CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203634Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	January 14, 2013
From	Anil Rajpal, MD, MPH, Clinical Team Leader Division of Gastroenterology and Inborn Errors Products
Subject	Cross-Discipline Team Leader Review
NDA/ BLA Supplement #	NDA 203634
Applicant	Santarus, Inc.
Date of Submission	December 14, 2011 (submitted) / December 16, 2011 (received)
PDUFA Goal Date	January 16, 2013 (includes 3-month extension due to Major Amendment)
Proprietary Name / Established (USAN) names	Uceris® / budesonide
Dosage forms / Strength	9 mg tablet
Proposed Indication	Induction of remission in patients with mild to moderate UC
Recommended Action:	Approval

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1. Introduction

This submission, received December 16, 2011, is the initial New Drug Application (NDA) for Uceris (budesonide), a synthetic corticosteroid with a high glucocorticosteroid activity and a substantial first-pass elimination. The Applicant is Santarus, Inc.

The Applicant proposes the following indication:

"… for induction of remission in patients with active mild to moderate ulcerative colitis."

The proposed product is an extended-release tablet. The proposed dose is 9 mg orally once daily (QD).

This is a 505(b)(2) application. Entocort EC (NDA 21-324) is the reference drug.

All the review disciplines recommend in favor of approval.

2. Background

2.1 Regulatory History

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

Table 1. Pertinent Regulatory History of Uceris (NDA 203634)*

Date	Event
June 8, 2006	Pre-IND / Pre-Phase 3 Meeting
November 30, 2007	Initial IND Submission / Special Protocol Assessments (SPAs) ▪ Study CB-01-02/01 ▪ Study CB-01-02/02
January 25, 2008	SPA No Agreement Letters sent
March 7, 2008	Meeting to discuss responses in SPA No Agreement Letters
April 13, 2010	Meeting to discuss Statistical Analysis Plans (SAPs)
May 31, 2011	Pre-NDA Meeting
December 16, 2011	NDA Submission received

*IND 74882

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:
- Dose: The Division recommended a dose exploration study. Agreement was not reached on the proposed Phase 3 dose.
- Treatment Duration: The Division advised the Sponsor that although the proposed indication is "induction of remission", the studies should be extended in order to provide data after a longer duration of treatment.

(2) SPAs: Agreement was not reached on the SPAs. However, the following recommendations were provided to the Sponsor [see SPA No Agreement Letters (January 25, 2008) and Meeting Minutes (March 7, 2008)]:

- Dose Exploration Plan: The Division stated that an acceptable approach would be to include dose exploration in both Phase 3 studies, but commented that it may be more efficient to do dose exploration in a smaller Phase 2 study.
- Treatment Duration: The Division stated that an eight week treatment duration appeared reasonable, but recommended the conduct of a smaller Phase 2 study in order to estimate the rate of onset of activity.
- Definition of Remission: The Division recommended that the definition for remission include the requirement that there be a finding of no friability on endoscopy.

(3) Meeting to Discuss SAPs and Pre-NDA Meeting: The following comments were communicated to the Sponsor (see April 13, 2010 and May 31, 2011 Meeting Minutes):

- Primary Endpoint Definition: The Division discouraged the Sponsor from changing the primary endpoint definition while the study is underway; the Sponsor agreed to use the original primary endpoint definition.
- Primary Analysis Population: The Division stated that the primary analysis population would be the ITT population, but the proposed analysis populations (i.e., exclusion of 50 patients with GCP violations, and exclusion of patients with normal histology at baseline) would be considered during the NDA review.

It should be noted that there was a change of sponsor from Cosmo Technologies, Ltd. to Santarus, Inc. on February 6, 2009.

See the Clinical Review by Marjorie Dannis for details of the Uceris regulatory history.

2.2 Current Application

The application was submitted on December 14, 2011, and received on December 16, 2011. It was classified as a ten-month submission with a PDUFA deadline of October 16, 2012. Because of a major amendment received on August 3, 2012, the PDUFA date was extended to January 16, 2013.

No Advisory Committee meeting was convened to discuss this application.

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

(1) Clinical Review by Marjorie Dannis, dated December 12, 2012
(2) Statistics Reviews:
  (a) Primary Statistics Review by Milton Fan, dated December 21, 2012
  (b) Secondary Statistics Memo by Mike Welch, dated December 31, 2012
(3) Clinical Pharmacology Review by Dilara Jappar, dated December 19, 2012
(4) Biopharmaceutics Review by Elsbeth Chikhale, dated December 12, 2012
(5) CMC Reviews:
  (a) CMC Review by Raymond Frankewich, dated November 9, 2012
  (b) CMC Addendum by Raymond Frankewich, dated January 14, 2013
(6) Pharmacology/Toxicology Review by Dinesh Gautam, dated October 15, 2012
(7) OSI Clinical Inspection Summary by Susan Leibenhaut, dated December 17, 2012

(8) QT Interdisciplinary Review Team (QT-IRT) Consult Review by Monica Fiszman, dated May 15, 2012
(9) OSI Clinical Inspection Summary by Susan Leibenhaut, dated December 17, 2012
(10) Division of Medication Error Prevention and Analysis (DMEPA) Reviews:
  (a) Label and Labeling Review by Anne Tobenkin, dated April 10, 2012
  (b) Proprietary Name Review by Anne Tobenkin, dated April 16, 2012
  (c) Proprietary Name Review by Denise Baugh, dated July 25, 2012
  (d) Proprietary Name Review by Denise Baugh, dated December 11, 2012
(11) Office of Professional Drug Promotion (OPDP) Labeling Reviews:
  (a) Review of Prescribing Information by Eunice Chung-Davies, dated December 20, 2012
  (b) Review of Patient Labeling by Kendra Jones, dated December 28, 2012
(12) Division of Medical Policy Programs (DMPP) Patient Labeling Review by Latonia Ford, dated December 21, 2012

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

3. CMC

The reader is referred to the CMC Review (dated November 9, 2012) and Addendum (dated January 14, 2013) by Raymond Frankewich, for complete information.

3.1 Overview

3.1.1 Overview of Drug Substance (DS)

The CMC Reviewer noted the following:

- Budesonide used for this drug product is sourced from (b) (4) and manufactured at a facility in (b) (4)
- The description of the manufacture of budesonide is described in DMF (b) (4) held by (b) (4). DMF (b) (4) was evaluated in support of this review. DMF (b) (4) currently is considered adequate to support this NDA.
- The Applicant's specification for budesonide DS is the same as the USP monograph for budesonide, with two more tests added: one for residual solvents (b) (4), and (b) (4); and the other for particle size.

3.1.2 Overview of Drug Product (DP)

The CMC Reviewer noted the following:

- The DP is formulated as a delayed and extended release tablet. It is intended to deliver budesonide directly into the colon and then slowly disperse the budesonide over a period of time. The tablet is coated with an acid-resistant polymer film which breaks down at or above pH 7.0, which is the normal pH in the terminal ileum. The acid-resistant coating allows the tablet to pass through the acidic condition of the stomach without significant decomposition. It is in the ileum where budesonide is released from the tablet core. The

tablet core contains budesonide with specific polymers that provide for the extended release of budesonide throughout the colon.

- The manufacturing process is a [redacted (b) (4)]
- DP specification includes tests for Appearance, Identification, Assay, Content Uniformity, and Degradants of the drug substance. Also included are compendial microbial tests (USP <61>, including the test for E. Coli, and tests for Dissolution and [redacted (b) (4)]. The Dissolution test includes both in an acid and buffer stages, and the buffer stage includes three time points (1, 4, and 8 hrs.) to evaluate the extended-release properties of the drug product.
- Two packaging presentations are proposed: a 30-count HDPE bottle and a physician sample blister pack.
- Stability data through 24 months storage is provided for samples of three (3) commercial batches of drug product, Data are provided for storage at both the ICH Controlled Room Temperature conditions (CRT) (25^0C / 60% RH) and ICH Accelerated conditions (40^0C / 75% RH). Statistical analysis was performed for the CRT storage condition for Assay, three of the four specified degradation products, Total Impurities, and Buffer Stage Dissolution at two time points (4 hrs. and 8 hrs.). Based on the submitted data, the proposed expiration dating period of 30 months for both proposed package presentations is granted.
- The DP is described as a delayed and extended release tablet in the Description section of the labeling, which is correct, but it will be designated as extended-release tablets in the labeling per ONDQA policy.

3.2 Issues

3.2.1 CMC Review

The CMC Reviewer noted the following unresolved deficiencies (in the CMC Review dated November 9, 2012):

A. Regarding the drug product

The test and acceptance criteria for dissolution are not satisfactorily established as of this review, pending completion of the Biopharmaceutics Review.

B. Regarding label/labeling

The following comments will be reflected in the draft labeling in the e-room, and will be sent to the applicant during the labeling negotiation.

1. The first two sentences of the Description section should be changed to read as follows: "UCERIS (budesonide) Tablets 9 mg contain budesonide, a synthetic corticosteroid, as the active ingredient. Budesonide is designated chemically as…"

2. The second sentence of the second paragraph of the Description section should read as follows: [redacted]

3. The second and third sentences of the third paragraph of the Description section contains language that is redundant. The second sentence should be changed to read "The tablet is coated with a polymer film, which breaks down at or above pH 7.0, [redacted] where budesonide then begins to be released from the tablet core". The third sentence should be changed to read: "The tablet core contains budesonide with polymers that provide for extended release of budesonide [redacted].

4. Dosage form and route of administration are not specifically expressed in the Description section. It appears the most appropriate place to put such an expression in the proposed PI is in the first sentence of the fourth paragraph. This sentence should be changed to read as follows: [redacted]

In addition to the above two deficiency items, the CMC Reviewer noted a third deficiency item: The facility intended to [redacted] budesonide DS has not yet been declared "Acceptable" by the Office of Compliance (at the time of the CMC Review). (The [redacted] facility is [redacted].)

3.2.1 Addendum to CMC Review

The CMC Reviewer noted the following (in the Addendum to the CMC Review):

Item A: Item A above has been resolved. In a teleconference on December 11, 2012, the Applicant was requested to submit the following information:

- Identification of the stability data sets that would have required USP <711> testing beyond Stage [redacted]
- Statistical analysis of current stability data against the four (4) hour dissolution time point acceptance criteria of [redacted]
- Proposal for expiry period based on updated analysis with revised dissolution acceptance criteria.

The Applicant submitted an amendment on December 12, 2012 that adequately addressed each of the items in this request. The CMC Reviewer noted that the Applicant accepted the dissolution acceptance criteria recommended by the ONDQA Biopharmaceutics group (see Section 5.1.2 of this CDTL Review), and submitted a revised drug product specification (see Addendum to CMC Review). The CMC Reviewer also noted that the expiration period of 30 months proposed for this drug product appears to be appropriate, even with the revised acceptance criteria for the Dissolution test, and that this conclusion is based on the following:

- Statistical analysis for pooled stability data collected using the HDPE bottle configuration (the one intended for commercial distribution) identifying a 37-month expiration date.
- Statement in the ONDQA Biopharmaceutics Review indicating that, in the authors' opinion, it can be expected based on the provided data that the stability batches would

have passed stage (b) (4) testing and occasionally stage (b) (4) testing using the newly agreed upon 4 hour buffer stage acceptance range of (b) (4)
The CMC Reviewer also noted that none of the samples tested in Stage 1 at the 36 month time point failed; that is, none of the samples stored in either package configuration for 36 months would have required testing beyond Stage 1.

Item B: All of the label revisions in Item B above have been resolved.

Inspection of (b) (4): The Office of Compliance issued an overall "Acceptable" recommendation on January 2, 2013.

3.3 Recommendation

Although the CMC Review noted that there were deficiencies identified in the NDA that precluded approval of this application, the Addendum to the CMC Review noted that those deficiencies had been resolved, and recommends approval.

4. Nonclinical Pharmacology/Toxicology

4.1 Issues

The reader is referred to the Nonclinical Pharmacology/Toxicology Review by Dinesh Gautam, dated October 15, 2012, for complete information.

The Nonclinical Reviewer noted the following key findings:

- This 505(b)(2) NDA is supported by reference to the Agency's previous findings of safety and available information on the toxicology of budesonide.
- The Applicant provided published literature on the pharmacology and pharmacokinetics of budesonide. The published studies showed that budesonide is an effective anti-inflammatory agent through modulation of translation of NF-κB. Budesonide also causes inhibition of cytokine release from MHC-1. Cytochrome P450 3A (CYP3A) plays a key role in the metabolism of budesonide.
- A 28-day repeated dose oral toxicity study in Cynomolgus monkeys was conducted as per the Agency's recommendation. There were no overt clinical reactions or serious toxicity in monkeys treated orally with budesonide at 18 mg/day once daily for 28 days.
- Budesonide was not genotoxic 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 and the mouse micronucleus test.
- Carcinogenicity studies with budesonide were conducted in rats and mice.
  - 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. Budesonide had no effect on fertility in rats at subcutaneous doses up to 80 µg/kg. 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 a subcutaneous dose of 20 µg/kg. No such effects were noted at 5 µg/kg.

The Nonclinical Reviewer recommends an Approval action based on the non-clinical review of the information submitted in the NDA.

The Nonclinical Reviewer agreed with the Applicant's proposed labeling for the following sections:

- Section 8.1 of Label (Pregnancy)
- Section 13.1 of Label (Carcinogenesis, Mutagenesis, Impairment of Fertility)

The Nonclinical Reviewer concluded that the following section is not required and should be deleted.

- Section (b) (4)

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 Issues

5.1.1 Clinical Pharmacology

The reader is referred to the Clinical Pharmacology Review by Dilara Jappar, dated December 19, 2012, for complete information. The following is summarized from the Clinical Pharmacology Review.

Dose Selection Rationale:

The Clinical Pharmacology Reviewer noted that one Phase 2 dose-finding study (using Uceris 3 mg and 9 mg) and two Phase 3 studies (using Uceris 6 mg and 9 mg) have demonstrated that the 9 mg dose was more efficacious compared to 3 mg or 6 mg based on the numerical comparison of measured efficacy assessments. The Clinical Pharmacology Reviewer commented that those studies were not powered to detect a statistical difference between 3 mg vs. 9 mg or 6 mg vs. 9 mg.

Single-Dose PK (based on Study CRO-PK-06-178):

Following single oral dose administration of Uceris 9 mg under fasted condition in healthy subjects, C_{max} was 1348.8 ± 958.8 pg/ml, AUC_{0-t} was 13555.9 ± 7816.9 pg.h/ml, $AUC_{0-\infty}$ was 16431.2 ± 10519.8 pg.h/m, and T_{max} was 13.3 ± 5.9 hours. The pharmacokinetic (PK) parameters of Uceris 9 mg have a high degree of variability among subjects with a CV ranging from 45% to 71%. In plasma concentration vs. time profile, there appears to be double peaks (based on both the mean profile and individual profiles) following single oral dose administration of Uceris 9 mg, occurring around 6 hours and 16 hours post-dose, respectively. Although the double peaks were observed in the majority of the subjects, these were not always present in all of the subjects.

Multiple-Dose PK (based on Study CRO-PK-03-105):

Following 7 days of oral dosing of Uceris 9 mg, the coefficient of accumulation was Css_{max}/C_{max} = 0.87 ± 0.51, AUC_{ss}/AUC_{inf} = 0.82 ± 0.47, and AUC_{ss}/AUC_{0-24} = 1.135 ± 0.6925, where AUC_{ss} was AUC_{0-tau} where 0-tau is 0-24 hours at steady state, indicating the absence of budesonide accumulation following multiple dose administration of Uceris 9 mg.

Relative Bioavailability (based on Study CRO-PK-06-178):

Relative bioavailability of Uceris 9 mg was compared with the reference product Entocort EC 3x3 mg. Uceris 9 mg has comparable exposure, but different PK profile compared to the reference product Entocort EC. AUC was 13555.9 ± 7816.9 and 13394.6 ± 5983.0, C_{max} was 1348.8 ± 958.8 and 1555.9 ± 588.0 for Uceris 9 mg and Entocort EC 3 x 3 mg, respectively. These two products are not statistically bioequivalent with respect to both rate (C_{max}) and extent (AUC) of budesonide absorption. In plasma concentration vs. time profile, Entocort EC appears to have one peak whereas the Uceris 9 mg appears to have double peaks, where the first peak is close to the T_{max} of the reference product Entocort EC.

Food Effect (based on Study CRO-PK-03-105):

The effect of food on absorption of Uceris 9 mg was studied following single dose administration of Uceris 9 mg under fed and fasted states. The presence of food increased the absorption lag time (7.4 hr vs. 9.8 hr) and decreased the rate of absorption (4.7 hr increase in t_{max} and 27% decrease in C_{max}). However, effect of food on extent of absorption was small, only by 9% reduction in AUC_{0-t} and 5% reduction in $AUC_{0-\infty}$.

HPA Axis Suppression:

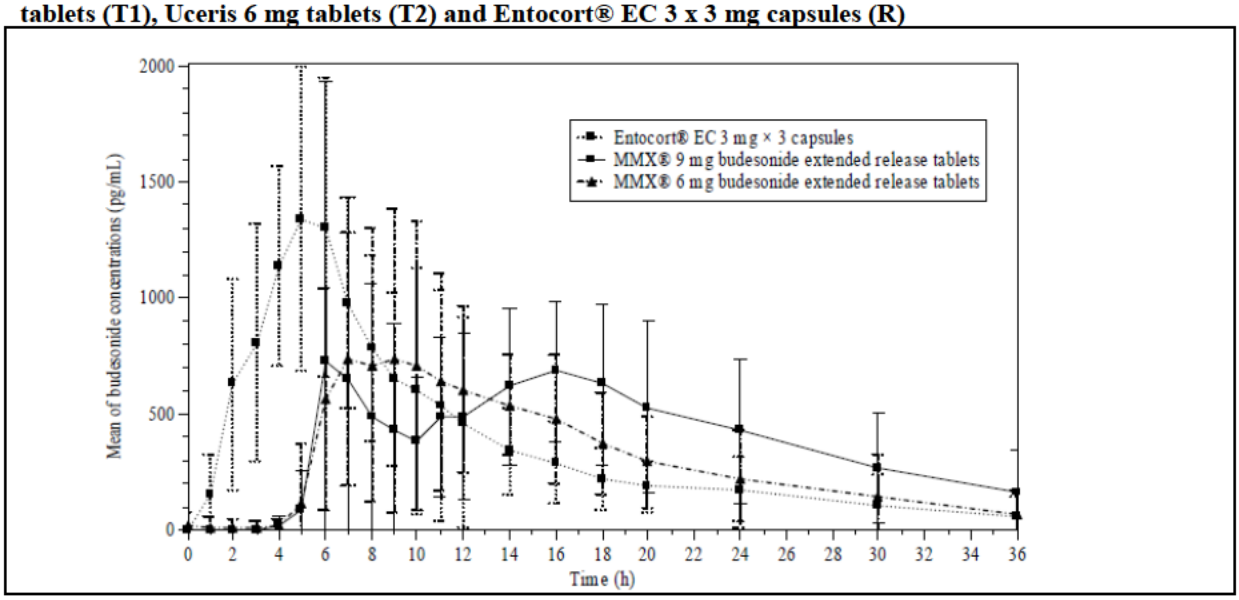
The Clinical Pharmacology Reviewer noted that Uceris 9 mg results in HPA axis suppression were as expected. Forty-seven percent (47%) of patient who were treated with Uceris 9 mg for 4 weeks and 79% of patients who were treated with Uceris 9 mg for 8 consecutive weeks had an abnormal response to the ACTH stimulation test indicating HPA axis suppression.

The Clinical Pharmacology Reviewer commented that compared to the reference product Entocort EC, Uceris 9 mg appears to have higher potential for HPA axis suppression.

However, this is based on a cross-study comparison. The Clinical Pharmacology Reviewer stated that according to the Medical Review for Entocort EC (NDA 21324), 54% of patients who received Entocort EC had an abnormal ACTH response after 8 weeks of treatment; for this duration of treatment in the Uceris 9 mg study, 79% had an abnormal ACTH response. The Clinical Pharmacology Reviewer noted the following limitations to the comparison with the Entocort EC data (in addition to being a cross-study comparison): (1) the study with Uceris 9 mg was based on a very limited number of patients, n= 14. (2) It is possible that the criteria to categorize an abnormal ACTH response differed between the two studies (it is not clear what criteria were used in the Entocort EC study).

The Clinical Pharmacology Reviewer also commented that the possible higher HPA axis suppression potential of Uceris 9 mg versus Entocort EC 3 X 3 mg may be due to the prolonged exposure of budesonide in this new formulation compared to Entocort EC (see figure below).

Figure 1. Mean Budesonide plasma concentration profiles following oral administration of Uceris 9 mg tablets (T1), Uceris 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules (R)



The figure above is taken from the Clinical Pharmacology Review by Dilara Jappar.

The Clinical Pharmacology Review stated "The warning section of the label should include this information." This point was clarified with the Clinical Pharmacology Reviewer; she agreed with the wording in the Warning section of the label about adrenal suppression and was not suggesting that additional information (i.e., comparison to Entocort EC) should be added.

5.1.2 Biopharmaceutics

The reader is referred to the Biopharmaceutics Review by Elsbeth Chikhale, dated December 12, 2012, for complete information.

The focus of the Biopharmaceutics Review is on the following: (1) dissolution method and acceptance criteria; (2) alcohol dose dumping method and data; and (3) extended release claim. The Biopharmaceutics Reviewer's conclusions are summarized below.

Dissolution Method and Acceptance Criteria: The Biopharmaceutics Reviewer noted that the dissolution method and acceptance criteria shown in the table below are acceptable.

Table 2. Dissolution Method and Acceptance Criteria

Product Name	USP Apparatus	Rotation Speed (rpm)	Dissolution Media/ Volume/Temperature	Acceptance Criteria (% Label Claim Dissolved)
UCERIS (budesonide) ER Tablets	USP 2 - Paddle	100 rpm	**Acid Stage:** **500 ml** of 0.1 M HCl containing 0.5%Macrogol Cetostearyl Ether at 37°C **Buffer Stage:** **1000 ml** of phosphate buffer containing 0.5% Macrogol Cetostearyl Ether at 37°C	**Acid Stage:** 2 hours: Not more than (b) (4) **Buffer Stage:** 2 hours : Not more than (b) (4) 4 hours: (b) (4) 8 hours: Not less than (b) (4) Meets USP <711> L1, L2, or L3 as appropriate

Table above is taken from the Biopharmaceutics Review by Elsbeth Chikhale, dated December 12, 2012

In Vitro Alcohol Dose Dumping Study: The Biopharmaceutics Reviewer noted that the results of the *in vitro* alcohol dose dumping study indicate that the presence of 40% ethanol did not significantly alter the release of the drug from the drug product. Thus, the Biopharmaceutics Reviewer concluded that no *in vivo* alcohol dose dumping is expected based on these *in vitro* results.

Extended Release Claim: The Biopharmaceutics Reviewer noted that the extended release claim is acceptable because it is supported by the provided dissolution data.

5.2 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

7.1 Issues

The reader is referred to the Clinical Review by Marjorie Dannis and the Statistics Review by Milton Fan for complete information.

7.1.1 Overview of Studies Submitted

UC Studies CB-01-02/01 and CB-01-02/02:

The table below summarizes the two controlled clinical trials (Studies CB-01-02/01 and CB-01-02/02) submitted in support of the NDA.

Table 3. UC Studies CB-01-02/01 and CB-01-02/02

Study	Region / Country	Design	Population	DB Treatment Period	Treatment Arms
CB-01-02/01	North America and India	R, DB, PC	▪ active mild or moderate UC*	8 weeks	➢ Uceris 6 mg/day (n=126) ➢ Uceris 9 mg/day (n=127) ➢ Asacol 2.4 g/day[#] (n=127) ➢ Placebo (n=129)
CB-01-02/02	Europe	R, DB, PC	▪ active mild or moderate UC*	8 weeks	➢ Uceris 6 mg/day (n=128) ➢ Uceris 9 mg/day (n=128) ➢ Entocort EC 9 mg/day[†] (n=126) ➢ Placebo (n=129)

R: Randomized; DB: Double-blind; PC: Placebo-controlled
* UCDAI ≥ 4 and ≤ 10
[#]Asacol two 400 mg tablets TID
[†] Entocort EC 3 x 3 mg/day

Other Studies:

A full listing of studies (including Phase 1 and 2 studies) is provided in Appendix 1 of this CDTL Review.

It should be noted that a long term (12 month) extension study was conducted (Study CB-01-02/04) that enrolled a total of 123 patients (62 patients receiving Uceris 6 mg QD and 61 patients receiving placebo) with mild or moderate UC in remission status from Studies CB-01-02/01, CB-01-02/02, and CB-01-02/06.

7.1.2 Key Design Features (Studies CB-01-02/01 and CB-01-02/02)

Key design features of Studies CB-01-02/01 and CB-01-02/02 are summarized below.

Key Entry Criteria:

Key entry criteria were a diagnosis of active mild to moderate severity UC with a UCDAI score ≥ 4 and ≤ 10 and suffering from UC for at least 6 months. (See Appendix 2 for the UCDAI scoring system.) Patients were excluded if they used oral or rectal steroids in the last 4 weeks, immunosuppressive agents in the last 8 weeks, or TNFα-antagonists in the last 3 months.

Study Visits / Key Assessments:

Five study visits were scheduled: Screening (Visit 1), Day 1 (Visit 2), and at the end of Weeks 2 (Visit 3), 4 (Visit 4), and 8 (Visit 5/Final Visit).

A colonoscopy was performed at Screening (unless the same procedure was performed within one month prior to screening, and the results were available to the Investigator at that time) and at Visit 5 (Day 56). During colonoscopy, three biopsies were taken from the colonic lesions considered to be most severe. All biopsy evaluations were performed at a single histopathology center by a blinded histopathologist; the Saverymuttu scoring system was used, and the Histological Activity Grade was determined from the total Saverymuttu Score (see Appendix 3). The result of the biopsy was available only after randomization. Patients were considered to have normal baseline histology if all available biopsies from a colonoscopy had a total Saverymuttu score ≤ 1 (corresponding to a Histological Activity Grade of 0). Patients were considered to have active disease only when at least one of the biopsies had a total Saverymuttu score > 1.

UCDAI was assessed at Screening and at Visit 5. The UCDAI is comprised of four components (stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity) (see Appendix 2).

Primary Endpoint:

The primary endpoint was clinical remission after 8 weeks of treatment. Clinical remission was defined as follows:

- UCDAI ≤ 1 with score of 0 for both rectal bleeding, stool frequency, and mucosal appearance; and
- ≥ 1-point reduction from baseline in a separate endoscopy-only score (see Appendix 4).

Secondary Endpoints:

Secondary endpoints were as follows:

- Clinical improvement, defined as a ≥ 3-point improvement in UCDAI from baseline to the end of Week 8
- Endoscopic improvement, defined as a ≥ 1-point improvement in a separate endoscopy-only score (see Appendix 4) from baseline to the end of Week 8

7.1.3 Conduct (Studies CB-01-02/01 and CB-01-02/02)

Dates of Enrollment, Completion, SAP Amendment, and Database Lock:

The dates of enrollment, completion, and database lock are shown below by study[1,2]:

- Study CB-01-02/01:
  - First patient randomized: August 20, 2008
  - Last patient completed: May 28, 2010
  - SAP amendment: July 16, 2010
  - Database lock: September 23, 2010
- Study CB-01-02/02:
  - First patient randomized: July 24, 2008
  - Last patient completed: February 13, 2010
  - SAP amendment: July 16, 2010
  - Database lock: November 4, 2010

Applicant's Proposal to Revise the Primary Analysis Population:

April 13, 2010 Meeting: In the meeting held on April 13, 2010, the Applicant proposed revising the primary analysis population (exclusion of patients with GCP violations from the ITT population) (see Section 2.1 of this CDTL Review). The Division's general response was that the primary analysis population would be the ITT population, but the proposed analysis population would be considered during the NDA review.

July 16, 2010 SAP Amendment: The Clinical Reviewer noted that on July 16, 2010, the Sponsor amended both SAPs, reportedly "prior to database lock and study unblinding." The Sponsor's new ITT population (referred to in the Clinical Review as the "mITT population" and in the Statistics Review as the "Sponsor's ITT population") is defined as follows:

All randomized patients who received one dose of drug but excluded patients who had:

1. No histological evidence of active UC ("normal histology") at Baseline
2. Major entry criteria violations
3. Major GCP violations

Applicant's Rationale for July 16, 2010 SAP Amendment: The Applicant's rationale for the revised primary analysis population is summarized below (full rationale is provided in the Clinical Review):

[1] Dates of enrollment and completion are taken from the Clinical Review by Marjorie Dannis.
[2] Dates of SAP amendment and database lock are taken from the Primary Statistics Review by Milton Fan.

- The protocols were developed in 2007 and early 2008
- EMA issued a Guidance in August 2008 specifying that only patients with confirmed active UC should be included in trials.
- In FDA registration trials such as ACT 1 and ACT 2 for Remicade, the absence of histological inflammation excluded the diagnosis of active UC
- The July 16, 2010 amendment to the SAPs was prior to database lock and study unblinding.
- Exclusion of patients with infectious colitis at study entry was a pre-specified exclusion criterion in the study protocol; exclusion of patients from study sites where GCP violations were identified is consistent with ICH Guidelines.
- Collection of mucosal biopsies at Screening was a prospectively-required procedure in the original Phase 3 protocols. All mucosal biopsies collected in Studies CB-01-02/01 and CB-01-02/02 were objectively reviewed by central histopathology laboratories in blinded fashion. All patients who were discovered to have no histologic evidence of active UC were removed from the primary analysis population prior to database lock and unblinding.

May 31, 2011 Meeting: In the meeting held on May 31, 2011, the Applicant again discussed with the Division their proposal to revise the primary analysis population (exclusion from the ITT population of 50 patients with GCP violations, and exclusion of patients with normal histology at baseline) (see Section 2.1 of this CDTL Review). The Division's general response was again that the primary analysis population would be the ITT population, but the proposed analysis population would be considered during the NDA review.

7.1.4 Patients Excluded from the Sponsor's ITT Analysis Populations (Studies CB-01-02/01 and CB-01-02/02)

The exclusions from the Sponsor's ITT analysis populations are summarized below by study.

Study CB-01-02/01:

The number of patients excluded from the Sponsor's ITT Analysis Population by treatment group and category of exclusion are summarized in the table below.

Table 4. Exclusions from the Sponsor's ITT Analysis Population (Study CB-01-02/01)

Category of Exclusion	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2.4 g	Total
"True" ITT	129	127	126	127	509
Sponsor's ITT* (mITT)	121	123	121	124	489
Patients Excluded from Sponsor's ITT	8 (5.5%)	4 (3.1%)	5 (4.7%)	3 (2.4%)	20 (3.9%)
Infectious Colitis at Entry[#]	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	3 (0.6%)
Normal Histology at Entry[†]	6 (4.7%)	3 (2.4%)	5 (3.9%)	3 (2.4%)	17 (3.3%)

*The Sponsor's ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline.
[#]Infectious colitis at entry was a major entry criteria violation.
[†]Normal histology at entry was defined as all available biopsies from a colonoscopy had a total Sayermattu Score ≤ 1 (corresponding to a Histological Activity Grade of 0) (see Appendix 3)
(Table above is modified from Table 8 on Page 54 of the Study Report for Study CB-01-02/01.)

The Clinical Reviewer noted the following from the table above:

- Normal Histology at Entry or Infectious Colitis at Entry: A total of 20 patients (3.9%) were excluded (17 patients with normal histology at entry, 3 patients with infectious colitis at entry).
- Major GCP Violations: There were no patients with major GCP violations in this study (Study CB-01-02/01).
- Number of Exclusions by Arm: There were slightly more excluded patients from the placebo arm (8) versus the other arms (4, 5, and 3) but the total numbers of patients excluded per arm were small.

Study CB-01-02/02:

The number of patients excluded from the Sponsor's ITT Analysis Population by treatment group and category of exclusion are summarized in the table below.

Table 5. Exclusions from the Sponsor's ITT Analysis Population (Study CB-01-02/02)

Category of Exclusion	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2.4 g	Total
"True" ITT	129	128	128	126	511
Sponsor's ITT* (mITT)	89	109	109	103	410
Patients Excluded from Sponsor's ITT	40 (31.0 %)	17 (13.5 %)	19 (14.8%)	23 (18.3%)	101 (19.8%)
Treated, but not randomized	1 (0.8%)	1 (0.8%)	0	0	2 (0.4%)
Infectious Colitis at Entry[#]	0	1 (0.8%)	0	0	1 (0.2%)
Major GCP Violation	20 (15.5%)	9 (7.1%)	9 (7.0%)	12 (9.5%)	50 (9.8%)
Normal Histology at Entry[†]	33 (25.6%)	12 (9.5%)	16 (12.5%)	16 (12.7%)	77 (15.1%)

*The Sponsor's ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline.
[#]Infectious colitis at entry was a major entry criteria violation.
[†]Normal histology at entry was defined as all available biopsies from a colonoscopy had a total Sayermattu Score ≤ 1 (corresponding to a Histological Activity Grade of 0) (see Appendix 3)
(Table above is modified from Table 8 on Page 55 of the Study Report for Study CB-01-02/02.)

The Clinical Reviewer noted the following from the table above:

- Normal Histology at Entry and Major GCP Violations: Twenty-nine of the 101 excluded patients had both normal histology at baseline and major GCP violations, and are thus included in both categories.
- Infectious Colitis at Entry: There was 1 patient with infectious colitis at entry.
- Major GCP Violations: There were 50 patients with GCP violations enrolled at 4 sites.
- Patients Not Randomized: There were 2 patients not randomized.
- Number of Exclusions by Arm: There appeared to be a disproportionate number of placebo patients excluded (40) compared to the other arms (17, 19, and 23).
- Total Number of Exclusions in Study CB-01-02/02 versus Study CB-01-02/01: The total number of exclusions in Study CB-01-02/02 was higher than in Study CB-01-02/01 (n=101) versus Study CB-01-02/01 (n=20).

Discussion:

The Clinical Reviewer commented that the Sponsor's exclusions were patients whose clinical data would not be appropriate to interpret for the following reasons:

- Patients with histology not consistent with the disease being studied should not be included in the patient population.

- Patients whose data were not reliable should not be included in the study.
- All patient data with these issues were eliminated prior to study unblinding.
- The interpretation of histology slides was performed at a central location and thus represents an objective measure.

Key concerns identified by the Primary Statistics Reviewer included the following:

- Change in the Primary Analysis Populations after Study Enrollment: The Primary Statistics Reviewer concluded that for each study, the sponsor's ITT analysis (based on the exclusion of all patients with normal histology at baseline) should be considered a subgroup analysis that is hypothesis generating (rather than the primary analysis) because the sponsor's ITT analysis population was not "clearly pre-specified"; he noted that for each study, the sponsor's ITT analysis population was pre-specified in the SAP but not the protocol, and although the SAP was finalized before database lock, the sponsor's ITT analysis population was introduced in the SAP after study enrollment.
- Disproportionate Numbers of Placebo Subjects with Normal Histology at Baseline (primarily Study CB-01-02/02): The Primary Statistics Reviewer commented that more patients were excluded from the placebo group compared to the Uceris 9 mg group in Study CB-01-02/01 (5.5% vs. 3.1%) and Study CB-01-02/02 (31.0% vs. 13.5%) (mostly due to normal histology at baseline in Study CB-01-02/02), and concluded that the results from each of the studies (particularly Study CB-01-02/02) may be biased in favor of the Uceris 9 mg group.
- Exclusion of Four Sites with Major GCP Violations (in Study CB-01-02/02): The Primary Statistics Reviewer noted that the exclusion of four sites with major GCP violations contributes to the difficulty in interpretation of results from Study CB-01-02/02.

The Secondary Statistics Reviewer addressed concerns about the change in the primary analysis populations of each study after study enrollment, disproportionate numbers of placebo subjects in Study CB-01-02/02 with normal histology at baseline, and data quality of CB-01-02/02 (as reflected by four sites with major GCP violations).

- Change in the Primary Analysis Populations (Each Study) after Study Enrollment: The Secondary Statistics Reviewer concluded that there does not appear to be a clear potential source of bias that should override the use of the modified ITT analysis population (i.e., the sponsor's ITT analysis population). His rationale included the following: (a) Performing the efficacy analysis on only histology positive subjects is consistent with antimicrobial trials (where this is done in a prospective fashion). (b) A diagnostic test that conclusively identifies the disease would not in theory invalidate the randomization provided the blind was maintained and critical study milestones were well-documented. (c) The sponsor's change to the SAP, although after completion of study enrollment, was made well before database lock and unblinding, and the data management procedures appear adequate.
- Disproportionate Numbers of Placebo Subjects with Normal Histology at Baseline (Study CB-01-02/02): The Secondary Statistics Reviewer concluded that since the primary analysis population excludes subjects with normal histology at baseline, the disproportionate numbers of placebo subjects with normal histology at baseline should not be an issue unless one was convinced that the randomization process was biased, and this does not appear to be the case. He noted the following: (a) Although one would

expect baseline characteristics to be balanced across treatment groups, imbalances occur in trials, and it should not be supposed that any particular imbalance invalidates the randomization or that the randomization process was flawed. (b) The imbalance may have occurred by chance or may suggest other procedural problems (related to the sites with major GCP issues). (c) The sponsor re-examined their randomization process and concluded it functioned as intended.

- Data Quality of CB-01-02/02 (as reflected by four sites with major GCP violations): The Secondary Statistics Reviewer concluded that although the removal of protocol violators from the primary analysis is inconsistent with statistical review practice (protocol violators would typically be removed from a per-protocol data set not an ITT or modified ITT data set), in this case, the site violations are major ones, including missing source data, so removal may be justified. He noted that it cannot be expected that treatment group balances would occur because of the randomization method (centrally controlled in blocks of size 4), and thus removal of sites from the primary analysis may bias the efficacy results; however, he further noted that the treatment difference with or without sites removed was similar (see further discussion in Section 7.1.7 Primary Efficacy Analysis of this CDTL Review).

7.1.5 Demographics and Baseline Disease Characteristics (Studies CB-01-02/01 and CB-01-02/02)

Demographics:

In Study CB-01-02/01, approximately 50% of patients were Caucasian, approximately 34% patients were Asian, 7% were African-American, and 7% were Hispanic. The median age was 42 years (minimum 18 years, maximum 77 years). Approximately 56% of patients were male.

In Study CB-01-02/02, More than 99% of patients were Caucasian. The median age was 44 years (minimum 18 years, maximum 75 years). Approximately 57% of patients were male.

Baseline Disease Characteristics:

Across treatment groups in both Studies CB-01-02/01 and CB-01-02/02, UC history was generally similar. The overall median time since diagnosis of UC was 3.3 years for Study CB-01-02/01 and 3.9 years for Study CB-01-02/02.

Across treatment groups in both Studies CB-01-02/01 and CB-01-02/02, the median baseline UCDAI score was generally similar. The overall median baseline UCDAI score was 7.0.

7.1.6 Disposition (Studies CB-01-02/01 and CB-01-02/02)

Disposition is summarized below by study.

Study CB-01-02/01: Among 489 patients in the mITT analysis population, 349 (71%) completed the study. The most common reasons for early withdrawal from the study were treatment failure (n = 44; 9%) and withdrawal of consent (n = 38; 8%). A slightly lower percent of patients in the placebo group (63%) completed the study as compared to the other treatment groups (72% to 77%).

Study CB-01-02/02: Among 410 patients in the mITT analysis population, 272 (66%) completed the study. The most common reasons for early withdrawal from the study were treatment failure (n = 85; 21%) and withdrawal of consent (n = 30; 7%).

7.1.7 Primary Efficacy Analysis (Studies CB-01-02/01 and CB-01-02/02)

The primary efficacy analysis is summarized below by study.

Study CB-01-02/01:

When the primary analysis of clinical remission was performed using the mITT population, the percentage of patients in clinical remission at Week 8 was statistically significantly higher for patients receiving Uceris 9 mg than for patients receiving placebo (17.9% vs. 7.4%, p = 0.0143). Thus, the treatment difference between Uceris 9 mg and placebo was 10.4%.

Clinical remission rates in the Uceris 6 mg group (13.2%) and in the Asacol group (12.1%) were numerically greater than placebo, but the differences did not reach statistical significance. See table below.

Table 6. Rates of Clinical Remission mITT Population (Study CB-01-02/01)

	Placebo N=121	Budes. MMX 9 mg N=123	Budes. MMX 6 mg N=121	Asacol 2400 mg N=124
Remission: n (%)	9 (7.4)	22 (17.9)	16 (13.2)	15 (12.1)
95% CI	2.8, 12.1	11.1, 24.7	7.2, 19.3	6.4, 17.8
Difference between active and placebo		10.4	5.8	4.7
95% CI		2.2, 18.7	-1.8, 13.4	-2.7, 12.1
p-value		0.0143*	0.1393	0.2200

Source: Table 14.2-1.1.1

Abbreviation: Budes., budesonide; CI: confidence interval

Notes: The denominator for calculating percentages was the number of patients in each treatment group in the ITT population. Patients with missing data that precluded determination of remission were analyzed as not having achieved remission in these analyses (i.e., worst case). All p-values were based on the Chi-square test; comparisons of budesonide MMX and placebo were conducted at the α = 0.025 level of significance and the comparison of Asacol and placebo were conducted a the α = 0.05 level of significance. The study was not powered to show statistical significance for Asacol versus budesonide MMX.

* Value is statistically significant at the α = 0.025 level.

Table above is taken from the Clinical Review by Marjorie Dannis. Source is CSR Study CB-01-02/01 Table 17.

Study CB-01-02/02:

When the primary analysis of clinical remission was performed using the mITT population, the percentage of patients in clinical remission at Week 8 was statistically significantly higher for patients receiving Uceris 9 mg than for patients receiving placebo (17.4% vs. 4.5%, p = 0.0047). Thus the treatment difference between Uceris 9 mg and placebo was 12.9%.

The clinical remission rate in the Uceris 6 mg group (8.3%) and the Entocort EC group (12.6%) was each numerically greater than placebo, but the differences did not reach statistical significance. See table below.

Table 7. Rates of Clinical Remission mITT Population (Study CB-01-02/02)

	Placebo N=89	Budes. MMX 9 mg N=109	Budes. MMX 6 mg N=109	Entocort EC 9 mg N=103
Remission, n (%)	4 (4.5)	19 (17.4)	9 (8.3)	13 (12.6)
95% CI	0.2, 8.8	10.3, 24.6	3.1, 13.4	6.2, 19.0
Difference vs. placebo		12.9	3.8	8.1
95% CI		4.6, 21.3	-3.0, 10.5	0.4, 15.9
p-value[d]		0.0047*	0.2876	0.0481†

Source: Tables 14.2-1.1.1

Abbreviations: Budes., budesonide; CI: confidence interval.

Notes: Patients with missing data that precluded determination of remission were analyzed as failures in these analyses (i.e., worst case). The denominator for calculating percentages was the number of patients in each treatment group in the ITT population. All p-values were based on the Chi-square test, with α = 0.025 for comparisons of budesonide MMX and placebo and α = 0.05 for the comparison of Entocort and placebo. The study was not powered to show statistical significance for Entocort EC versus budesonide MMX.

* Value is statistically significant at the α = 0.025 level.

† Value is statistically significant at the α = 0.05 level.

Table above is taken from the Clinical Review by Marjorie Dannis. Source is CSR Study CB-01-02/02 Table 17.

Discussion / Conclusions:

The Clinical Reviewer concluded that substantial evidence of efficacy was demonstrated based on the results in the mITT analysis population (i.e., sponsor's ITT analysis population) of each of the two studies (Studies CB-01-02/01 and CB-01-02/02).

The Primary Statistics Reviewer concluded that the two studies (Study CB-01-02/01 and Study CB-01/02/02) did not provide substantial evidence (from a statistical perspective) demonstrating superiority of Uceris 9 mg over placebo for the "all randomized" population. He summarized the results in the "true" ITT analysis population (i.e., "all randomized" population) and in the population with positive histology at baseline as follows:

- "True" ITT analysis Population (each study): The Primary Statistics Reviewer performed "true" ITT analyses for both studies (see Appendix 5). For Study CB-01-02/01, the Statistics Reviewer concluded that the remission rates for Uceris 9 mg and Uceris 6 mg were each numerically greater than placebo, but the differences did not reach statistical significance. For Study CB-01-02/02, the Primary Statistics Reviewer concluded that the remission rate for Uceris 9 mg was numerically greater than placebo, but the difference did not reach statistical significance.
- Positive Histology at Baseline (each study): The Primary Statistics Reviewer noted that for patients with positive histology at baseline in each study, Uceris 9 mg was numerically better than placebo, but the subgroup of patients with positive histology at baseline was not pre-specified in the protocol, and thus without "clear pre-specification", this subgroup analysis should be considered exploratory and hypothesis generating in nature (see also discussion in Section 7.1.4 of this CDTL Review).

The results for each of the three populations ["true" ITT analysis population, baseline histology positive population, and modified ITT population (i.e., sponsor's ITT analysis population)] are summarized by study in the two tables below.

Table 8. Clinical Remission Rates by Analysis Population - Study CB-01-02/01

Population	Treatment Arms				Uceris 9 mg - Placebo
	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2400 mg	
"True" ITT*	**10.9%** (14/129)	**17.3%** (22/127)	15.1% (19/126)	12.6% (16/127)	**6.4%** (p=0.1365)
Histology Positive[#]	**8.2%** (10/122)	**18.5%** (23/124)	13.8% (17/123)	12.1% (15/124)	**10.3%** (p=0.0238)
mITT[†]	**7.4%** (9/121)	**17.9%** (22/123)	13.2% (16/121)	12.1% (15/124)	**10.5%** (p=0.0143)

*"True" ITT Population results from Statistics Review by Milton Fan Page 20 (p value based on chi-squared test).
[#]Histology Positive Population results from Statistics Review by Milton Fan Page 27 (p-value based on Fisher's exact test).
[†]mITT (i.e., Sponsor's ITT) Population results from CSR Study CB-01-02/01 Table 17 (p value based on chi-squared test).

Table 9. Clinical Remission Rates by Analysis Population - Study CB-01-02/02

Population	Treatment Arms				Uceris 9 mg - Placebo
	Placebo	Uceris 9 mg	Uceris 6 mg	Asacol 2400 mg	
"True" ITT*	**14.0%** (18/129)	**17.2%** (22/128)	12.5% (16/128)	15.9% (20/126)	**3.2%** (p=0.4746)
Histology Positive[#]	**6.3%** (6/96)	**16.7%** (19/114)	8.0% (9/112)	14.5% (16/110)	**10.4%** (p=0.0308)
mITT[†]	**4.5%** (4/89)	**17.4%** (19/109)	8.3% (9/109)	12.6% (13/103)	**12.9%** (p=0.0047)

*True ITT Population results from Statistics Review by Milton Fan Page 43 (p value based on chi-squared test).
[#]Histology Positive Population results from Statistics Review by Milton Fan Page 44 (p-value based on Fisher's exact test).
[†]mITT (i.e., Sponsor's ITT) Population results from CSR Study CB-01-02/02 Table 17 (p value based on chi-squared test).

The Secondary Statistics Reviewer concluded the following regarding the primary analysis population of each study (to include patients with positive histology at baseline) and the interpretation of results of Study CB-01-02/02 (given the GCP violation issues and apparent randomization imbalance in subjects with normal histology at baseline) (see also discussion in Section 7.1.4 of this CDTL Review):

- Primary Analysis Population of Each Study (to include patients with positive histology at baseline): The Secondary Statistics Reviewer noted that introduction of bias due to this change is not evident, and that based on this analysis population both studies showed statistically significant results (with an effect of about 10%).
- Interpretation of Results of Study CB-01-02/02 (given the GCP violation issues and apparent randomization imbalance in subjects with normal histology at baseline): The

Secondary Statistics Reviewer noted that Study CB-01-02/02 should be considered supportive to the principle trial given both of these issues.

The Secondary Statistics Reviewer concluded that the overall level of statistical evidence of efficacy based on both studies is sufficient to support a recommendation for product approval by the Clinical Team. He also recommended that the Clinical Studies section of labeling should describe the studies as originally designed but should present results for only the biopsy positive subjects; he noted that the nature of the site violations for study CB-01-02/02 would support removal of these sites from the analysis tables (see Section 12.3 of this CDTL Review).

7.1.8 Secondary Efficacy Analyses (Studies CB-01-02/01 and CB-01-02/02)

Both the Clinical Reviewer and the Primary Statistical Reviewer noted that for both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement) in both studies, the rates were numerically higher in the Uceris 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

7.1.9 Subgroup Analyses (Studies CB-01-02/01 and CB-01-02/02)

The Primary Statistics Reviewer noted that in Study CB-01-02/01, the treatment difference in the rate of clinical remission at Week 8 (Uceris 9 mg versus placebo) was inconsistent between the ≤ 42 years and > 42 years age subgroups. The treatment difference was 1.2% in the ≤ 42 years age subgroup (Uceris 9 mg 11.1% versus placebo 9.9%) and was 21.0% in the > 42 years age subgroup (Uceris 9 mg 25.0% versus placebo 4.0%).

7.2 Recommendation

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

8. Safety

8.1 Issues

The reader is referred to the Clinical Review by Marjorie Dannis dated December 12, 2012, for complete information.

8.1.1 Exposure

A summary of Uceris exposure in UC patients in shown in the table below.

Table 10. Number of UC Patients* by Duration of Dosing

Dose#	≥ 1 dose	≥ 1 wk	≥ 2 wks	≥ 4 wks	≥ 8 wks	≥ 3 mos	≥ 6 mos	≥ 9 mos	≥ 12 mos	≥ 15 mos
9 mg	352	329	324	300	251	13	0	0	0	0
6 mg	300	280	271	233	202	42	31	26	23	1
3 mg	17	17	17	17	15	0	0	0	0	0

*UC patients in any of the six Phase 2 or 3 trials.
#once per day (QD) dosing
Table above summarized from the Clinical Review by Marjorie Dannis; source is Response to Information Request dated March 26, 2012 (Page 5 of "0012-safety-information-amendment")

A total of 669 UC patients received at least one dose of Uceris across the three dose groups. The cumulative patient-years of exposure across the three dose groups was 113 patient-years. The majority of patients received the 9 mg dose strength (58%).

8.1.2 Safety Findings

Deaths:

No deaths were reported in any of the clinical studies conducted for the Uceris clinical program.

Serious Adverse Events:

Serious adverse events (SAEs) are summarized below for the Primary Analysis Group (i.e., Studies CB-01-02/01 and CB-01-02/02) and for the Long-Term Analysis Group (i.e., Study CB-01-02/04).

- Primary Analysis Group: Overall, SAEs occurred in 3% (25/1020) of patients. SAEs occurred in a similar percentage of patients in all treatment groups (2% to 3%), with the exception of the Entocort group, which had a lower incidence (<1%). SAEs were most frequently reported in the gastrointestinal disorders System Organ Class (SOC) (2%); the incidence was similar across all treatment groups (<1% to 2%). SAEs in all other SOCs were reported in <1% of all patients. SAEs occurring in more than one patient by Preferred Term (PT) were UC (1%) and treatment failure (<1%). The incidence of UC was similar in the Uceris 9 mg (2%) and placebo (2%) groups and lower in the Uceris 6 mg (<1%), Asacol (<1%), and Entocort (<1%) groups. Treatment failure was reported as an SAE in 2 patients; both were in the Uceris 9 mg group.

- Long-Term Analysis Group: A total of 2 SAEs were reported in the long-term analysis group, 1 SAE in the placebo group (severe lobar pneumonia) and 1 SAE in the Uceris 6 mg group (moderate hypertension). These SAEs were considered by the investigators to be not related to study treatment. The Clinical Reviewer agreed that severe lobar pneumonia is probably not related to study treatment; however, the Clinical Reviewer noted that it is possible that moderate hypertension could be related to study treatment.

Dropouts and/or Discontinuations:

Dropouts and/or discontinuations are summarized below for the Primary Analysis Group and for the Long-Term Analysis Group.

- Primary Analysis Group: Overall, 16% (166/1020) of patients had at least one adverse event (AE) leading to withdrawal. The incidence of AEs leading to withdrawal was similar in all treatment groups (15% to 19%), with the exception of the Asacol group, which had a lower incidence (11%). The most frequently reported AE by PT leading to withdrawal was UC, occurring in 12% of patients. The incidence of UC leading to withdrawal was similar in all treatment groups (11% to 16%), with the exception of the Asacol group, which had a lower incidence (8%).

- Long-Term Analysis Group: In the long-term analysis group, a greater percentage of patients in the placebo group than in the Uceris 6 mg group experienced an AE that led to withdrawal from the study (30% [17/61] and 16% [10/62], respectively). The most frequent AE that led to withdrawal in both treatment groups was UC and was reported in a greater percentage of patients in the placebo group (23%) than in the Uceris 6 mg group (15%). No other AEs that led to withdrawal were reported by more than one patient in either treatment group.

Potential Glucocorticoid-related Effects:

Potential glucocorticoid-related effects are summarized below for the Primary Analysis Group and for the Long-Term Analysis Group.

- Primary Analysis Group: Glucocorticoid effects were observed for 10% (104/1020) of patients in the primary analysis group. These effects occurred most frequently in the Entocort group (14%) and Asacol group (12%) and least frequently in the budesonide Uceris 6 mg group (8%). Glucocorticoid effects occurred in similar percentages of patients in placebo (11%) and Uceris 9 mg (10%). Overall, the most common individual glucocorticoid effects were mood changes and sleep changes (4% each). Review of the individual events showed that the frequency of events was similar or lower with Uceris 9 mg when compared with placebo. (See table below.)

Table 11. Potential Glucocorticoid Effects in the Primary Analysis Group

	Phase III Randomized, Double-blind					
Glucocorticoid Effect	Placebo N=258 n (%)	MMX 9 mg N=255 n (%)	MMX 6 mg N=254 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)	Total N=1020 n (%)
Overall	27 (10.5)	26 (10.2)	19 (7.5)	15 (11.8)	17 (13.5)	104 (10.2)
Moon face	4 (1.6)	3 (1.2)	3 (1.2)	2 (1.6)	2 (1.6)	14 (1.4)
Striae rubrae	2 (0.8)	0	0	0	0	2 (0.2)
Flushing	3 (1.2)	0	1 (0.4)	2 (1.6)	1 (0.8)	7 (0.7)
Fluid retention	3 (1.2)	2 (0.8)	3 (1.2)	3 (2.4)	0	11 (1.1)
Mood changes	11 (4.3)	9 (3.5)	10 (3.9)	3 (2.4)	6 (4.8)	39 (3.8)
Sleep changes	12 (4.7)	7 (2.7)	10 (3.9)	1 (0.8)	9 (7.1)	39 (3.8)
Insomnia	8 (3.1)	6 (2.4)	6 (2.4)	2 (1.6)	5 (4.0)	27 (2.6)
Acne	5 (1.9)	6 (2.4)	2 (0.8)	6 (4.7)	3 (2.4)	22 (2.2)
Hirsutism	0	1 (0.4)	0	1 (0.8)	1 (0.8)	3 (0.3)

Table above is taken from the Clinical Review by Marjorie Dannis. Source is Summary Clinical Safety Page 48 Table 35.

- Long-Term Analysis Group: Most of the patients in both the placebo and the Uceris 6 mg treatment groups did not experience any potential glucocorticoid effects with up to 12 months of treatment with study drug. A similar percentage of patients in both treatment groups reported any potential glucocorticoid effect (12% of patients in the placebo group versus 15% of patients in the Uceris 6 mg group). The most common events were insomnia (7% of all patients), followed by moon face, mood change, and sleep change (all at 5%). (See table below.)

Table 12. Summary of Patients with Potential Glucocorticoid Effects in the Long-term Analysis Group

	Uceris 6 mg (N = 62) n (%)	Placebo (N = 61) n (%)
Overall	9 (14.5)	7 (11.5)
Insomnia	4 (6.5)	4 (6.6)
Mood changes	4 (6.5)	2 (3.3)
Moon face	3 (4.8)	3 (4.9)
Sleep changes	3 (4.8)	3 (4.9)
Acne	3 (4.8)	0
Hirsutism	3 (4.8)	0
Flushing	1 (1.6)	1 (1.6)
Fluid retention	1 (1.6)	1 (1.6)

Table above is taken from the Clinical Review by Marjorie Dannis. The table is adapted from the Summary of Clinical Safety page 49 Table 37.

Common Adverse Events:

Common adverse events (AEs) are summarized below for the Primary Analysis Group and for the Long-Term Analysis Group.

- Primary Analysis Group: Overall, a total of 57% (585/1020) of patients experienced at least one AE, and the percentage of patients experiencing AEs was similar across all treatment groups (54% to 63%). The most frequently affected SOCs were

gastrointestinal disorders (33% of patients); nervous system disorders (14%); and infections and infestations (11%). The incidence of AEs was similar across all treatment groups for the gastrointestinal disorders SOC (29% to 36%) and the infections and infestations SOC (10% to 13%). The most frequently reported treatment-emergent AEs by PT were ulcerative colitis in 14% of patients and headache in 11%. Among common AEs (occurring in ≥5% of patients in any group), the following AEs occurred in a higher percentage of patients receiving Uceris (either 9 mg or 6 mg) compared with placebo: (a) ulcerative colitis; (b) nausea; (c) flatulence; and (d) headache. In addition, the Clinical Reviewer noted that there appeared to be a potential relationship between the dose of Uceris and the AE of decreased blood cortisol (4% of patients receiving Uceris 9 mg, 2% receiving Uceris 6 mg, and <1% receiving placebo), although the frequency of these events was low overall (no more than 4% of patients in any group). The Clinical Reviewer noted that this potential dose relationship is not unexpected for this class of drug (a glucocorticoid).

- Long-Term Analysis Group: Overall, AEs occurred in a slightly higher percentage of patients in the placebo group (72% [44/61]) than in the Uceris 6 mg group (65% [40/62]). The most frequently reported AE was UC, which was reported at a numerically higher percentage for patients in the placebo treatment group than for patients in the Uceris 6 mg treatment group (26% vs.18%). Osteopenia was more commonly reported in the placebo group than Uceris 6 mg treatment group (8% and 2% , respectively), while frequent bowel movements (2% vs. 7%), haematochezia (2% vs.7%), constipation (0% and 7%), abdominal pain (8% vs.10%) and headache (3% vs. 7%) were more commonly reported in the Uceris 6 mg group. However, the overall frequencies of these events were low (none were reported by more than five patients in any treatment group). The Clinical Reviewer noted that several potentially glucocorticoid related AEs occurred in a slightly higher percentage in the Uceris 6 mg treatment group vs. the placebo group. These were: cushinoid (5% vs. 3%), acne (5% vs. 0), flushing (3% vs. 2%), hirsutism (5% vs.0) and blood cortisol decreased (3% vs. 2%). However, the Clinical Reviewer pointed out that these all occurred in only one to three patients.

8.2 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

The application was presented to the Pediatric Research Committee (PeRC) on November 28, 2012.

The PeRC agreed with the Division to grant a partial waiver in patients birth to <5 years of age because studies are impossible or highly impractical because there are too few patients with disease/condition to study. The PeRC also agreed with the Division to grant a deferral in patients 5 to 17 years of age because the product is ready for approval in adults.

PeRC recommendations included the following: (1) Request the sponsor to adjust the timelines for studies; (2) Conduct of a growth study is not needed; (3) Evaluate this product for (b) (4); (4) Include assessment of PK in the study to ensure similar exposures; (5) The sponsor should be encouraged to submit a revised Pediatric Plan.

Other items discussed included the following: (1) The Division currently believes that the tablet is appropriate for use down to five years of age, but there will need to be additional discussion between the Division and the Sponsor about the development of an age-appropriate formulation. (2) Committee members questioned if it may have been possible for pediatric studies in this age group to have already been completed for this product. (3) (b) (5)

11. Other Relevant Regulatory Issues

11.1 QT Evaluation

The reader is referred to the QT-IRT Consult Review by Monica Fiszman dated May 15, 2012 for complete information.

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

- Budesonide (capsules) is being marketed since 1997. The Cmax with the approved formulation Entocort EC is slightly higher than that expected with Uceris (tablets).
- No AEs of concerns as per ICH E14 Guidance have been reported post-marketing.

11.2 Office of Scientific Investigations (OSI) Audits

The reader is referred to the OSI Clinical Inspection Summary by Susan Leibenhaut, dated December 17, 2012 for complete information.

11.2.1 Site Inspections

The site inspections are summarized in the tables below.

Table 13. Overview of Sites Inspected (Study CB-01-02/01)

Site Number/ Investigator/ Location	No. pts	Inspector's Key Findings	Final Classification
Site 5005[#] Neil Cohen, M.D. Marlton, NJ	10	• Minor Protocol Violations: – Neither the Principal Investigator nor Sub-Investigator signed the Informed Consent Documents. – IBDQ used prior to IRB approval – Cortisol levels taken at 2:55 PM (one subject) and 2:00 PM (another subject) instead of between 8:00 and 10:00 AM – Four subjects used concomitant antibiotics • Minor Concerns about Study Conduct: – Correlation between colonoscopy reports (which included pictures) and table of endoscopic index assessments (EIA) in source documents. – No documentation of physician input to the endosopic index assessment, UCDAI, and Clinical Activity Index (CAI) assessment forms. – UCDAI and CAI for 3 subjects signed/dated at Visit 1 but information from subject diaries not reviewed until Visit 2 – Temperature excursions below lower limit of 59 ^{0}F (one day of 58.5 ^{0}F, two days of between 56 and 57.5 ^{0}F, and two days of 58.5 ^{0}F) • Overall Assessment: The data from this site can be used in support of the NDA.	VAI
Site 5003[†] Tawfik Chami, M.D. Zephyrhills, FL	9	• No significant regulatory violations • Overall Assessment: The data from this site can be used in support of the NDA.	NAI
Site 9004* Umesh Jalihal, M.D. Bangalore-Karnataka, India	20	• Minor Protocol Violations: – No documentation of eligibility determination in screening visit 1 for 2 subjects. – Failure to prepare or maintain adequate case histories: ▪ notes for Visit 1 not maintained for two subjects ▪ source document differs from subject diary for one subject's CAI at Visit 1 ▪ source document differs from eCRF for one subject's EIA ▪ source document differs from eCRF for one subject's CAI • Overall Assessment: The data from this site can be used in support of the NDA.	VAI

*Site 9004 was initially requested for inspection in a consult request to OSI dated February 13, 2012.
[#]Site 5005 was requested for inspection in a consult request to OSI dated June 21, 2012.
[†]Site 5003 was selected by OSI
NAI: No Action Indicated; VAI: Voluntary Action Indicated
Information in the table above is taken from the OSI Clinical Inspection Summary

Table 14. Overview of Sites Inspected (Study CB-01-02/02)

Site Number/ Investigator/ Location	No. pts	Inspector's Key Findings	Final Classification[§]
Site 1055* Limas Kupcinskas, M.D. Kaunas, Lithuania	27	• Minor Protocol Violations: – Pre-study mesalamine not recorded for most patients. Investigator interpreted requirement to discontinue mesalamines prior to entry to mean that recording of pre-study medication use not needed. – Discrepancies noted between the source documents and the eCRFs (inaccurate records) that resulted in lower UCDAI scores for 2 subjects (in the Uceris 9 mg arm) but no change in remisison status (neither subject achieved remission). • Overall Assessment: The data from this site can be used in support of the NDA.	VAI
Site 1059[†] Robert Petryka, M.D. Warszawa, Poland	17	• No significant regulatory violations. – This site was noted by the sponsor as one of the sites that should be excluded from the safety and efficacy analysis. • Overall Assessment: The data from this site can be used in support of the NDA.	NAI
Site 1122[#] Ivan Bunganic, M.D. Presov, Slovakia	22	• Numerous GCP violations. – Numerous GCP violations at this site. – This site was noted by the sponsor as one of the sites that should be excluded from the safety and efficacy analysis. • Overall Assessment: Based on the FDA inspection of this site, OSI cannot conclude that the GCP violations noted impact primary efficacy assessment or subject safety.	VAI[§]

*Site 1055 was initially requested for inspection in a consult request to OSI dated February 13, 2012.
[#]Site 1122 was requested for inspection in a consult request to OSI dated June 21, 2012.
[†]Site 1059 was selected by OSI
[§]Preliminary classification for Site 1122 is VAI; final classification is pending as of the date of this CDTL Review
NAI: No Action Indicated; VAI: Voluntary Action Indicated
Information in the table above is taken from the OSI Clinical Inspection Summary

Four of the sites (sites 5005, 9004, 1055, and 1122) were selected by the clinical reviewers due to enrollment of large numbers of subjects per site relative to other sites, and high proportion of treatment responders at each site. Two of the sites (sites 5003 and 1059) were selected by OSI.

Three of the sites (5005, 9004, 1055) were given a final classification of VAI (Voluntary Action Indicated). The final classification of one site (site 1122) is pending as of the date of this CDTL Review; the preliminary classification is VAI. Two sites (sites 5003 and 1059) were given a final classification of NAI (No Action Indicated). No sites were given a classification of OAI (Official Action Indicated).

Because the protocol violations at each of the sites did not affect the validity of the data or markedly affect the calculation of the primary efficacy endpoint, the overall assessment of the inspectors from the inspection of the six clinical sites was that the data are reliable and can be used in support of the NDA.

11.2.2 Review of Sponsor Audit Reports

For-cause investigations identified 2 sites (sites 1040 and 1106) that required audits (both from Study CB-01-02/02). The process of Data Validation and External Data Reconciliation identified 5 additional sites from that study (sites 1082, 1122, 1059, and 1098, and 1111) that required audits. The Applicant submitted the audit reports for these 7 sites in a Response to Information Request dated August 3, 2012.

The results of the audits are summarized in the table below.

Table 15. Summary of Audit Reports (Study CB-01-02/02)

Site Number/ Country	No. pts	Critical Findings
Site 1040 Italy	11	• No interaction of SI's with PI. • SI not a gastroenterologist and had no training in assessment of colonoscopy reports or clinical assessment related to the study. • A number of inconsistencies concerning colonoscopy reports for 3 subjects; overall impression that the reports had not been reviewed before the subjects were enrolled.
Site 1106 Russia	11	• Quality of source data not adequate as per ICH GCP requirements (e.g., corrections/insertions not initialed/dated, use of correction fluid, illegible records). • Limited GCP knowledge and lack of GCP training of the study team; SI not able to communicate in English, and thus could not review subject data entered into eCRFs in English by the data manager.
Site 1082 Slovakia	6	• No consistent GCP approach to protocol modifications (e.g., changes to diary, and memos to staff concerning use of diary data); not clear if protocol modifications would be retroactive for subjects already participating. • Protocol did not state how UCDAI/CAI/EIA should be assessed, and that UCDAI and CAI should be cross-linked with diary data. For 2 subjects, it was not clear who made EIA assessments. • No written instructions regarding how investigators should instruct subjects to complete diaries. • Inadequate study notes: (a) There was not accurate documentation of which investigators had seen which subjects for each visit; (b) Laboratory reports not legible; (c) Correction fluid used on source documents; (d) Duplicate sets of notes for a single subject had different content. • Large number of discrepancies between the source and eCRF data.
Site 1122 Slovakia	22	• No consistent GCP approach to protocol modifications (e.g., changes to diary, and memos to staff concerning use of diary data); not clear if protocol modifications would be retroactive for subjects already participating. • Protocol did not state how UCDAI/CAI/EIA should be assessed, and that UCDAI and CAI should be cross-linked with diary data. • Diary data not consistently collected and accuracy in eCRF could not be confirmed: (a) investigators assisted in filling out subjects diary (which had large sections blank at time of visit); (b) confusion about whether "normal" stools meant normal for the subject versus normally formed stools; (c) confusion about stool frequency assessment. • Could not be confirmed that the original source data was present for all subjects, and there was no audit trail for changes to the source data. For some source data, the notes had been retyped and the old versions destroyed.
Site 1059 Poland	17	• Audit showed no critical findings
Site 1098 Ukraine	17	• Audit showed no critical findings
Site 1111 Russia	22	• Audit showed no critical findings

PI: Principle Investigator; SI: Sub-Investigator.
Information in table above summarized from the OSI Clinical Inspection Summary

12. Labeling

12.1 Proprietary Name

For complete information, see the DMEPA Proprietary Name Review by Anne Tobenkin, dated April 16, 2012, and DMEPA Proprietary Name Reviews by Denise Baugh, dated July 25, 2012, and December 11, 2012.

DMEPA concluded in the review dated April 16, 2012, that the proprietary name of "Uceris" was acceptable. This was communicated to the Applicant in the Proprietary Name Request Conditionally Acceptable Letter dated April 17, 2012, along with a statement that the proposed proprietary name of "Uceris" will be re-reviewed 90 days prior to the approval of the NDA.

DMEPA conducted re-evaluations of the proposed proprietary name of "Uceris" (see reviews dated July 25, 2012, and December 11, 2012); again, DMEPA concluded that the proprietary name of "Uceris" was acceptable.

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 Anne Tobenkin, dated April 16, 2012, and Proprietary Name Reviews by Denise Baugh, dated July 25, 2012, and December 11, 2012.

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): The recommendation for (b) (4) of Uceris (originally proposed by the Applicant) was removed.
- Drug Interactions (Section 7 of Label): A sub-section entitled "Inhibitors of Gastric Acid Secretion" was added that included the following statement: "Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H2 blockers and antacids)."
- Clinical Studies (Section 14 of Label): The following revisions were made:
  - In the description of the study design, the total number of patients enrolled (not including GCP violations) (i.e., 970 patients) was stated, but an additional statement was added describing the primary analysis population ("Eight-hundred ninety-nine of these patients had histology consistent with active UC; this was considered the primary analysis population.")
  - The sub-section entitled (b) (4) (originally proposed by the Applicant) was removed.

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 December 14, 2012 (see DMEPA Label and Labeling Review by Anne Tobenkin, dated April 10, 2012).

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.

13.2 Risk Benefit Assessment

The benefit of Uceris in mild to moderate UC 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

A postmarketing required pediatric study under PREA is recommended for the current application, with the following language for the Approval Letter:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 5 years because necessary studies are impossible or highly impracticable.

We are deferring submission of your pediatric study for ages 5 to 17 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

> An 8-week randomized, double-blind, placebo-controlled trial in children 5 to 17 years of age with active, mild to moderate ulcerative colitis. The trial will evaluate pharmacokinetics (PK), efficacy for induction of remission, and safety of at least 2 doses of Uceris (budesonide). The effects of 8 weeks of Uceris (budesonide) on the HPA axis will be assessed.
>
> Final Protocol Submission: 09/2013
> Trial Completion: 06/2016
> Final Report Submission: 09/2016

Submit the protocol to your IND 074882 with a cross-reference letter to this NDA.

Reports of this required pediatric postmarketing study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

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)

None of the primary review disciplines had recommendations for postmarketing commitments.

13.7 Recommended Comments to Applicant

None.

APPENDIX 1: Clinical Studies Conducted with Uceris

Table 16: Clinical Studies Conducted with Uceris

Study # Status Country/Region	Study Description	Study Population	Treatment Regimen Dose and Duration	Participants Dosed
PRIMARY STUDIES				
CB-01-02/01 Complete Canada, Mexico, US, India	Phase III, multi-center, randomized, double-blind, placebo-controlled, double-dummy, parallel-group comparative study with reference arm CSR CB-01-02/01	Patients with active mild or moderate UC Age: 18-77 years	Budesonide MMX 6 mg/day x 8 wk Budesonide MMX 9 mg/day x 8 wk Asacol 2 x 400 mg t.i.d. x 8 wk (2400 mg/day) Placebo x 8 wk	126 127 127 129 (509 total)
CB-01-02/02 Complete Italy, France, UK, Belgium, Sweden, Romania, Poland, Slovakia, Ukraine, Estonia, Latvia, Lithuania, Russia, Israel, Australia	Phase III, multi-center, randomized, double-blind, placebo-controlled, double-dummy, parallel-group comparative study with additional reference arm CSR CB-01-02/02	Patients with active mild or moderate UC Age: 18-75 years	Budesonide MMX 6 mg/day x 8 wk Budesonide MMX 9 mg/day x 8 wk Entocort EC 3 x 3 mg/day x 8 wk Placebo x 8 wk	128 128 126 129 (511 total)
SUPPORTIVE STUDIES				
CB-01-02/06[a] Complete India	Phase III, multi-center, open-label efficacy and safety companion study (Parent study: CB-01-02/01) CSR CB-01-02/06	Patients with active mild or moderate UC Age: 19-62 years	Budesonide MMX 9 mg/day x 8 wk	61
CB-01-02/05 Complete Romania	Phase II, dose-finding, double-blind, multi-center, comparative, pilot efficacy and safety study CSR CB-01-02/05	Patients with active mild or moderate UC Age: 26-66 years	Budesonide MMX 3 mg/day x 8 wk Budesonide MMX 9 mg/day x 8 wk Placebo x 8 wk	17 15 17 (49 total)
CRO-03-53 Complete France, Austria, Belgium, Hungary	Period 1: Phase II, randomized, double-blind, placebo-controlled, parallel-group, pilot multi-center efficacy study Period 2: Phase II, open-label, pilot multi-center efficacy study CSR CRO-03-53	Patients with active mild or moderate left-sided UC Age: 18-66 years	Group A: Budesonide MMX 9 mg/day x 8 wk (Period 1) Group B: Placebo x 4 wk (Period 1), then budesonide MMX 9 mg/day x 4 wk (Period 2)	18 18 (36 total)
CB-01-02/04[a] Complete Canada, US, Italy, Russia, Ukraine, India	Phase III, multi-center, randomized, double-blind, placebo-controlled, 12-month efficacy and safety extension study (Parent studies: CB-01-02/01, CB-01-02/02, CB-01-02/06) CSR CB-01-02/04	Patients with mild or moderate UC in remission status Age: 18-75 years	Budesonide MMX 6 mg/day x 12 mo Placebo x 12 mo	62 61 (123 total)
CRO-PK-06-178 Complete Switzerland	Phase I, single-dose, single-center, open-label, randomized, 3-way cross-over, exploratory bioavailability and pharmacokinetics study CSR CRO-PK-06-178	Healthy subjects Age: 22-51 years	Budesonide MMX 6 mg single dose Budesonide MMX 9 mg single dose Entocort EC 3 x 3 mg single dose	13 13 13 (13 total)
CRO-PK-03-105 Complete Switzerland	Phase I, single-center, open-label, randomized, balanced, single-dose food effect and multiple-dose pharmacokinetics study CSR CRO-PK-03-105	Healthy male subjects Age: 18-30 years	Budesonide MMX 9 mg single dose, fasted or fed (first phase) Budesonide MMX 9 mg/day x 7 days, fasted (second phase)	12 12 (12 total)
CRO-01-28 Complete Austria	Phase I, single-dose, single-center, open-label pilot study CSR CRO-01-28	Healthy male subjects Age: 26-40 years	^{152}Sm-budesonide MMX 9 mg, single dose (^{152}Sm-oxide 5 mg)	12

t.i.d. = three times daily; UC = ulcerative colitis; UK = United Kingdom; US = United States.
[a] CB-01-02/04 and CB-01-02/06 enrolled patients who may have previously received budesonide MMX in a parent study (i.e., CB-01-02/01 or CB-01-02/02).

(Table above is taken from the Clinical Review by Marjorie Dannis.)

APPENDIX 2: UCDAI Score

Table 17. Ulcerative Colitis Disease Activity Index Score

Index	Description	Score
1. Stool frequency	Normal	0
	1- 2 stools/day more than normal	1
	3 to 4 stool/day more than normal	2
	>4 stools/day more than normal	3
2. Rectal bleeding	None	0
	Streaks of blood	1
	Obvious blood	2
	Mostly blood	3
3. Mucosal Appearance	Normal	0
	Mild friability	1
	Moderate friability	2
	Exudation	3
4. Physician Rating of Disease Activity	Normal	0
	Mild Moderate	1 2
	Severe	3

(The table above is taken from the Clinical Review by Marjorie Dannis.)

APPENDIX 3: Saverymuttu Scoring System and Histological Activity Grade

The table below shows the Saverymuttu Scoring System.

Table 18. Saverymuttu Scoring System

Histopathological Observations		Score
Enterocytes	Normal	0
	Loss of Single Cells	1
	Loss of Groups of Cells	2
	Frank Ulceration	3
Crypts	Normal	0
	Single Inflammatory Cells	1
	Cryptitis	2
	Crypt Abscesses	3
Lamina Propria Mononuclear Cells	Normal	0
	Slight Increase	1
	Moderate Increase	2
	Marked Increase	3
Lamina Propria Neutrophils	Normal	0
	Slight Increase	1
	Moderate Increase	2
	Marked Increase	3
	Total Score	**0-12**

The table above is taken from the Clinical Review by Marjorie Dannis.

The table below shows the conversion from the total Saverymuttu Score to the Histological Activity Grade.

Table 19. Determination of Histological Activity Grade (Conversion from Total Saverymuttu Score to Histological Activity Grade)

Total Score Obtained	Histological Activity Grade
0-1	0
2-4	1
5-8	2
9-12	3

The table above is taken from the Clinical Review by Marjorie Dannis.

APPENDIX 4: Endoscopy-Only Scoring System

The following endoscopy-only scoring system[3] was used as part of the primary endpoint definition (see Section 7.1.2 of this CDTL Review):

Table 20. Endoscopy-Only Scoring System*

1	**Granulation scattering reflected light:**	**Score**
	No	0
	Yes	2
2	**Vascular pattern:**	
	Normal	0
	Faded/disturbed	1
	Completely absent	2
3	**Vulnerability of mucosa:**	
	Normal	0
	Slightly increased (contact bleeding)	2
	Greatly increased (spontaneous bleeding)	4
4	**Mucosal damage (mucus, fibrin, erosions, ulcer):**	
	None	0
	Slight	2
	Pronounced	4

*Note: This endoscopy-only scoring system is not part of the UCDAI.
(Table above is taken from Page 49 of the CB-01/02/01 Protocol.)

[3]Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298: 82-6.

APPENDIX 5: Additional Analyses from Primary Statistics Review

The following additional analyses are taken from the Primary Statistics Review. The Statistics Reviewer performed "true" ITT analyses (i.e., including all randomized patients) for each of the two studies (Studies CB-01-02/01 and CB-01-02/02). The results from the true "ITT" analyses are shown in the tables below.

Study CB-01-02/01:

Table 21. Rate of Clinical Remission – "True" ITT Population (Study CB-01-02/01)

	Placebo N=129	MMX 9 mg N=127	MMX 6 mg N=126	Asacol 2400 mg N=127
Remission, n (%)	14 (10.9%)	22 (17.3%)	19 (15.1%)	16 (12.6%)
95% CI	(6.1, 17.5)	(11.1, 25.0)	(9.3, 22.5)	(7.4, 19.7)
Difference vs. placebo		6.3%	4.2%	1.7%
95% CI		(-2.0, 15.0)	(-4.0, 12.5)	(-6.1, 9.6)
p-value		0.1365	0.3147	0.6642

p-value was obtained by Chi-square test

(Table above is taken from Page 27 of the Statistics Review by Milton Fan.)

The Statistics Reviewer concluded that based on the "True" ITT Population, remission rates for Uceris 9 mg and Uceris 6 mg were numerically greater than placebo, but the differences did not reach statistical significance.

Study CB-01-02/02:

Table 22. Rate of Clinical Remission – "True" ITT Population (Study CB-01-02/02)

	Placebo N=129	MMX 9 mg N=128	MMX 6 mg N=128	Entocort EC N=126
Remission, n (%)	18 (14.0%)	22 (17.2%)	16 (12.5%)	20 (15.9%)
95% CI	(8.5, 21.21)	(1.1, 24.9)	(17.3, 19.5)	(10.0, 23.4)
Difference vs. placebo		3.2%	-1.5%	1.9%
95% CI		(-5.6, 12.1)	(-9.7, 6.8)	(-6.8, 10.7)
p-value		0.4746	0.7309	0.6669

p-value was obtained by Chi-square test.

(Table above is taken from Page 43 of the Statistics Review by Milton Fan.)

The Statistics Reviewer concluded that based on the "True" ITT Population, the remission rate for Uceris 9 mg was numerically greater than placebo, but the difference did not reach statistical significance.

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/s/

ANIL K RAJPAL
01/14/2013