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RESEARCH**

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Established Name	Budesonide MMX
(Proposed) Trade Name	Uceris
Therapeutic Class	Corticosteroid
Applicant	Santarus, Inc
Formulation(s)	Extended Release Tablet
Dosing Regimen	9 mg once daily
Indication(s)	Induction of remission in patients with active, mild to moderate ulcerative colitis
Intended Population(s)	Adults with active, mild to moderate ulcerative colitis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From the clinical standpoint, the submitted clinical data are adequate to support the recommendation of US marketing approval for Budesonide MMX 9 mg for the indication of induction of remission of ulcerative colitis.

1.2 Risk Benefit Assessment

Review of the current Application reveals that the benefit of Budesonide MMX for the induction of remission of ulcerative colitis outweighs the risk of Budesonide MMX in an appropriate patient population.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Adult studies are completed and ready for approval, but the safety and efficacy have not been established for the pediatric population ages 5 to 17 years old (UC studies have typically been waived for the pediatric subgroup age less than five).

The Sponsor will need to complete the following clinical study¹:

A randomized, double-blind, placebo- controlled, parallel group safety, efficacy and PK study of 8 weeks of treatment with Budesonide MMX, in children 5 to 17 years of age, with active, mild or moderate UC. Study should include appropriate dose ranging to establish the effective dose in this patient population.

Safety assessments should include an evaluation of the effects of 8 weeks of Budesonide MMX treatment on the HPA axis in a pediatric study population.

Timeline for this study should be:

Protocol Submission: 01/2014

Study Completion: 01/2018

Study Submission: 06/2018

¹ Only a brief description of this study is described here; further details will to be discussed with the Sponsor in the near future.

2 Introduction and Regulatory Background

2.1 Product Information

The sponsor proposes that Budesonide MMX 9 mg tablets, an enteric coated, extended release, oral dosage formulation is designed for the induction of remission in adult patients with mild to moderate active ulcerative colitis. According to the Sponsor, to provide an enhanced standard of treatment for ulcerative colitis, budesonide, a topically active glucocorticoid was selected as the active ingredient and then combined with the novel patented MMX delivery technology.

Each Budesonide MMX tablet is enterically coated to provide delayed release characteristics at the appropriate pH, so as to protect the drug substance from gastric acid and enzyme degradation. The tablet core contains 9 mg of budesonide and a mixture of polymers that further control the extended release characteristics of the drug substance, along with other excipients. According to the Sponsor, this recently developed technology was patented and applied to the delivery of mesalamine (as Lialda) which was approved by the FDA for once daily treatment of ulcerative colitis.

Budesonide, the active ingredient in budesonide MMX, is a synthetic glucocorticosteroid with topical anti-inflammatory properties, weak mineralocorticoid activity, and substantial first pass elimination. This extensive first pass metabolism by the liver ensures little systemic availability, which may result in less glucocorticoid (GCS)-related side effects compared to conventional systemically available steroids.

2.2 Currently Available Treatments for Proposed Indications

Sulfasalazine and 5-aminosalicylates (mesalamine, olsalazine, and balsalazide), given orally, rectally (by means of suppository or enema), or both, represent first-line treatment for ulcerative colitis. Mild-to-moderate proctitis can be treated with mesalamine suppositories or enemas; clinical remission occurs in most patients within 2 weeks, with repeated treatments as needed. If this fails, 5-aminosalicylate enemas or glucocorticoid enemas are a next step. Patients who do not have a response to rectally administered agents may be given oral glucocorticoids.

Patients with mild-to-moderate ulcerative colitis that is refractory to rectal therapies and to oral 5-aminosalicylate are candidates for oral glucocorticoids or immunosuppressive agents (azathioprine or 6-mercaptopurine).²

² Silvio Danese, M.D., and Claudio Fiocchi, M.D. N Engl J Med 2011; 365:1713-1725

2.3 Availability of Proposed Active Ingredient in the United States

Budesonide is widely commercially available in both the United States and other countries. It has several formulations including an inhalation powder, nebulized suspension, and metered dose inhaler for the treatment of chronic asthma; an aerosol nasal spray suspension for the localized treatment of allergic rhinitis; and for the treatment of Crohn's disease, modified-release and controlled-ileal release oral capsules and a retention enema (not approved in the United States).

2.4 Important Safety Issues With Consideration to Related Drugs

Budesonide is a synthetic glucocorticosteroid. Side effects 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 side effects 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.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Relevant Clinical Pre-submission Regulatory Background	
Date	Action
June 2006	<p>Pre- IND Meeting:</p> <ul style="list-style-type: none"> ➤ The Division advised the Sponsor that it would be useful to extend their Phase 3 studies to capture maintenance data. ➤ The Division clarified that a dose exploration study is not required but is strongly recommended to determine the lowest effective dose for their specific product. ➤ The Division clarified that an approved steroid with the indication of “colitis,” or similar historical term for ulcerative colitis, could be used as a comparator. The Division further clarified that different comparators may be used in different studies. ➤ The Division acknowledged that the dosing proposed appeared to be reasonable. However, since sufficient information from Phase 2 studies was not available, there was no agreement that the proposed dose was appropriate for Phase 3 investigations.
November 2007	<p>Submission of IND 74,882 (Special Protocol Assessment):</p> <ul style="list-style-type: none"> ➤ The Sponsor submitted a Special Protocol Assessment (SPA) for two Phase 3 trials to evaluate the safety and efficacy of Budesonide-MMX in ulcerative colitis. The first protocol, CB-01-02/01 (Asacol study) proposed to compare Budesonide-MMX 9mg and 6mg daily to placebo and Asacol 2,400 mg daily over four weeks. The second protocol, CB-01-02/02 (Entocort study) proposed to compare Budesonide-MMX 9mg daily to placebo and Entocort EC 9 mg daily over eight weeks.
March 2008	<p>Type A Meeting (including SPA discussion):</p> <ul style="list-style-type: none"> ➤ The Division stated that it may be more efficient to do dose exploration in a smaller Phase 2 study, but an acceptable approach would be to include dose explorations in both Phase 3 studies. The Division noted that this agreement was limited to <u>agreement with the plan</u> to include dose exploration in both studies; however, the Division reserved the right to critique choice of dose when the study results were reviewed. ➤ The Division stated that an eight week treatment duration appeared reasonable. However, a Phase 2 study could be used to estimate the rate of onset of activity, which could be helpful in selecting the most advantageous time for the primary endpoint assessment. As mentioned previously (in the pre-IND meeting and SPA responses), in the absence of a complete Phase 2 development program, the Division has no firm basis for evaluating the adequacy of the choice of eight weeks as the treatment duration. ➤ The Division recommended that the definition for remission also include the requirement that there be a finding of no friability on endoscopy.

Relevant Clinical Pre-submission Regulatory Background	
Date	Action
April 2010	<p>April 12, 2010 Teleconference:</p> <ul style="list-style-type: none"> ➤ The Sponsor asked whether the Division concurred with their statistical methodologies as proposed within the SAPs for U.S. Study Protocol CB-01-02/01 and E.U. Study Protocol CB-01-02/02. (Both SAPs were identical regarding the statistical methodology.) The Division strongly discouraged any changes in the primary endpoint analysis once the study was underway. ➤ The Division further stated: “As your current studies are nearly completed, this presents a serious review issue regarding the integrity of your analysis. In addition to the analysis you proposed, you will need to provide in your NDA an analysis according to the protocol in place at study commencement. You should provide justification for proposing alternative analyses, and you should provide documentation of the measures taken to preserve blinding of study results and ensure that those results could not have influenced analysis plans.”
May 2011	<p>Pre NDA Meeting:</p> <ul style="list-style-type: none"> ➤ The Division stated that they would review all of the data and would consider the proposed population (excluding patients with normal histology) in its determination of efficacy; however, the primary analysis population would remain the true ITT population. ➤ The Division acknowledged that the Sponsor was planning to exclude 50 patients from their ITT analysis due to GCP violations. The Division reiterated (as discussed in the April 13, 2010 meeting) that this was a review issue and that the true ITT population would remain the primary analysis population. ➤ The Division acknowledged that no formal agreement was reached for protocols CB-01- 02/01 and CB-01-02/02 which were submitted under Special Protocol Assessments (SPAs).
December 2011	NDA 203634 was submitted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The Sponsor certified that all of the studies contained in the NDA submission were performed in compliance with guidelines for Good Clinical Practice (GCP) and were conducted under the supervision of an IRB, or IEC equivalent, with adequate informed consent procedures.

According to the Sponsor, twenty-seven investigator site audits were performed throughout studies CB-01-02/01 and CB-01-02/02. Critical audit findings related to Good Clinical Practice (GCP) that could adversely affect product quality, the rights, safety or well being of subjects and/or the quality and/or integrity of the data were noted at four investigator sites (from Study CB-01-02/02 only). These critical GCP violations (see Appendix A for detailed description) led the Sponsor to conclude that all efficacy data from these four sites should be excluded (a total of 50 patients). Consequently, all the patient results for these four sites were excluded from the ITT population.

Due to this finding, the Division of Scientific Investigations (DSI) performed inspections of two domestic and four foreign sites.³ Only preliminary results of these inspections were available at the time of this review (5 December 2012). However, four sites were VAI, two sites were NAI and none were OAI (data unreliable). See Appendix C for further details.

This reviewer agrees that the patient results (which would not be reliable data) for these four sites should be excluded from the efficacy analyses.

3.3 Financial Disclosures

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

On 29 March 2012, the Sponsor amended their Financial Disclosure to include a Form 3455 for study (b) (6) clinical investigator Dr. (b) (6). According to the Sponsor, during a recent review they discovered new information regarding Dr. (b) (6) financial disclosure.

“The original Sponsor for Study (b) (6) was Cosmo Technologies Ltd. During the conduct of study (b) (6) in 2008, the clinical investigator did not have any financial interest in Cosmo Technologies Ltd. The investigator did however purchase shares of

³ This is as opposed to the inspection of one to two Investigator sites which is typically done for NDA/BLA submissions.

Santarus, Inc. common stock in 2008. At the time of his initial financial disclosure, Santarus was not the Sponsor of study [REDACTED] (b) (6).”

According to Form 3455, Dr. [REDACTED] (b) (6) 75,000 shares of Santarus in “about 2008”.

This reviewer believes that the Investigator’s stock purchase information should have been made available to the Sponsor at an earlier date; however, this oversight does not appear to affect the approvability of budesonide MMX at this time.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

UCERIS Tablets contain budesonide, a synthetic corticosteroid, as the active ingredient. Budesonide is designated chemically as (RS)-11 β , 16 α , 17,21 tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5.

According to CMC Reviewer, Raymond P. Frankewich, Ph.D., “specification of the drug product has not been satisfactorily established due to unresolved issues on dissolution test.” Thus:

- “The applicant has **not** submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.
- The Office of Compliance has **not** issued an overall “Acceptable” recommendation for the facilities involved in this application.
- Also, issues on labels/labeling are **not** satisfactorily resolved yet.
- Therefore, from the ONDQA perspective, this NDA is not recommended for approval per 21 CFR 314.125(b),(6) and (13) in its present form until the above issues are satisfactorily resolved.”

See complete CMC Review dated 9 November 2012 for further details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

For nonclinical safety, the Sponsor relied on the Agency's previous assessment of safety of budesonide. In addition, as per the Agency's recommendation, a 28-day repeated dose oral toxicity study in Cynomolgus monkeys was conducted and the study report was submitted in this NDA application. This repeated dose toxicology study showed that budesonide was well tolerated in this species. No treatment-related toxicological adverse effects were observed in animals receiving the drug.

According to Pharmacology/Toxicology Reviewer, Dinesh Gautam, Ph.D., "From a nonclinical standpoint, approval of the NDA application is recommended." See complete pharmacology/toxicology review dated 15 October 2012 for further details.

4.4 Clinical Pharmacology

The Clinical Pharmacology Draft review or Final Review was not available prior to the time of this review's completion (5 December 2012). The following clinical pharmacology details were obtained from the draft label that includes initial draft revisions by the Clinical Pharmacology Reviewer.⁴

4.4.1 Mechanism of Action

Budesonide has a high topical glucocorticosteroid activity and a substantial first-pass elimination. The formulation contains budesonide in an extended release tablet core. The tablet core is coated with a gastro-resistant film to protect dissolution in gastric juice which delays budesonide release until exposure to a pH \geq 7, by the time the tablet reaches the terminal ileum. Upon disintegration of the coating, the core matrix provides extended release of budesonide in a time dependent manner.

4.4.2 Pharmacodynamics

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

⁴ Label negotiations with the Sponsor are not completed.

Treatment with systemically active GCS, including UCERIS, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to ACTH stimulation.

4.4.3 Pharmacokinetics

Absorption

Following single oral administration of Uceris 9 mg in healthy subjects, peak plasma concentration (C_{max}) was 1.35 ± 0.96 ng/mL and the area under the plasma concentration time curve (AUC) was approximately 16.43 ± 10.52 ng·hr/mL.

Food Effect

A food-effect study involving administration of Uceris to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased by 27% while there was no significant decrease in AUC. Additionally, a mean delay in absorption lag time of 2.4 hours is observed under fed conditions.

Distribution

The mean volume of distribution (VSS) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range 1 to 230 nmol/L, independent of gender.

Metabolism

Following absorption, budesonide is subject to high first-pass metabolism (80-90%). In vitro experiments in human liver microsomes demonstrate that budesonide is rapidly and extensively biotransformed, mainly by CYP3A4, to its 2 major metabolites, 6 β -hydroxy budesonide and 16 α -hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (<1/100) in relation to that of the parent compound.

Excretion

Budesonide is excreted in urine and feces in the form of metabolites. After oral as well as intravenous administration of micronized [3H]-budesonide, approximately 60% of the recovered radioactivity is found in urine. The major metabolites, including 6 β -hydroxy budesonide and 16 α -hydroxy prednisolone, are mainly renally excreted, intact or in conjugated forms. No unchanged budesonide is detected in urine.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1: Clinical Studies Conducted with Budesonide MMX

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	126
					Budesonide MMX 9 mg/day x 8 wk	127
					Asacol 2 x 400 mg t.i.d. x 8 wk (2400 mg/day)	127
					Placebo x 8 wk	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	128
					Budesonide MMX 9 mg/day x 8 wk	128
					Entocort EC 3 x 3 mg/day x 8 wk	126
					Placebo x 8 wk	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	17
					Budesonide MMX 9 mg/day x 8 wk	15
					Placebo x 8 wk	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)	18
					Group B: Placebo x 4 wk (Period 1), then budesonide MMX 9 mg/day x 4 wk (Period 2)	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	62
					Placebo x 12 mo	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	13
					Budesonide MMX 9 mg single dose	13
					Entocort EC 3 x 3 mg single dose	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)	12
					Budesonide MMX 9 mg/day x 7 days, fasted (second phase)	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).

5.2 Review Strategy

For this submission, pivotal studies CB-01-02/01 and CB-01-02/02 were reviewed in detail. Details of the study design and conduct are contained in Section 5. Study results are discussed in Sections 6 (efficacy) and 7 (safety). Aspects of supportive studies are discussed when relevant. The remaining studies safety results are included in the various populations of the safety section.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol Summary

Title

Study CB-01-02/01

Efficacy and Safety of New Oral Budesonide MMX 6 mg and 9 mg Extended Release Tablet Formulations in Patients with Mild or Moderate, Active Ulcerative Colitis. A Multicenter, Randomized, Double-Blind, Double Dummy, Comparative Study Versus Placebo, With an Additional Reference Arm Evaluating Asacol® 2400 mg.

Study CB-01-02/02

Efficacy and Safety of Oral Budesonide MMX 6 mg and 9 mg Extended Release Tablets in Patients with Mild or Moderate Active Ulcerative Colitis. A Multicenter, Randomized, Double-Blind, Double-Dummy, Comparative Study Versus Placebo with an Additional Reference Arm Evaluating Entocort® EC.

Study Centers and Study Period

Study CB-01-02/01

This study was conducted from 20 August 2008 to 28 May 2010 in 108 centers in four countries. Participating countries included: Canada, Mexico, India, and the United States.

Study CB-01-02/02

The study was conducted from 24 July 2008 to 13 February 2010 at 69 study sites in 15 countries. Participating countries included:

- Western Europe (Italy, France, UK, Belgium and Sweden)
- Eastern Europe (Romania, Poland, Slovakia, Ukraine, Estonia, Lithuania, Russia and Latvia)
- Remaining countries (Israel and Australia)

Study Objectives

Study CB-01-02/01 and Study CB-01-02/02

The *primary objective* of both of the studies was to evaluate the efficacy and safety of oral budesonide MMX 6 mg and 9 mg extended-release tablets compared with placebo for the induction of remission (see definition in Study Endpoints section below) in patients with active, mild or moderate UC, when administered for 8 weeks.

The *secondary objective* of both of the studies was to evaluate clinical and endoscopic improvement of oral budesonide MMX 6 mg and 9 mg extended-release tablets when compared with placebo in patients with active, mild or moderate UC after 8 weeks of treatment.

Study Design

Study CB-01-02/01

This was a multi-center, randomized, double-blind, double-dummy, parallel group, comparative study of 8 weeks of treatment with budesonide MMX 6 mg or 9 mg tablets or placebo in patients with active, mild or moderate UC. A reference arm using Asacol 400 mg (2 x 400 mg tablets three times daily (TID)) was also included.

After confirmation of eligibility and provision of signed informed consent, eligible patients were to undergo full colonoscopy to evaluate mucosal appearance of all colonic districts; three biopsies were taken from the most severe areas of colonic lesions. Biopsies were evaluated in accordance with the criteria of Saverymuttu⁵ at an independent central lab. Additional biopsies were taken for comparison at Week 8.

Following completion of screening and confirmation of eligibility, patients discontinued their current treatment and underwent a *2-day washout period during which they received no treatment for UC*. Following the washout period, patients were randomized (by a centralized interactive voice response system (IVRS)) to one of the following four treatment groups:

- placebo (budesonide MMX-matched and Asacol-matched)
- budesonide MMX 9 mg
- budesonide MMX 6 mg
- Asacol 2400 mg

All treatments were administered once per day. A double-dummy procedure was used to maintain the blind, with each treatment group receiving the combinations of drugs three times daily, for up to 8 weeks.

Thus, each patient took 1 tablet and 6 over-encapsulated tablets per day (for 8 weeks), corresponding to active or placebo study drug according to the randomized treatment assignment.

⁵ See Table 1 in Appendix A for Saverymutta Scale

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 follow-up safety visit was to be conducted 2 weeks after the Final Visit. Patients were considered to have completed the study if they completed 8 weeks of treatment.

Study CB-01-02/02

This was a multi-center, randomized, double-blind, double-dummy, parallel group, comparative study of 8 weeks of treatment with budesonide MMX 6 or 9 mg tablets or placebo in patients with active, mild or moderate UC. A reference arm using Entocort EC 9 mg (3 x 3 mg capsules daily) was also included.

After confirmation of eligibility and provision of signed informed consent, patients discontinued their current treatment and underwent a *2-day washout period during which they received no treatment for UC*. Following the washout period, patients were randomized (by a centralized interactive voice response system (IVRS)) to one of the following four treatment groups:

- placebo (budesonide MMX-matched and Entocort EC-matched)
- budesonide MMX 9 mg
- budesonide MMX 6 mg
- Entocort EC 3 x 3 mg

All treatments were administered once per day. A double-dummy procedure was used to maintain the blind, with each treatment group receiving the combinations of drugs once daily, for up to 8 weeks.

Thus, each patient took one tablet and three capsules per day (for 8 weeks), corresponding to active or placebo study drug according to the randomized treatment assignment.

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 follow-up safety visit was to be conducted 2 weeks after the Final Visit. Patients were considered to have completed the study if they completed 8 weeks of treatment.

Efficacy Measurements

Study CB-01-02/01 and Study CB-01-02/02

Colonoscopy, mucosal biopsies and histological assessment

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 Visit 5 (Day 56). During colonoscopy, three biopsies were taken from the colonic lesions considered to be most severe.

Each specimen was examined by a histopathologist to determine severity of enterocyte and crypt changes, and the cellularity of the lamina propria. All biopsy evaluations were performed at a single histopathology center by a blinded histopathologist, using the Saverymuttu scoring system (see Table 1 in Appendix A). The result of the biopsy was available only after randomization. The histological activity grade was determined from the total Saverymuttu score (see Table 2 in Appendix A). Patients were considered to have active disease only when at least one of the biopsies had a score > 1 (according to Table 2 in Appendix A); patients were considered to have histological healing, or to have normal baseline histology if all available biopsies from a colonoscopy had a score ≤ 1 (corresponding to a histological activity grade of 0) (according to Table 2 in Appendix A).

Mucosal appearance results from the colonoscopy were used in calculating the UCDAI (see Ulcerative Colitis Disease Activity Index below).

Ulcerative Colitis Disease Activity Index

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), which were scored as described in the table below. Stool frequency and rectal bleeding were based on information recorded in the patient diaries, and mucosal appearance was based on colonoscopy results. *The total UCDAI score is the sum of the scores for all four components. To be eligible for the study, patients were required to have a total UCDAI score of ≥ 4 and ≤ 10.*

Of note, at this time, there is no rigorous standard to evaluate the efficacy of therapy for UC. While there are many empiric indices for the assessment of disease activity in UC, none of them have been formally validated. However, the UCDAI has been used to determine efficacy in previous registration trials.

Table 2: UCDAI Assessments and Scores

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	1
	Moderate	2
	Severe	3

Study Population

Study CB-01-02/01 and Study CB-01-02/02

Key Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

- 18-75 years old, suffering from UC for at least 6 months
- Diagnosis of UC in active phase, of mild or moderate severity, with UCDAI ≥ 4 and ≤ 10
- If female of childbearing potential had to have a negative serum pregnancy test immediately prior to enrolment, and had to agree to be completely abstinent or be using an accepted form of contraception throughout the entire study period.

Key Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

- Presence of limited distal proctitis (from anal verge up to 15 cm above the pectineal line)
- Diagnosis of severe UC (UCDAI > 10)
- Presence of infectious colitis
- Evidence or history of toxic megacolon
- Presence of severe anemia, leucopenia or granulocytopenia
- Use of oral or rectal steroids in the last 4 weeks
- Use of immunosuppressive agents in the last 8 weeks before the study
- Use of anti-TNF α agents in the last 3 months
- Concomitant use of any rectal preparation
- Concomitant use of antibiotics or cytochrome P450 3A4 (CYP3A4) inducers or CYP3A4 inhibitors
- Verified, presumed or expected pregnancy or ongoing lactation
- Presence of liver cirrhosis, evident hepatic or renal disease/ insufficiency or severe diseases in other organs and systems
- Presence of local/ systemic complications or other pathological states requiring a therapy with corticosteroids and/or immunosuppressive agents
- Diagnosis of type 1 diabetes, hepatitis B, hepatitis C or HIV
- Diagnosis or family history of glaucoma

Blinding

Study CB-01-02/01 and Study CB-01-02/02

Both were double-blind studies. A double-dummy approach was required to maintain the blind because budesonide MMX tablets were distinguishable from both Asacol and Entocort EC capsules.

Prior and Concomitant Therapy

Study CB-01-02/01 and Study CB-01-02/02

Patients were advised not to use any medication without approval from the Investigator. Concomitant medication for the treatment of UC was not allowed during the study. Patients had to refrain from taking other medications throughout the study; in particular, use of antibiotics, pro-kinetic and anti-motility agents were prohibited. CYP3A4, 5 and 7 inhibitors and inducers prohibited in this study are listed in Table 5 in Appendix A.

Study Visits and Procedures

Study CB-01-02/01 and Study CB-01-02/02

The study visits and related safety assessments are summarized in the tables below.

Clinical Review
 Marjorie F. Dannis, M.D.
 NDA 203634
 Uceris (Budesonide MMX)

Table 3: Schedule of Events

Visit	Visit 1 Screening Day -16 to -2	Visit 2 Day 1 (post 2-day Washout ¹)	Visit 3 Day 14 ± 2	Visit 4 Day 28 ± 2	Visit 5 Day 56 ± 2	Final visit ² (Early withdrawal or Day 56)	Follow up (14 days after final visit)
Signing of informed consent	X						
Demographic data	X						
Medical history	X						
UC history	X						
Eligibility criteria check	X						
Physical examination	X	X ^{3,4}	X	X		X	X ³
Evaluation of potential glucocorticoid effects	X			X		X	X
Blood sampling for hematology and biochemistry laboratory assessments ⁵	X		X ⁶	X ⁶		X	
Morning plasma cortisol	X	X ⁴	X	X		X	
Stool sampling	X						
Urinalysis	X		X	X		X	
Pregnancy test (for females) ⁷	X	X ⁴	X	X		X	
Vital signs ⁸	X	X ⁴	X	X		X	
Adverse events	X ⁹	X ⁴	X	X	X	X ¹²	X
Prior/Concomitant medications	X	X ⁴	X	X	X	X ¹²	
Full colonoscopy	X ¹⁰				X		
Mucosal biopsy	X ¹⁰				X		
CAI	X		X	X	X		
UCDAI	X				X		
EI	X				X		
IBD-QoL	X		X	X	X		
Issue of study drugs		X ¹¹		X			

Visit	Visit 1 Screening Day -16 to -2	Visit 2 Day 1 (post 2-day Washout ¹)	Visit 3 Day 14 ± 2	Visit 4 Day 28 ± 2	Visit 5 Day 56 ± 2	Final visit ² (Early withdrawal or Day 56)	Follow up (14 days after final visit)
Diary issue	X ¹³	X		X			
Diary assessment		X	X	X	X	X ¹²	
Compliance check				X	X	X ¹²	
Collection of unused drugs				X	X	X ¹²	

Abbreviations: UC, ulcerative colitis, UCDAI, Ulcerative Colitis Disease Activity Index; CAI, Clinical Activity Index; EI, Endoscopic Index; IBD-QoL, Inflammatory Bowel Disease Quality of Life Questionnaire.

- ¹ Washout of current UC therapy occurred 2 days prior to the first planned dose of study drug (Day -2 to Day -1) after informed consent was obtained and eligibility criteria were confirmed.
- ² Final visit assessments also had to be performed for patients who completed Visit 5 (Day 56) assessments.
- ³ Only an abbreviated physical examination was performed.
- ⁴ Assessments were performed before administration of study drug.
- ⁵ Hematology assessments were as follows: red blood cells (RBC), white blood cell count (WBC), platelets, hemoglobin, hematocrit and erythrocyte sedimentation rate (ESR). Biochemistry assessments were as follows: C-reactive protein (CRP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), creatinine, urea (blood urea nitrogen [BUN]), glucose, total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, sodium, potassium.
- ⁶ After completion of blood sampling procedures, patients received a light breakfast appropriate to the given country. After breakfast, patients received their morning dose of study drug.
- ⁷ For females of childbearing potential only. A serum pregnancy test was performed at the screening and final visits and a urine pregnancy test was performed at Visit 2 (Day 1), Visit 3 (Day 14) and Visit 4 (Day 56).
- ⁸ Vital signs were oral temperature, respiratory rate, pulse and blood pressure after 5 minutes seated.
- ⁹ Any AEs that occurred prior to signing the inform consent form were to be captured in the medical history section of the CRF.
- ¹⁰ Full colonoscopy and mucosal biopsies unless the same procedures were performed within one previous month and the results were available.
- ¹¹ Patients received their first dose of study drug after vital signs, concomitant medications and baseline AEs were recorded and an abbreviated physical examination had been performed.
- ¹² These assessments were to be performed if not already performed at Visit 5 (Day 56).
- ¹³ Diary was to record patient symptoms for Days -16 to -2 only. Patients were not required to make diary entries during the washout period.

Study Endpoints

Study CB-01-02/01 and Study CB-01-02/02

The primary endpoint for both studies was clinical remission after 8 weeks of treatment.

To be considered in remission, patients had to meet all of the following criteria:

- UCDAI score of ≤ 1 , with subscores of 0 for both rectal bleeding and stool frequency
- A normal mucosa (no friability) by endoscopy (via colonoscopy) at the end of Week 8
- A ≥ 1 -point reduction in the endoscopy score from baseline to the end of Week 8

Colonoscopies were required for the evaluation of the mucosa at both Screening and Week 8.

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 the mucosal appearance subscore from baseline to the end of Week 8

Other endpoints were as follows:

- Symptom resolution (stool frequency and rectal bleeding subscores [from the UCDAI] of 0)
- Histologic healing (total histologic score of ≤ 1 for all biopsy specimens)
- Levels of the bio-humoral markers ESR and CRP
- IBD-QoL scores
- CAI score ≤ 4
- Treatment failure (worsening of UC), after 8 weeks of treatment

6 Review of Efficacy

Efficacy Summary

The efficacy of budesonide MMX 9 mg in inducing remission was established by the results of the two randomized, double-blind, double-dummy, placebo-controlled, parallel group, multi-center studies (CB-01-02/01 and CB-01-02/02). Each of these studies demonstrated that budesonide MMX 9 mg was statistically significantly superior to placebo in inducing clinical remission, the primary endpoint of both studies.

A stringent definition of the primary endpoint was applied in CB-01-02/01 and CB-01-02/02, incorporating symptomatic (clinical), endoscopic, and Investigator-based criteria into the definition of remission.

According to the Sponsor, the ITT population was defined prospectively in the Statistical Analysis Plan (SAP) for each study; it included all randomized patients who received at least one dose of study drug, had no major entry criteria violations, had no major GCP violations, and had histological evidence of active UC disease at baseline.

The timing of the Sponsor's changes in analysis populations was not ideal, and presented challenging review issues. However, according to this reviewer, the Sponsor's ITT population does represent the appropriate population for the primary analyses, as it includes only patients who have active, mild/moderate UC and includes only reliable patient data.

6.1 Indication

The Applicant is proposing that budesonide MMX receive an indication "for the induction of remission in patients with active, mild to moderate ulcerative colitis".

6.1.1 Methods

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

Efficacy Issues for Study CB-01-02/01 and Study CB-01-02/02

Dates of Study CB-01-02/01

1st patient randomized - 20 Aug 2008
Last patient completed - May 28, 2010

Dates of Study CB-01-02/02

1st patient randomized - 24 July 2008
Last patient completed -13 February 2010

During and after these studies, the Sponsor wanted to alter the primary analysis population of both studies protocols; however, FDA recommended against this, stating it would be a "serious review issue(s) regarding the integrity of study."

On July 16, 2010, the Sponsor amended both SAPs, reportedly "prior to database lock and study unblinding."

The Sponsor's new "ITT" population⁶ now included all randomized patients who received one dose of drug but *excluded* patients who had:

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

The Sponsor provided the following justification for the modification to the primary analysis population:

1. The protocols were developed in 2007 and early 2008 and represented the current clinical understanding of UC and accepted study designs at the time.

2. While the studies were ongoing, the EMA issued a new Guidance on 1 August 2008 which specified that only patients with confirmed, active UC should be included in clinical trials. It stated:

- *"Only patients having confirmed ulcerative colitis should be included in trials. Extent as well as severity of the disease should be defined by recent clinical and endoscopic evaluation. The absence of histological evidence of inflammation at trial entry excludes a diagnosis of active colitis."*

3. FDA has accepted registration studies that required histological confirmation of active disease as an entry criterion. The absence of histologically proven disease was an exclusion criterion in the ACT 1 and ACT 2 infliximab trials, as the absence of histological inflammation excluded the diagnosis of active UC.

4. In 2009, the budesonide MMX IND was transferred from one Sponsor to another. At that time, the new (current) Sponsor assessed the adequacy of the analysis populations, endpoints and statistical analyses described in the protocol in light of the current clinical thinking, the European Guidance, and regulatory precedence in the US.

5. The current Sponsor amended the SAPs (dated 16 July 2010) for the two Phase III studies prior to database lock and study unblinding and included in the ITT population only those patients demonstrated to have active UC.

6. Additionally, the SAP-defined ITT population also excluded patients with major entry criteria violations (i.e., C. difficile infection) at Screening, and patients enrolled at sites with major GCP violations. Rationale for these further exclusions was as follows:

- *The exclusion of patients with infectious colitis at study entry was a pre-specified exclusion criterion in the study protocol.*

⁶ Will be referred to as mITT population

- *The exclusion of patients from study sites where GCP violations were identified is consistent with ICH Guidelines which mandate that any results obtained in substantial noncompliance with GCP must be excluded*

7. *The Sponsor claimed that the revision of the SAPs did not introduce bias into the existing budesonide MMX clinical studies because:*

- *The collection of mucosal biopsies at Screening was a prospectively-required procedure in the original Phase III 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.*

Analysis Populations

Study CB-01-02/01

A total of 509 patients were randomized (129 placebo, 127 MMX 9 mg, 126 MMX 6 mg, and 127 Asacol).

A total of 489 patients were included in the sponsor's ITT population (mITT): placebo, n = 121; budesonide MMX 9 mg, n = 123; budesonide MMX 6 mg, n = 121; and Asacol 2400 mg, n = 124.

Thus, a total of 20 patients were excluded from the mITT population (8 placebo, 4 MMX 9 mg, 5 MMX 6 mg, and 3 Asacol)⁷. These 20 patients included 3 patients with infectious colitis and 17 patients with "normal" histology. There were no GCP violations in this study.

Study CB-01-02/02

A total of 509 patients were randomized and treated and a total of 410 patients were included in the mITT population.

The 101 excluded patients (40 placebo; 19 MMX 9 mg; 19 MMX 6 mg; 23 Entocort) comprised: 1 patient who was confirmed following randomization to have infectious colitis at study entry; 2 who were not randomized; all 50 patients enrolled at 4 sites that were found to have committed major GCP violations; and 77 patients with normal histology at baseline⁸ (33 placebo; 12 MMX 9 mg; 16 MMX 6 mg; 16 Entocort). There

⁷ There were slightly more excluded patients from the placebo group, but the total numbers per group were small

⁸ Twenty-nine of the 101 excluded patients had both normal histology at baseline and major GCP violations, and are thus included in both categories. See Tables in Appendix B for individual patient data

were more patients excluded from this study (compared to Study CB-01-02/01) and it appears as if there is a disproportionate number of a placebo patients excluded. See Table below.

Table 4: Exclusions from Total randomized/Treated Population which resulted in Sponsor’s mITT Analysis Population

Category	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Entocort EC 9 mg	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Safety	129	128	128	126	511
ITT	89	109	109	103	410
Patients excluded from 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)
Major entry criteria violation	0	1 (0.8)	0	0	1 (0.2) ^b
GCP violation	20 (15.5)	9 (7.1)	9 (7.0)	12 (9.5)	50 (9.8)
Normal histology	33 (25.6)	12 (9.5)	16 (12.5)	16 (12.7)	77 (15.1) ^c

Source: Table 14.1-1 and Table 14.1-5

Abbreviations: Budes., budesonide.

Notes: Patients could have more than one reason for being excluded. The denominator for calculating percentages is the number of patients in each treatment group in the Safety population. The ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry

SCR Study CB-01-02/02 Table 8

GCP Violations

According to the Sponsor, inspections performed at four different sites “did not meet the level of GCP and data integrity requirements”. Thus, all of the data from these sites was excluded from the mITT analysis (20 placebo; 9 MMX 9 mg; 9 MMX 6 mg; 12 Entocort) Specific information about the nature of the violations is available in Appendix A.

Efficacy Discussion

There were two ways to analyze data for the efficacy evaluation of this drug. The first is a purely statistical approach and the second is an approach taking many clinical factors into consideration. These clinical factors are relevant to the disease process and the integrity of the study. The primary analysis population was changed during/after the study; however, the Sponsor’s exclusions were patients whose clinical data would not be appropriate to interpret. 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. In addition, the interpretation of histology slides was performed at a central location and thus represents an objective measure.

According to ICH-E9, there are a limited number of circumstances that might lead to the exclusion of randomized subjects from the full analysis set: failure to satisfy major entry criteria, failure to take at least one dose of trial medication and lack of any data post randomization. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

- The entry criterion was measured prior to randomization
- The detection of the relevant eligibility violations can be made completely objectively
- All subjects receive equal scrutiny for eligibility violations; data should not be unblinded prior to this scrutiny
- All detected violations of the particular entry criterion are excluded.

Thus, this reviewer concludes that the Sponsor's mITT population can be considered as valid and evaluable.

6.1.2 Demographics

Study CB-01-02/01 and Study CB-01-02/02

Baseline demographic characteristics for the mITT population of Studies CB-01-02/01 and CB-01-02/02 are presented in the table below. As discussed in Section 6.1.1, these populations represent the primary efficacy analysis populations of each of these studies. Both studies randomized a predominance of Caucasian male patients. In Study CB-01-02/02, practically all patients were Caucasian. In Study CB-01-02/01, approximately one-third of the patients were Asian. Both studies had similar median ages and age ranges.

Table 5: Demographics Study 02/01 and 02/02

Demographic Subgroup	Study CB-01-02/01 *(mITT Population)				Study CB-01-02/02 *(mITT Population)			
	Placebo N=121	Budesonide MMX 9 mg N=123	Budesonide MMX 6 mg N=121	Asacol 2400 mg N=124	Placebo N=89	Budesonide MMX 9 mg N=109	Budesonide MMX 6 mg N=109	Entocort EC 2400 mg N=103
Sex (n,%)								
Male	68 (56)	77 (63)	59 (49)	69 (56)	57 (64)	64 (59)	57 (52)	55 (53)
Female	53 (44)	46 (37)	62 (51)	55 (44)	32 (36)	45 (41)	52 (48)	48 (47)
Age (years)								
median	39	42	43	45	42	44	43	45
Min, Max	18, 77	19, 68	18, 75	18, 72	19, 74	20, 69	18, 74	19, 75
Race (n,%)								
Caucasian	64 (53)	60 (49)	60 (50)	61 (49)	89 (100)	107 (98)	109 (100)	103 (100)
Black	7 (6)	9 (7)	11 (9)	8 (7)	0	0	0	0
Hispanic	9 (7)	8 (7)	7 (6)	12 (10)	0	0	0	0
Asian	39 (32)	44 (36)	42 (35)	43 (35)	0	1 (1)	0	0
Other	2 (2)	2 (2)	1 (1)	0	0	1 (1)	0	0

Adapted from Study 02/01 CSR, Table 12 p 58 and Study 02/02 CSR Table 11 p 59

* mITT population is ITT population excluding patients with: GCP violations, histological evidence of normal mucosa and infectious colitis

Ulcerative Colitis History

UC history was generally similar across treatment groups in both pivotal studies (see Table 3 and 4: Summary of Ulcerative Colitis History (mITT Population) for Study CB-01-02/01 and Study CB-01-02/02 respectively in Appendix A). 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 with similar ranges of 0 to approximately 50 years. Time since diagnosis was longest for the Asacol group (4.8 years) and Entocort EC group (4.6 years). For both pivotal studies:

- The overall median age at diagnosis was approximately 35 years.
- The median number of flares in the last two years was 2.
- The severity of last flare was moderate for the majority (66%) of patients.
- The median scores of 7.0 for baseline UCDAI and Endoscopic Index were consistent with mild to moderate disease, as required for participation in the study.

6.1.3 Subject Disposition

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%). See table below for additional patient disposition information.

Study CB-01-02/02

Among 410 patients in the mITT analysis population, 272 (66%) completed the study. Once again, the most common reasons for early withdrawal from the study were treatment failure (n = 85; 21%) and withdrawal of consent (n = 30; 7%). However, there was a higher treatment failure rate across all treatment groups in this study, 19%-24% vs. 7%-12%. See table below for additional patient disposition information.

Table 6: Patient Disposition of Pivotal Studies

Category	Study CB-01-02/01 *(mITT Population)				Study CB-01-02/02 *(mITT Population)			
	Placebo N=121	Budesonide MMX 9 mg N=123	Budesonide MMX 6 mg N=121	Asacol 2400 mg N=124	Placebo N=89	Budesonide MMX 9 mg N=109	Budesonide MMX 6 mg N=109	Entocort EC 2400 mg N=103
Completed Study								
Yes	76 (63)	89 (72)	89 (74)	95 (77)	61 (69)	76 (70)	67 (62)	68 (67)
No	45 (37)	34 (28)	32 (26)	29 (23)	28 (32)	33 (30)	42 (39)	35 (34)
Discontinued due to:								
AE	10 (8)	6 (5)	5 (4)	7 (6)	1 (1)	2(2)	2(2)	3 (3)
Protocol violation	2(2)	1 (1)	1 (1)	1 (1)				
Withdrew consent	10 (8)	11 (9)	8 (7)	9 (7)	7 (8)	6 (6)	10 (9)	7 (7)
Lost to follow-up	4 (3)	5 (4)	1 (1)	2(2)	1 (1)	1 (1)	0	0
Investigator Decision	2(2)	2(2)	3 (3)	2(2)	1 (1)	2(2)	3 (3)	2(2)
Sponsor Decision	0	0	1 (1)	0	0	0	0	1 (1)
Treatment Failure	14 (12)	9 (7)	13 (11)	8 (7)	17 (19)	21 (20)	26 (24)	21 (20)
Other	3 (3)	0	0	0	1 (1)	1 (1)	1 (1)	1 (1)

Adapted from Study 02/01 CSR, Table 11 p 56 and Study 02/02 CSR Table 11 p 58

6.1.4 Analysis of Primary Endpoint(s)

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 budesonide MMX 9 mg than for patients receiving placebo (17.9% vs. 7.4%, $p = 0.0143$). Thus, the treatment effect between budesonide MMX 9 mg and placebo was 10.4%. Clinical remission rates in the budesonide MMX 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 7: 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 $\alpha = 0.025$ level of significance and the comparison of Asacol and placebo were conducted at the $\alpha = 0.05$ level of significance. The study was not powered to show statistical significance for Asacol versus budesonide MMX.

* Value is statistically significant at the $\alpha = 0.025$ level.

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 budesonide MMX 9 mg than for patients receiving placebo (17.4% vs. 4.5%, $p = 0.0047$). Thus the treatment effect between budesonide MMX 9 mg and placebo was 12.9%. Clinical remission rate in the budesonide MMX 6 mg group (8.3%) was numerically greater than placebo, but the differences did not reach statistical significance. The percentage of patients achieving remission in the Entocort EC group (12.6%) was statistically higher than that of patients receiving placebo ($p = 0.0481$). See table below.

Table 8: 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 $\alpha = 0.025$ for comparisons of budesonide MMX and placebo and $\alpha = 0.05$ 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 $\alpha = 0.025$ level.

[†] Value is statistically significant at the $\alpha = 0.05$ level.

CSR Study CB-01-02/01 Table 17

6.1.5 Analysis of Secondary Endpoints(s)

Clinical Improvement

Study CB-01-02/01

Results for clinical improvement in the mITT population (worst case and observed case methods) are shown in the table below. Differences in clinical improvement rates (using both methods) between all active treatment groups and placebo were not statistically significant.

Table 9: Rates of Clinical Improvement mITT Population Study CB-01-02/01

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Asacol 2400 mg
Worst case, N	121	123	121	124
Clinical Improvement, n (%)	30 (24.8)	41 (33.3)	37 (30.6)	42 (33.9)
95% CI	17.1, 32.5	25.0, 41.7	22.4, 38.8	25.5, 42.2
Difference between active and placebo		8.5	5.8	9.1
95% CI		-2.8, 19.9	-5.5, 17.0	-2.3, 20.4
p-value		0.1420	0.3146	0.1189
Observed case, N	64	72	75	80
Improvement, n (%)	30 (46.9)	41 (56.9)	37 (49.3)	42 (52.5)
95% CI	34.6, 59.1	45.5, 68.4	38.0, 60.6	41.6, 63.4
Difference between active and placebo		10.1	2.5	5.6
95% CI		-6.7, 26.8	-14.2, 19.1	-10.8, 22.0
p-value		0.2406	0.7725	0.5023
Worst case, N	121	123	121	124
Clinical Improvement, n (%)	30 (24.8)	41 (33.3)	37 (30.6)	42 (33.9)

Source: [Table 14.2-2.1.1](#)

Abbreviation: Budes., budesonide; ITT, intent-to-treat; CI: confidence interval

Notes: Patients with missing data that precluded determination of clinical improvement were analyzed as indicated (worst case and observed case methods). For the worst case analysis, the denominator for calculating percentages was the number of patients in each treatment group in the ITT population. For the observed case analysis, the denominator for calculating percentages is the number of patients in each treatment group with non-missing values. All p-values were based on the Chi-square test; comparisons of budesonide MMX and placebo were conducted at the $\alpha = 0.025$ level of significance and the comparison of Asacol and placebo were conducted at the $\alpha = 0.05$ level of significance. The study was not powered to show statistical significance for Asacol versus budesonide MMX.

CSR Study CB-01-02/01 Table 20

Study CB-01-02/02

Results for clinical improvement in the mITT population (worst case and observed case methods) are shown in the table below. Differences in clinical improvement rates between the active treatment groups and placebo were not statistically significant, although Budesonide MMX 9 mg achieved a numerically higher rate of clinical improvement than all other groups using both methods.

Table 10: Rates of Clinical Improvement mITT Population Study CB-01-02/02

	Placebo	Budes.MMX 9 mg	Budes. MMX 6 mg	Entocort EC 9 mg
Worst case, N	89	109	109	103
Clinical Improvement, n (%)	30 (33.7)	46 (42.2)	28 (25.7)	34 (33.0)
95% CI	23.9, 43.5	32.9, 51.5	17.5, 33.9	23.9, 42.1
Difference vs. Placebo		8.5	-8.0	-0.7
95% CI for the Difference		(-5.0, 22.0)	(-20.8, 4.8)	(-14.1, 12.7)
p-value		0.2215	0.2174	0.9185
Observed case, N	54	69	58	58
Improvement, n (%)	30 (55.6)	46 (66.7)	28 (48.3)	34 (58.6)
Difference vs. Placebo		11.1	-7.3	3.1
95% CI for the Difference		(-6.2, 28.4)	(-25.7, 11.2)	(-15.3, 21.4)
p-value		0.2082	0.4411	0.7433

Source: [Table 14.2-2.1.1](#)

Abbreviation: Budes., budesonide; ITT, intent-to-treat; CI: confidence interval

Notes: Patients with missing data that precluded determination of remission were analyzed as indicated (worst case or observed case methods). For the worst case analysis, the denominator for calculating percentages was the number of patients in each treatment group in the ITT population. For the observed case analysis, the denominator for calculating percentages is the number of non-missing observations within the imputation method in each treatment group in the ITT population. All p-values were based on the Chi-square test; comparisons of budesonide MMX and placebo were conducted at the $\alpha = 0.025$ level of significance and the comparison of Entocort EC and placebo were conducted at the $\alpha = 0.05$ level of significance. Study was not powered to show statistical significance for Entocort EC versus budesonide MMX.

CSR Study CB-01-02/02 Table 20

Endoscopic Improvement **Study CB-01-02/01**

Results for endoscopic improvement in the mITT population (worst case and observed case methods) are shown in the table below. Using both methods, the rate of endoscopic improvement was higher in the budesonide MMX 9 mg group (42% and 57%) than in the other treatment groups. However, according to the Sponsor, as per the hierarchical testing procedure for secondary endpoints, because clinical improvement was not statistically significant in the mITT population, formal statistical comparisons of endoscopic improvement between the two budesonide MMX groups and placebo were not conducted.

Table 11: Rates of Endoscopic Improvement mITT Population Study CB-01-02/01

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Asacol 2400 mg
Worst case, N	121	123	121	124
Endoscopic improvement: n (%)	40 (33.1)	51 (41.5)	43 (35.5)	41 (33.1)
95% CI	24.7, 41.4	32.8, 50.2	27.0, 44.1	24.8, 41.3
Difference between active and placebo		8.4	2.5	0.0
95% CI		ND	ND	-11.8, 11.8
p-value		ND	ND	0.9991
Observed case, N	75	89	85	95
Endoscopic improvement: n (%)	40 (53.3)	51 (57.3)	43 (50.6)	41 (43.2)
95% CI	42.0, 64.6	47.0, 67.6	40.0, 61.2	33.2, 53.1
Difference between active and placebo		4.0	-2.7	-10.2
95% CI		ND	ND	-25.2, 4.9
p-value		ND	ND	0.1872

CSR Study CB-01-02/01 Table 22

Study CB-01-02/02

Results for endoscopic improvement in the mITT population (worst case and observed case methods) are shown in the table below. Using both methods, the rate of endoscopic improvement was higher in the budesonide MMX 9 mg group (42% and 63%) than in the other treatment groups. However, according to the Sponsor, as per the hierarchical testing procedure for secondary endpoints, because clinical improvement was not statistically significant in the mITT population, formal statistical comparisons of endoscopic improvement between the two budesonide MMX groups and placebo were not conducted.

Table 12: Rates of Endoscopic Improvement mITT Population Study CB-01-02/02

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Entocort EC 9 mg
Worst case, N	89	109	109	103
Endoscopic Improvement, n (%)	28 (31.5%)	46 (42.2%)	28 (25.7%)	38 (36.9%)
95% CI	21.8, 41.1	32.9, 51.5	17.5, 33.9	27.6, 46.2
Difference vs. placebo	--	10.7	-5.8	5.4
95% CI for the Difference	--	--	--	(-8.0, 18.8)
p-value	--	--	--	0.4293
Observed case, N	57	73	64	65
Improvement, n (%)	28 (49.1%)	46 (63.0%)	28 (43.8%)	38 (58.5%)
Difference vs. placebo	--	13.9	-5.4	9.3
95% CI for the Difference	--	--	--	-8.3, 27.0
p-value	--	--	--	0.3017

Source: [Table 14.2-2.2.1](#)

Abbreviations: Budes., budesonide; ITT, intent-to-treat; CI: confidence interval

Notes: Patients with missing data that precluded determination of remission were analyzed as indicated (worst case or observed case methods). For the worst case analysis, The denominator for calculating percentages was the number of patients in each treatment group in the ITT population. For the observed case analysis, the denominator for calculating percentages is the number of non-missing within the imputation method in each treatment group in the ITT population. All p-values were based on the Chi-square test; comparisons of budesonide MMX and placebo were conducted at the $\alpha = 0.025$ level of significance and the comparison of Entocort EC and placebo were conducted at the $\alpha = 0.05$ level of significance. The study was not powered to show statistical significance for Entocort EC versus budesonide MMX.

CSR Study CB-01-02/02 Table 22

6.1.6 Other Endpoints

For both pivotal studies, there were many other endpoints investigated; however, most evaluations did not show a statistically significant treatment difference between budesonide MMX 9 mg and placebo.

6.1.7 Subpopulations

A comparison of remission rates was done in the budesonide MMX 9 mg and placebo groups after stratifying for age, sex and geographic region.

Study CB-01-02/01

This analysis indicated that there were numerical differences (at the $\alpha = 0.05$ level) for patients in the following subsets: 1) > 42 years of age (21.0% difference; 95% CI: 8.8% to 33.2%, $p = 0.0024$); 2) female (13.9% difference; 95% CI: 0.9% to 26.9%, $p = 0.0345$); and 3) treated in North America (9.6% difference; 95% CI: 0.7% to 18.5%, $p = 0.0376$). See table below.

Table 13: Rates of Clinical Remission mITT Population Stratified by Age, Sex, and Geographic Region Study CB-01-02/01

	Placebo	Budes. MMX 9 mg	p-value
Remission rate by age			
≤ 42 years: n (%)	7 (9.9)	7 (11.1)	0.8131
> 42 years: n (%)	2 (4.0)	15 (25.0)	0.0024
Remission rate by sex			
Female: n (%)	3 (5.7)	9 (19.6)	0.0345
Male: n (%)	6 (8.8)	13 (16.9)	0.1512
Remission rate by geographic region			
North America: n (%)	4 (4.9)	12 (14.5)	0.0376
India: n (%)	5 (12.8)	10 (25.0)	0.1676

Source: [Tables 14.2-1.3.1, 14.2-1.3.2, and 14.2-1.3.3](#)

North America comprised the US, Canada, and Mexico.

CSR Study CB-01-02/01 Table 18

Study CB-01-02/02

This analysis indicated that there were numerical differences (at the $\alpha = 0.05$ level) for patients in the following subsets: 1) ≤ 43.5 years of age (15.9% difference; 95% CI: 3.6% to 28.2%, $p=0.0195$); 2) male (13.5% difference; 95% CI: 2.3% to 24.7%, $p=0.0246$); and 3) Eastern European (14.0% difference; 95% CI: 3.3% to 24.8%, $p=0.0227$). See table below.

Table 14: Rates of Clinical Remission mITT Population Stratified by Age, Sex, and Geographic Region Study CB-01-02/02

	Placebo	Budes. MMX 9 mg	p-value
Remission rate by age			
≤ 43.5 years: n (%)	2 (4.4)	11 (20.4)	0.0195
> 43.5 years: n (%)	2 (4.5)	8 (14.5)	0.1009
Remission rate by sex			
Female: n (%)	1 (3.1)	7 (15.6)	0.1296
Male: n (%)	3 (5.3)	12 (18.8)	0.0246
Remission rate by geographic region			
Western Europe: n (%)	0 (0.0)	2 (11.1)	0.4866
Eastern Europe: n (%)	1 (2.3)	9 (16.4)	0.0227
Rest of the World: n (%)	3 (10.0)	8 (22.2)	0.1846

Source: [Tables 14.2-1.3.1](#), [14.2-1.3.2](#), and [14.2-1.3.3](#)

Western Europe comprised Italy, France, UK, Belgium, and Sweden. Eastern Europe comprised Romania, Poland, Slovakia, Ukraine, Estonia, Lithuania, and Latvia. Rest of the World comprised Russia, Israel, and Australia.

CSR Study CB-01-02/02 Table 18

From these analyses, it appears that the remission rates were not consistent among certain subgroups. The reason behind this disparity is unclear; however, the overall efficacy of budesonide MMX appears to have been demonstrated.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

For complete information, see the Clinical Pharmacology Review by Dilara Jappar.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Aspects of the long-term Study CB-01-02/04 will be discussed here since in this study, budesonide MMX was used chronically for up to 12 months.⁹

Study Design

Study CB-01-02/04 was a multi-center, randomized, double-blind, parallel group, comparative study designed to evaluate the safety and tolerability of budesonide MMX 6 mg¹⁰ for up to 12 months. However, according to the Sponsor's Statistical Analysis Plan (SAP) the study was not powered to show statistically significant differences between budesonide MMX and placebo, there was no formal sample size calculation performed and the study was planned to be exploratory in nature. In meetings with the Sponsor, it was confirmed that they (b) (4)

⁹ Of note, the dose used was 6 mg as compared to the 9 mg dose used in the short-term pivotal studies.

¹⁰ "and to assess the efficacy of budesonide MMX 6 mg in the maintenance of clinical remission"

(b) (6) would be using the data in support of safety. Nonetheless, some aspects of the study will be briefly described here.

Patients who achieved UCDAI remission in studies CB-01-02/01, CB-01-02/02, and CB-01-02/06¹¹ were eligible to enroll. Clinical remission status was assessed after 1, 3, 6, and 9 months of treatment or at Early Withdrawal. Endoscopic relapse status was assessed by a full colonoscopy performed at the beginning of the study and a flexible sigmoidoscopy performed at the End of Study/Early Withdrawal Visit.

Primary efficacy endpoints were clinical remission after 1, 3, 6, and 9 months of treatment and at the End of Study (12 months) or the Early Withdrawal Visit.

In this study, the Sponsor defined the Intent-to-Treat (ITT) population as: all randomized patients who received at least one dose of a study drug.

Another population was defined as the Efficacy Evaluable (EE) population which was defined as all randomized patients who:

- received at least one dose of a study drug
- were in UCDAI remission at the end of previous short-term study¹²
- had abnormal histology at baseline in short-term studies
- were not enrolled in a site that had GCP violations
- were not withdrawn early from present study due to insufficient bone density at Visit 1

The EE population was the primary population for the efficacy analyses.

Results

A total of 153 patients were screened for study entry, 123 patients were enrolled into the study, and a total of 122 patients were randomized. The majority of the enrolled patients had participated in studies CB-01-02/01 or CB-01-02/02 immediately prior to enrolling into the present study. A summary of patient disposition by treatment group is presented in the table below. As seen below, the EE population is a much smaller patient population.

¹¹ An open label study, see Section 5.1

¹² CB-01-02/01, CB-01-02/02 or CB-01-02/06

Table 15: Study CB-01-02/04 Patient Disposition by Analysis Population

	Placebo	MMX 6 mg	Total
Randomized	60	62	122
Safety Population	61	62	123
Parent Study:			
CB-01-02/01 n (%)	39 (63.9%)	38 (61.3%)	77 (62.6%)
CB-01-02/02 n (%)	18 (29.5%)	19 (30.6%)	37 (30.1%)
CB-01-02/06 n (%)	4 (6.6%)	5 (8.1%)	9 (7.3%)
Efficacy Evaluable Population	32	39	71
Intent-to-Treat (ITT) Population	60	62	122

Summary Clinical Efficacy Table 38

Clinical Remission

In the EE and ITT populations, the percentages of patients in clinical remission in the placebo and budesonide MMX treatment groups after 1, 3, 6, 9, and 12 months of treatment, and at the End of Study/Early Withdrawal Visit, are presented in the table below.

Table 16: Patients in Clinical Remission by Study Visit and Population

Patients in Clinical Remission at:	EE Population		ITT Population	
	Placebo N = 32 x/n (%)	MMX 6 mg N = 39 x/n (%)	Placebo N = 61 x/n (%)	MMX 6 mg N = 61 x/n (%)
1 month	23/30 (76.7%)	30/34 (88.2%)	36/47 (76.6%)	40/46 (87.0%)
3 month	23/25 (92.0%)	30/31 (96.8%)	38/41 (92.7%)	37/41 (90.2%)
6 month	16/21 (76.2%)	20/25 (80.0%)	28/35 (80.0%)	27/34 (79.4%)
9 month	13/15 (86.7%)	19/20 (95.0%)	23/27 (85.2%)	26/28 (92.9%)
12 month	11/13 (84.6%)	14/15 (93.3%)	18/23 (78.3%)	19/22 (86.4%)
End of Study/Early Withdrawal Visit	12/28 (42.9%)	15/26 (57.7%)	22/44 (50.0%)	22/36 (61.1%)

P-values are based on the Chi-square test.
 x = number of patients in clinical remission.
 n = number of patients with sufficient diary data to enable determination of clinical remission status at the indicated visit.
 Adapted from SCE Tables 38 and 39

As shown in the table above, the numbers of patients that remained in clinical remission decreased over the 12-month period in both treatment groups and in both patient populations. The percentages of patients that remained in clinical remission in the budesonide MMX group were numerically higher at each time point when compared

with placebo in both patient populations. According to the Sponsor, no statistically significant differences were observed between groups; however, this was an exploratory study so no statistical comparisons should be made.¹³

Endoscopic Relapse

Summarized in the table below are the percentages of patients (for both study populations) in endoscopic relapse in the placebo and the budesonide MMX groups. The results show that in both study populations numerically more patients in the budesonide MMX group had endoscopic relapses than patients in the placebo group (although much more pronounced in the EE population). Once again, formal statistical comparisons were not relevant here, although it is noted that in the ITT population, the endoscopic relapse rates were similar in both treatment groups.

Table 17: Patients in Endoscopic Relapse

	EE Population		ITT Population	
	Placebo N=61	MMX 6mg N=61	Placebo N=61	MMX 6mg N=61
Patients Experiencing Endoscopic Relapse (n [%]) 95% Confidence Interval	16 (50.0%) (32.7, 67.3)	27 (69.2%) (54.7, 83.7)	39 (63.9%) (51.9, 76.0)	42 (68.9%) (57.2, 80.5)
Difference Between Placebo and Budesonide MMX 95% Confidence Interval	19.2 (-6.2, 44.7)		4.9 (-13.5, 23.3)	
P-value	0.0990		0.5653	

The denominator for calculating percentages is the number of patients in each treatment group or the total number of patients in the ITT population.

Confidence intervals calculated based on the normal approximation

Adapted from SCE Tables 43 and 44

6.1.10 Additional Efficacy Issues/Analyses

Additional analyses were performed on the subset of patients (in each of the pivotal studies) who had “normal histology”. The following definitions were provided by the Sponsor:

1. “Histological healing” or “normal baseline histology”: all available biopsies from a colonoscopy had a score ≤ 1 (corresponding to a histological activity grade of 0)

2. Conversion from Total Score to Histological Activity Grade:

¹³ Since the denominators for calculating percentages included only those patients with sufficient diary information at each time point to determine remission/relapse status, the percentages of patients in clinical remission were not monotonically decreasing, but were generally the same over time.

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

The following trends were apparent from the analyses of this subset of patients:

- Many patients with “normal” histology at Baseline did not have “normal” histology at End of Study.
- Many patients with “normal” histology at Baseline had high Baseline UCDAI scores and some had high Final UCDAI scores.
- Patients with “normal” histology at Baseline would be expected to be in remission at end of study; however, most were not.

See Appendix B for tabulations of individual patient data. It is difficult to draw definitive conclusions from these analyses, but the subset of patients with “normal” histology at Baseline seems to represent a heterogeneous group which may not be appropriate to be included as part of the patient population in UC studies.

7 Review of Safety

Safety Summary

7.1 Methods

Five analysis groups were defined in order to analyze the cumulative safety data from the nine clinical studies in the budesonide MMX clinical development program as shown in the table below.

The first three analysis groups were defined for five short-term induction studies (of 4 to 8 weeks in duration) evaluating budesonide MMX under the intended indication of patients with active, mild to moderate UC. Each of the five studies included one treatment arm with budesonide MMX at the 9 mg dosage strength.

The short-term treatment data is subdivided into a *primary analysis group* (Phase 3 randomized, double blind studies [CB-01-02/01 and CB-01-02/02]) and two *supportive analysis groups* (Phase 2/3 randomized, double blind studies and Phase 2/3 open-label studies). The fourth analysis group (*long-term analysis group*) presents long-term safety data for the 6 mg dosage strength compared to placebo in the “maintenance of remission” in patients with UC. The fifth analysis group combines the Phase 1 data

from three studies in normal, healthy volunteers; however, this group will not be separately evaluated.

Table 18: Safety Analysis Groups

Sections	Analysis Groups	Studies
Short-term (up to 8 weeks) Treatment for Induction of Remission in Patients with UC (ISS Section 4)	Phase III Randomized, Double-blind Studies (Primary Analysis Group)	CB-01-02/01
		CB-01-02/02
	Phase II/III Randomized, Double-blind Studies (Supportive Analysis Group)	CB-01-02/01
		CB-01-02/02 CB-01-02/05 CRO-03-53 (Period 1)
	Phase II/III Open-label studies (Supportive Analysis Group)	CB-01-02/06
		CRO-03-53 (Period 2)
Long-term Treatment (up to 12 months) in Patient with UC (ISS Section 5)	Phase III Randomized, Double-blind 12-month Extension Study	CB-01-02/04
Phase I Clinical Experience in Healthy Volunteers (ISS Section 6)	Phase I Clinical Studies	CRO-01-28 CRO-PK-06-178 CRO-PK-03-105

Source: Applicant's Summary of Clinical Safety

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from:

- Randomized, Double-blind Studies-(CB-01-02/01, CB-01-02/02, CB-01-02/05, CRO-03-53 -Period 1)
- Open Label Studies- CB-01-02/06, CRO-03-53 -Period 2)
- 12-month Extension Study-CB-01-02/04
- Phase I Clinical Studies- (CRO-01-28, CRO-PK-06-178 and CRO-PK-03-105)

Additionally, safety information was obtained from the 120-day safety update that provided updated clinical data on budesonide MMX and new relevant literature involving budesonide from 29 September 2011 through 31 January 2012.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary, Version 11.0.

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

Adverse event incidence data were included from all of the Phase 2 and Phase 3 studies. See Section 7.1 for a description of how pooled data is presented in this review.

7.2 Adequacy of Safety Assessments

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

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

In the overall budesonide MMX clinical development program, a total of 669 patients received at least one dose of budesonide MMX at any dosage strength (3, 6, or 9 mg). The cumulative patient-years of exposure in the entire program was 113 patient-years. The majority of patients who received budesonide MMX (58%) received the 9 mg dosage strength.

The vast majority (95%) of the budesonide MMX patient exposures occurred in patients with UC who participated in the Phase 2 and 3 efficacy and safety studies. While the majority of the exposures have been for up to 8 weeks, exposures of up to 450 days (15 months) have also occurred in the clinical development program.

The dosage strength with the largest numbers of exposures of up to 8 weeks was the 9 mg dosage strength (251 patients with ≥ 8 weeks of exposure). The majority of the exposures beyond 8 weeks occurred in patients who received the 6 mg dosage strength. See table below.

Table 19: Summary of Budesonide MMX Exposure

	Total Patient Years of Exposure ****	Duration of Dosing									
		>= 1 dose	>= 1 wk	>= 2 wks	>= 4 wks	>= 8 wks	>= 3 mo.	>= 6 mo.	>= 9 mo.	>= 12 mo.	>= 15 mo.
Overall *	113.0										
9 mg	47.1	389	341	324	300	251	13	0	0	0	0
6 mg	63.4	313	280	271	233	202	42	31	26	23	1
3 mg	2.5	17	17	17	17	15	0	0	0	0	0
Ulcerative Colitis **	112.6										
9 mg	46.7	352	329	324	300	251	13	0	0	0	0
6 mg	63.4	300	280	271	233	202	42	31	26	23	1
3 mg	2.5	17	17	17	17	15	0	0	0	0	0
Healthy Volunteers ***	0.4										
9 mg	0.4	37	12	0	0	0	0	0	0	0	0
6 mg	0.0	13	0	0	0	0	0	0	0	0	0
3 mg	NA	0	0	0	0	0	0	0	0	0	0

Notes:

All doses of Budesonide MMX were to have been taken once per day.

* Overall includes all patients who received at least one dose of Budesonide MMX in any of the nine Phase I, II, or III trials.

** Ulcerative Colitis includes all patients who received at least one dose of Budesonide MMX in any of the six Phase II or III trials.

*** Healthy Volunteers includes all patients who received at least one dose of Budesonide MMX in any of the three Phase I trials.

**** Total patient years of exposure = (sum of all patient duration of exposure days / 365.25). This is a cumulative frequency table; patients could be counted more than once in each row depending upon their duration of drug exposure. Patients who received more than one dosage strength of Budesonide MMX (e.g. 6 mg and 9 mg) are counted in each of their respective dosage strengths. One month was 30.25 days. Patients with an incalculable duration of exposure were placed in the >= 1 dose group only.

Windows were used to calculate the duration of dosing as follows:

1. >= 1 week includes all patients exposed for at least 6 days
2. >= 2 weeks includes all patients exposed for at least 12 days
3. >= 4 weeks includes all patients exposed for at least 25 days
4. >= 8 weeks includes all patients exposed for at least 50 days
5. >= 3, 6, 9, 12 and 15 months includes all patients exposed for at least 6 days less than the indicated number of months.

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7.2.2 Explorations for Dose Response

The two pivotal studies (CB-01-02/01 and CB-01-02/02) included both a 6 mg budesonide MMX dose and a 9 mg budesonide MMX dose. The higher dose group was shown to have more efficacy (higher percentage of patients reaching remission as defined by the primary endpoint) than the lower dose group. In general, there was no clear trend of higher incidence of AEs with increasing dose seen in the UC studies. However, an adverse event which showed a possible dose-response effect was the AE

“blood cortisol decreased”, although the overall percentages of patients with this AE were low (<1% of patients receiving placebo, 2% budesonide 6 mg, and 4% budesonide MMX 9 mg). An apparent dose trend was observed with respect to morning plasma cortisol levels in the budesonide MMX groups. Larger decreases in mean morning plasma cortisol levels were observed with increasing dosage strength of budesonide MMX from 6 mg to 9 mg. Mean percentage changes for morning plasma cortisol levels relative to baseline in the primary analysis group were +18% for placebo versus -10% for budesonide MMX 6 mg, and -19% for budesonide MMX 9 mg.

Decreased blood cortisol is an expected AE in patients with UC treated with corticosteroids. Of note, there did not appear to be a dose trend in budesonide MMX for overall glucocorticoid effects, AEs related to infections or AEs related to blood pressure increases. (But, the lack of overall glucocorticoid effects also could be due to the short-term nature of the pivotal studies.

7.2.3 Special Animal and/or In Vitro Testing

For more information see the Pharm Tox and Clinical Pharmacology Review

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information see the Clinical Pharmacology Review

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

The studies were adequately designed to allow for safety analyses. The submitted studies also adequately monitored for potential adverse effects known to be related to corticosteroid use. This included monitoring morning cortisol concentrations and performing ACTH stimulation tests, observing for overall glucocorticoid effects and checking bone mineral density scans. The studies did not reveal any new safety signals.

7.3 Major Safety Results

Table 20: Short-term Treatment Analysis Population

	Placebo n (%)	MMX 9 mg n (%)	MMX 6 mg n (%)	MMX 3 mg n (%)	Asacol n (%)	Entocort n (%)	Total n (%)
PRIMARY ANALYSIS GROUP							
Phase III Randomized, Double-blind Studies							
Randomized							1022
Safety Population	258 (100.0)	255 (100.0)	254 (100.0)	0	127 (100.0)	126 (100.0)	1020 ^a (100.0)
Study CB-01-02/01	129 (50.0)	127 (49.8)	126 (49.6)	0	127 (100.0)	0	509 (49.9)
Study CB-01-02/02	129 (50.0)	128 (50.2)	128 (50.4)	0	0	126 (100.0)	511 (50.1)
SUPPORTIVE ANALYSIS GROUPS							
Phase II/III Randomized, Double-blind Studies							
Randomized							1107
Safety Population	293 (100.0)	288 (100.0)	254 (100.0)	17 (100.0)	127 (100.0)	126 (100.0)	1105 ^a (100.0)
Study CB-01-02/01	129 (44.0)	127 (44.1)	126 (49.6)	0	127 (100.0)	0	509 (46.1)
Study CB-01-02/02	129 (44.0)	128 (44.4)	128 (50.4)	0	0	126 (100.0)	511 (46.2)
Study CB-01-02/05	17 (5.8)	15 (5.2)	0	17 (100.0)	0	0	49 (4.4)
Study CRO-03-53 (Period 1)	18 (6.1)	18 (6.3)	0	0	0	0	36 (3.3)
Phase II/III Open-label Studies							
Safety Population	0	89 (100.0)	0	0	0	0	89 (100.0)
Study CB-01-02/06 ^b	0	60 (67.4)	0	0	0	0	60 (67.4)
Study CRO-03-53 (Period 2)	0	29 (32.6)	0	0	0	0	29 (32.6)

Note: Patients are summarized based on the treatment they received.

^a Two randomized patients did not receive study drug and not included in the analysis population for the ISS.

^b Study CB-01-02/06 enrolled patients who failed to achieve clinical remission in Study CB-01-02/01 (parent study); therefore, some patients in Study CB-01-02/06 may have also received budesonide MMX in Study CB-01-02/01.

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7.3.1 Deaths

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

7.3.2 Nonfatal Serious Adverse Events

Primary Analysis Group

SAEs reported for patients in the primary analysis group are presented in the table below. 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 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 PT were UC (1%) and treatment failure (<1%). The incidence of UC was similar in the budesonide MMX 9 mg (2%) and placebo (2%) groups and lower in the budesonide MMX 6 mg (<1%), Asacol (<1%), and Entocort (<1%) groups. Treatment failure was reported as an SAE in 2 patients; both were in the budesonide MMX 9 mg group. See table below.

Table 21: Serious Adverse Events in the Primary Analysis Group

System Organ Class Preferred Term	Phase III Randomized, Double-blind					
	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 (%)
Patients with any SAE	8 (3.1)	7 (2.7)	5 (2.0)	4 (3.1)	1 (0.8)	25 (2.5)
Gastrointestinal Disorders	4 (1.6)	4 (1.6)	4 (1.6)	2 (1.6)	1 (0.8)	15 (1.5)
Colitis Ulcerative	4 (1.6)	4 (1.6)	2 (0.8)	1 (0.8)	1 (0.8)	12 (1.2)
Diarrhoea	0	1 (0.4)	0	0	0	1 (0.1)
Enterocolitis	0	0	1 (0.4)	0	0	1 (0.1)
Gastric Ulcer	0	0	0	0	1 (0.8)	1 (0.1)
Large Intestine Perforation	0	1 (0.4)	0	0	0	1 (0.1)
Nausea	0	0	1 (0.4)	0	0	1 (0.1)
Pancreatitis	0	0	0	1 (0.8)	0	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (0.4)	1 (0.4)	0	1 (0.8)	0	3 (0.3)
Colon Cancer	0	1 (0.4)	0	0	0	1 (0.1)
Renal Cell Carcinoma	0	0	0	1 (0.8)	0	1 (0.1)
Signet-Ring Cell Carcinoma	1 (0.4)	0	0	0	0	1 (0.1)
General Disorders and Administration Site Conditions	0	2 (0.8)	0	0	0	2 (0.2)
Treatment Failure	0	2 (0.8)	0	0	0	2 (0.2)
Infections and Infestations	1 (0.4)	0	0	0	0	1 (0.1)
Pelvic Abscess	1 (0.4)	0	0	0	0	1 (0.1)
Nervous System Disorders	0	0	1 (0.4)	0	0	1 (0.1)
Cerebrovascular Accident	0	0	1 (0.4)	0	0	1 (0.1)
Psychiatric Disorders	1 (0.4)	0	0	0	0	1 (0.1)
Personality Disorder	1 (0.4)	0	0	0	0	1 (0.1)
Renal and Urinary Disorders	0	0	1 (0.4)	0	0	1 (0.1)
Urge Incontinence	0	0	1 (0.4)	0	0	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.4)	0	0	0	1 (0.1)
Asthma	0	1 (0.4)	0	0	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (0.8)	0	1 (0.1)
Pyoderma Gangrenosum	0	0	0	1 (0.8)	0	1 (0.1)
Vascular Disorders	1 (0.4)	0	0	0	0	1 (0.1)
Deep Vein Thrombosis	1 (0.4)	0	0	0	0	1 (0.1)

Source: ISS Table 1.13.1

Supportive Analysis Groups

The same 25 SAEs were reported for the Phase 2/3 randomized double-blind studies as in the primary analysis group, as these groups overlap (see description of analysis populations above). One additional SAE (nephrolithiasis) was experienced by a patient receiving budesonide MMX 3 mg, for a total of 26/1105 (2%) patients overall

experiencing SAEs in this supportive analysis group. The SAE of nephrolithiasis was not considered related to study treatment by the investigator.

In the Phase 2/3 open-label studies, SAEs were reported for two patients receiving budesonide MMX 9 mg: one patient experienced an SAE of UC and one experienced an SAE of endometrial hyperplasia. These SAEs were considered not related to study treatment according to the investigator. This reviewer agrees that UC and endometrial hyperplasia are probably not related to study treatment.

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 budesonide MMX 6 mg group (moderate hypertension). These SAEs were considered by the investigators not related to study treatment. This reviewer agrees that severe lobar pneumonia is probably not related to study treatment; however, it is a possible that moderate hypertension could be related to study treatment.

7.3.3 Dropouts and/or Discontinuations

Primary Analysis Group

Overall, 16% (166/1020) of patients had at least one 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%). Among all other AEs leading to withdrawal reported in $\geq 1\%$ of patients in any group, abdominal pain was most commonly reported in the placebo and entocort groups; diarrhea and frequent bowel movements were most commonly reported in the placebo group; nausea and anemia were most commonly reported in either of the budesonide MMX groups; and treatment failure was most commonly reported in the entocort group. See the table below for a tabulation of AEs leading to withdrawal in 1% or more patients.

Table 22: Adverse Events Leading to Withdrawal in $\geq 1\%$ of Patients in the Primary Analysis Group

System Organ Class Preferred Term	Phase III Randomized, Double-blind					
	Placebo N=258	MMX 9 mg N=255	MMX 6 mg N=254	Asacol N=127	Entocort N=126	Total N=1020
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with any AE leading to withdrawal	43 (16.7)	39 (15.3)	48 (18.9)	14 (11.0)	22 (17.5)	166 (16.3)
Gastrointestinal Disorders	39 (15.1)	32 (12.5)	43 (16.9)	11 (8.7)	17 (13.5)	142 (13.9)
Colitis Ulcerative	31 (12.0)	29 (11.4)	40 (15.7)	10 (7.9)	15 (11.9)	125 (12.3)
Abdominal Pain	4 (1.6)	1 (0.4)	1 (0.4)	1 (0.8)	2 (1.6)	9 (0.9)
Diarrhoea	3 (1.2)	1 (0.4)	0	1 (0.8)	0	5 (0.5)
Nausea	0	0	4 (1.6)	1 (0.8)	0	5 (0.5)
Frequent Bowel Movements	4 (1.6)	0	0	0	0	4 (0.4)
General Disorders and Administration Site Conditions	3 (1.2)	4 (1.6)	3 (1.2)	2 (1.6)	3 (2.4)	15 (1.5)
Treatment Failure	2 (0.8)	3 (1.2)	3 (1.2)	0	3 (2.4)	11 (1.1)
Skin and Subcutaneous Tissue Disorders	0	1 (0.4)	1 (0.4)	3 (2.4)	1 (0.8)	6 (0.6)
Blood and Lymphatic System Disorders	0	3 (1.2)	0	0	1 (0.8)	4 (0.4)
Anaemia	0	3 (1.2)	0	0	0	3 (0.3)
Nervous System Disorders	0	0	3 (1.2)	1 (0.8)	0	4 (0.4)
Vascular Disorders	0	0	1 (0.4)	2 (1.6)	0	3 (0.3)

Source: ISS Table 1.15.1

Supportive Analysis Groups

AEs leading to withdrawal in 1% or more patients by SOC and PT in the Phase 2/3 randomized, double-blind studies are presented in the table below. Similar to the primary analysis group, AEs led to withdrawal in 16% (175/1105) of patients. Patients most frequently withdrew due to AEs of UC (12% of patients overall). Withdrawal due to UC occurred most frequently in the budesonide MMX 6 mg group (16%), and least frequently in the budesonide MMX 3 mg group (9%). According to the Applicant, the apparent imbalance in events leading to withdrawal in the budesonide MMX 3 mg group relative to the other treatment groups could be due to its very small number of patients (N = 17). In the Phase 2/3 open-label studies, a total of 4 AEs led to withdrawal in 3/89 patients (3%). These AEs were UC, defecation urgency, flatulence, and fluid retention.

Table 23: Adverse Events Leading to Withdrawal in $\geq 1\%$ of Patients in the Supportive Analysis Group

System Organ Class Preferred Term	Phase II/III Randomized, Double-blind					
	Placebo N=293 n (%)	MMX 9 mg N=288 n (%)	MMX 6 mg N=254 n (%)	MMX 3 mg N=17 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)
Patients with any AE leading to withdrawal	48 (16.4)	41 (14.2)	48 (18.9)	2 (11.8)	14 (11.0)	22 (17.5)
Gastrointestinal Disorders	43 (14.7)	33 (11.5)	43 (16.9)	2 (11.8)	11 (8.7)	17 (13.5)
Colitis Ulcerative	33 (11.3)	30 (10.4)	40 (15.7)	1 (5.9)	10 (7.9)	15 (11.9)
Abdominal Pain	6 (2.0)	1 (0.3)	1 (0.4)	0	1 (0.8)	2 (1.6)
Diarrhoea	3 (1.0)	1 (0.3)	0	0	1 (0.8)	0
Nausea	0	0	4 (1.6)	0	1 (0.8)	0
Frequent Bowel Movements	4 (1.4)	0	0	0	0	0
Haematochezia	0	1 (0.3)	0	1 (5.9)	0	0
General Disorders and Administration Site Conditions	4 (1.4)	5 (1.7)	3 (1.2)	0	2 (1.6)	3 (2.4)
Treatment Failure	2 (0.7)	3 (1.0)	3 (1.2)	0	0	3 (2.4)
Skin and Subcutaneous Tissue Disorders	0	1 (0.3)	1 (0.4)	0	3 (2.4)	1 (0.8)
Blood and Lymphatic System Disorders	0	3 (1.0)	0	0	0	1 (0.8)
Anaemia	0	3 (1.0)	0	0	0	0
Nervous System Disorders	0	0	3 (1.2)	0	1 (0.8)	0
Vascular Disorders	0	0	1 (0.4)	0	2 (1.6)	0

Source: ISS Table 3.16.1

Long-term Analysis Group

In the long-term analysis group, AEs that led to withdrawal are summarized in the table below. A greater percentage of patients in the placebo group than in the budesonide MMX 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 budesonide MMX 6 mg group (15%). No other AEs that led to withdrawal were reported by more than one patient in either treatment group.

Table 24: Summary of Adverse Events Leading to Withdrawal in the Long-term Analysis Group

Preferred Term	Placebo N = 61 n (%)	MMX 6 mg N = 62 n (%)	Total N = 123 n (%)
Patients With an AE Leading to Withdrawal	17 (29.9%)	10 (16.1%)	27 (22.0%)
Colitis Ulcerative	14 (23.0%)	9 (14.5%)	23 (18.7%)
Frequent Bowel Movements	1 (1.6%)	1 (1.6%)	2 (1.6%)
Cushingoid	0	1 (1.6%)	1 (0.8%)
Hirsutism	0	1 (1.6%)	1 (0.8%)
Lobar Pneumonia	1 (1.6%)	0	1 (0.8%)
Mood Altered	0	1 (1.6%)	1 (0.8%)
Psoriasis	1 (1.6%)	0	1 (0.8%)

Source: CSR CB-01-02/04 Table 14.3-1.7

7.3.4 Significant Adverse Events

Potential Glucocorticoid-related Effects

Exposure to systemic corticosteroids is known to produce adverse effects related to hypercorticism (glucocorticoid effects). Budesonide MMX is a topically-active corticosteroid with significant first-pass hepatic metabolism and limited systemic bioavailability; however, glucocorticoid-related effects have been previously described in currently approved formulations of oral Budesonide.

Thus, in the budesonide MMX clinical program, adverse signs and symptoms potentially related to the use of glucocorticoids were pre-specified in the Phase 2/3 protocols and were evaluated. These included moon face, striae, flushing, fluid retention, mood changes, sleep changes, insomnia, acne, and hirsutism. Laboratory results potentially related to the use of glucocorticoids (morning plasma cortisol) are presented below in Section 7.4.2 Other significant adverse effects including long-term effects potentially related to the use of glucocorticoids, such as infections, glucose intolerance, blood pressure elevations, and losses in bone mineral density have also been analyzed and are discussed below.

Primary Analysis Group

The table below provides a summary of patients with glucocorticoid effects at any post baseline visit in the primary analysis group. Included in this table are all newly emergent

glucocorticoid effects reported at any time post baseline and, if present at baseline, any post baseline worsening of existing glucocorticoid effects. 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 MMX 6 mg group (8%). Glucocorticoid effects occurred in similar percentages of patients in placebo (11%) and budesonide MMX 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 budesonide MMX 9 mg when compared with placebo.

Table 25: Potential Glucocorticoid Effects in the Primary Analysis Group

Glucocorticoid Effect	Phase III Randomized, Double-blind					
	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)

Source: Summary Clinical Safety; page 48 Table 35

Supportive Analysis Groups

The table below provides a summary of patients with glucocorticoid effects at any post baseline visit in the supportive analysis groups. In general, the percentage of patients with glucocorticoid effects was consistent with findings for the primary analysis group. One exception is the budesonide MMX 3 mg group, which experienced the fewest glucocorticoid effects (6% [1/17]). However, the small sample size of the budesonide MMX 3 mg group may limit comparison of glucocorticoid effects with the other treatment groups. But, the similar frequencies between the placebo and budesonide MMX 9 mg group may suggest a lack of dose-related increases for glucocorticoid effects with budesonide MMX administration, consistent with findings for the primary analysis group

Table 26: Potential Glucocorticoid Effects in the Supportive Analysis Groups

Glucocorticoid Effect	Phase II/III Randomized, Double-blind						Phase II/III Open-label
	Placebo N=275 n (%)	MMX 9 mg N=270 n (%)	MMX 6 mg N=254 n (%)	MMX 3 mg N=17 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)	MMX 9 mg N=60 n (%)
Overall	27 (9.8)	26 (9.6)	19 (7.5)	1 (5.9)	15 (11.8)	17 (13.5)	5 (8.3)
Moon face	4 (1.5)	3 (1.1)	3 (1.2)	0	2 (1.6)	2 (1.6)	3 (5.0)
Striae rubrae	2 (0.7)	0	0	0	0	0	0
Flushing	3 (1.1)	0	1 (0.4)	0	2 (1.6)	1 (0.8)	0
Fluid retention	3 (1.1)	2 (0.7)	3 (1.2)	1 (5.9)	3 (2.4)	0	1 (1.7)
Mood changes	11 (4.0)	9 (3.3)	10 (3.9)	0	3 (2.4)	6 (4.8)	0
Sleep changes	12 (4.4)	7 (2.6)	10 (3.9)	0	1 (0.8)	9 (7.1)	0
Insomnia	8 (2.9)	6 (2.2)	6 (2.4)	0	2 (1.6)	5 (4.0)	1 (1.7)
Acne	5 (1.8)	6 (2.2)	2 (0.8)	0	6 (4.7)	3 (2.4)	1 (1.7)
Hirsutism	0	1 (0.4)	0	0	1 (0.8)	1 (0.8)	0

Source: Summary Clinical Safety; page 49 Table 36

Long-term Analysis Group

Potential glucocorticoid effects reported for patients in the long-term analysis group are presented in the table below. Most of the patients in both the placebo and the budesonide MMX 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 budesonide MMX 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%).

Table 27: 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)

Adapted from Summary Clinical Safety; page 49 Table 37

Long-Term Adverse Effects and other Adverse Events of Interest Associated with the Administration of Glucocorticosteroids

Study CB-01-02/04 evaluated patients for up to 12 months and assessed patients for potential long-term adverse effects not assessed in the short-term treatment studies, including HPA axis suppression, reductions in bone mineral density, and impaired glucose tolerance/diabetes. These effects have been described with prolonged use of conventional systemic steroids (e.g., prednisone, prednisolone, etc.).

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression

Reduction in plasma cortisol concentrations and abnormalities in ACTH stimulation test results are known pharmacodynamic effects of glucocorticosteroids.

Mean morning plasma cortisol concentrations in the primary safety analysis population were within normal limits in all treatment groups over the 8-week treatment period. Although mean morning plasma cortisol concentrations appeared to decrease from baseline to the final visit in a dose-dependent manner in the budesonide MMX treatment groups, these changes were not associated with clinically meaningful increases in the number of potential glucocorticoid effects that were reported. A similar pattern of results was observed in the supportive safety analysis populations.

Bone Density

Long-term Analysis Group

Bone density loss was evaluated at Baseline (Visit 1) and at the End of Study/Early Withdrawal Visit in patients who participated in the 12-month maintenance study¹⁴. Abnormally low bone density was observed at Baseline for 16% (10/61) of the patients in the placebo group and 21% (13/62) of the patients in the budesonide MMX 6 mg treatment group. All patients who were identified as having abnormally low bone density at Visit 1 were discussed between the Sponsor and the Investigator with regard to their eligibility to continue receiving study drug. Based on these discussions, 5 patients each in the placebo and the budesonide MMX 6 mg treatment groups were withdrawn from the study due to abnormally low bone density at Baseline.

There were no clinically important differences between the treatment groups with regard to bone density at the End of Study/Early Withdrawal Visit or with regard to changes in bone density following treatment with study drug. At the time of the End of Study/Early Withdrawal Visit, the majority of the patients in the placebo and the budesonide MMX 6 mg treatment groups had normal scans (74% [29/39] and 77% [27/35], respectively). Five patients each in the placebo and the budesonide MMX 6 mg treatment groups had

¹⁴ using either a dual-energy X-ray absorptiometry (DXA) scan or an alternative radiographic method (typically using plain X-rays) if DXA equipment was not available.

abnormally low bone density at the End of Study/Early Withdrawal Visit; for three of these patients in the placebo group and for two of these patients in the budesonide MMX 6 mg group, the abnormally low bone density at the End of Study/Early Withdrawal Visit was a worsening relative to the result of their Visit 1 scan.

These results suggest that there are no clinically meaningful effects on bone mineral density after treatment with budesonide MMX 6 mg for up to 12 months.

7.3.5 Submission Specific Primary Safety Concerns

There were no submission specific primary safety concerns identified.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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 SOC's 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 $\geq 5\%$ of patients in any group), the following AEs occurred in a higher percentage of patients receiving budesonide MMX (either 9 mg or 6 mg) compared with placebo:

- Colitis Ulcerative (also higher incidence than Asacol and Entocort)
- Nausea (lower incidence than Asacol; higher incidence than Entocort)
- Flatulence (lower incidence than Asacol and Entocort)
- Headache (also higher incidence than Asacol and Entocort)

In addition, there appeared to be a potential relationship between the dose of budesonide MMX and the AE of blood cortisol decreased (4% of patients receiving budesonide MMX 9 mg, 2% receiving budesonide MMX 6 mg, and <1% receiving placebo), although the frequency of these events was low overall (no more than 4% of patients in any group). However, this potential dose related relationship is not

unexpected for this class of drug (a glucocorticoid). See table 6 in Appendix A for the most common Treatment-Emergent Adverse Events reported in the Primary Analysis Group.

Supportive Analysis Groups

In the Phase 2/3 randomized, double-blind studies, overall, 614/1105 (56%) patients experienced at least one AE. Of the 559 patients in this analysis group who received budesonide MMX, 317 (56%) experienced at least one AE. In general, the nature and percentage of AEs were similar to the primary analysis group.

See Table 7 in Appendix A for the most common Treatment-Emergent Adverse Events reported in the Phase 2/3 randomized, double-blind studies,

Long-term Analysis Group

Overall, AEs occurred in a slightly higher percentage of patients in the placebo group (72% [44/61]) than in the budesonide MMX 6 mg group (65% [40/62]). Treatment-related AEs occurred in a similar percentage of patients in both treatment groups (21%).

The most frequently reported treatment-emergent AE was UC, which was reported at a numerically higher percentage for patients in the placebo treatment group than for patients in the budesonide MMX 6 mg treatment group (26% vs.18%). Osteopenia was more commonly reported in the placebo group than budesonide MMX 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 budesonide MMX 6 mg group. However, the overall frequencies of these events were low (none were reported by more than five patients in any treatment group).

Of note, several potentially glucocorticoid related AEs occurred in a slightly higher percent in the budesonide MMX 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, these all occurred in only one to three patients. See Table 8 in Appendix A for the most common Treatment-Emergent Adverse Events reported in the Long-term Analysis Group

7.4.2 Laboratory Findings

Hematology and Chemistry

Primary Analysis Group

For the primary analysis group, evaluation of routine hematology and clinical chemistry results revealed no clinically important differences across the treatment groups from

baseline to the final visit. All mean parameters remained within normal limits for all treatment groups at all visits. Individual shifts in hematologic and clinical chemistry parameters from baseline to worst postbaseline values were similar across all treatment groups. Few patients experienced shifts in any parameter from normal to Grade 1 or higher abnormalities from baseline to any postbaseline visit.

Treatment with budesonide MMX was not associated with clinically significant increases in transaminases or bilirubin. No patients met criteria for Hy's Law (defined as an elevation of ≥ 3 x upper limit of normal [ULN] in AST or ALT with an elevation of ≥ 2 x ULN in bilirubin).

Treatment with corticosteroids can also be associated with glucose intolerance; however, no clinically meaningful changes in mean fasting serum glucose concentrations were observed in the primary analysis group.

Supportive Analysis Groups

Hematologic and clinical chemistry parameters for the supportive analysis groups were similar to the primary analysis groups. Mean values for all routine parameters remained within normal limits for all treatment groups and all time points. Few patients experienced shifts in any parameter from normal at baseline to abnormal at any postbaseline visit.

Long-term Analysis Group

Mean hematology and clinical chemistry test results were similar throughout the 12-month treatment period in both the placebo and the budesonide MMX 6 mg treatment groups. At all visits, the majority of the patients in both treatment groups had test results for all hematology and clinical chemistry test parameters that were within the normal range.

The highest frequencies of abnormal hematology test results were observed for hemoglobin concentrations, which were abnormally low for up to one-quarter of the patients in both treatment groups at all study visits. Low hemoglobin is not unexpected in the UC population. There was no evidence of a trend in either treatment group with regard to changes in any hematology test results over time.

The highest frequencies of abnormal clinical chemistry results were observed for total cholesterol and triglyceride concentrations. Total cholesterol concentrations were elevated for up to 40% of the patients in both treatment groups at all study visits, and triglyceride concentrations were elevated for up to 20% of the patients in both treatment groups at all study visits. There were no clinically important differences between the treatment groups with regard to the percentage of on-study changes from baseline to any postbaseline visit in clinical chemistry test results. There was also no evidence of a

trend in either treatment group with regard to increases or decreases in any of the clinical chemistry tests results over time.

Plasma Cortisol

Primary Analysis Group

At all visits, in all treatment groups (including the two budesonide MMX groups), mean morning plasma cortisol levels remained within normal limits (138 to 690 nmol/L).

Morning plasma cortisol levels decreased from baseline to the final visit in both budesonide MMX treatment groups. Summary statistics for the changes in morning plasma cortisol levels from baseline are presented in Table 9 in Appendix A.

The mean percentage decrease was largest in the budesonide MMX 9 mg group, suggesting a dose trend. Specifically, from baseline to end-of-study, the mean percentage change from baseline was +18% for the placebo group, -19% for budesonide MMX 9 mg, -10% for budesonide MMX 6 mg, <1% for Asacol, and -8% for Entocort. Although the percentage changes in mean morning plasma cortisol levels were higher in the budesonide MMX groups, there was no increase in the overall number of potential glucocorticoid effects, as these events occurred with similar frequencies between placebo and budesonide MMX 9 mg, and to a lesser extent in budesonide MMX 6 mg (see Section 7.3.4).

Supportive Analysis Groups

In the Phase 2/3 randomized, double-blind studies, mean morning plasma cortisol levels decreased from baseline to the final visit in all budesonide MMX treatment groups. The mean percentage decreases in the budesonide MMX groups suggested a dose trend, consistent with findings in the primary analysis group. However, as in the primary analysis group, changes in this supportive analysis group were not associated with an increase in the overall number of potential glucocorticoid effects.

Long-term Analysis Group

Morning plasma cortisol concentrations were assessed at each visit for up to 12 months during the 12-month treatment period. A summary and change from baseline of morning plasma cortisol (nmol/L) is presented in Table 10 in Appendix A. Beginning at the time of study entry and continuing throughout the treatment period, mean morning plasma cortisol concentrations were numerically lower in the budesonide MMX 6 mg treatment group than in the placebo treatment group, although all mean morning plasma cortisol concentrations were within the normal range for both treatment groups at all visits. In both treatment groups, mean morning plasma cortisol levels increased from baseline to the Final Visit for completers (patients who completed 12 months of study treatment) as well as for all patients (including those who withdrew early).

7.4.3 Vital Signs

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

7.4.4 Electrocardiograms (ECGs)

Electrocardiograms (ECGs) were performed at baseline and at the final study visits of the Phase 1 studies; there were no ECGs performed as part of the protocol for the Phase 2 and 3 studies. In the combined Phase 1 analysis group, 16/37 (43%) subjects had abnormal ECG results at baseline, and 24/37 (65%) subjects had abnormal ECG findings at the final visit. According to the Applicant, these differences were not considered clinically meaningful given the small sample size of the Phase 1 analysis group. In addition, according to the Applicant, there were no changes from baseline to final visit in any of the key ECG parameters, including heart rate, PR/PQ interval, QRS interval, or QT interval.

Of note, budesonide (the active ingredient in budesonide MMX) is currently an approved and marketed drug in the United States; thus, the amount of ECG safety information submitted with this application appeared sufficient.

7.4.5 Special Safety Studies/Clinical Trials

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

7.4.6 Immunogenicity

The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The only event showing a possible dose-response effect was for the AE blood cortisol decreased, although the overall percentages of patients with this AE were low (<1% of patients receiving placebo, 2% budesonide MMX 6 mg, and 4% budesonide MMX 9

mg). An apparent dose trend was observed with respect to morning plasma cortisol levels in the budesonide MMX groups. Larger decreases in mean morning plasma cortisol levels were observed with increasing dosage strength of budesonide MMX from 6 mg to 9 mg. Mean percentage changes for morning plasma cortisol levels relative to baseline in the primary analysis group were +18% for placebo versus -10% for budesonide MMX 6 mg, and -19% for budesonide MMX 9 mg.

However, decreased blood cortisol is an expected AE in patients with UC treated with corticosteroids (see prescribing information for Entocort EC).

In the long-term treatment analysis group (up to 12 months of budesonide MMX 6 mg/day), a dose-response effect could not be analyzed because only one dose of budesonide MMX was tested.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

7.5.3 Drug-Demographic Interactions

Subgroup Analyses by Age, Sex, Race, and Region

In the primary analysis group, subgroup analyses were performed by age (patients ≤ 60 years and >60 years), sex, race, and geographical region. In general, the safety findings were consistent across all subgroups compared with the overall population. Exceptions include the following:

Subgroup Analysis by Age

A numerically higher percentage of patients >60 years old in the budesonide MMX 6 mg group (N = 32 patients >60 years) experienced treatment-related AEs, severe AEs, and AEs leading to discontinuation compared with patients ≤ 60 years old (N = 907 patients ≤ 60 years) and compared with the overall analysis population (N = 1020). However, this finding was not observed for patients >60 years old in the budesonide MMX 9 mg group, perhaps suggesting this may have been due to age or dose of budesonide MMX, but rather due to the small sample size of the subpopulation >60 years. See table below.

Table 1.9.2.2: Summary of Treatment Emergent Adverse Events by Age: > 60 years
 Phase 3 Randomized Double-blind Studies
 Protocols: CB-01-02/01 and CB-01-02/02
 Safety Population

	Placebo N=34 n (%)	MMX 9 mg N=18 n (%)	MMX 6 mg N=32 n (%)	Asacol N=14 n (%)	Entocort N=15 n (%)	Total N=113 n (%)
Treatment Emergent AEs	16 (47.1)	10 (55.6)	21 (65.6)	10 (71.4)	7 (46.7)	64 (56.6)
Related	7 (20.6)	4 (22.2)	12 (37.5)	3 (21.4)	5 (33.3)	31 (27.4)
Not Related	9 (26.5)	6 (33.3)	9 (28.1)	7 (50.0)	2 (13.3)	33 (29.2)
Mild	6 (17.6)	3 (16.7)	7 (21.9)	4 (28.6)	2 (13.3)	22 (19.5)
Moderate	8 (23.5)	5 (27.8)	7 (21.9)	5 (35.7)	5 (33.3)	30 (26.5)
Severe	2 (5.9)	2 (11.1)	7 (21.9)	1 (7.1)	0 (0.0)	12 (10.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leading to Discontinuation	5 (14.7)	2 (11.1)	11 (34.4)	1 (7.1)	3 (20.0)	22 (19.5)
Serious Treatment Emergent AEs	0 (0.0)	1 (5.6)	2 (6.3)	2 (14.3)	0 (0.0)	5 (4.4)
Related	0 (0.0)	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)	1 (0.9)
Not Related	0 (0.0)	1 (5.6)	1 (3.1)	2 (14.3)	0 (0.0)	4 (3.5)
Leading to Discontinuation	0 (0.0)	1 (5.6)	2 (6.3)	0 (0.0)	0 (0.0)	3 (2.7)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Note: Related = Possibly, Probably or Missing. The denominator for calculating percentages is the number of patients in each treatment group or the total number of patients within each subgroup.
 Program: Tables\snts-tsteael.sas (11NOV2011)

ISS Table 1.9.2.2 Summary of Treatment Emergent Adverse Events by Age: > 60 years

Similar to the overall population, gastrointestinal disorders was the most commonly affected SOC (10/32 [31.1%]) for patients >60 years old in the budesonide MMX 6 mg group. The only individual AEs reported for more than 2 patients >60 years old in the budesonide MMX 6 mg group were UC (7/32 [22%]), muscle spasms (4/32 [13%]), headache (3/32 [9%]), and treatment failure (3/32 [9%]). These AEs were reported for fewer patients >60 years old in the budesonide MMX 9 mg group, again possibly suggesting that any numerical differences were due to the small sample size of this subpopulation.

Subgroup Analysis by Race/Ethnicity

A numerically higher percentage of Hispanic/Latino patients in the budesonide MMX 6 mg group (86%; N = 7) experienced at least one AE compared with the overall analysis group (57%; N = 1020)¹⁵. However, the percentage of patients in this group

¹⁵ Although the percentage of Hispanic/Latino patients who experienced at least one AE in the placebo group was 70%; N=10.

experiencing treatment-related AEs, severe AEs, and AEs leading to discontinuation was not increased, and there were no SAEs reported.

A numerically lower percentage of Asian patients (40%; N = 181) reported any AEs compared with the overall analysis population and compared with the other race subgroups; this finding was consistent across treatment groups. AEs reported for Asian patients were generally similar to the overall population.

Subgroup Analysis by Region

A numerically higher percentage of patients in North America (72%; N = 335) and Western Europe (77%; N = 93) reported any AEs compared with the overall analysis population (57%; N = 1020) and compared with other regional subgroups; this finding was consistent across treatment groups for these two regions. There were also increases in the percentage of patients experiencing treatment-related AEs, severe AEs, and AEs leading to discontinuation; however, these increases were variable across treatment groups and did not suggest a dose related trend for budesonide MMX. Similar to the overall analysis population, the most commonly affected SOCs were gastrointestinal disorders (UC, nausea), nervous system disorders (headache), and infections and infestations (nasopharyngitis) across all treatment groups for both regions.

A numerically lower percentage of patients in India (39%; N = 174) reported any AEs compared with the overall analysis population and compared with the other regional subgroups; this finding was consistent across treatment groups and is consistent with results for the subgroup analysis of Asian patients

Taken together, the results of the demographic subgroup analyses suggest that there are no major drug-demographic interactions for the populations studied in the budesonide MMX clinical program.

7.5.4 Drug-Disease Interactions

No subgroup analyses were conducted in patients with different disease severities. In addition, no subgroup analyses were conducted in patients with particular concomitant illnesses, renal insufficiency or hepatic insufficiency. However, the following two passages taken from the Entocort EC Prescribing Information/Package Insert pertain to the renal impairment and hepatic impairment subpopulations respectively.

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

budesonide (<1/100). Thus, patients with impaired renal function taking budesonide are not expected to have an increased risk of adverse effects.”

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

7.5.5 Drug-Drug Interactions

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

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The applicant did not provide any clinical or adverse event data regarding human carcinogenicity in this application.

7.6.2 Human Reproduction and Pregnancy Data

The safety experience with the use of budesonide MMX in pregnancy and lactation is limited. One pregnancy was reported during Study CB-01-02/04.

- A 35 year old Caucasian female randomized to budesonide MMX 6 mg, became pregnant during the study and withdrew on Day 39. The patient entered the study on September 11, 2009. On October 19, 2009 (Day 39), a routine pregnancy test

indicated that she was pregnant. The patient discontinued her study drug and was withdrawn from the study on that day. On [REDACTED] (b) (6) the patient delivered a normal, [REDACTED] (b) (6) weeks gestation) female infant weighing 3.2 kg. There were no complications during the delivery and the patient experienced no SAEs during the course of her pregnancy.

Budesonide MMX is not recommended for use in women who are pregnant or breastfeeding. Glucocorticoids are secreted in human milk. The amount of budesonide secreted in breast milk has not been determined, but a decision to discontinue nursing, or discontinue the drug should be made on an individual basis.

In addition, according to the Entocort EC package insert budesonide was teratogenic and embryocidal in rabbits and rats. There are no adequate and well-controlled studies in pregnant women, thus budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Pregnancy Category C)

Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The effects of budesonide MMX on pediatric populations were not studied in the budesonide MMX program, as all studies required participants to be at least 18 years old for study eligibility. The safety and effectiveness of budesonide in pediatric patients has not been established. Systemic and inhaled corticosteroids, including budesonide MMX, may cause a reduction of growth velocity in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

One patient in the budesonide MMX 9 mg group in Study CB-01-02/01 experienced a mild, non serious AE of overdose. The event did not lead to discontinuation from the study, no action was taken, and the event resolved ten days after onset. The event arose due to patient confusion over the number of tablets/capsules required by the double-blind, double-dummy design of the protocol.

Acute overdosage with budesonide, even at very high doses, is not expected to lead to an acute clinical crisis. Treatment consists of supportive and symptomatic therapy. Chronic overdosage may lead to systemic corticosteroid effects, such as Cushingoid features. If such changes occur, the dose should be gradually reduced until treatment is

discontinued, in accordance with normal procedures for the discontinuation of prolonged oral glucocorticosteroid therapy.¹⁶

If glucocorticoids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism and adrenal suppression may occur.

Single oral doses of 200 and 400 mg/kg were lethal in female and male mice, respectively. The signs of acute toxicity were decreased motor activity, piloerection and generalized edema.¹⁷

7.7 Additional Submissions

A 120-Day Safety Update Report was submitted on 26 March 2012 which covered the safety data from 29 September 2011 to 31 January 2012. The Applicant reported that no new safety information from the UCERIS™ (budesonide) clinical development program was presented in this update because all clinical studies were completed and analyzed prior to the NDA filing.

According to the Applicant, one new study of budesonide MMX was initiated by Santarus, Inc. since the NDA filing. The Phase 3b study, C2011-0401 (A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Budesonide MMX 9 mg Extended-release Tablets as Add-on Therapy in Patients with Active, Mild or Moderate Ulcerative Colitis not Adequately Controlled on a Background Oral 5-ASA Regimen), was initiated in February 2012. The first patient enrolled in this study on 9 February 2012 and was treated with blinded study drug budesonide MMX 9 mg; therefore, no data from this study was available yet to be included in this update.

The Applicant performed an updated literature search (using budesonide) covering the period from 29 September 2011 through 31 January 2012. The results showed a safety profile for budesonide that was consistent with what has previously been reported in the literature. The events described in the literature were generally consistent with the known pharmacodynamic and clinical activity of budesonide.

8 Postmarket Experience

Budesonide MMX is not approved for use and has not been marketed in any country.

¹⁶ Entocort EC Prescribing Information

¹⁷ Entocort EC Prescribing Information

9 Appendices

9.1 Literature Review/References

See individual references noted throughout this review.

9.2 Labeling Recommendations

At the time of this review (5 December 2012) labeling was not yet negotiated with the Sponsor. See Appendix C for the most recent draft label (with track changes and comments included).

9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

Appendix A

Study CB-01-02/02 Sites with Major GCP Violations:

Site 1040-Italy

- The PI did not have adequate oversight of the study conduct, or of the sub-investigators delegated study responsibilities in accordance with ICH GCP. The PI was unable to answer questions on study conduct and had no involvement with any of the patients recruited.
- The sub-investigator had no previous experience of clinical trials prior to joining the team and has had no formal ICH GCP training. The current sub-investigator is not a GI specialist, but has been delegated responsibility for reviewing colonoscopy reports for study purposes; hence, the results of the colonoscopy could not be verified.
- Many discrepancies were noted with the review of colonoscopy reports for the completion of UCDAI, and Endoscopic Activity Index scoring.
 - In one case (1040002) it was stated in the baseline colonoscopy report that the patient was in remission at randomization, inconsistent with the protocol eligibility criteria. The Endoscopic Index scores entered into the eCRF for subject 1040002 at baseline were inconsistent with the colonoscopy report on file. In a further case (1040014) It was noted in the baseline colonoscopy report that the subject only had active disease in the

rectum and should therefore have been excluded due to exclusion criteria No.1 (limited distal proctitis).

- Several other inconsistencies between the colonoscopy reports and the information in some patient's eCRFs were noted.
- Therefore quality of the colonoscopy data was in doubt.

Site: 1106-Russia

- Limited GCP knowledge was demonstrated during the audit interview by the PI and by the study team members. The sub-investigator who was responsible for treating all study patients had no previous clinical trial experience.
- The quality of source data for all reviewed patients was found to be inadequate to substantiate that recorded in the patient's eCRF. There was no traceability for corrections and insertions that had been made in the notes, correction fluid had been used and discrepancies between the UCDAI scores and the patients' notes were seen.

Site: 1082-Russia

- It could not be confirmed that diary data was accurate for all patients. Diaries were being completed inconsistently, there was no record in the source notes that diaries were reviewed with the patients during study visits, and in one case many corrections had been made to diary data with no traceability with regards to who made the changes and why.
- The Study Typed Notes (STN) were not completed in accordance with ICH GCP. Examples are as follows:
 - It was not accurately documented in the STN which Investigators had seen which subjects for each visit (subject/visit). Whilst an Investigator's name had been printed at the top of each entry (with a computerized date and time stamp), this did not accurately document which Investigator had seen that subject
 - The investigators confirmed that they had 'cut and pasted' entire sections of notes from one visit to the next e.g. the Follow Up (FU) visit for subject 1082001 stated 'diary filled and study medications taken'. This should not have been the case as implementation of the diaries should have stopped at the previous visit (V5) and no diaries should have been with the subject. It was confirmed by the CRA (during the audit) that this was the case for medical history, diagnosis, objective and conclusion for the V5/FU visit for subject 1082001 and for V2-V5 for subject 1082006 which included physical examination in addition to the parameters above.
 - Many handwritten changes had been made to the STN and it had not always been documented who had made changes and when. Where there was documentation of who had made these changes, the amendments

were not always made by the investigator who was documented as having written the STN (see first bullet above).

- Liquid paper/correction fluid had been used on a number of key source documents;
- **Reduced or partial colonoscopies were preformed for some patients at visit 5, despite the fact that the protocol required a full colonoscopy**

Site: 1122-Slovakia

- Diary data was not consistently collected and its accuracy in the eCRF could not be confirmed.
- Patients had not completed the diaries in a consistent and timely manner. Inclusion criteria could not be confirmed for some patients. It could not be confirmed that the original source data (STN) was present for all subjects.
- Additionally, there was no audit trail for changes to the source data, as the source data for a number of subjects had all been retyped and the original versions destroyed.
- The site did not always conduct a full colonoscopy as required by the protocol. Use of a less complete examination such as sigmoidoscopy may have lead to underestimates of disease severity.

Table 1: Saverymuttu Scale

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

Table 2: Conversion from Total Score to Histological Activity Grade

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

Table 3: Summary of Ulcerative Colitis History (mITT Population) Study 02/01

	Placebo N = 121	Budesonide MMX 9 mg N = 123	Budesonide MMX 6 mg N = 121	Asacol 2400 mg N = 124)	Total N = 489
Age at diagnosis					
Median	33.0	34.0	36.0	35.0	34.0
Min, Max	16, 73	13, 66	7, 69	5, 68	5, 73
Disease duration (years)					
Median	2.8	3.2	3.5	4.8	3.3
Min, Max	0, 38	0, 40	0, 50	0, 49	0, 50
Duration ≤ 1 year (n [%])	35 (28.9)	34 (27.6)	26 (21.5)	23 (18.5)	118 (24.1)
Duration > 1 to ≤ 5 years (n [%])	44 (36.4)	43 (35.0)	43 (35.5)	42 (33.9)	172 (35.2)
Duration > 5 years (n [%])	42 (34.7)	46 (37.4)	52 (43.0)	59 (47.6)	199 (40.7)
Disease extent					
Proctosigmoiditis (n [%])	41 (33.9)	34 (27.6)	28 (23.1)	37 (29.8)	140 (28.6)
Left-sided colitis (n [%])	34 (28.1)	32 (26.0)	41 (33.9)	35 (28.2)	142 (29.0)
Extensive/pancolitis (n [%])	40 (33.1)	56 (45.5)	50 (41.3)	52 (41.9)	198 (40.5)
Missing	6	1	2	0	9
Number of Flares in last 2 years					
Median	2.0	2.0	3.0	2.0	2.0
Min, Max	0, 24	0, 90	0, 30	0, 80	0, 90
Severity of last flare: n (%)					
Mild	30 (24.8)	31 (25.2)	29 (24.0)	25 (20.2)	115 (23.5)
Moderate	79 (65.3)	82 (66.7)	80 (66.1)	81 (65.3)	322 (65.8)
Missing	12	10	12	18	52
Baseline UCDAI score					
Median	7.0	7.0	6.0	7.0	7.0
Min, Max	1, 11	2, 10	2, 11	2, 11	1, 11
Missing	13	9	6	10	38
Baseline Endoscopic Index score					
Median	7.0	7.0	7.0	8.0	7.0
Min, Max	0, 12	3, 12	1, 12	1, 12	0, 12

Source: [Table 14.1-13.1](#)

Note: In the instances where the date of diagnosis was partial, it was assumed that the diagnosis was performed on the first day of the month (if only the day was missing) or the first of January (if the day and month were missing). For the duration of current flare, it was assumed that a month represented 30.4375 days.

Source: Adapted from Table 13 Clinical Study Report Study 02/01 pg 59

Table 4: Summary of Ulcerative Colitis History (mITT Population) Study 02/02

	Placebo N=89	Budes. MMX 9 mg N=109	Budes.MMX 6 mg N=109	Entocort EC 9 mg N=103	Total N=410
Age at diagnosis					
Median	35.0	35.0	36.0	37.0	36.0
Min, Max	14, 68	13, 66	14, 66	12, 67	12, 68
Disease duration (years)					
Median	4.0	3.2	3.9	4.6	3.9
Min, Max	0, 49	0, 38	0, 31	0, 31	0, 49
Duration ≤ 1 year (n [%])	15 (16.9)	22 (20.2)	15 (13.8)	19 (18.4)	71 (17.3)
Duration > 1 to ≤ 5 years (n [%])	36 (40.4)	49 (45.0)	52 (47.7)	39 (37.9)	176 (42.9)
Duration > 5 years (n [%])	38 (42.7)	38 (34.9)	42 (38.5)	45 (43.7)	163 (39.8)
Disease extent					
Proctosigmoiditis (n [%])	41 (46.1)	47 (43.1)	48 (44.0)	41 (39.8)	177 (43.2)
Left-sided colitis (n [%])	28 (31.5)	32 (29.4)	32 (29.4)	39 (37.9)	131 (32.0)
Extensive/pancolitis (n [%])	20 (22.5)	29 (26.6)	28 (25.7)	23 (22.3)	100 (24.4)
Number of Flares in last 2 years					
Median	2.0	3.0	2.0	2.0	2.0
Min, Max	0, 15	0, 8	0, 10	0, 15	0, 15
Severity of last flare: n (%)					
Mild	25 (28.1)	34 (31.2)	33 (30.3)	31 (30.1)	123 (30.0)
Moderate	63 (70.8)	66 (60.6)	74 (67.9)	67 (65.0)	270 (65.9)
Baseline UCDAI score					
Median	7.0	7.0	7.0	7.0	7.0
Min, Max	2, 10	3, 10	3, 11	2, 11	2, 11
Baseline Endoscopic Index score					
Median	7.0	7.0	8.0	7.0	7.0
Min, Max	3, 12	3, 12	4, 12	3, 12	3, 12

Source: Adapted from Table 13 Clinical Study Report Study 02/02 pg 59-60

Table 5: Prohibited Cytochrome P450 3A4, Cytochrome P450 3A5 & Cytochrome P450 3A7 Inhibitors and Inducers

CYP3A4, 5 & 7 Inhibitors		CYP3A4, 5 & 7 Inducers
<i>HIV Antivirals:</i>		<i>HIV Antivirals:</i>
delavirdine		efavirenz
indinavir		nevirapine
nelfinavir		
ritonavir		<i>Other Inducers:</i>
saquinavir		barbiturates
<i>Other Inhibitors:</i>		carbamazepine
amiodarone	grapefruit juice	glucocorticoids
cimetidine	itraconazole	modafinil
ciprofloxacin	ketoconazole	phenobarbital
clarithromycin	mifepristone	phenytoin
diethyl-dithiocarbamate	nefazodone	rifampin
diltiazem	norfloxacin	St. John's wort
erythromycin	norfluoxetine	troglitazone
fluconazole	mibefradil	pioglitazone
fluvoxamine	verapamil	rifabutin
gestodene		

Note: azithromycin is not an inhibitor of CYP3A4.
 Abbreviations: HIV: human immunodeficiency virus

Table 6: Treatment-Emergent Adverse Events in ≥2% of Patients in the Primary Analysis Group

System Organ Class Preferred Term	Phase III Randomized, Double-blind					
	Placebo N=258 n (%)	MMX 9		Asacol N=127 n (%)	Entocort N=126 n (%)	Total N=1020 n (%)
		mg N=255 n (%)	MMX 6 mg N=254 n (%)			
Patients with any AE	138 (53.5)	144 (56.5)	154 (60.6)	80 (63.0)	69 (54.8)	585 (57.4)
Gastrointestinal Disorders	80 (31.0)	81 (31.8)	86 (33.9)	46 (36.2)	36 (28.6)	329 (32.3)
Colitis Ulcerative	36 (14.0)	34 (13.3)	42 (16.5)	13 (10.2)	16 (12.7)	141 (13.8)
Nausea	11 (4.3)	13 (5.1)	12 (4.7)	10 (7.9)	3 (2.4)	49 (4.8)
Abdominal Pain	15 (5.8)	9 (3.5)	7 (2.8)	10 (7.9)	7 (5.6)	48 (4.7)
Diarrhoea	11 (4.3)	3 (1.2)	7 (2.8)	8 (6.3)	4 (3.2)	33 (3.2)
Flatulence	5 (1.9)	6 (2.4)	8 (3.1)	7 (5.5)	7 (5.6)	33 (3.2)
Abdominal Pain Upper	5 (1.9)	10 (3.9)	8 (3.1)	2 (1.6)	2 (1.6)	27 (2.6)
Vomiting	6 (2.3)	0	9 (3.5)	3 (2.4)	1 (0.8)	19 (1.9)
Abdominal Distension	2 (0.8)	6 (2.4)	4 (1.6)	4 (3.1)	2 (1.6)	18 (1.8)
Dyspepsia	5 (1.9)	3 (1.2)	3 (1.2)	5 (3.9)	1 (0.8)	17 (1.7)
Frequent Bowel Movements	5 (1.9)	1 (0.4)	2 (0.8)	4 (3.1)	0	12 (1.2)
Abdominal Tenderness	2 (0.8)	1 (0.4)	3 (1.2)	3 (2.4)	0	9 (0.9)
Constipation	2 (0.8)	5 (2.0)	1 (0.4)	1 (0.8)	0	9 (0.9)
Nervous System Disorders	32 (12.4)	32 (12.5)	46 (18.1)	18 (14.2)	14 (11.1)	142 (13.9)
Headache	27 (10.5)	29 (11.4)	37 (14.6)	12 (9.4)	9 (7.1)	114 (11.2)
Dizziness	1 (0.4)	3 (1.2)	8 (3.1)	4 (3.1)	2 (1.6)	18 (1.8)
Somnolence	0	1 (0.4)	1 (0.4)	3 (2.4)	0	5 (0.5)
Infections and Infestations	25 (9.7)	28 (11.0)	31 (12.2)	16 (12.6)	13 (10.3)	113 (11.1)
Nasopharyngitis	6 (2.3)	4 (1.6)	13 (5.1)	3 (2.4)	6 (4.8)	32 (3.1)
Upper Respiratory Tract Infection	3 (1.2)	2 (0.8)	6 (2.4)	1 (0.8)	0	12 (1.2)
Urinary Tract Infection	1 (0.4)	5 (2.0)	1 (0.4)	3 (2.4)	2 (1.6)	12 (1.2)
General Disorders and Administration Site Conditions	21 (8.1)	20 (7.8)	24 (9.4)	9 (7.1)	9 (7.1)	83 (8.1)
Pyrexia	11 (4.3)	5 (2.0)	6 (2.4)	3 (2.4)	2 (1.6)	27 (2.6)
Fatigue	5 (1.9)	8 (3.1)	5 (2.0)	0	1 (0.8)	19 (1.9)
Treatment Failure	2 (0.8)	3 (1.2)	4 (1.6)	0	3 (2.4)	12 (1.2)
Asthenia	1 (0.4)	2 (0.8)	5 (2.0)	1 (0.8)	2 (1.6)	11 (1.1)
Musculoskeletal and Connective Tissue Disorders	22 (8.5)	18 (7.1)	23 (9.1)	11 (8.7)	6 (4.8)	80 (7.8)
Back Pain	8 (3.1)	6 (2.4)	6 (2.4)	2 (1.6)	0	22 (2.2)
Arthralgia	4 (1.6)	5 (2.0)	5 (2.0)	4 (3.1)	0	18 (1.8)
Muscle Spasms	3 (1.2)	4 (1.6)	6 (2.4)	2 (1.6)	3 (2.4)	18 (1.8)
Musculoskeletal Pain	0	0	1 (0.4)	3 (2.4)	0	4 (0.4)

Table 6: Treatment-Emergent Adverse Events in $\geq 2\%$ of Patients in the Primary Analysis Group

System Organ Class Preferred Term	Phase III Randomized, Double-blind					
	Placebo N=258 n (%)	MMX 9		Asacol N=127 n (%)	Entocort N=126 n (%)	Total N=1020 n (%)
		mg N=255 n (%)	MMX 6 mg N=254 n (%)			
Investigations	13 (5.0)	27 (10.6)	16 (6.3)	12 (9.4)	10 (7.9)	78 (7.6)
Blood Cortisol Decreased	1 (0.4)	11 (4.3)	6 (2.4)	0	4 (3.2)	22 (2.2)
Alanine Aminotransferase Increased	0	0	1 (0.4)	3 (2.4)	1 (0.8)	5 (0.5)
Blood Urine Present	0	1 (0.4)	1 (0.4)	3 (2.4)	0	5 (0.5)
Psychiatric Disorders	17 (6.6)	18 (7.1)	13 (5.1)	10 (7.9)	7 (5.6)	65 (6.4)
Insomnia	12 (4.7)	7 (2.7)	9 (3.5)	3 (2.4)	4 (3.2)	35 (3.4)
Mood Altered	4 (1.6)	4 (1.6)	4 (1.6)	3 (2.4)	4 (3.2)	19 (1.9)
Skin and Subcutaneous Tissue Disorders	13 (5.0)	14 (5.5)	14 (5.5)	12 (9.4)	5 (4.0)	58 (5.7)
Acne	5 (1.9)	6 (2.4)	2 (0.8)	4 (3.1)	3 (2.4)	20 (2.0)
Rash	5 (1.9)	4 (1.6)	1 (0.4)	3 (2.4)	0	13 (1.3)
Respiratory, Thoracic and Mediastinal Disorders	7 (2.7)	9 (3.5)	7 (2.8)	7 (5.5)	4 (3.2)	34 (3.3)
Pharyngolaryngeal Pain	1 (0.4)	4 (1.6)	3 (1.2)	2 (1.6)	3 (2.4)	13 (1.3)
Blood and Lymphatic System Disorders	10 (3.9)	9 (3.5)	4 (1.6)	3 (2.4)	1 (0.8)	27 (2.6)
Anaemia	5 (1.9)	5 (2.0)	4 (1.6)	2 (1.6)	0	16 (1.6)
Vascular Disorders	4 (1.6)	5 (2.0)	8 (3.1)	4 (3.1)	2 (1.6)	23 (2.3)
Flushing	3 (1.2)	2 (0.8)	0	3 (2.4)	1 (0.8)	9 (0.9)
Metabolism and Nutrition Disorders	5 (1.9)	2 (0.8)	8 (3.1)	3 (2.4)	0	18 (1.8)
Reproductive System and Breast Disorders	1 (0.4)	6 (2.4)	6 (2.4)	1 (0.8)	0	14 (1.4)
Eye Disorders	1 (0.4)	4 (1.6)	1 (0.4)	6 (4.7)	0	12 (1.2)
Injury, Poisoning and Procedural Complications	3 (1.2)	4 (1.6)	0	3 (2.4)	1 (0.8)	11 (1.1)
Renal and Urinary Disorders	0	2 (0.8)	6 (2.4)	2 (1.6)	0	10 (1.0)
Hepatobiliary Disorders	0	1 (0.4)	0	3 (2.4)	0	4 (0.4)

Adapted from Applicant's Table 16, ISS p 38-40

Table 7: Treatment-Emergent Adverse Events in $\geq 2\%$ of Patients in the Supportive Analysis Group

System Organ Class Preferred Term	Phase II/III Randomized, Double-blind					
	Placebo N=293 n (%)	MMX 9 mg N=288 n (%)	MMX 6 mg N=254 n (%)	MMX 3 mg N=17 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)
Patients with any Treatment Emergent AEs	148 (50.5)	157 (54.5)	154 (60.6)	6 (35.3)	80 (63.0)	69 (54.8)
Gastrointestinal Disorders	86 (29.4)	86 (29.9)	86 (33.9)	2 (11.8)	46 (36.2)	36 (28.6)
Colitis Ulcerative	38 (13.0)	36 (12.5)	42 (16.5)	1 (5.9)	13 (10.2)	16 (12.7)
Abdominal Pain	18 (6.1)	10 (3.5)	7 (2.8)	1 (5.9)	10 (7.9)	7 (5.6)
Nausea	12 (4.1)	13 (4.5)	12 (4.7)	0	10 (7.9)	3 (2.4)
Flatulence	5 (1.7)	8 (2.8)	8 (3.1)	0	7 (5.5)	7 (5.6)
Diarrhoea	11 (3.8)	4 (1.4)	7 (2.8)	0	8 (6.3)	4 (3.2)

Table 7: Treatment-Emergent Adverse Events in ≥2% of Patients in the Supportive Analysis Group

System Organ Class Preferred Term	Phase II/III Randomized, Double-blind					
	Placebo N=293 n (%)	MMX 9 mg N=288 n (%)	MMX 6 mg N=254 n (%)	MMX 3 mg N=17 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)
Abdominal Pain Upper	6 (2.0)	10 (3.5)	8 (3.1)	0	2 (1.6)	2 (1.6)
Abdominal Distension	3 (1.0)	6 (2.1)	4 (1.6)	0	4 (3.1)	2 (1.6)
Vomiting	6 (2.0)	0	9 (3.5)	0	3 (2.4)	1 (0.8)
Dyspepsia	6 (2.0)	3 (1.0)	3 (1.2)	0	5 (3.9)	1 (0.8)
Frequent Bowel Movements	5 (1.7)	1 (0.3)	2 (0.8)	0	4 (3.1)	0
Abdominal Tenderness	2 (0.7)	1 (0.3)	3 (1.2)	0	3 (2.4)	0
Haematochezia	4 (1.4)	1 (0.3)	0	1 (5.9)	0	1 (0.8)
Nervous System Disorders	33 (11.3)	37 (12.8)	46 (18.1)	1 (5.9)	18 (14.2)	14 (11.1)
Headache	28 (9.6)	34 (11.8)	37 (14.6)	1 (5.9)	12 (9.4)	9 (7.1)
Dizziness	1 (0.3)	3 (1.0)	8 (3.1)	0	4 (3.1)	2 (1.6)
Somnolence	0	1 (0.3)	1 (0.4)	0	3 (2.4)	0
Infections and Infestations	25 (8.5)	31 (10.8)	31 (12.2)	1 (5.9)	16 (12.6)	13 (10.3)
Nasopharyngitis	6 (2.0)	4 (1.4)	13 (5.1)	0	3 (2.4)	6 (4.8)
Urinary Tract Infection	1 (0.3)	6 (2.1)	1 (0.4)	0	3 (2.4)	2 (1.6)
Upper Respiratory Tract Infection	3 (1.0)	2 (0.7)	6 (2.4)	0	1 (0.8)	0
Acute Tonsillitis	2 (0.7)	0	0	1 (5.9)	0	0
General Disorders and Administration Site Conditions	23 (7.8)	24 (8.3)	24 (9.4)	1 (5.9)	9 (7.1)	9 (7.1)
Pyrexia	12 (4.1)	6 (2.1)	6 (2.4)	0	3 (2.4)	2 (1.6)
Fatigue	5 (1.7)	9 (3.1)	5 (2.0)	0	0	1 (0.8)
Asthenia	1 (0.3)	2 (0.7)	5 (2.0)	1 (5.9)	1 (0.8)	2 (1.6)
Treatment Failure	2 (0.7)	3 (1.0)	4 (1.6)	0	0	3 (2.4)
Musculoskeletal and Connective Tissue Disorders	23 (7.8)	20 (6.9)	23 (9.1)	0	11 (8.7)	6 (4.8)
Back Pain	8 (2.7)	7 (2.4)	6 (2.4)	0	2 (1.6)	0
Muscle Spasms	3 (1.0)	5 (1.7)	6 (2.4)	0	2 (1.6)	3 (2.4)
Arthralgia	4 (1.4)	5 (1.7)	5 (2.0)	0	4 (3.1)	0
Musculoskeletal Pain	0	1 (0.3)	1 (0.4)	0	3 (2.4)	0
Investigations	15 (5.1)	29 (10.1)	16 (6.3)	0	12 (9.4)	10 (7.9)
Blood Cortisol Decreased	1 (0.3)	12 (4.2)	6 (2.4)	0	0	4 (3.2)
Alanine Aminotransferase Increased	0	0	1 (0.4)	0	3 (2.4)	1 (0.8)
Blood Urine Present	0	1 (0.3)	1 (0.4)	0	3 (2.4)	0
Psychiatric Disorders	18 (6.1)	19 (6.6)	13 (5.1)	0	10 (7.9)	7 (5.6)
Insomnia	12 (4.1)	7 (2.4)	9 (3.5)	0	3 (2.4)	4 (3.2)
Mood Altered	4 (1.4)	4 (1.4)	4 (1.6)	0	3 (2.4)	4 (3.2)
Skin and Subcutaneous Tissue Disorders	13 (4.4)	15 (5.2)	14 (5.5)	0	12 (9.4)	5 (4.0)

Table 7: Treatment-Emergent Adverse Events in ≥2% of Patients in the Supportive Analysis Group

System Organ Class Preferred Term	Phase II/III Randomized, Double-blind					
	Placebo N=293 n (%)	MMX 9 mg N=288 n (%)	MMX 6 mg N=254 n (%)	MMX 3 mg N=17 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)
Acne	5 (1.7)	6 (2.1)	2 (0.8)	0	4 (3.1)	3 (2.4)
Rash	5 (1.7)	4 (1.4)	1 (0.4)	0	3 (2.4)	0
Respiratory, Thoracic and Mediastinal Disorders	7 (2.4)	11 (3.8)	7 (2.8)	0	7 (5.5)	4 (3.2)
Pharyngolaryngeal Pain	1 (0.3)	4 (1.4)	3 (1.2)	0	2 (1.6)	3 (2.4)
Cough	2 (0.7)	6 (2.1)	1 (0.4)	0	2 (1.6)	1 (0.8)
Blood and Lymphatic System Disorders	10 (3.4)	9 (3.1)	4 (1.6)	1 (5.9)	3 (2.4)	1 (0.8)
Anaemia	5 (1.7)	5 (1.7)	4 (1.6)	1 (5.9)	2 (1.6)	0
Vascular Disorders	4 (1.4)	6 (2.1)	8 (3.1)	0	4 (3.1)	2 (1.6)
Flushing	3 (1.0)	3 (1.0)	0	0	3 (2.4)	1 (0.8)
Metabolism and Nutrition Disorders	6 (2.0)	3 (1.0)	8 (3.1)	1 (5.9)	3 (2.4)	0
Fluid Retention	3 (1.0)	0	2 (0.8)	1 (5.9)	2 (1.6)	0
Reproductive System and Breast Disorders	2 (0.7)	6 (2.1)	6 (2.4)	0	1 (0.8)	0
Eye Disorders	1 (0.3)	5 (1.7)	1 (0.4)	0	6 (4.7)	0
Injury, Poisoning and Procedural Complications	3 (1.0)	4 (1.4)	0	0	3 (2.4)	1 (0.8)
Renal and Urinary Disorders	0	2 (0.7)	6 (2.4)	1 (5.9)	2 (1.6)	0
Nephrolithiasis	0	1 (0.3)	0	1 (5.9)	0	0
Hepatobiliary Disorders	0	1 (0.3)	0	0	3 (2.4)	0

Adapted from Applicant's Table 16, ISS p 40-42

Table 8: Treatment-Emergent Adverse Events in $\geq 2\%$ of Patients in the Long-term Analysis Group

Preferred Term	Placebo N = 61 n (%)	MMX 6 mg N = 62 n (%)	Total N = 123 n (%)
Patients With Any AE	44 (72.1)	40 (64.5)	84 (68.3)
Colitis Ulcerative	16 (26.2)	11 (17.7)	27 (22.0)
Abdominal Pain	5 (8.2)	6 (9.7)	11 (8.9)
Diarrhoea	3 (4.9)	3 (4.8)	6 (4.9)
Headache	2 (3.3)	4 (6.5)	6 (4.9)
Osteopenia	5 (8.2)	1 (1.6)	6 (4.9)
Cushingoid	2 (3.3)	3 (4.8)	5 (4.1)
Frequent Bowel Movements	1 (1.6)	4 (6.5)	5 (4.1)
Haematochezia	1 (1.6)	4 (6.5)	5 (4.1)
Back Pain	3 (4.9)	1 (1.6)	4 (3.3)
Constipation	0	4 (6.5)	4 (3.3)
Urinary Tract Infection	1 (1.6)	3 (4.8)	4 (3.3)
Acne	0	3 (4.8)	3 (2.4)
Alanine Aminotransferase Increased	3 (4.9)	0	3 (2.4)
Blood Cholesterol Increased	1 (1.6)	2 (3.2)	3 (2.4)
Blood Cortisol Decreased	1 (1.6)	2 (3.2)	3 (2.4)
Blood Triglycerides Increased	1 (1.6)	2 (3.2)	3 (2.4)
Cough	1 (1.6)	2 (3.2)	3 (2.4)
Dizziness	0	3 (4.8)	3 (2.4)
Flushing	1 (1.6)	2 (3.2)	3 (2.4)
Haemoglobin Decreased	1 (1.6)	2 (3.2)	3 (2.4)

Adapted from Applicant's Table 39, ISS p 76-77

Table 9: Summary and Change from Baseline in Morning Plasma Cortisol by Visit in the Primary Analysis Group

Visit Cortisol Level (nmol/L)	Phase III Randomized, Double-blind				
	Placebo N=258	MMX 9 mg N=255	MMX 6 mg N=254	Asacol N=127	Entocort N=126
Screening					
Cortisol Level, N	252	249	250	126	125
Mean ± SD	334.4 ± 152.45	363.4 ± 230.13	347.5 ± 146.03	349.2 ± 153.63	374.3 ± 159.96
Median	312.0	334.0	327.0	315.0	364.0
Min, Max	14, 982	14, 3064	14, 850	80, 905	14, 1137
Visit 2 (Baseline)					
Cortisol Level, N	254	248	246	126	121
Mean ± SD	338.0 ± 135.20	341.1 ± 137.98	357.5 ± 124.53	357.1 ± 127.19	368.6 ± 145.61
Median	317.0	323.0	345.0	349.5	348.0
Min, Max	14, 690	14, 836	50, 723	14, 822	72, 941
Visit 3 (Week 2)					
Cortisol Level, N	214	220	211	114	110
Mean ± SD	345.8 ± 139.75	214.1 ± 161.57	255.7 ± 158.38	333.1 ± 117.53	299.8 ± 163.50
Median	323.0	202.5	244.0	316.0	296.0
Min, Max	14, 822	14, 1057	14, 993	110, 773	14, 792
Change from baseline, N	213	220	210	113	110
Mean ± SD	13.3 ± 122.75	-141.2 ± 184.73	-90.2 ± 145.23	-15.4 ± 117.84	-72.8 ± 143.59
Mean % change ± SD	11.9 ± 58.51	-35.1 ± 54.70	-24.7 ± 43.70	0.7 ± 39.15	-17.8 ± 39.77
Median change	11.0	-142.0	-75.8	-26.0	-56.0
Min, Max change	-311, 381	-1362, 764	-498, 574	-312, 407	-407, 297

Table 9: Summary and Change from Baseline in Morning Plasma Cortisol by Visit in the Primary Analysis Group

Visit Cortisol Level (nmol/L)	Phase III Randomized, Double-blind				
	Placebo N=258	MMX 9 mg N=255	MMX 6 mg N=254	Asacol N=127	Entocort N=126
Visit 4 (Week 4)					
Cortisol Level, N	194	201	189	99	103
Mean ± SD	333.3 ± 130.17	194.4 ± 159.46	260.1 ± 155.56	313.1 ± 107.95	282.1 ± 154.18
Median	320.0	161.0	251.0	287.0	265.0
Min, Max	38, 858	14, 607	14, 707	69, 604	14, 695
Change from baseline, N	193	200	188	99	103
Mean ± SD	-2.9 ± 110.93	-163.3 ± 183.08	-83.5 ± 143.99	-35.2 ± 119.80	-95.2 ± 135.12
Mean % change ± SD	4.9 ± 46.79	-42.3 ± 45.47	-23.3 ± 42.55	-5.3 ± 32.70	-24.5 ± 37.36
Median change	-2.5	-161.5	-69.0	-29.0	-83.5
Min, Max change	-361, 417	-1208, 240	-511, 280	-426, 268	-445, 327
Final Visit					
Cortisol Level, N	237	235	242	118	118
Mean ± SD	347.5 ± 143.28	253.5 ± 172.94	299.4 ± 172.19	331.9 ± 133.94	322.9 ± 160.79
Median	331.0	237.0	299.5	310.5	312.0
Min, Max	50, 1073	14, 1115	14, 1002	14, 709	14, 767
Change from baseline, N	235	234	240	117	118
Mean ± SD	14.9 ± 126.87	-101.0 ± 208.50	-50.7 ± 168.86	-25.3 ± 152.47	-47.0 ± 153.50
Mean % change ± SD	17.5 ± 101.67	-18.8 ± 66.06	-10.0 ± 56.34	0.9 ± 50.04	-8.2 ± 42.82
Median change	4.0	-76.0	-49.0	-20.5	-32.3
Min, Max change	-326, 501	-1420, 763	-502, 601	-392, 388	-597, 330

Source: ISS Table 1.30.1

Note: The normal range for morning plasma cortisol is 138 – 690 nmol/L. Baseline is the average of the results collected prior to or on the day of the first study drug administration.

Table 10: Summary and Change from Baseline of Morning Plasma Cortisol by Visit in the Long-term Analysis Group

	Placebo N=61	Budesonide MMX 6 mg N=62	Total N=123
Visit 1 (Baseline)			
Cortisol level, n	59	59	118
Mean ± SD	287.3 ± 153.49	244.6 ± 141.90	265.9 ± 148.73
Median	279.0	226.0	256.5
Min, Max	14, 640	14, 591	14, 640

Table 10: Summary and Change from Baseline of Morning Plasma Cortisol by Visit in the Long-term Analysis Group

	Placebo N=61	Budesonide MMX 6 mg N=62	Total N=123
Visit 2 (Month 1)			
Cortisol level, n	45	49	94
Mean ± SD	287.3 ± 98.20	224.7 ± 132.19	254.6 ± 120.70
Median	295.0	220.0	274.5
Min, Max	14, 483	14, 497	14, 497
Change from baseline, n	43	47	90
Mean ± SD	-17.9 ± 162.87	-36.8 ± 164.16	-27.8 ± 162.90
Mean % change ± SD	109.5 ± 450.11	67.1 ± 507.44	87.4 ± 478.69
Median change	-15.7	-20.0	-17.8
Min, Max change	-428, 356	-499, 483	-499, 483
Visit 3 (Month 3)			
Cortisol Level, n	40	45	85
Mean ± SD	309.6 ± 96.83	223.4 ± 158.09	264.0 ± 139.00
Median	305.0	203.0	251.0
Min, Max	144, 494	14, 649	14, 649
Change from baseline, n	38	44	82
Mean ± SD	-1.9 ± 159.58	-44.3 ± 142.70	-24.6 ± 151.31
Mean % change ± SD	98.5 ± 332.10	25.2 ± 171.16	59.1 ± 259.39
Median change	3.7	-51.0	-35.5
Min, Max change	-370, 331	-433, 274	-433, 331
Visit 4 (Month 6)			
Cortisol Level, n	35	31	66
Mean ± SD	337.3 ± 124.83	290.6 ± 134.74	315.4 ± 130.70
Median	334.0	284.0	328.0
Min, Max	149, 604	14, 568	14, 604
Change from baseline, n	33	31	64
Mean ± SD	48.3 ± 165.64	23.7 ± 151.76	36.4 ± 158.29
Mean % change ± SD	195.2 ± 714.83	172.9 ± 666.28	184.4 ± 686.34
Median change	33.0	30.0	30.5
Min, Max change	-326, 552	-218, 499	-326, 552
Visit 5 (Month 9)			
Cortisol Level, n	30	29	59
Mean ± SD	345.6 ± 116.42	284.1 ± 108.10	315.4 ± 115.66
Median	374.0	262.0	304.0
Min, Max	130, 580	108, 516	108, 580
Change from baseline, n	28	29	57
Mean ± SD	45.4 ± 209.67	5.6 ± 188.62	25.2 ± 198.46

Table 10: Summary and Change from Baseline of Morning Plasma Cortisol by Visit in the Long-term Analysis Group

	Placebo N=61	Budesonide MMX 6 mg N=62	Total N=123
Mean % change ± SD	241.7 ± 819.29	206.2 ± 671.66	223.7 ± 741.29
Median change	64.5	-20.0	22.0
Min, Max change	-370, 566	-249, 441	-370, 566
Final Visit/Completers (Month 12)^a			
Cortisol Level, n	21	22	43
Mean ± SD	348.0 ± 121.66	310.3 ± 141.72	328.7 ± 132.11
Median	375.0	288.5	328.0
Min, Max	144, 571	36, 668	36, 668
Change from baseline, n	21	22	43
Mean ± SD	64.7 ± 205.42	48.0 ± 129.40	56.2 ± 168.93
Mean % change ± SD	386.4 ± 1144.61	134.8 ± 479.26	257.6 ± 868.86
Median change	53.0	31.5	43.0
Min, Max change	-279, 557	-158, 368	-279, 557
Final Visit/All Patients^b			
Cortisol Level, n	41	39	80
Mean ± SD	359.7 ± 113.43	287.4 ± 160.87	324.5 ± 142.43
Median	370.0	284.0	340.5
Min, Max	144, 591	14, 668	14, 668
Change from baseline, n	41	36	77
Mean ± SD	74.7 ± 194.99	50.4 ± 174.87	63.3 ± 185.05
Mean % change ± SD	248.7 ± 833.63	233.2 ± 704.55	241.5 ± 770.99
Median change	35.0	41.0	41.0
Min, Max change	-279, 557	-350, 475	-350, 557

Source: CSR CB-01-02/04 Table 14.3-3.4.1

Notes: The normal range for morning plasma cortisol is 138 – 690 nmol/L. Baseline is the last non-missing assessment prior to or on the day of the first dose of study drug administration in the Extension study.

^a Includes data from only those patients who completed 12 months of study drug. Patients who completed 12 months of study drug were on drug up to the time of the Final Visit

^b Includes data from the Final Visit for all patients, including both those patients who completed 12 months of study drug, and those who withdrew early.

Appendix B

Clinical remission

- UCDAI score ≤ 1 point with a score of 0 for both rectal bleeding and stool frequency,
- a normal mucosa (with no evidence of friability), and
- ≥ 1-point reduction from baseline in the Endoscopic Index score.

Study 02-01 “Normal Histology” Scores with UCDAI Scores

Subject	Treatment Group	Baseline UCDAI	Final UCDAI	Histology Specimen 1 Baseline Score	Histology Specimen 1 Final Score	Histology Specimen 2 Baseline Score	Histology Specimen 2 Final Score	Histology Specimen 3 Baseline Score	Histology Specimen 3 Final Score	Remission (yes or no)
5096004										(b) (4)
7000001										
9001005										
9004015										
9008008										
9008012										
5008001										
5100029										
9016009										
5077006										
5079013										
9002021										
9006001										
9012008										
5096002										
5097009										
9008007										

Study 02-01 “Normal Histology” Scores with UCDAI Scores

Subject	Treatment Group	Baseline UCDAI	Final UCDAI	Histology Specimen 1 Baseline Score	Histology Specimen 2 Baseline Score	Histology Specimen 3 Baseline Score	Histology Specimen 1 Final Score	Histology Specimen 2 Final Score	Histology Specimen 3 Final Score	Remission (yes or no)
5096004										(b) (4)
7000001										
9001005										
9004015										
9008008										
9008012										
5008001										
5100029										
9016009										
5077006										
5079013										
9002021										
9006001										
9012008										
5096002										
5097009										
9008007										

Clinical Review
 Marjorie F. Dannis, M.D.
 NDA 203634
 Uceris (Budesonide MMX)

O2-02 Normal Histology Grades with UCDAI Scores By Site

Patient Number	SITE	Treatment	UCDAI Baseline	UCDAI Final	Histo Specimen 1 Baseline Grade	Histo Specimen 2 Baseline Grade	Histo Specimen 3 Baseline Grade	Histo Specimen 1 Final Grade	Histo Specimen 2 Final Grade	Histo Specimen 3 Final Grade	Remission
1023001	1023										(b) (4)
1039015	1039										
1056006	1056										
1056010	1056										
1056015	1056										
1056018	1056										
1056020	1056										
1057010	1057										
1057014	1057										
1057015	1057										
1059006	1059										
1059007	1059										
1059008	1059										
1059010	1059										
1065008	1065										
1067005	1067										
1070003	1070										
1071004	1071										
1071012	1071										
1072002	1072										
1074008	1074										
1083001	1083										
1083004	1083										
1083005	1083										
1083009	1083										
1083011	1083										
1083012	1083										
1083018	1083										
1083019	1083										
1098003	1098										
1098007	1098										
1098011	1098										
1098015	1098										
1098016	1098										
1098017	1098										
1098019	1098										
1098020	1098										
1100003	1100										
1104002	1104										
1107007	1107										
1112004	1112										
1112007	1112										
1112011	1112										
1113007	1113										
1114001	1114										
1114002	1114										
1114004	1114										
1118007	1118										

Clinical Review
 Marjorie F. Dannis, M.D.
 NDA 203634
 Uceris (Budesonide MMX)

02-02 Normal Histology Grades with UCDAI Scores by Treatment Group

Patient Number	SITE	Treatment	UCDAI Baseline	UCDAI Final	Histo Specimen 1 Baseline Grade	Histo Specimen 2 Baseline Grade	Histo Specimen 3 Baseline Grade	Histo Specimen 1 Final Grade	Histo Specimen 2 Final Grade	Histo Specimen 3 Final Grade
1056006	1056									
1056010	1056									
1057015	1057									
1059007	1059									
1067005	1067									
1072002	1072									
1083001	1083									
1083009	1083									
1098016	1098									
1098019	1098									
1112004	1112									
1039015	1039									
1056015	1056									
1059006	1059									
1070003	1070									
1083011	1083									
1098015	1098									
1100003	1100									
1107007	1107									
1113007	1113									
1118007	1118									
1065008	1065									
1071012	1071									
1083012	1083									
1083019	1083									
1098003	1098									
1112011	1112									
1114001	1114									
1023001	1023									
1056018	1056									
1056020	1056									
1057010	1057									
1057014	1057									
1059008	1059									
1059010	1059									
1071004	1071									
1074008	1074									
1083004	1083									
1083005	1083									
1083018	1083									
1098007	1098									
1098011	1098									
1098017	1098									
1098020	1098									
1104002	1104									
1112007	1112									
1114002	1114									
1114004	1114									

(b) (4)

Study 02/02 Patients with Normal Histology from Sites with GCP Violations

Patient	Site	Treatment	Country	UC	UC Extent
1040002	1040	Placebo	Italy	Mild	Proctosigmoiditis/distal UC
1040008	1040	MMX 9 mg	Italy	Mild	Proctosigmoiditis/distal UC
1082001	1082	Placebo	Slovakia	Mild	Proctosigmoiditis/distal UC
1082004	1082	MMX 9 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1082005	1082	Placebo	Slovakia	Mild	Proctosigmoiditis/distal UC
1082006	1082	MMX 6 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1106004	1106	Placebo	Russia	Moderate	Left-sided UC
1106005	1106	Entocort	Russia	Moderate	Extensive UC
1106006	1106	Entocort	Russia	Moderate	Left-sided UC
1106007	1106	Placebo	Russia	Moderate	Left-sided UC
1106009	1106	Placebo	Russia	Moderate	Left-sided UC
1106010	1106	MMX 6 mg	Russia	Moderate	Left-sided UC
1106011	1106	MMX 6 mg	Russia	Moderate	Left-sided UC
1106012	1106	Placebo	Russia	Moderate	Left-sided UC
1122001	1122	MMX 6 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1122002	1122	MMX 6 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1122005	1122	Entocort	Slovakia	Mild	Proctosigmoiditis/distal UC
1122006	1122	Placebo	Slovakia	Mild	Left-sided UC
1122008	1122	Entocort	Slovakia	Moderate	Proctosigmoiditis/distal UC
1122009	1122	MMX 9 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1122011	1122	Placebo	Slovakia	Mild	Proctosigmoiditis/distal UC
1122015	1122	Placebo	Slovakia	Moderate	Proctosigmoiditis/distal UC
1122016	1122	MMX 9 mg	Slovakia	Mild	Left-sided UC
1122017	1122	MMX 6 mg	Slovakia	Mild	Left-sided UC
1122019	1122	Placebo	Slovakia	Mild	Left-sided UC
1122020	1122	Placebo	Slovakia	Mild	Left-sided UC
1122021	1122	Placebo	Slovakia	Mild	Proctosigmoiditis/distal UC
1122022	1122	MMX 9 mg	Slovakia	Mild	Proctosigmoiditis/distal UC
1122023	1122	Entocort	Slovakia	Mild	Left-sided UC

Appendix C

Pivotal Study Site Inspections

Name of CI Address	Protocol Number; Site Number: Subject Number	Results	Rationale for site inspection
Dr. Neil Cohen Marlton, NJ 08053	CB-01-02/01 Site 5005 11 subjects	VAI: All subjects records reviewed, 483 issued for minor issues concerning ICF, blood plasma cortisol, and use of cipro and levoquin: Confusion on dates due to screening as noted above.	Large enrollment/US site
Tawfik Chami Zephyrhillis, FL 33542	CB-01-02/01 Site 5003 9 subjects	NAI. No notable observations.	Large enrollment/US site
Dr. Umesh Jalihal Bangalore-560 086, India	CB-01 02/01 Site 9004 20 Subjects	VAI: There is no documentation of eligibility criteria in screening visit 1 for 2 subjects. S20 (MMX 6) endoscopy index score 5 in source, but 7 in eCRF. CI response is that originally recorded Jan 2010, then it was reassessed and revised in June to 7.	Large enrollment/India site
Prof. Kupcinkas Kaunas, LT 50009, Lithuania	CB-01 02/02 Site 1055 27 Subjects	VAI: 20 subjects' records. 483 issued for 2 subjects enrolled with UC hx < 6 m, concomitant UC meds not listed. The other violation was discrepancies noted between the source documents and the eCRFs (inaccurate records)	---largest percentage of patients who completed study at any site --- high budesonide MMX 9 mg remission rate, (2/10 or 20 %) and low placebo remission rate (0/4 or 0%) thus a large difference between remission rates
Dr. Robert Petryka Warszawa, 03-580, Poland	CB-01 02/02 Site # 1059 17 Subjects	NAI, good site	Per OSI
Dr. Ivan Bunganic Presov, 08001, Slovakia	CB-01 02/02 Site # 1122 22 Subjects	VAI: Violations in data listings, S19 had UCDAI <4 at screening; S22 had high GGT, 7 subjects did not begin meds on Day 1, missing oral temps Drug account did not match for 2 subjects (only 1 or 2 pills off)	Per OSI ¹⁸

Adapted from OSI Summary Draft prepared 25 October 2012

¹⁸ This site was inspected by Sponsor and found to have critical GCP violations; this reviewer agrees with Sponsor's assessment.

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

/s/

MARJORIE F DANNIS
12/12/2012

ANIL K RAJPAL
12/12/2012
I concur with Dr. Dannis.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: NDA 203634 **Applicant:**
Santarus, Inc

Stamp Date: Dec. 16, 2011

Drug Name: Uceris (budesonide MMX) **NDA/BLA Type:** 505(b)(2).

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			Individual TOC per section
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			From clinical standpoint
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?		X		
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(2). <i>Budesonide</i>
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? See comment	X			<i>The Sponsor was advised to do a dose ranging study.</i> <i>According to the Sponsor, the efficacious dose levels of glucocorticosteroids are similar in UC and CD The 9 mg dose of budesonide MMX that was used in both adequate and well-controlled Phase III studies was chosen based on</i> <i>(1) the average dosage strength of oral budesonide that is used as standard of care in CD;</i> <i>(2) published literature indicating that single daily oral doses of</i>

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					<p><i>budesonide 9 mg are more efficacious than multiple daily divided doses in patients with active distal UC</i></p> <p><i>(3) the budesonide MMX Phase II studies that demonstrated improved efficacy with budesonide MMX 9 mg once daily relative to budesonide MMX 3 mg and placebo., (Budesonide MMX 6 mg was included in the Phase III trials to identify the lowest effective dose for treatment of patients with active, mild to moderate UC.)</i></p>
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p><i>Pivotal Study #1 CSR CB-01-02/01</i> <i>Indication Induction of Remission* in Active Mild or Moderate Ulcerative Colitis</i></p> <p><i>Pivotal Study #2: CSR CB-01-02/02</i> <i>Indication Induction of Remission* in Active Mild or Moderate Ulcerative Colitis</i></p>	X			<p><i>* Remission defined as patients had to meet all of the following criteria</i></p> <ul style="list-style-type: none"> <i>• UCDAI score of ≤ 1, with subscores of 0 for both rectal bleeding and stool frequency</i> <i>• A normal mucosa (with no evidence of friability) by endoscopy at the end of Week 8</i> <i>• A ≥ 1-point reduction in the endoscopy score from baseline to the end of Week 8</i>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			<i>The approvability of this product and the proposed draft labeling will be determined during/after the review of the data submitted.</i>
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		<i>Second pivotal study is entirely international. Rationale is requested.</i>
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			<i>But need to quantify exposure more clearly and In SCS need to tabulate with links to narratives all SAEs, AE dropouts</i>
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		<p><i>EKGs only done in phase I studies- In the Phase I analysis group, 16/37 (43.2%) patients had abnormal ECG results at baseline, and 24/37 (64.9%) patients had abnormal ECG findings at the final visit According to the Sponsor, these differences are not clinically meaningful given the small sample size of the Phase I analysis group. In addition, there were no changes from baseline to final visit in any of the key ECG parameters, including heart rate, PR/PQ interval, QRS interval, or QT interval (ISS Table 5.39).</i></p>

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					<i>Link to ISS table referenced from SCS not working and no word EKG in ISS. (Budesonide is marketed in the United States as Entocort EC).</i>
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	<i>Budesonide MMX is not approved for use and has not been marketed in any country.</i>
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			<i>Directed Sponsor to ICH guidance EIA 62 patients received budesonide MMX 6 mg for up to 12 months. Response may change based on exposure information to be obtained from Sponsor.</i>
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		<i>Requested</i>
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?		X		<i>Deaths-none SAEs-yes Adverse event dropouts-no Not in ISS or SCS-should be compiled together not only separate</i>
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			<i>They want (b) (4) -will need to discuss with Sponsor the inappropriateness of this request</i>

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

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

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		<i>Second pivotal study is entirely international. Rationale is requested.</i>
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			X	<i>As per Stats</i>
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	<i>As per Stats</i>
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	<i>As per Stats</i>
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		<i>Information requested via email-Sponsor response pending</i>

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __ Yes _____

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

Please quantify exposure to budesonide MMX (i.e. how many patients exposed at each dose and for what length of time).

Please submit:

1. the coding dictionary used for mapping investigator verbatim terms to preferred terms.
2. a tabulation of all SAEs and AE dropouts with links to their respective narratives
3. benefit-risk analysis for your product
4. a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine
5. adequate information to assess the arrhythmogenic potential of your product (e.g., QT interval studies, if needed)

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Table 10. Summary of Study Drug Exposure for Supportive Analysis Groups

Duration of Exposure (days) ^a	Phase II/III Randomized, Double-blind						Phase II/III Open-label
	Placebo N=293	MMX 9 mg N=288	MMX 6 mg N=254	MMX 3 mg N=17	Asacol N=127	Entocort N=126	MMX 9 mg N=89
n	277	272	245	17	120	121	85
Mean	48.0	48.6	47.0	53.1	50.8	49.8	45.3
SD	28.31	15.93	17.98	9.50	13.94	13.79	15.67
Median	56.0	56.0	56.0	56.0	56.0	56.0	55.0
Minimum	3	1	3	28	7	8	8
Maximum	421	106	89	59	70	73	62
Missing	16	16	9	0	7	5	4

Source: ISS Table 3.7, Table 4.7

Abbreviations: MMX = budesonide MMX; SD = standard deviation.

^a Duration of exposure = study drug returned date (or last date study drug was collected) - study drug dispensed date.

See appended signature page

2/6/12

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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/s/

MARJORIE F DANNIS
02/06/2012

ANIL K RAJPAL
02/06/2012