeding score of 0 and improvement of no change from baseline in MMDAI Bowel frequency score. From the data analysis in Table 3, it appears that the most difficult clinical component to remit is the rectal

bleeding, and endoscopy subscsores. This doesn't make clinical sense in that bleeding should be reflected in the endoscopy subscore. From the additional analyses, concomitant oral 5-ASA use at baseline 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 (reference Table 7, Dr. Rajpal, and CDTL memorandum). In regards to other baseline disease characteristics, including 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 5** below). Other Baseline Disease Characteristics are pictured below in Table 5 which apparently does not offer clear etiologies for the discrepancy in low remission rates between placebo and active treatment.

Table 5: Baseline Characteristics in Pivotal Clinical Trials

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
Extent of Disease – n (%)[f]				
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)
Normal Number of Stools per Day[a]				
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)
Type of Disease – n (%)				
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)
Duration of Disease (years)				
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)

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

a The question asked was "Think back to a time when you were not suffering from your most recent flare of Proctitis/Proctosigmoiditis. What was the normal number of bowel movements you had in a 24-hour period?"

For the normal bowel movement calculation (ie, when no UP/UPS symptoms were present), a bowel movement represented when stool was passed. Table is reproduced from CDTL memorandum

Table 6 demonstrates that the disease severity does imply a potential relationship to efficacy remission as the moderate disease activity reflected by higher MMDAI scores trends higher to remission than the mild disease activity. These data are further supported by an analysis of the extent of disease classified as more proximal or extending more distal, as proctosigmoiditis or proctitis (**Table 7**, below). It is clear that the trend towards higher remission rates is correlated with extent of disease activity, with the extent of disease a characteristic that likely is clinically

important. It is interesting to also note that the placebo responders are also higher in the more extensive disease category which remains unclear to this Signatory.

Table 6: Analysis of the Primary Endpoint by Disease Severity

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

Source: Reviewer

Reproduced from Statistical Review, Dr. Farrar

Table 7: Analysis of the Primary Endpoint by Disease Severity

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

Reproduced from Statistical Review, Dr. Farrar

In toto, I agree with the reviews and recommendations of the Statistical reviewer, Dr. Farrar, and the CDTL, Dr. Rajpal who recommend approval of this NDA based upon two statistically significant trials demonstrating efficacy of Budesonide rectal foam (b) (4)

8. Safety

Overall, the safety profile of Budesonide rectal foam supports an approval recommendation. The safety profile of the Uceris Rectal foam is akin to that observed with the Uceris oral formulation of budesonide. Budesonide and synthetic glucocorticosteroid products are generally associated with the following adverse reactions, Warnings and Precautions as identified in the current labeling. Adverse reactions typical of systemic glucocorticosteroids include adrenal suppression, sleep and mood disturbance, acne, striae, hirsutism, proximal myopathy, glucose intolerance, hypertension, narrow angle glaucoma, cataracts, bone loss, aseptic necrosis and reduced growth velocity. These adverse reactions are generally dependent on dose, treatment time, concomitant and previous glucocorticosteroid intake, and individual

sensitivity. Other adverse reactions reported in clinical trials include dyspepsia, muscle cramps, tremor, palpitations, blurred vision, skin reactions, menstrual disorders, hypokalemia, and behavioral changes.

From the review of safety, data associated Total AE's leading to Discontinuation and AE's Leading to Discontinuation in > 1 Subject reported for patients in the primary analysis group are presented in **Table 8** below:

Table 8: 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 (%)
Total [n (%)]	12 (4%)	26 (10%)
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 adrenocorticotropic hormone (ACTH).
Numbers of AEs in the table above are taken from Pages 108-111 of the Summary of Clinical Safety.
Data table reproduced from CDTL memorandum, Dr. Rajpal.

Table 9 below reflects on the commonly observed potential glucocorticoid related effects which do not reflect any new adverse events associated with this molecule.

Table 9: All Budesonide Population: Potential Glucocorticoid Related Effects

Adverse Event	Budesonide Foam N=718 n (%)	Budesonide Enema N=268 n (%)
Blood cortisol decreased*	58 (8.1%)	0
Adrenal insufficiency#	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 adrenocorticotropic hormone (ACTH).
Numbers of AE's in the table above are taken from Pages 119-120 of the Summary of Clinical Safety.
Data table reproduced from CDTL memorandum, Dr. Rajpal.

For further review of the safety issues, the reader is referred to Dr. Marks' Clinical review.

I agree with the approval recommendation based on review of the Safety of Uceris Budeosnide Rectal foam in this population.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application as there were no decisional issues that required input from the Advisory Committee during the review cycle.

10. Pediatrics

This application concerns an orphan indication and therefore the Sponsor is not bound by PREA regulation.. The local action of the drug is expected to be the same in children as in adults. Although the treatment effectiveness of Uceris Rectal foam might be able to be extrapolated from the adult indication to the pediatric patients due to disease pathology being the same in both age groups and the same mechanism of action of the drug, one cannot extrapolate an effective pediatric dosage for a topically acting drug from adult studies. The rectal foam formulation is predominantly locally acting and systemic absorption is not needed for efficacy; nonetheless, a dose ranging trial evaluating smaller dosages stratified by age with drug-exposure information could have yielded useful prescribing information for patients, especially in the younger age cohort. Oral mesalamines are not approved for use in pediatric patients with inflammatory bowel disease. Both the oral and suppository mesalamines act by "local action." It is likely that various dosages based on body size or age that account for systemic exposures would be important to understand the comparison to adult systemic exposure for understanding safety and tolerability with Uceris rectal formulation. Efficacy is determined by the impact on altering mucosal inflammation and cannot be extrapolated by systemic exposure of the molecule and therefore requires a clinical efficacy endpoint. It should be noted though that adolescents would be a suitable first population akin to the adult population based on colonic length and potential for improvement. The study of younger children with UP and proctosigmoiditis could be done sequentially. The Sponsor has agreed to a PMC for a pediatric study which is described below

11. Other Relevant Regulatory Issues

A. DSI audits

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 Dr. Marks' summary).

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.

B. Financial disclosures
No active issues

C. 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:

> "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."

These issues therefore result in a tentative approval as discussed below in Section 13.1.

D. **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 Vuniqi, and CDRH Human Factors Consult Review by QuynhNhu Nguyen and the CDTL memorandum. All reviewers recommend approval of the sNDA and all issues are approvable.

12. Labeling

Labeling reflects changes to the following sections of the label which the reader is referred to the approved labeling for further details. The specific issues are cited below as summarized by Dr. Rajpal:

- 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 (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.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action:

All of the review divisions recommended an Approval for which gained concurrence from the Clinical reviewer and CDTL. I agree with the recommendations from these disciplines for Tentative Approval for Uceris (Budesonide) rectal foam for the indication proposed for (b) (4) 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"). 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.

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.

13.2 Risk Benefit Assessment:
I have concluded that the data in these submissions do reflect a risk and benefit supporting the proposed use of Uceris for management in adults.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
There are no requirements for postmarketing risk evaluation and mitigation strategies.

Recommendation for other Postmarketing Requirements and Commitments:

1) 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 HPA axis will be assessed.

    Final Protocol Submission: 4/2015
    Trial Completion: 1/2018
    Final Report Submission: 4/2018

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/s/

ANDREW E MULBERG
09/15/2014
Deputy Director Summary review