

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203634Orig1s000**

**STATISTICAL REVIEW(S)**

## Statistical Team Leader Memorandum

Submission: NDA 203634  
Product: Uceris (budesonide)  
Sponsor: Santarus  
Indication: Induction of remission of ulcerative colitis  
Medical Div: DGIEP

This memorandum presents the Team Leader's summary of statistical issues and recommendations as discussed with the Clinical Review Team during the course of this NDA review. The three main issues are the change in the primary analysis populations made after the enrollment period for studies 01 and 02; the disproportionate number of placebo patients in study 02 who had normal histology; and the data quality of study 02 as reflected by four sites with major GCP violations.

### *Change in primary analysis population*

Performing the efficacy analysis on only histology positive subjects is consistent with antimicrobial trials where this is done in a prospective fashion. From a statistical perspective, a diagnostic test conducted prior to randomization that conclusively identifies disease (in this case, active UC) would in theory not invalidate the randomization and should be acceptable provided the blind was maintained and critical study milestones were well documented. The sponsor's change to their SAP identifying the primary analysis to include only subjects with positive histology at baseline was made after completion of study enrollment but well before database lock and unblinding, and the sponsor's data management procedures appear adequate. The sponsor's rationale for the change was based on release of new EMA guidelines, while the studies were ongoing, which state in part that absence of histological evidence excludes a diagnosis of active colitis. There does not appear to be a clear potential source of bias that should override the use of the modified analysis population to judge the efficacy of this product.

### *Placebo subjects with normal histology*

In study 02, a larger-than-expected number of placebo subjects had normal histology at baseline. In randomizing, one would expect baseline characteristics to be balanced across treatment groups. Imbalances however do occur in trials, and it should not be supposed that any particular imbalance invalidates the randomization or that the randomization process was flawed. The imbalance may have occurred by chance or it may suggest that there were other procedural problems in study 02 possibly tied in with the sites that were identified by the sponsor to have critical GCP issues. The sponsor re-examined their randomization process for study 02 and concluded it functioned as intended. Since the primary analysis population excludes subjects with normal baseline histology, this would not be an issue unless one was convinced the randomization process was biased, and this does not appear to be the case.

## Statistical Team Leader Memorandum

### *Study 02 site violations*

The GCP violations and the imbalance of placebo subjects with normal histology raise a cautionary note regarding the quality of results from study 02. The removal of protocol violators from the primary analyses is inconsistent with statistical review practice as protocol violators would typically be removed from a per-protocol data set not an ITT or modified ITT data set. However, in this case, the site violations are major ones, including missing source data, so removal may be justified. Since the randomization was centrally controlled in blocks of size 4, it cannot be expected that treatment group balances would occur within site and hence removal of sites from the primary analysis may bias the efficacy results; however, a similar treatment effect size is shown with or without sites removed.

### *Conclusions and recommendations for labeling*

There appears to be adequate documentation supporting the sponsor's change to the primary analysis population to include subjects with positive histology at baseline, and the introduction of bias due to this change is not evident. Based on this analysis population, both studies show statistically significant results, each with an effect of about 10%. Study 02 has the GCP violation issues as well as the apparent randomization imbalance in subjects with normal histology; for these reasons, this study should be considered supportive to the principle trial, study 01.

The overall level of statistical evidence of efficacy based on both studies is, in this reviewer's opinion, sufficient to support a recommendation for product approval by the Clinical Team.

Labeling should specifically identify an indicated population based on positive results from mucosal biopsy to identify active UC. The clinical trials section of labeling should describe the studies as originally designed but should present results for only the biopsy positive subjects. The nature of the site violations for study 02 would support removal of these sites from the analysis tables.

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/s/  
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MICHAEL E WELCH  
12/31/2012



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Science  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**BLA/Serial Number:** 203634  
**Drug Name:** Uceris (budesonide) 9 mg tablets  
**Indication(s):** Induction of remission in patients with active, mild to moderate ulcerative colitis  
**Applicant:** Santarus, Inc.  
**Date(s):** Received December 16, 2011 PDFUA: January 16, 2013  
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## 1. EXECUTIVE SUMMARY

### 1.1 Conclusions and Recommendations

The sponsor submitted two induction trials (Study CB-01-02/01 and CB-01-02/02) and one maintenance trial (Study CB-01-02/04).

Study CB-01-02/01 showed that in the sponsor's ITT population, the percentage of patients achieving clinical remission at Week 8 in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group. Remission rates for budesonide MMX 6 mg was numerically greater than placebo, but the difference did not reach statistical significance.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

Study CB-01-02/02 conducted in Europe was problematic with regard to the sponsor's ITT population. The sponsor's ITT population excluded four sites with significant GCP violations, and significantly more patients were excluded from the placebo group compared to the budesonide MMX 9 mg group (31.0% vs. 13.5%) mainly due to normal histology at baseline.

Results for this study in sponsor's ITT population tended to be biased against placebo and might not be interpretable statistically with placebo.

Study CB-01-02/02 showed that in the sponsor's ITT population, the percentage of patients in clinical remission at Week 8 was significantly higher for patients receiving budesonide MMX 9 mg than for patients receiving placebo.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

This reviewer performed "true" ITT analyses including all randomized patients for both studies (CB-01-02/01 and CB-01-02/02). Results showed that remission rates for budesonide MMX 9 mg was numerically greater than placebo for both studies, but differences did not reach statistical significance for this "true" ITT population. The treatment differences between budesonide MMX 9 and placebo were 6.3% with 95% CI (-2%, 15.0%) and 3.2% with 95% CI (-5.6%, 12.1%) for Study CB-01-02/01 and Study CB-01-02/02, respectively.

In Study CB-01-02/01, the number of patients with normal histology at baseline was comparable among treatment groups. Rate of clinical remission for budesonide MMX9 mg group was

numerically higher than for placebo for patients with positive baseline histology (18.5% vs. 8.2%) with nominal p-value of 0.0238 (Fisher's exact test).

In Study CB-01-02/01, 5 of 6 placebo patients with normal histology at baseline had clinical remission. None of the 3 budesonide MMX 9 mg patients with normal histology at baseline had clinical remission. The p-value changed from 0.0238 in "positive histology" population to 0.1365 in the reviewer's "true" ITT population. So, the p-value for the sponsor's ITT analysis was at best at borderline significant compared to the pre-specified threshold of 0.025. .

In Study CB-01-02/02, statistically significant more placebo patients with normal histology at baseline were observed as compared to other treatment groups. So, results from the sponsor's ITT analysis excluding patients with normal histology might not be statistically interpretable. The rate of clinical remission for the budesonide MMX 9 mg group was numerically higher than that for placebo for patients with positive baseline histology (16.7% vs. 6.3%) with nominal p-value of 0.0308 (Fisher's exact test). The p-value changed from 0.0308 in the "positive histology" population to 0.4746 in "true" ITT population. Results from the sponsor's ITT analysis might not be considered robust.

Furthermore, since the sponsor's ITT analysis excluded all patients with normal histology at baseline, the sponsor's ITT analysis should not be considered as a modified ITT analysis but a subgroup analysis for patients with abnormal histology at baseline. Basing the primary analysis on the subgroup of patients with abnormal histology was not pre-specified in the original protocols but was introduced in the SAP after study enrollment but before database lock. Without clear pre-specification, this subgroup analysis should be considered as exploratory and hypothesis generating in nature.

For the maintenance trial (Study CB-01-02/04), the SAP stated that this study was an exploratory in nature with no formal sample size calculation. This study was not powered to show statistically significant differences between budesonide MMX 6 mg and placebo. So, this study should be considered as an exploratory study.

In conclusion, for induction, both studies (Study CB-01-02/01 and Study CB-01/02/02) did not provide substantially statistical evidence demonstrating superiority of the budesonide MMX 9 mg over placebo for all randomized population. For patients with positive histology at baseline, the budesonide MMX 9 mg was numerically better than placebo. But, subgroup of patients with positive histology was not pre-specified in the protocol. Without clear pre-specification, this subgroup analysis should be considered exploratory and hypothesis generating in nature.

## **1.2. Brief Overview of Clinical Studies**

### **1.2.1 Study CB-01-02/01**

This is a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, parallel-group study comparing budesonide MMX (6 mg and 9 mg) with placebo in patients with active, mild or moderate UC. A reference arm using Asacol® (hereafter referred to as Asacol)

2400 mg (2 x 400 mg tablets TID) was also included. To maintain the blind, placebos for both budesonide MMX and Asacol were given in each treatment group.

The primary objective of this study is to evaluate the efficacy and safety of oral budesonide MMX® (hereafter referred to as budesonide MMX) 6 mg and 9 mg extended-release tablets when compared with placebo in patients with active, mild or moderate ulcerative colitis (UC) after 8 weeks of treatment.

Efficacy was assessed using the 4-component Ulcerative Colitis Disease Activity Index (UCDAI) score, UCDAI sub-scores for stool frequency and rectal bleeding, endoscopic and histologic assessment of the colonic mucosa.

The primary endpoint was clinical remission after 8 weeks of treatment. Clinical remission was defined as meeting all of the following criteria:

- UCDAI score of  $\leq 1$ , with subscores of 0 for both rectal bleeding and stool frequency
- A normal mucosa (with no evidence of friability) by endoscopy at the end of Week 8
- A  $\geq 1$ -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.

With objection from the FDA, the sponsor modified the definition of the primary analysis population for efficacy as follows:

Protocol	SAP
The primary analysis population for efficacy was defined as the Full analysis set (FAS)	The primary analysis population for efficacy was defined as the ITT Population
The FAS included all randomized patients who received at least one dose of study drug, and with at least one post-baseline efficacy assessment.	The ITT population included all randomized patients who received at least one dose of study drug, excluding patients with major GCP or entry criteria violations or normal histology (no active disease) at baseline.

Study CB-01-02/01 was performed at 108 centers throughout the US, Canada, Mexico, and India.

### 1.2.2 Study CB-01-02/02

The study design of this study was nearly identical to Study CB-01-02/01. Both studies were randomized, double-blind, double-dummy, placebo-controlled, parallel group, multicenter studies which evaluated up to 8 weeks of once daily therapy with budesonide MMX 9 mg and 6 mg and placebo in adult patients with active, mild to moderate ulcerative colitis. The studies shared identical entry criteria and identical primary, secondary, and other efficacy endpoints.

The only difference between the two studies was the addition of different, non-powered active reference arms; CB-01-02/01 included Asacol® (mesalamine [hereafter referred to as Asacol]) 2400 mg while CB-01-02/02 included Entocort EC (budesonide) 9 mg. The dosage strength of Entocort EC that was used in study CB-01-02/02 is approved in the US for treatment of CD and was included as an active comparator to compare localized GI delivery of budesonide. The

dosage strength of Asacol that was used in study CB-01-02/01 is approved in the US for treatment of active mild to moderate UC and for maintenance of remission of UC. Asacol was included in CB-01-02/01 to provide a study design that was similar to that of CB-01-02/02.

Both studies were powered for the comparisons of budesonide MMX 9 mg and 6 mg arms to placebo and were adjusted for multiplicity, but were not powered for comparisons between budesonide MMX and the active reference groups.

Study CB-01-02/02 was performed at 69 centers throughout Western and Eastern Europe, Israel, and Australia.

### **1.2.3 Study CB-01-02/04**

Additionally, a 12-month, double-blind, placebo-controlled Phase III study enrolling patients achieving remission in any of the previous three Phase III studies followed 123 patients for up to 12 months with the objective of assessing long-term safety and maintenance of remission with budesonide MMX 6 mg.

The SAP stated that this study was an exploratory in nature and such there was no formal sample size calculation. It is planned that approximately 150 patients will be randomized, giving 75 patients per treatment group.

The SAP also stated that this study is not powered to show statistically significant differences between budesonide MMX and placebo. So, this study should be considered as exploratory study.

Furthermore, the SAP stated that the primary efficacy endpoints are clinical remission at 1, 3, 6, 9 months and at the End of Study/Early Withdrawal Visit.

If no multiplicity adjustments were to be applied to primary efficacy endpoints, results for primary efficacy endpoints should be considered exploratory.

So, Study CB-01-02/04 should be considered as exploratory.

### 1.3 Statistical Issues and Findings

The sponsor submitted two induction trials (Study CB-01-02/01 and CB-01-02/02) and one maintenance trial (Study CB-01-02/04).

Study CB-01-02/01 showed that in the sponsor's ITT population, the percentage of patients achieving clinical remission at Week 8 in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group. Remission rates for budesonide MMX 6 mg was numerically greater than placebo, but the difference did not reach statistical significance.

Result of subgroup analysis of rate of clinical remission at Week 8 was inconsistent between  $\leq 42$  years vs.  $> 42$  years (1.2% vs. 21.0%).

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

Study CB-01-02/02 conducted in Europe was problematic with the sponsor's ITT population. Sponsor's ITT population excluded significantly more patients in placebo than in budesonide MMX 9 mg group (31.0% vs. 13.5%) mainly due to normal histology at baseline.

Results for this study in sponsor's ITT population tended to be biased against placebo and might not be interpretable with placebo.

Study CB-01-02/02 showed that in the sponsor's ITT population, the percentage of patients in clinical remission at Week 8 was significantly higher for patients receiving budesonide MMX 9 mg than for patients receiving placebo.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

The sponsor's ITT population was not pre-specified in the protocol but was pre-specified in the protocol. But, proposed SAP excluding patients with normal histology at baseline and critical GCP violations was submitted FDA just 17 days before the last patient out. The SAP was finalized about 5 months after last patient out. The SAP did not state clearly which analysis (randomized or ITT) was to be the primary efficacy analysis. In the Teleconference dated April 13, 2010, the agency clearly stated that "true" ITT analysis should be considered as the primary efficacy analysis. The agency assumed the primary analysis was to be based on the as-randomized and recommended the sponsor's ITT analysis would be a sensitivity analysis to support the primary analysis.

In the pre-NDA meeting on May 31, 2011, the Agency restated that the “true” ITT population should be used as the primary analysis population.

This reviewer performed “true” ITT analysis including all randomized patients for both studies (CB-01-02/01 and CB-01-02/02). Results showed that remission rates for budesonide MMX 9 mg was numerically greater than placebo for both studies, but differences did not reach statistical significance for “true” ITT population. The treatment differences between budesonide MMX 9 and placebo were 6.3% with 95% CI (-2%, 15.0%) and 3.2% with 95% CI (-5.6%, 12.1%) for Study CB-01-02/01 and Study CB-01-02/02, respectively.

In Study CB-01-02/01, the number of patients with normal histology at baseline was comparable among treatment groups. Rate of clinical remission for budesonide MMX9 mg group was numerically higher than for placebo for patients with positive baseline histology (18.5% vs. 8.2%) with nominal p-value of 0.0238 (Fisher’s exact test).

In Study CB-01-02/01, 5 of 6 placebo patients with normal histology at baseline had clinical remission. None of 3 budesonide MMX 9 mg patients with normal histology at baseline had clinical remission. The p-value changed from 0.0238 in “positive histology” population to 0.1365 in “true” ITT population. So, the p-value for the sponsor’s ITT analysis was at best at borderline significant.

In Study CB-01-02/02, statistically significant more placebo patients with normal histology at baseline were observed as compared to other treatment groups. So, results from the sponsor’s ITT analysis excluding patients with normal histology might not be interpreted statistically. Rate of clinical remission for budesonide MMX 9 mg group was numerically higher than that for placebo for patients with positive baseline histology (16.7% vs. 6.3%) with nominal p-value of 0.0308 (Fisher’s exact test). The p-value changed from 0.0308 in “positive histology” population to 0.4746 in “true” ITT population. Results from the sponsor’s ITT analysis might not be robust.

Furthermore, the sponsor’s ITT analysis excluded all patients with normal histology at baseline. So, the sponsor’s ITT analysis should not be considered as a modified ITT analysis but a subgroup analysis for patients with abnormal histology at baseline. Subgroup of patients with abnormal histology was not pre-specified in the protocol.

Without clear pre-specification, this subgroup analysis should be considered as exploratory and hypothesis generating in nature.

For maintenance trial (Study CB-01-02/04), the SAP stated that this study was an exploratory in nature and such there was no formal sample size calculation. This study was not powered to show statistically significant differences between budesonide MMX 6 mg and placebo. So, this study should be considered as an exploratory study.

In conclusion, for induction, both studies (Study CB-01-02/01 and Study CB-01/02/02) did not provide substantially statistical evidence demonstrating superiority of the budesonide MMX 9 mg over placebo for total population. For patients with positive histology at baseline, the

budesonide MMX 9 mg was numerically better than placebo. But, subgroup of patients with positive histology was not pre-specified in the protocol. Without clear pre-specification, this subgroup analysis should be considered as exploratory and hypothesis generating in nature.

For maintenance, Study CB-01-02/04 was designed as exploratory in nature. Results cannot be interpreted statistically

## **2. INTRODUCTION**

### **2.1 Overview**

Budesonide MMX 9 mg tablet is an enteric coated, extended release, oral dosage formulation designed for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC). UC is a chronic, relapsing/remitting inflammatory bowel disease (IBD) involving the colorectal mucosa. To provide an enhanced standard of treatment for UC, budesonide, a topically-active glucocorticosteroid, was selected as the active ingredient and combined with the novel, patented multimatrix (MMX) delivery technology.

The sponsor seeks marketing approval for budesonide MMX 9 mg for induction of remission in patients with active, mild to moderate ulcerative colitis.

### **2.2 Data Sources**

The sponsor has submitted four Phase III studies, CB-01-02/01 and CB-01-02/02, CB-01-02/06, and CB-01-02/04. Studies CB-01-02/01 and CB-01-02/02 were submitted as two adequate well-controlled studies (CB-01-02/01 and CB-01-02/02) for induction of remission in patients with active, mild to moderate UC. CB-01-02/01 was conducted in the US, Canada, Mexico and India while CB-01-02/02 was conducted in Europe, Russia, Israel, and Austria. With the exception of the reference comparator arm (Asacol in CB-01-02/01 and Entocort in CB-01-02/02), these two studies were identical in design. CB-01-02/06 was an open-label efficacy and safety study in patients with mild to moderate, active ulcerative colitis. CB-01-02/04 was a 12 month, double-blind, placebo-controlled Phase III extension study in maintenance of remission in subjects with ulcerative colitis.

These four studies were entitled as follows:

- Protocol CB-01-02/01: Efficacy and Safety of New Oral Budesonide MMX (CB—01-02) 9 mg and 6 mg Extended Release Tablet Formulation 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.
- Protocol CB-01-02/02: Efficacy and Safety of Oral Budesonide MMX (CB-01-02) 6 mg and 9 mg Extended Release Tablet Formulation 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.

- Protocol CB-01-02/04: Randomized, Double-Blind, Multi-Center, Twelve Month Extension Study to Evaluate the Safety and Efficacy of Daily Budesonide MMX 6 mg vs. Placebo in the Maintenance of Remission in Subjects with Ulcerative Colitis.
- Protocol CB-01-02/06: A Multicenter, Open-Label Efficacy and Safety Study of Oral Budesonide MMX 9 mg Extended Release Tablets in Patients with Mild to Moderate, Active Ulcerative Colitis

The Statistical Analysis Plan (SAP) for Study CB-01-2/04 stated that this study is an exploratory in nature and such there is no formal sample size calculation.

The SAP also stated that this study is not powered to show statistically significant differences between budesonide MMX and placebo. So, this study should be considered as an exploratory study.

This review mainly focuses two induction studies (CB-01-02/01 and CB-01-02/02). Some comments are also provided on Study CB-01-02/04.

The original submission was submitted in eCTD and dated December 14, 2011.

The electronic submission is located at <\\Cdsub1\evsprod\NDA203634\0000>.

The sponsor submitted responses to requests for information dated March 9, 2012, March 26, 2012, May 2, 2012, May 9, 2012, May 29, 2012, and July 20, 2012.

### **3. STATISTICAL EVALUATION**

#### **3.1 Evaluation of Efficacy**

##### **3.1.1 Study CB-01-02/01**

###### **3.1.1.1 Study Design**

This is a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, parallel-group study comparing budesonide MMX (6 mg and 9 mg) with placebo in patients with active, mild or moderate UC. A reference arm using Asacol® (hereafter referred to as Asacol) 2400 mg (2 x 400 mg tablets TID) was also included. To maintain the blind, placebos for both budesonide MMX and Asacol were given in each treatment group.

The primary objective of this study is to evaluate the efficacy and safety of oral budesonide MMX® (hereafter referred to as budesonide MMX) 6 mg and 9 mg extended-release tablets when compared with placebo in patients with active, mild or moderate ulcerative colitis (UC) after 8 weeks of treatment.

The secondary objective is to evaluate the clinical improvement and endoscopic improvement of budesonide MMX 6 mg and 9 mg oral tablets when compared with placebo in patients with active, mild or moderate UC after 8 weeks of treatment

The other objective is to evaluate symptom resolution; histologic healing; improvement in the Clinical Activity Index (CAI); changes in C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR); improvement in the Inflammatory Bowel Disease-Quality of Life (IBD-QoL) questionnaire after 8 weeks of treatment

A full colonoscopy was performed at Screening and Visit 5 (Day 56). At Screening and Visit 5, three biopsies were taken from the colonic lesions considered as most severe during each endoscopy. Each bioptic specimen was examined by a histopathologist in terms of severity of enterocytes and crypt changes, and the cellularity of the lamina propria. All biopsy sample evaluations was performed at the central laboratory.

Key inclusion criteria were:

1. Male or female patients; 18-75 years old
2. Diagnosed with UC in active phase, of mild to moderate severity with an Ulcerative Colitis Disease Activity Index (UCDAI) score  $\geq 4$  and  $\leq 10$  according to Sutherland and suffering from UC for at least 6 months.

Eligible patients underwent a 2-day washout period and were then randomized to one of the following four treatment groups:

- Placebo
- Budesonide MMX 9 mg
- Budesonide MMX 6 mg
- Asacol

Study drug was to be given as follows:

Placebo: One budesonide MMX-matching placebo tablet once daily in the morning, after breakfast; two Asacol-matching over-encapsulated placebo tablets three times daily, after breakfast, lunch, and dinner

Budesonide MMX 9 mg: One budesonide MMX 9 mg tablet once daily in the morning, after breakfast; two Asacol-matching over-encapsulated placebo tablets three times daily, after breakfast, lunch, and dinner

Budesonide MMX 6 mg: One budesonide MMX 6 mg tablet once daily in the morning, after breakfast; two Asacol-matching over-encapsulated placebo tablets three times daily, after breakfast, lunch, and dinner

Asacol: One budesonide MMX-matching placebo tablet once daily in the morning, after breakfast; two Asacol 400 mg over-encapsulated tablets three times daily, after breakfast, lunch, and dinner

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) or Final Visit.

Efficacy was assessed using the 4-component Ulcerative Colitis Disease Activity Index (UCDAI) score, UCDAI sub-scores for stool frequency and rectal bleeding, endoscopic and histologic assessment of the colonic mucosa, changes in CRP levels and ESR, scores from the 32-item IBD-QoL, and scores from the 7-component CAI.

UCDAI was assessed at Screening and at Visit 5 (Day 56). The UCDAI is comprised of four components (stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity). 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  $\geq 4$  and  $\leq 10$  according to the Sutherland method ([Sutherland, 1987](#)) for determining disease activity. Investigators were instructed to determine study eligibility using the most severe episode (highest score) of stool frequency and rectal bleeding that were recorded in the patient diary during the last 7 calendar days prior to Visit 2. Stool frequency and rectal bleeding diary entries on the colonoscopy and colonoscopy preparation days were not included in the 7 days used to determination of the UCDAI score.

Several key opinion leaders indicated that the UCDAI score was best understood and interpreted when the scores for stool frequency and rectal bleeding are based the average of the 3 days that were closest to Visit 5 and occurred within the first 5 days before Visit 5. This methodology was also confirmed by reviewing the results of recent UC trials ([Kamm, 2007](#); [Lichtenstein, 2007](#)). Therefore, to be most meaningful clinically, remission status at Visit 5 (Day 56) was based on the average of the 3 days closest to Visit 5 that: 1) were closest to Visit 5, 2) did not have missing diary data, and 3) occurred within the first 5 non-colonoscopy related days closest to Visit 5).

Safety was assessed by monitoring treatment-emergent adverse events (AEs), treatment-emergent serious AEs (SAEs), potential glucocorticoid effects, vital signs (pulse, systolic and diastolic blood pressure, temperature), clinical laboratory test results (including morning plasma cortisol), and physical examination findings.

Patients were considered to have completed the study if they completed 8 weeks of treatment. Patients withdrawn from the study before completion of Week 8 were asked to undergo the Final Visit as soon as possible after withdrawal.

With objection from the FDA, the sponsor modified the definition of the primary analysis population for efficacy as follows:

Protocol	SAP
The primary analysis population for efficacy was defined as the Full analysis set (FAS)	The primary analysis population for efficacy was defined as the ITT Population
The FAS included all randomized patients who received at least one dose of study drug, and with at least one post-baseline efficacy assessment.	The ITT population included all randomized patients who received at least one dose of study drug, excluding patients with major GCP or entry criteria violations or normal histology (no active disease) at baseline.

The following analysis populations were defined:

- Safety: All patients who received at least one dose of the study drug
- Intent-to-Treat (ITT): All randomized patients who received at least one dose of the study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.
- Per-protocol (PP): All patients in the ITT who completed the study without major protocol violations.
- Sensitivity: All randomized patients who received at least 1 dose of the study drug, and had mucosal histology consistent with active UC at baseline; this population was defined after the database was unblinded.

The ITT population was the primary population for the analysis of all efficacy endpoints. Patients in the ITT population were analyzed according to their randomized treatment assignment.

The PP population was used for a secondary analysis of the primary and secondary endpoints. Patients in the PP population were analyzed according to their randomized treatment assignment.

The Sensitivity population was used for supplementary analysis of the primary endpoint (clinical remission), both secondary endpoints (clinical improvement and endoscopic improvement), and two other endpoints (symptom resolution and histologic healing).

Since the sensitivity population was defined after the data were unblended, this reviewer think that results from the sensitivity analyses for primary and secondary endpoints should be considered as exploratory. Results from this sensitivity population will not be discussed in this review.

The primary endpoint was clinical remission after 8 weeks of treatment. Clinical remission was defined as meeting all of the following criteria:

- UCDAI score of  $\leq 1$ , with subscores of 0 for both rectal bleeding and stool frequency
- A normal mucosa (with no evidence of friability) by endoscopy at the end of Week 8
- A  $\geq 1$ -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 are:

- Clinical improvement, defined as a  $\geq 3$ -point improvement in UCDAI from baseline to the end of Week 8
- Endoscopic improvement, defined as a  $\geq 1$ -point improvement in the mucosal appearance subscore from baseline to the end of Week 8

Other endpoints are symptom resolution (UCDAI stool frequency and rectal bleeding subscores of 0), histologic healing (total histologic score of  $\leq 1$  for all biopsy specimens), ESR,CRP; IBD-QoL scores; CAI score  $\leq 4$ , and treatment failure defined as a worsening of clinical conditions (worsening of UC), which, in the opinion of the Investigator, required immediate specific medical treatment).

A non-powered active reference arm, Asacol® (mesalamine [hereafter referred to as Asacol]) 2400 mg, was included in study CB-01-02/01. The dosage strength of Asacol that was used in study CB-01-02/01 is approved in the US for treatment of active mild to moderate UC and for the maintenance of remission of UC.

This study was powered for the comparisons between budesonide MMX 9 mg and placebo and between budesonide 6 mg and placebo. They were adjusted for multiplicity, but were not powered for comparisons between budesonide MMX and the active reference groups.

Study CB-01-02/01 was performed at 108 centers throughout the US, Canada, Mexico, and India and conducted from August 20, 2008 to May 28, 2010..

### **3.1.1.2 Sponsor's Analysis**

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: placebo, n = 121; budesonide MMX 9 mg, n = 123; budesonide MMX 6 mg, n = 121; and Asacol 2400 mg, n = 124.

A total of 20 patients were excluded in the sponsor's ITT population (8 placebo; 4 MMX 9 mg; 5 MMX 6 mg; and 3 Asacol). The sponsor's ITT analysis excluded 17 patients with normal histology at baseline ((6 placebo; 3; MMX 9 mg; 5 MMX 6 mg; 3 Asacol). A total of 3 patients were excluded in the sponsor's ITT population (2 placebo; 1 MMX 9 mg) for infectious colitis at entry. Summary of patients excluded from the sponsor's ITT analysis population is given below.

**Table 8. Exclusions from the ITT Analysis Population**

Category	Placebo	Budesonide MMX 9 mg	Budesonide MMX 6 mg	Asacol 2400 mg	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Safety	129	127	126	127	509
ITT <sup>a</sup>	121	123	121	124	489
Patients excluded from ITT	8 (5.5)	4 (3.1)	5 (4.7)	3 (2.4)	20 (3.9)
Infectious colitis at entry	1 (0.8)	1 (0.8)	1 (0.8)	0	3 (0.6)
Normal histology at entry	6 (4.7)	3 (2.4)	5 (3.9)	3 (2.4)	17 (3.3)

Source: [Table 14.1-1](#) and [Table 14.1-5](#)

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.

<sup>a</sup> The ITT population included all randomized patients who received at least 1 dose of study drug, excluding those with major entry criteria violations, major GCP violations, and normal histology at baseline.

### 3.1.1.2.1 Sponsor's Rationale for Exclusions for the Sponsor's ITT Analysis Population

The sponsor provided a detailed rationale for exclusions based on 1) major entry criteria violations (confirmation of infectious colitis at the time of randomization), 2) presence of normal histology at baseline (and thus, non-active UC), and 3) major violations of GCP.

Sponsor's rationale for exclusions for the sponsor's ITT analysis population briefly summarized below.

- The exclusion of patients with infectious colitis at study entry was a pre-specified exclusion criterion in the study protocol. Compared to UC, infectious colitis may present with similar signs and symptoms and can be difficult to distinguish endoscopically from UC.
- Analysis of efficacy in patients with active disease based on histology is supported by the scientific literature ([Riley, 1991](#); [Robert, 2004](#); [Stange, 2008](#); [Travis, 2008](#); [Thomas, 2009](#)). The requirement for performing mucosal biopsies at screening was prospectively incorporated in the study protocols. The exclusion of patients with normal histology from the ITT analysis was prospectively defined in the SAP. Exclusion of patients with normal histopathology allows for the accurate assessment of the treatment effect of budesonide MMX on the intended patient population. The application of this exclusion did not introduce bias because:
  - In all instances, baseline mucosal biopsies were sampled *prior* to randomization
  - All histopathology assessments were made in a completely objective manner by a blinded pathologist at a central laboratory using the standardized scoring system described by Saverymuttu ([Saverymuttu, 1986](#)). Thus, all patients received equal scrutiny for the presence (or absence) of active UC.
  - All patients who were discovered to have had normal histopathology (no active UC) were removed from the ITT analysis population prior to database lock and unblinding.
- 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. These exclusions were planned for consistency with study CB-01-02/02. In the current study, CB-01-02/01, no patients were excluded for this reason.

### **3.1.1.2.2 Planned Analysis**

For primary endpoint analyses, clinical remission rates were compared between each budesonide MMX treatment group and the placebo group using the Chi-square test. Patients with missing data that precluded the determination of remission status were considered as not having met the endpoint (using a worst case imputation method).

Because both budesonide MMX groups were tested in parallel, the two primary endpoint comparisons were conducted at the  $\alpha = 0.025$  level of significance.

For secondary endpoints analyses, clinical improvement (secondary endpoint 1) and endoscopic improvement (secondary endpoint 2) were analyzed hierarchically in the ITT and PP populations. If at least one primary endpoint comparison was statistically significant, clinical improvement was to be compared between each budesonide MMX dose group and placebo. If at least one comparison of clinical improvement was statistically significant, then endoscopic improvement was to be compared between each budesonide MMX dose group and placebo. All secondary endpoint comparisons were conducted at the  $\alpha = 0.025$  level of significance. Patients with missing data that precluded the determination of clinical or endoscopic improvement were analyzed using both worst case and observed case imputation (all patients with missing data were excluded from the analysis) methods.

For other endpoints analyses, if at least one primary endpoint comparison was statistically significant, analyses of the remaining endpoints were to be conducted in the ITT population at the  $\alpha = 0.05$  level of significance. For the endpoints of symptom resolution, histological healing, and  $\text{CAI} \leq 4$ , patients with missing data were analyzed using both worst case and observed case imputation methods. For the endpoints of IBDQoL, CRP, and ESR, patients with missing data were handled using last observation carried forward (LOCF) and observed case imputation methods.

The percentages of patients with AEs were summarized by treatment group. AEs were categorized by system organ class (SOC) and preferred term. Vital signs, laboratory parameters including morning plasma cortisol (value and change from baseline) were summarized at each visit and for change from baseline for each treatment group. Baseline cortisol results were calculated as the average result from two samples (when available) taken on different days before the study drug treatment was started. If only one sample was available then it was taken as the baseline evaluation of cortisol for the study. In addition, shift tables were produced for each laboratory parameter and by treatment group.

Physical examinations were summarized by treatment group and by visit. Potential glucocorticoid effects were also tabulated.

### **3.1.1.2.3 Treatment Group Comparability**

The summary of the results for comparability of the treatment groups at baseline for the sponsor's ITT population is given in Appendix Table 1.

As seen from Appendix Table 1, demographic characteristics were similar across the treatment groups, except that the percentage of males in the budesonide MMX 9 mg group was 62.6% as compared with 48.8% to 56.2% in the other groups. The median age at study entry was 42.0 years (range: 18 to 77 years). UCDAI baseline scores appeared similar across treatment groups.

### 3.1.1.2.4 Sponsor's Analysis of Primary Efficacy Variable

The primary endpoint was analyzed in the sponsor's ITT (primary), PP, and sensitivity populations. For these analyses, missing data were handled using the worst case method (i.e., patients with missing data were treated as not achieving remission).

The primary analysis of clinical remission was performed using the sponsor's ITT population. Results are summarized in Table 1.

**Table 1 Rates of Clinical Remission (Sponsor's ITT 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.

As seen in table above, in the sponsor's ITT population, the percentage of patients achieving clinical remission in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group. Remission rates for budesonide MMX 6 mg and Asacol were numerically greater than placebo, but the differences did not reach statistical significance. Similar results were observed in the PP population

The difference in remission rates in the budesonide MMX 9 mg and placebo groups remained significant at the  $\alpha = 0.025$  level after adjusting for age ( $p = 0.0180$ ), sex ( $p = 0.0151$ ) and geographic region ( $p = 0.0141$ ) when using the Cochran-Mantel-Haenszel test.

#### 3.1.1.2.4.1 Subgroup Analysis

Results of subgroup analyses of rates of clinical remission by age ( $\leq 42$  vs.  $> 42$ ), gender, and geographic region are given in Table 2.

**Table 2 Rates of Clinical Remission Stratified by Age, Sex, and Geographic Region  
Study CB-01-02/01  
(Sponsor’s ITT Population)**

	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.

As seen from table above, a comparison of remission rates in the budesonide MMX 9 mg and placebo groups after stratifying for age, sex and geographic region indicated statistically significant 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%,  $p = 0.0376$ ), where North America comprised the United States, Canada, and Mexico.

#### 3.1.1.2.4.2 Data for Patients with Normal and Abnormal Histology Combined

Based on the FDA’s suggestion the data for patients with normal and abnormal histology be combined in an assessment of the primary efficacy endpoint, an analysis of remission status by treatment group (budesonide 9 mg, placebo) was conducted, stratifying by baseline histology status (normal, abnormal) using the Mantel-Haenszel statistic. The result of this analysis was not statistically significant ( $p=0.0909$ ). However, the Breslow-Day test for the homogeneity of odds ratios across the two histology groups was statistically significant ( $p= 0.0029$ ), indicating that pooling odds ratios across baseline histology groups is not valid, since the odds ratios in the two groups are not constant. In other words, this analysis provides additional statistical support for the view that these are distinctly different populations, and therefore the data from both groups should not be combined for an assessment of efficacy.

### 3.1.1.2.5 Sponsor's Analyses of Secondary Variables

Secondary endpoints were analyzed in the ITT and PP populations. In the ITT and PP populations, the missing clinical and endoscopic improvement outcome data were assessed using both the worst case and observed case methods.

#### 3.1.1.2.5.1 Rate of Clinical Improvement

Results for clinical improvement in the sponsor's ITT population (worst case and observed case methods) are given in Table 3.

**Table 3 Rates of Clinical Improvement  
Study CB-01-02/01  
(Sponsor's ITT Population)**

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Asacol 2400 mg
<b>Worst case, N</b>	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
<b>Observed case, N</b>	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

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.

As seen from table above, in the worst case analysis in the sponsor's ITT population, the clinical improvement rate was numerically higher in the budesonide MMX 9 mg group (33.3%) than in the placebo group (24.8%), but the difference did not reach statistical significance. The rates of clinical improvement were similar in the budesonide MMX 9 mg, budesonide MMX 6 mg and Asacol groups. Differences in clinical improvement rates between all active treatment groups and placebo were not statistically significant. Rates of clinical improvement using the observed case method yielded a similar pattern of results with numerically greater rates in budesonide MMX 9 mg compared to placebo, budesonide MMX 6 mg, and Asacol.

The rates of clinical improvement in the PP population were similar to those observed in the sponsor's ITT population, with the exception that the budesonide MMX 9 mg group had a

significantly higher rate of clinical improvement ( $p = 0.0182$ ) when compared with placebo when the observed case method was used.

### 3.1.1.2.5.2 Rate of Endoscopic Improvement

Results for endoscopic improvement in the sponsor's ITT population (worst case and observed case methods) are given in Table 4.

**Table 4 Rates of Endoscopic Improvement  
Study CB-01-02/01  
(Sponsor's ITT Population)**

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Asacol 2400 mg
<b>Worst case, N</b>	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
<b>Observed case, N</b>	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

Source: [Table 14.2-2.2.1](#)

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

Notes: Patients with missing data that precluded determination of endoscopic improvement 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 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.

As seen from table above, using the worst case method, the rate of endoscopic improvement was higher in the budesonide MMX 9 mg group (41.5%) than in any other treatment group, including the Asacol group. However, as per the hierarchical testing procedure for secondary endpoints, because clinical improvement was not statistically significant in the ITT population, formal statistical comparisons of endoscopic improvement between the two budesonide MMX groups and placebo were not conducted. Rates of endoscopic improvement using the observed case method in the ITT population yielded a similar pattern of results with rates in budesonide MMX 9 mg again being numerically greater than in all other groups.

The rates of endoscopic improvement in the PP population were similar to those observed for the ITT population,

### **3.1.1.3 Reviewer's Comments and Evaluation**

#### **3.1.1.3.1 UCDAI Assessment**

The UCDAI was comprised of four components (stool frequency, rectal bleeding, mucosal appearance and physician's rating of disease activity). Stool frequency and rectal bleeding were based on information recorded in the patient diaries and mucosal appearance was based on colonoscopy results. The UCDAI score was the sum of the scores of these four components and was assessed at Visit 2 (Screening) and at Visit 5 (Week 8) for remission.

The protocol did not pre-specify how to compute scores for stool frequency and rectal bleeding from the patient diaries.

The SAP stated the following:

At the start of the study, Investigators were instructed to determine study eligibility (and remission status) by using the most severe episode (highest score) of stool frequency and rectal bleeding that were recorded in the patient diary during the last 7 calendar days prior to Visit 2 (and Visit 5), after reviewing the diary and consulting with the patient. If the colonoscopy day (and the preparation day, if different from the colonoscopy day) fell within the 7 calendar days, they were not used to determine the scores for these two parameters.

Subsequent to the start of the study, it was learned from key opinion leaders (and confirmed by reviewing the results of the most recent UC trials) that the UCDAI score is best understood and interpreted only when the scores for stool frequency and rectal bleeding are based on an average of the diary entries for the 3 days closest to the evaluation visit in the week prior to the visit. Study eligibility will continue to be based on the most severe episode of stool frequency and rectal bleeding that were recorded in the last 7 days prior to Visit 2. However, to be most clinically meaningful, remission status will be based on the average of the 3 days closest to Visit 5 with non-missing diary data within the first 5 non-colonoscopy related days closest to Visit 5 (for example, if the colonoscopy occurred at Visit 5 and the day prior to the visit was the preparation day, then the 5 days prior to the preparation day will be used to evaluate remission).

At Visit 5, the scores for all four components must be non-missing; otherwise, the UCDAI score will be set to missing.

The method to compute scores for stool frequency and rectal bleeding at Visit 5 was specified in the SAP. The scores for stool frequency and rectal bleeding were based on an average of the diary entries for the 3 days closest to the evaluation visit in the week prior to the visit.

The method to compute scores for stool frequency and rectal bleeding should be pre-specified in the protocol or protocol amendment not in the SAP. If the method was specified in the SAP, it might be based on blinded data and data driven.

#### **3.1.1.3.2 Histological Assessment**

All biopsy evaluations were performed at single histopathology center by a blinded histopathologist. The result of the biopsy was available only after randomization. However, the determination of histological activity grade was not pre-specified in the protocol but was pre-specified in the SAP. The SAP was finalized very late about five months after last patient out.

Patients were considered to have active disease only when at least one of biopsies had a score > 2. Patients were considered to have normal baseline histology if all available biopsies from a colonoscopy had score ≤ 1.

So, the determination whether patient had normal baseline histology was done late after last patient out for protocol CB-01-02/02 and 17 days before last patient out in this study.

### **3.1.1.3.3 Sponsor's ITT Population**

After the last patient out for protocol CB-01-02/02, the sponsor had concerns regarding normal histology results from protocol CB-01-02/02. Later, the SAP excluding patients with normal histology at baseline was proposed.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of the study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

A Special Protocol Assessment (SAP) for this study was submitted on November 30, 2007, and the ITT population was pre-specified as

- ITT – include all randomized patients with at least one dose administered and with at least a post-baseline efficacy assessment

About a month and half before this study completed (May 28, 2010), the sponsor conducted a Teleconference with the Agency on April 13, 2010 to present the proposed Full Analysis Set. In the Tcon, the sponsor proposed the following: as

- Use original definition as specified in the protocol
- Propose to exclude from the FAS patients that were not compliant with Good Clinical Practice; these patients will be included in a sensitivity analysis as responders
- Observe three of Eastern European Sites (Study CB-01-02/02) had reported unusually high remission rate (67%-73% vs. 9.2% for Western Europe)
- Expand the histological evaluation to all patients enrolled in the studies.
- Propose to remove these patients from the FAS

Our responses for about the proposed analysis population were:

- Your Full Analysis Set (FAS) population is not a “true” Intent-to-Treat (ITT) population, which is defined as including all randomized subjects. The FAS population is commonly defined as modified ITT (mITT) population.
- Analysis based on the “true” ITT population should be considered as the primary analysis. Analysis based on the mITT population should be considered as sensitivity analysis.
- Your newly proposed primary endpoint analysis will be viewed as supportive only.

The summary of Meeting Minutes is given Appendix A.

The sponsor revised their Statistical Analysis Plan (SAP) on July 15, 2010. The SAP was revised more than a month and half after the last patient completed (May 28, 2010).

The SAP stated:

#### **4.2 Analysis Populations**

The following analysis populations are defined.

##### **4.2.1 Randomized Set**

The Randomized Set (RS) is defined as all patients who are randomized into the study.

##### **4.2.2 Intent-to-Treat Population**

The Intent-to-Treat (ITT) population is the primary population for the analysis of all efficacy endpoints. The ITT population is defined as all randomized patients who received at least one dose of a study drug and who had no GCP or major entry criteria violations (e.g., a *C. difficile* infection during Screening) or normal histology at Baseline as determined by biopsy. These exclusions are consistent with ICH E9 and the Statistical and Medical reviews for Lialda, Attachments 1 – 3).

The SAP included the proposed ITT population. But, the SAP did not state which analysis (randomized or ITT) was to be the primary efficacy analysis. In the Teleconference dated April 13, 2010, the Agency clearly stated that “true” ITT analysis should be considered as the primary efficacy analysis. The Agency assumed that the primary analysis was to be based on the as-randomized set and recommended the sponsor’s ITT analysis would be a sensitivity analysis to support the primary analysis.

In the pre-NDA meeting on May 31, 2011, the Agency restated that the “true” ITT population should be used as the primary analysis population.

The summary of Meeting Minutes is given Appendix B

The detailed timeline for change of the sponsor’s ITT population is given Appendix C.

The sponsor provided timeline for Studies CB-01-02/01 and timeline of activities leading to revision of the Statistical Analysis Pan (SAP) is given Appendix D and E, respectively.

Furthermore, the sponsor’s ITT analysis excluded all patients with normal histology at baseline. So, the sponsor’s ITT analysis was more than modified ITT analysis but a subgroup analysis for patients with positive histology at baseline. Analysis of the subgroup of patients with positive histology at baseline was not pre-specified in the protocol.

Without clear pre-specification, this subgroup analysis should be considered exploratory and hypothesis generating in nature.

### 3.1.1.3.4 Sponsor's ITT Analysis of Primary Efficacy Variable

The sponsor's ITT analysis excluded 20 patients (8 placebo; 4 MMX 9 mg; 5 MMX 6 mg; 3 Asacol). Of these, 17 patients had normal histology at baseline (6 placebo; 3 MMX 9 mg; 5 MMX 6 mg; 3 Asacol).

The sponsor's ITT analysis excluded more placebo patients (8 placebo; 4 MMX 9 mg; 5 MMX 6 mg; 3 Asacol). The sponsor's ITT analysis might be biased in favor of MMX 9 mg.

#### 3.1.1.3.4.1 Subgroup Analysis of Primary Efficacy Variable for Sponsor's ITT Analysis

This reviewer performed subgroup analyses of remission rates for age (<65 vs. ≥65), race, smoking status, country, baseline UCDAI score, baseline CRP (<10 mg/L vs. ≥10 mg/L), and concomitant medication use status for sponsor's ITT analysis. The summary of results is given in Table 5.

**Table 5 Analysis of Remission  
Study CB-01-02/01  
Sponsor's ITT Analysis**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	13/77 (16.9%)	6/68 (8.8%)	8.1%	(-2.7%, 18.8%)
Female	9/46 (19.6%)	3/53 (5.7%)	13.9%	(0.9%, 27.0%)
<b>Age</b>				
<65	21/119 (17.7%)	9/114 (7.9%)	9.8%	(1.3%, 18.2%)
≥65	1/4 (25.0%)	0/7 (0%)	25.0%	(-17.4%, 67.4%)
<b>Race</b>				
White	10/60 (16.7%)	4/64 (6.3%)	10.4%	(-0.7%, 21.6%)
Black	2/9 (22.2%)	0/7 (0.0%)	22.2%	(-4.9%, 49.4%)
Asian	10/44 (22.7%)	5/39 (12.8%)	9.9%	(-6.3%, 26.1%)
Other	0/10 (0.0%)	0/11 (0.0%)		
<b>Country</b>				
Canada	0/7 (0.0%)	0/5 (0.0%)		
India	10/40 (25.0%)	5/39 (12.8%)	12.2%	(-4.9%, 29.2%)
US	12/76 (15.8%)	4/77 (5.2%)	10.6%	(0.1%, 20.2%)
<b>Baseline UCDAI Score</b>				
1		0/1 (0.0%)		
2	1/3 (33.3%)	0/1 (0.0%)	33.3%	(-20.0%, 86.7%)
3	0/11 (0.0%)	1/5 (20.0%)	-20.0%	(-55.1%, 15.1%)
4	4/14(28.6%)	3/11(27.3%)	1.6%	(-34.1%, 36.7%)
5	6/13 (46.2%)	1/17 (5.9%)	40.3%	(11.0%, 69.6%)
6	3/15 (20.0%)	0/16 (0.0%)	20.0%	(-0.2%, 40.2%)
7	4/19 (21.1%)	2/20 (10.0%)	11.1%	(-11.5%, 33.6%)
8	3/19 (15.8%)	1/17 (5.9%)	9.9%	(-9.9%, 29.8%)
9	0/16 (0.0%)	0/11 (0.0%)	0.0%	
10	1/4 (25.0%)	1/8 (11.1%)	13.9%	(-35.7%, 60.7%)
11		0/1 (0.0%)		

Obtained by this reviewer.

As seen from the table above, remission rates were statistically significantly higher at 5% significance level for budesonide MMX 9 mg for female, age <65 , US for the sponsor’s ITT analysis.

Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of scores 3, 4, and 9.

### 3.1.1.3.4.2 Reviewer’s “true” ITT Analysis of Primary Efficacy Variable

This reviewer performed “true” ITT analysis including all randomized patients. Results from the true “ITT” analysis are given in Table 6.

**Table 6 Rate of Clinical Remission  
 (“True” ITT Population)  
 Study CB-01-02/01**

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

p-value was obtained by Chi-square test

As seen from the table above, remission rates for budesonide MMX 9 mg and MMX 6 mg were numerically greater than placebo, but the differences did not reach statistical significance for the true “ITT” population.

Furthermore, the sponsor’s ITT analysis excluded more placebo responders (8 for placebo vs. 4 for MMX 9 mg). The sponsor’s ITT analysis might be biased in favor of MMX 9 mg.

### 3.1.1.3.4.3 Sponsor’s “True” ITT Analysis

As per request from this reviewer, the sponsor performed a “true” ITT analysis for the primary efficacy endpoint. The results were given in Appendix Table 2.

As seen from Appendix Table 2, the results from sponsor’s “true” ITT analysis were similar to those obtained by this reviewer’s “true” ITT analysis.

### 3.1.1.3.5 Rate of Clinical Remission by Baseline Histology Status

#### 3.1.1.3.5.1 Number of Subjects by Baseline Histology Status

The number of subjects with normal histology at baseline was comparable among treatment groups as seen from Table 7.

**Table 7 Number of Subjects with Normal Histology at Baseline Study CB-01-02/01**

Placebo	MMX 9 mg	MMX 6 mg	Asacol	MMX 9 mg vs. Placebo p-value
6/128 (4.7%)	3/127 (2.4%)	5/128 (3.9%)	3/127 (2.4%)	0.3140

p-value was obtained by Chi-square test.

### 3.1.1.3.5.2 Reviewer's Analysis of Rate of Clinical Remission by Baseline Histology Status

This reviewer performed analysis of rate of clinical remission by baseline histology status. The results are given in Table 8.

**Table 8 Rate of Clinical Remission by Baseline Histology Status Study CB-01-02/01**

Baseline Histology	Placebo	MMX 9 mg	MMX 6 mg	Asacol	MMX 9 mg vs. Placebo p-value
positive	10/122 (8.2%)	23/124 (18.5%)	17/123 (13.8%)	15/124 (12.1%)	0.0238
normal	5/6 (83.3%)	0/3 (0.0%)	3/5 (60.0%)	2/3 (66.7%)	0.0476
Total	15/128 (11.7%)	23/127 (18.1%)	20/128 (15.6%)	17/127 (13.4%)	

Copied from Tables 2 and 3, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

p-value was obtained by Fisher's exact test

All randomized patients who received at least one dose a study drug were included.

As seen from the table above, the rate of clinical remission for the MMX 9 mg group was numerically higher than that for placebo for subjects with positive baseline histology.

Among subjects with normal baseline histology, the rate of clinical remission was 83.3% (5/6) for placebo vs. 0.0% (0/3) for MMX 9 mg.

Comparing MMX 9 mg versus placebo, CMH yielded the stratified analysis by baseline history:  $p = 0.0909$ ; Breslow-Day  $p = 0.0029$ . While using the Dersimonian and Laird test, the 95% CI of pooled estimate of treatment effect was (-1.27, 0.56) including zero.

### 3.1.1.3.5.3 Sponsor's Analysis of Rate of Clinical Remission by Baseline Histology Status

Per our request, the sponsor also performed analysis of rate of clinical remission by baseline histology status. The results were given in Appendix Tables 3 and 4 for patients with positive histology at baseline and patient with normal histology at baseline, respectively.

As seen from the Appendix Tables 3 and 4, this result was similar to that obtained by this reviewer for abnormal baseline histology.

### 3.1.1.3.6 Subgroup Analyses for All Randomized Population, Positive Histology, and Normal Histology subpopulation

Per our request, the sponsor performed subgroup analyses of remission rates for age (<65 vs. ≥65), race, smoking status, country, baseline UCDAI score, baseline CRP (<10 mg/L vs. ≥10 mg/L), and concomitant medication use status for all randomized patients, all randomized patients with positive histology at baseline and all randomized patients with normal histology at baseline.

Summary of results for subgroup analyses for all randomized patients is given Table 9.

**Table 9 Analysis of Remission  
Study CB-01-02/01  
All Randomized Patients**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	13/80 (16.3%)	9/73 (12.3%)	4.0%	(-7.1%, 15.0%)
Female	9/47 (19.2%)	5/55 (9.1%)	10.1%	(-3.5%, 23.6%)
<b>Age</b>				
<65	22/123 (17.9%)	15/121 (12.4%)	5.5%	(-3.5%, 14.5%)
≥65	1/4 (25.0%)	0/7 (0%)	25.0%	(-17.4%, 67.4%)
<b>Race</b>				
White	10/62 (16.1%)	5/65 (7.7%)	8.4%	(-2.8%, 19.7%)
Black	2/9 (22.2%)	0/7 (0.0%)	22.2%	(-4.9%, 49.4%)
Hispanic	0/8 (0.0%)	1/10 (10.0%)	-10.0%	(-28.6%, 8.6%)
Asian	11/46 (23.9%)	9/44 (20.5%)	3.5%	(-13.7%, 20.6%)
Other	0/2 (0%)	0/2 (0.0%)		
<b>Country</b>				
Canada	0/7 (0.0%)	0/5 (0.0%)		
India	11/42 (26.2%)	9/44 (20.5%)	5.7%	(-12.1%, 23.6%)
Mexico		1/1 (100.0%)		
US	12/78 (15.4%)	5/78 (6.4%)	9.0%	(-0.7%, 18.7%)
<b>Baseline UCDAI Score</b>				
4	4/16 (25.0%)	4/13 (30.8%)	-5.8%	(-38.6%, 27.1%)
5	6/13 (46.2%)	4/20 (20.0%)	26.2%	(-6.1%, 58.4%)
6	3/15 (20.0%)	0/16 (0.0%)	20.0%	(-0.2%, 40.2%)
7	4/21 (19.0%)	2/20 (10.0%)	9.0%	(-12.3%, 30.4%)
8	4/19 (21.1%)	1/17 (5.9%)	15.2%	(-6.3%, 36.6%)
9	0/16 (0.0%)	0/11 (0.0%)		
10	1/4 (25.0%)	1/9 (11.1%)	13.9%	(-33.3%, 61.0%)
< 4 or > 10	1/23 (4.3%)	3/22 (13.6%)	-9.3%	(-25.9%, 7.3%)
<b>Baseline CRP</b>				
< 10 mg/L	20/95 (21.1%)	13/99 (13.1%)	7.9%	(-2.6%, 18.5%)
≥ 10 mg/L	3/32 (9.4%)	2/28 (7.1%)	2.2%	(-11.7%, 16.1%)

Copied from Tables 10 to 32, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were numerically higher for budesonide MMX 9 mg for female and US for all randomized patients analysis.

Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of scores 4, 9, and <4 or >10.

Summary of results for subgroup analyses for all randomized patients with positive histology at baseline is given Table 10.

**Table 10 Analysis of Remission  
Study CB-01-02/01  
All Randomized Patients with Positive Histology at Baseline**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	10/77 (13.0%)	6/69 (8.7%)	4.3%	(-5.7%, 14.3%)
Female	9/47 (19.1%)	3/53 (5.7%)	13.4%	(0.6%, 26.3%)
<b>Age</b>				
<65	22/120 (18.3%)	10/115 (8.7%)	9.6%	(1.0%, 18.3%)
≥65	1/4 (25.0%)	0/7 (0%)	25.0%	(-17.4%, 67.4%)
<b>Race</b>				
White	10/60 (16.7%)	4/64 (6.3%)	10.4%	(-0.7%, 21.6%)
Black	2/9 (22.2%)	0/7 (0.0%)	22.2%	(-4.9%, 49.4%)
Hispanic	0/8 (0.0%)		0/9 (0.0%)	
Asian	11/45 (24.4%)	6/40 (15.0%)	9.4%	(-7.3%, 26.2%)
Other	0/2 (0%)	0/2 (0.0%)		
<b>Country</b>				
Canada	0/7 (0.0%)	0/5 (0.0%)		
India	11/41 (26.8%)	6/40 (15.0%)	11.8%	(-5.7%, 29.3%)
US	12/76 (15.8%)	4/77 (5.2%)	10.6%	(1.0%, 20.2%)
<b>Baseline UCDAI Score</b>				
4	4/14 (28.6%)	3/12 (25.0%)	3.6%	(-30.5%, 37.6%)
5	6/13 (46.2%)	2/17 (11.8%)	34.4%	(3.3%, 65.5%)
6	3/15 (20.0%)	0/16 (0.0%)	20.0%	(-0.2%, 40.2%)
7	4/20 (20.0%)	2/20 (10.0%)	10.0%	(-11.9%, 31.9%)
8	4/19 (21.1%)	1/17 (5.9%)	15.2%	(-6.3%, 36.6%)
9	0/16 (0.0%)	0/11 (0.0%)		
10	1/4 (25.0%)	1/9 (11.1%)	13.9%	(-33.3%, 61.0%)
< 4 or > 10	1/23 (4.3%)	1/20 (5.0%)	-0.7%	(-13.3%, 12.0%)
<b>Baseline CRP</b>				
< 10 mg/L	20/92 (21.7%)	8/93 (8.6%)	13.1%	(3.0%, 23.3%)
≥ 10 mg/L	3/32 (9.4%)	2/28 (7.1%)	2.2%	(-11.7%, 16.1%)

Copied from Tables 33 to 55, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were statistically significantly higher at 5% significance level for budesonide MMX 9 mg for female, age <65 , US, baseline CRP < 10 mg/L for all randomized patients with positive histology at baseline.

Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of scores 4, 9, and <4 or >10.

Summary of results for subgroup analyses for all randomized patients with normal histology at baseline is given Table 11.

**Table 11 Analysis of Remission  
Study CB-01-02/01**

<b>All Randomized Patients with Normal Histology at Baseline</b>				
	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	0/3 (0.0%)	3/4 (75.0%)	-75.0%	(-100.0%, -32.6%)
Female		2/2 (100.0%)		
<b>Age</b>				
<65	0/3 (0.0%)	5/6 (83.3%)	-83.3%	(-100.0%, -53.5%)
<b>Race</b>				
White	0/2 (0.0%)	1/1 (100.0%)	-100.0%	(-100.0%, 100.0%)
Hispanic		1/1 (100.0%)		
Asian	0/1 (0.0%)	1/4 (75.0%)	-75.0%	(-100.0%, -32.6%)
<b>Country</b>				
India	0/1 (0.0%)	3/4 (75.0%)	-75.0%	(-100.0%, -32.6%)
Mexico		1/1 (100.0%)		
US	0/2 (0.0%)	1/1 (100.0%)	-100.0%	(-100.0%, 100.0%)
<b>Baseline UCDAI Score</b>				
4	0/2 (0.0%)	1/1 (100.0%)	-100.0%	(-100.0%, 100.0%)
5		2/3 (66.7%)		
7	0/1 (0.0%)			
< 4 or > 10		2/2 (100.0%)		
<b>Baseline CRP</b>				
< 10 mg/L	0/3 (0.0%)	5/6 (83.3%)	-83.3%	(-100.0%, -53.5%)

Copied from Tables 56 to 78, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were lower for budesonide MMX 9 mg for male, age <65, Indian, baseline CRP < 10 mg/L for all randomized patients with normal histology at baseline.

However, due to inadequate sample size, results were difficult to be interpreted statistically.

### 3.1.2 Study CB-01-02/02

#### 3.1.2.1 Study Design

The study design of this study was nearly identical to Study CB-01-02/01. Both studies were randomized, double-blind, double-dummy, placebo-controlled, parallel group, multicenter studies which evaluated up to 8 weeks of once daily therapy with budesonide MMX 9 mg and 6

mg and placebo in adult patients with active, mild to moderate ulcerative colitis. The studies shared identical entry criteria and identical primary, secondary, and other efficacy endpoints.

The only difference between the two studies was the addition of different, non-powered active reference arms; CB-01-02/01 included Asacol® (mesalamine [hereafter referred to as Asacol]) 2400 mg while CB-01-02/02 included Entocort EC (budesonide) 9 mg. The dosage strength of Entocort EC that was used in study CB-01-02/02 is approved in the US for treatment of CD and was included as an active comparator to compare localized GI delivery of budesonide. The dosage strength of Asacol that was used in study CB-01-02/01 is approved in the US for treatment of active mild to moderate UC and for maintenance of remission of UC. Asacol was included in CB-01-02/01 to provide a study design that was similar to that of CB-01-02/02.

Both studies were powered for the comparisons of budesonide MMX 9 mg and 6 mg arms to placebo and were adjusted for multiplicity, but were not powered for comparisons between budesonide MMX and the active reference groups.

Study CB-01-02/02 was performed at 69 centers throughout Western and Eastern Europe, Israel, and Australia.

The primary efficacy endpoint of clinical remission at Week 8 was rigorously defined in both study protocols, and required an Ulcerative Colitis Disease Activity Index (UCDAI) score of  $\leq 1$ , with scores of 0 for both rectal bleeding and stool frequency at Week 8, a normal mucosa at Week 8 (with no evidence of mucosal friability), and a  $\geq 1$ -point reduction in the Endoscopic Index (EI) score from baseline to Week 8. Thus, the UCDAI incorporates symptomatic, endoscopic, and investigator-judged measures and provides a comprehensive determination of disease status. All endoscopy procedures at baseline and at end of study were performed via colonoscopy.

Secondary efficacy endpoints were clinical improvement and endoscopic improvement at Week 8. Other efficacy assessments were symptom resolution, histologic healing, inflammatory markers (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), improvement in the Inflammatory Bowel Disease Quality of life (IBD-QoL) questionnaire responses, Clinical Activity Index scores  $\leq 4$ , and treatment failure.

### **3.1.2.2 Sponsor's Analysis**

A total of 511 patients were in the safety population. Among the 509 patients who were randomized and treated, 410 patients were included in the sponsor's ITT population. The 101 excluded patients comprised 1 patient who was confirmed following randomization to have infectious colitis at study entry (a pre-specified exclusion criterion); all 50 patients enrolled at 4 sites that were found to have committed major GCP violations; and 77 patients with normal histology at baseline. Twenty-nine of the 101 excluded patients had both normal histology at baseline and major GCP violations, and are thus included in both categories. Summary of patients excluded from the sponsor's ITT analysis is given in Table 12.

**Table 12 Exclusions from the Sponsor's ITT Analysis Population  
Study CB-01-02/02**

Category	Placebo n (%)	Budes. MMX 9 mg n (%)	Budes. MMX 6 mg n (%)	Entocort EC 9 mg n (%)	Total 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) <sup>b</sup>
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) <sup>c</sup>

Source: Table 14.1-1 and Table 14.1-5

Abbreviations: Budes., budesonide.

Disposition of patients in the sponsor's ITT population is given Table 13.

**Table 13 Summary of Patient Disposition (Sponsor's ITT Population)  
Study CB-01-02/02**

Category	Placebo N = 89 n (%)	Budes. MMX 9 mg N = 109 n (%)	Budes. MMX 6 mg N = 109 n (%)	Entocort EC 9 mg N = 103 n (%)	Total N = 410 n (%)
Completed Study					
Yes	61 (68.5)	76 (69.7)	67 (61.5)	68 (66.0)	272 (66.3)
No	28 (31.5)	33 (30.3)	42 (38.5)	35 (34.0)	138 (33.7)
Primary Reason for Discontinuation					
Adverse event	1 (1.1)	2 (1.8)	2 (1.8)	3 (2.9)	8 (2.0)
Consent withdrawn	7 (7.9)	6 (5.5)	10 (9.2)	7 (6.8)	30 (7.3)
Lost to Follow-up	1 (1.1)	1 (0.9)	0	0	2 (0.5)
Investigator Decision	1 (1.1)	2 (1.8)	3 (2.8)	2 (1.9)	8 (2.0)
Sponsor Decision	0	0	0	1 (1.0)	1 (0.2)
Treatment Failure	17 (19.1)	21 (19.3)	26 (23.9)	21 (20.4)	85 (20.7)
Other	1 (1.1)	1 (0.9)	1 (0.9)	1 (1.0)	4 (1.0)

Source: Table 14.1-4

Abbreviations: Budes., budesonide

As seen from the table above, among the 410 patients that were in the ITT analysis population, 272 (66%) completed the study. The most common reasons for early withdrawal from the study were treatment failure (n = 85; 20.7%) and withdrawal of consent (n = 30; 7.3%).

### 3.1.2.2.1 Sponsor's Rationale for Exclusions for the Sponsor's ITT Analysis Population

The sponsor provided a detailed rationale for exclusions based on 1) major entry criteria violations (confirmation of infectious colitis at the time of randomization), 2) presence of normal histology at baseline (and thus, non-active UC), and 3) major violations of GCP.

Sponsor's rationale for exclusions for the sponsor's ITT analysis population briefly summarized below.

- The exclusion of patients with infectious colitis at study entry was a pre-specified exclusion criterion in the study protocol. Compared to UC, infectious colitis may present with similar signs and symptoms and can be difficult to distinguish endoscopically from UC.
- Analysis of efficacy in patients with active disease based on histology is supported by the scientific literature (Riley, 1991; Robert, 2004; Stange, 2008; Travis, 2008; Thomas, 2009). The requirement for performing mucosal biopsies at screening was prospectively incorporated in the study protocols. The exclusion of patients with normal histology from the ITT analysis was prospectively defined in the SAP. Exclusion of patients with normal histopathology allows for the accurate assessment of the treatment effect of budesonide MMX on the intended patient population. The application of this exclusion did not introduce bias because:
  - In all instances, baseline mucosal biopsies were sampled *prior* to randomization
  - All histopathology assessments were made in a completely objective manner by a blinded pathologist at a central laboratory using the standardized scoring system described by Saverymuttu (Saverymuttu, 1986). Thus, all patients received equal scrutiny for the presence (or absence) of active UC.
  - All patients who were discovered to have had normal histopathology (no active UC) were removed from the ITT analysis population prior to database lock and unblinding.
- 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. The ITT population was defined to remove patients from sites with significant GCP violations (Sites 1040, 1082, 1122, and 1106). Exclusion of data from patients enrolled at these sites was necessary because:
  - It complies with ICH requirements which require the removal of data obtained in substantial noncompliance with GCP
  - It was performed in accordance with all internal standard operating procedures
- Moreover, the exclusion of patients from these sites did not introduce bias because:
  - All patients from the 4 sites where substantial GCP violations occurred were removed from the ITT analysis
  - The removal of all such patients occurred prior to database lock and unblinding

#### 3.1.2.2.2 Planned Analysis

The planned analysis was identical to that for Study CB-01-02/01.

#### 3.1.2.2.3 Treatment Group Comparability

The summary of results for the comparability of treatment groups at baseline for the sponsor's ITT population is given in Appendix Table 5.

As seen from Appendix Table 5, with the exception of sex, baseline demographic characteristics were similar across treatment groups. A slightly greater percentage of male patients were randomized to the placebo group (59.7%) compared to the active treatment groups (52.3% to 54.7%).

### 3.1.2.2.4 Sponsor's Analysis of Primary Efficacy Variable

The primary analysis of clinical remission was performed using the sponsor's ITT population. Results are summarized in Table 14.

**Table 14 Rates of Clinical Remission (Sponsor's ITT 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 <sup>d</sup>		0.0047*	0.2876	0.0481 <sup>†</sup>

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.

<sup>†</sup> Value is statistically significant at the  $\alpha = 0.05$  level.

As seen from the table above, in the sponsor's ITT population, the percentage of patients in clinical remission at Week 8 was significantly higher for patients receiving budesonide MMX 9 mg than for patients receiving placebo.

The difference in remission rates in the budesonide MMX 9 mg and placebo groups remained statistically significant at the  $\alpha = 0.025$  level after adjusting for age ( $p=0.0048$ ), sex ( $p=0.0045$ ), and geographic region ( $p=0.0048$ ) when using the Cochran-Mantel-Haenszel test.

#### 3.1.2.2.4.1 Subgroup Analysis

Results of subgroup analyses of rates if clinical remission by age ( $\leq 43.5$  vs.  $>43.5$ ), gender, and geographic region are given in Table 15.

**Table 15 Rate of Clinical Remission Stratified by Age, Sex, and Geographic Region  
(Sponsor’s ITT Population)  
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.

As seen from the table above, in the sponsor’s ITT population, a comparison of remission rates in the budesonide MMX 9 mg and placebo groups after stratifying for age, sex and geographic region indicated statistically significant differences (at the  $\alpha = 0.05$  level) for patients in the following subsets: 1)  $\leq 43.5$  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%,  $p=0.0227$ ), where Eastern Europe comprised Romania, Poland, Slovakia, Ukraine, Estonia, Lithuania, and Latvia.

#### **3.1.2.2.4.2 Data for Patients with Normal and Abnormal Histology Combined**

Based on the FDA’s suggestion that the data for patients with normal and abnormal histology be combined in an assessment of the primary efficacy endpoint, an analysis of remission status by treatment group (budesonide 9 mg, placebo) was conducted, stratifying by baseline histology status (normal, abnormal) using the Mantel-Haenszel statistic. The result of this analysis was not statistically significant ( $p=0.1300$ ). However, the Breslow-Day test for the homogeneity of odds ratios across the two histology groups was statistically significant ( $p= 0.0447$ ), indicating that pooling odds ratios across baseline histology groups is not valid, since the odds ratios in the two groups are not constant. In other words, this analysis provides additional statistical support for the view that these are distinctly different populations, and therefore the data from these two groups should not be combined for an assessment of efficacy.

#### **3.1.2.2.5 Sponsor’s Analyses of Secondary Variables**

Secondary endpoints were analyzed in the ITT and PP populations. In the ITT and PP populations, the missing clinical and endoscopic improvement outcome data were assessed using both the worst case and observed case methods.

### 3.1.2.2.5.1 Rate of Clinical Improvement

Results for clinical improvement in the sponsor's ITT population (worst case and observed case methods) are given in Table 16.

**Table 16 Rates of Clinical Improvement (Sponsor's ITT Population)  
Study CB-01-02/02**

	Placebo	Budes.MMX 9 mg	Budes. MMX 6 mg	Entocort EC 9 mg
<b>Worst case, N</b>	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
<b>Observed case, N</b>	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.

As seen from the table above, in the worst case analysis, the clinical improvement rate was numerically higher in the budesonide MMX 9 mg group than in any other treatment group, but the difference between budesonide MMX 9 mg and placebo did not reach statistical significance.

The rates of clinical improvement were similar for patients in the Entocort EC or placebo groups, and lower in the budesonide MMX 6 mg group. Differences in clinical improvement rates between the active treatment groups and placebo were not statistically significant.

Rates of clinical improvement using the observed case method yielded a similar pattern of results, with budesonide MMX 9 mg again being numerically higher than placebo.

The rates of clinical improvement in the PP population were similar to those observed in the sponsor's ITT population.

### 3.1.2.2.5.2 Rate of Endoscopic Improvement

Results for endoscopic improvement in the sponsor's ITT population (worst case and observed case methods) are given in Table 17.

**Table 17 Rates of Endoscopic Improvement (Sponsor’s ITT Population)  
Study CB-01-02/02**

	Placebo	Budes. MMX 9 mg	Budes. MMX 6 mg	Entocort EC 9 mg
<b>Worst case, N</b>	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
<b>Observed case, N</b>	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.

As seen from the table above, in the worst case analysis, the endoscopic improvement rate was higher in the budesonide MMX 9 mg group than in any other treatment group, including the Entocort EC group. However, as per the hierarchical testing procedure for secondary endpoints, because clinical improvement was not statistically significant in the sponsor’s ITT population, formal statistical comparisons for endoscopic improvement between the two budesonide MMX groups and placebo were not conducted.

Rates of endoscopic improvement using the observed case method in the sponsor’s ITT population yielded a similar pattern of results with the 9 mg group again achieving the highest rates of endoscopic improvement compared to all other groups.

The rates of clinical improvement in the PP population were similar to those observed in the sponsor’s ITT population.

### 3.1.2.3 Reviewer’s Comments and Evaluation

#### 3.1.2.3.1 UCDAI Assessment

See Section 3.1.1.3.1.

#### 3.1.2.3.2 Histological Assessment

See Section 3.1.1.3.2.

### 3.1.2.3.3 Sponsor's ITT Population

After the last patient out for protocol CB-01-02/02, the sponsor had concerns regarding normal histology results from blinded database. Later, the SAP excluding patients with normal histology at baseline was proposed. However, the application of this exclusion did introduce bias against placebo.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

A Special Protocol Assessment (SPA) for this study was submitted on November 30, 2007, and the ITT population was pre-specified as

- ITT – include all randomized patients with at least one dose administered and with at least a post-baseline efficacy assessment

About two months after this study was completed (February 13, 2010), the sponsor conducted a Teleconference on April 13, 2010 to present the proposed the Full Analysis Set. In the Tcon, the sponsor proposed the following: as

- Use original definition as specified in the protocol
- Propose to exclude from the FAS patients that were not compliant with Good Clinical Practice; these patients will be included in a sensitivity analysis as responders
- Observe that three of Eastern European Sites had reported unusually high Remission Rate (67%-73% vs. 9.2% for Western Europe)
- Expand the histological evaluation to all patients enrolled in the studies.
- Propose to remove these patients from the FAS

Our responses about the proposed analysis population were:

- Your Full Analysis Set (FAS) population is not a “true” Intent-to-Treat (ITT) population, which is defined as including all randomized subjects. The FAS population is commonly defined as modified ITT (mITT) population.
- Analysis based on the “true” ITT population should be considered as the primary analysis. Analysis based on the mITT population should be considered as the sensitivity analysis.
- Your newly proposed primary endpoint analysis will be viewed as supportive only.

The summary of Meeting Minutes is given Appendix A.

The sponsor revised their Statistical Analysis Plan (SAP) on July 15, 2010. The SAP was revised five months after the last patient completed (February 13, 2010). The SAP stated:

## 4.2 Analysis Populations

The following analysis populations are defined.

### 4.2.1 Randomized Set

The Randomized Set (RS) is defined as all patients who are randomized into the study.

### 4.2.2 Intent-to-Treat Population

The Intent-to-Treat (ITT) population is the primary population for the analysis of all efficacy endpoints. The ITT population is defined as all randomized patients who received at least one dose of a study drug and who had no GCP or major entry criteria violations (e.g., a *C. difficile* infection during Screening) or normal histology at Baseline as determined by biopsy. These exclusions are consistent with ICH E9 and the Statistical and Medical reviews for Lialda, Attachments 1 – 3).

The SAP included the proposed ITT population. But, the SAP did not state which analysis (randomized or ITT) was to be the primary efficacy analysis. In the Teleconference dated April 13, 2010, the Agency clearly stated that “true” ITT analysis should be considered the primary efficacy analysis. The Agency assumed that the primary analysis was to be based on the as-randomized set and recommended the sponsor’s ITT analysis would be the sensitivity analysis to support primary analysis.

In the pre-NDA meeting on May 31, 2011, the Agency restated that the “true” ITT population should be used as the primary analysis population.

The summary of Meeting Minutes is given Appendix B

The detailed timeline for change of the sponsor’s ITT population is given Appendix C.

The sponsor provided timeline for Studies CB-01-02/01 and timeline of activities leading to revision of the Statistical Analysis Plan (SAP) is given Appendix D and E, respectively.

Furthermore, the sponsor’s ITT analysis excluded all patients with normal histology at baseline. So, the sponsor’s ITT analysis was more than modified ITT analysis but a subgroup analysis for patients with positive histology at baseline.

This European study was designed mainly for European approval. So, it was my understanding that this study followed European Medicines Agency (EMA) guidelines for clinical trials in active UC.

EMA guideline was issued a week after first patient in for CB-01-02/02. The inclusion criteria in the guideline stated that only patients having confirmed ulcerative colitis should be included in trials. The absence of histological evidence of inflammation at trial entry excludes a diagnosis of active colitis. The exclusion of patients with normal histology should be made at randomization and not after randomization.

ICH E9 stated that subjects who fail to satisfy an entry criterion may be excluded from the analysis with possibility of introduce bias under some circumstances. But, data from this study showed exclusion of all patients with normal histology at baseline introduced bias against placebo. There was imbalanced in the number of patients with positive histology at baseline

among treatment groups. Due to imbalance, results from the sponsor's ITT analysis might not be interpreted statistically.

Furthermore, the sponsor's ITT analysis excluded all patients with normal histology at baseline. So, the sponsor's ITT analysis was more than modified ITT analysis but a subgroup analysis for patients with positive histology at baseline. Analysis of the subgroup of patients with positive histology at baseline was not pre-specified in the protocol.

Without clear pre-specification, this subgroup analysis should be considered exploratory and hypothesis generating in nature.

#### **3.1.2.3.4 Sponsor's ITT Analysis of Primary Efficacy Variable**

The sponsor's ITT analysis excluded 101 patients (40 placebo; 19 MMX 9 mg; 19 MMX 6 mg; 23 Entocort). The sponsor's ITT analysis excluded 77 patients with normal histology at baseline (33 placebo; 12 MMX 9 mg; 16 MMX 6 mg; 16 Entocort). A total of 50 patients for 4 sites (1040, 1106, 1082, 1122) were excluded from the sponsor's ITT analyses due to critical GCP violations.

The sponsor's ITT analysis excluded more placebo patients (40 placebo; 19 MMX 9 mg; 19 MMX 6 mg; 23 Entocort). The sponsor's ITT analysis might be biased in favor of MMX 9 mg. Results from the sponsor's ITT analysis might be difficult to be interpreted statistically.

##### **3.1.2.3.4.1 Subgroup Analysis of Primary Variable for Sponsor's ITT Analysis**

This reviewer performed subgroup analyses of remission rates for age (<65 vs. ≥65), race, smoking status, country, and baseline UCDAI score for the sponsor's ITT analysis. Results from subgroup analyses are given Table 18.

**Table 18 Analysis of Remission  
Study CB-01-02/02  
Sponsor's ITT Analysis**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	12/64 (18.8%)	3/57 (5.3%)	13.5%	(2.3%, 24.7%)
Female	7/45 (15.6%)	1/32 (3.1%)	12.5%	(0.3%, 24.6%)
<b>Age</b>				
<65	19/105 (18.1%)	3/79 (3.8%)	14.3%	(5.8%, 22.8%)
≥65	0/4 (0.0%)	1/10 (10.0%)	-10.0%	(-28.6%, 8.6%)
<b>Race</b>				
White	19/107 (17.8%)	4/89 (4.5%)	13.3%	(4.8%, 21.7%)
Asian	0/1 (0.0%)			
Other	0/1 (0%)			
<b>Country</b>				
Australia	0/1 (0.0%)	0/2 (0.0%)		
Estonia	0/6 (0.0%)	0/5 (0.0%)		
France	0/1 (0.0%)	0/1 (0.0%)		
Great Britain	0/4 (0.0%)			
Italy	2/12 (16.7%)	0/13 (0.0%)	16.7%	(-4.4%, 37.8%)
Latvia	0/2 (0.0%)	0/2 (0.0%)		
Lithuania	3/17 (17.6%)	0/12 (0.0%)	17.6%	(-0.5%, 35.8%)
Poland	3/14 (21.4%)	1/9 (11.1%)	10.3%	(-19.4%, 40.0%)
Romania	2/5 (40.0%)	0/3 (0.0%)	40.0%	(-2.9%, 82.9%)
Russia	8/35 (22.9%)	3/28 (10.7%)	12.2%	(-5.9%, 30.2%)
Slovakia	1/4 (25.0%)	0/7 (0.0%)	25.0%	(-17.4%, 67.4%)
Sweden	0/1 (0.0%)	0/2 (0.0%)		
Ukraine	0/6 (0.0%)	0/5 (0.0%)		
<b>Baseline UCDAI Score</b>				
2		0/1 (0.0%)		
3	0/3 (0.0%)	0/1 (0.0%)		
4	2/10 (20.0%)	0/9 (0.0%)	20.0%	(-4.8%, 44.8%)
5	6/12 (50.0%)	1/8 (12.5%)	37.5%	(1.1%, 73.9%)
6	4/19 (21.1%)	2/16 (12.5%)	8.6%	(-15.9%, 33.0%)
7	4/23 (17.4%)	0/19 (0.0%)	17.4%	(1.9%, 32.9%)
8	2/21 (9.5%)	1/14 (7.1%)	2.4%	(-16.1%, 20.8%)
9	1/17 (5.9%)	0/10 (0.0%)	5.9%	(-5.3%, 17.1%)
10	0/3 (0.0%)	0/5 (0.00%)		

Obtained by this reviewer.

As seen from the table above, remission rates were statistically significantly higher at 5% significance level for budesonide MMX 9 mg for male and female, white, and age <65 for the sponsor's ITT analysis.

Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of scores 8 and 10.

However, the sponsor’s ITT analysis excluded more placebo patients (40 placebo; 19 MMX 9 mg; 19 MMX 6 mg; 23 Entocort). The sponsor’s ITT analysis might be biased in favor of MMX 9 mg. Results from subgroup analyses for the sponsor’s ITT analysis might be difficult to be interpreted statistically.

### 3.1.2.3.4.2 Reviewer’s “True” ITT Analysis for Primary Efficacy Endpoint

This reviewer performed “true” ITT analysis including all randomized patients. Results from the true “ITT” analysis are given in Table 19.

**Table 19 Rate of Clinical Remission  
 (“True“ ITT Population)  
 Study CB-01-02/02**

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

p-value was obtained by Chi-square test.

As seen from the table above, remission rates for budesonide MMX 9 mg was slightly numerically greater than placebo, but the difference did not reach statistical significance for the true “ITT” population.

### 3.1.2.3.4.3 Sponsor’s “True“ ITT Analysis

As per our request from this reviewer, the sponsor performed a “true” ITT analysis for the primary efficacy endpoint. The results were given in Appendix Table 6.

As seen from Appendix Table 6, the results from the sponsor’s “true” ITT analysis were similar to those obtained by this reviewer’s “true” ITT analysis.

### 3.1.2.3.5 Rate of Clinical Remission by Baseline Histology Status

#### 3.1.2.3.5.1 Number of Subjects by Baseline Histology Status

More placebo subjects with normal histology at based were observed as compared to other treatment groups as seen in Table 20.

**Table 20 Number of Subjects with Normal Histology at Baseline  
Study CB-01-02/02**

Placebo	MMX 9 mg	MMX 6 mg	Entocort EC	MMX 9 mg vs. Placebo p-value
33/129 (25.6%)	12/126 (9.5%)	16/128 (12.5%)	16/126 (12.7%)	0.0008

p-value was obtained by Chi-square test.

### 3.1.2.3.5.2 Reviewer’s Analysis of Rate of Clinical Remission by Baseline Histology Status

This reviewer performed analysis of rate of clinical remission by baseline histology status. The results are given in Table 21.

**Table 21 Rate of Clinical Remission by Baseline Histology Status  
Study CB-01-02/02**

Baseline Histology	Placebo	MMX 9 mg	MMX 6 mg	Entocort EC	MMX 9 mg vs. Placebo p-value
positive	6/96 (6.3%)	19/114 (16.7%)	9/112 (8.0%)	16/110 (14.5%)	0.0308
normal	13/33 (39.4%)	3/12 (25.0%)	7/16 (43.8%)	5/16 (31.3%)	0.4913
Total	19/129 (14.7%)	22/126 (17.5%)	16/128 (12.5%)	21/126 (16.7%)	

p-value was obtained by Fisher’s exact test

All randomized patients who received at least one dose a study drug were included.

As seen from the table above, the rate of clinical remission for the MMX 9 mg group was numerically high than that for placebo for subjects with abnormal baseline histology.

Among subjects with normal baseline histology, the rate of clinical remission was 39.4% (13/33) for placebo vs. 25.0% (3/12) for MMX 9 mg.

Comparing MMX 9 mg vs. placebo, CMH yield stratified analysis by baseline histology: p= 0.1300; Breslow-Day p=0.0447. While using the Dersimonian and Laird test, 95% CI of pooled estimate of treatment effect was (-0.21, 0.25) including zero.

### 3.1.2.3.5.3 Sponsor’s Analysis of Rate of Clinical Remission by Baseline Histology Status

Per our request, the sponsor also performed analysis of rate of clinical remission by baseline histology status. The results were given in Appendix Tables 7 and 8 for patients with positive histology at baseline and patient with normal histology at baseline, respectively.

As seen from the Appendix Tables 7 and 8, this result was similar to that obtained by this reviewer for abnormal baseline histology.

Contrary to the sponsor's finding, if Fisher's exact method were used, p-value between the MMX 9 mg and the placebo would be 0.0310. The result would be negative ( $> 0.0250$ ). So, the result from this analysis was method dependent and not robust.

### 3.1.2.3.6 Sensitivity Analyses for Primary Efficacy Endpoint

A total of 50 patients for 4 sites (1040, 1106, 1082, 1122) were excluded from the sponsor's all efficacy analyses due to critical GCP violations.

**Table 22 Summary of Audits and Critical Findings in Study CB-01-02/02**

Site	Country	# Patients Randomized	Critical Audit Findings
1040	Italy	11	3
1106	Russia	11	2
1082	Slovakia	6	5
1122	Slovakia	22	4

Summary of patients in treatment by site for these four sites is given in Table 23.

**Table 23 Summary of Patients in Treatment by Site in Study CB-01-02/02**

Treatment	1040	1106	1082	1122	Total
Placebo	4	4	3	9	20
MMX 9 mg	3	1	1	5	9
MMX 6 mg	1	3	1	4	9
Entocort	3	3	1	4	12

Per the medical officer's request, the sponsor performed a sensitivity analysis including data from 4 sites with critical GCP violations with natural remission outcome.

The results of the sensitivity analysis are given in Table 24.

**Table 24 Sensitivity Analysis Including Data from 4 Sites with Critical GCP Violations with Natural Remission Outcome Study CB-01-02/02**

	Placebo N=96	MMX 9 mg N=114	MMX 6 mg N=112	Entocort EC N=110
Remission, n (%)	6 (6.3.0%)	19 (16.7%)	9 (8.0%)	16 (14.5%)
95% CI	(1.4, 11.1)	(9.8, 23.5)	(3.0, 13.1)	(8.0, 21.1)
Difference vs. placebo		10.4%	1.8%	8.3%
95% CI		(2.0, 18.8)	(-5.2, 8.8)	(0.1, 16.5)
p-value		0.0202	0.6197	0.0545

Copied from Sequence 0000, CSR CB-01-02/02 Table 14.2-1.1.3.

As seen from the table above, the result is the same result as obtained by this reviewer for abnormal baseline histology.

Contrary to the sponsor's finding, if Fisher's exact method were used, p-value between the MMX 9 mg and the placebo would be 0.0308. The result would be negative ( $> 0.0250$ ). So, the result from this sensitivity analysis was not robust.

This reviewer performed analysis of remission rates including all randomized without GCP violations by baseline histology status. Results are summarized in Table 25.

**Table 25 Rate of Clinical Remission for All Randomized Patients without GCP Violations by Baseline Histology Status Study CB-01-02/02**

Baseline Histology	Placebo	MMX 9 mg	MMX 6 mg	Entocort EC	MMX 9 mg vs. Placebo
					p-value
positive	5/89 (5.6%)	19/111 (17.1%)	9/109 (8.3%)	13/105 (12.4%)	0.0154
normal	5/20 (25.0%)	1/7 (14.3%)	3/10 (30.0%)	2/11 (18.2%)	1.0000
Total	10/109 (9.2%)	20/118 (16.9%)	12/119 (10.1%)	15/116 (12.9%)	0.1158

Compiled from Tables 1- 3, Efficacy Information Amendment, May 29, 2012

p-value was obtained by Fisher's exact test

All randomized patients who received at least one dose a study drug were included.

As seen from table above, for subjects without GCP violations, rate of clinical remission for MMX 9 mg group was numerically high than that for placebo for subjects with positive baseline histology.

Among subjects with normal baseline histology, rate of clinical remission was 25.0% (5/20) for placebo vs. 14.3% (1/7) for MMX 9 mg.

Comparing MMX 9 mg vs. placebo, CMH yield pooled analysis:  $p= 0.0392$ ; Breslow-Day  $p=0.1183$ . While using the Dersimonian and Laird test, 95% CI of pooled estimate of treatment effect was (-0.13, 0.25) including zero.

This reviewer performed analysis of remission rates including all randomized with GCP violations by baseline histology status. Results are summarized in Table 26

**Table 26 Rate of Clinical Remission for All Randomized Patients with GCP Violations by Baseline Histology Status Study CB-01-02/02**

Baseline Histology	Placebo	MMX 9 mg	MMX 6 mg	Entocort EC	MMX 9 mg vs. Placebo
					p-value
positive	1/7 (14.3%)	0/5 (0.0%)	0/3 (0.0%)	3/5 (60.0%)	1.0000
normal	8/13 (61.5%)	2/5 (40.0%)	4/6 (66.7%)	2/5 (40.0%)	0.6078
Total	9/20 (45.0%)	2/10 (20.0%)	4/9 (44.4%)	5/10 (50.0%)	0.2465

p-value was obtained by Fisher's exact test

All randomized patients who received at least one dose a study drug were included.

As seen from the table above, rates of remission for budesonide MMX 9 mg was higher than that for placebo for all randomized patients with GCP violations for total patients, patients with abnormal histology at baseline, and patients with normal histology at baseline. But, due to adequate sample size, the treatment differences failed to reach statistical significance.

Comparing MMX 9mg vs. placebo, CMH yielded pooled analysis:  $p=0.2730$ ; Breslow-Day  $p=0.5690$ . With using Dersimonian and Laird test, 95% CI of pooled estimate of treatment effect was  $(-0.39, 0.07)$  including zero.

This reviewer also performed analysis of remission rates including all randomized with GCP violations by baseline histology status by site.

Results of analyses are given Appendix Table 9.

As seen from Appendix Table 9, there was no difference in site 1040. Rates were higher for placebo in sites 1106 and 1122. Rate was slight higher for MMX 9 mg in site 1082.

### **3.1.2.3.7 Subgroup Analyses for All Randomized Population, Positive Histology, and Normal Histology subpopulation**

Per our request, the sponsor performed subgroup analyses of remission rates for age ( $<65$  vs.  $\geq 65$ ), race, smoking status, country, baseline UCDAI score, baseline CRP ( $<10$  mg/L vs.  $\geq 10$  mg/L), and concomitant medication use status for all randomized patients, all randomized patients with positive histology at baseline and all randomized patients with normal histology at baseline.

Summary of results for subgroup analyses for all randomized patients is given Table 27.

**Table 27 Analysis of Remission  
Study CB-01-02/02  
All Randomized Patients**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	14/70 (20.0%)	9/76 (11.8%)	8.2%	(-3.7%, 20.0%)
Female	8/56 (14.3%)	9/53 (17.0%)	-2.7%	(-16.3%, 11.0%)
<b>Age</b>				
<65	22/123 (17.9%)	17/115 (14.9%)	3.1%	(-6.3%, 12.5%)
≥65	0/4 (0.0%)	2/14 (14.3%)	-14.3%	(-32.6%, 4.0%)
<b>Race</b>				
White	22/125 (17.6%)	19/129 (14.7%)	2.9%	(-6.2%, 11.9%)
Asian	0/1 (0.0%)			
Other	0/1 (0%)			
<b>Country</b>				
Australia	0/1 (0.0%)	0/2 (0.0%)		
Estonia	0/6 (0.0%)	0/6 (0.0%)		
France	0/1 (0.0%)	0/1 (0.0%)		
Italy	2/15 (13.3%)	0/17 (0.0%)	13.3%	(-3.9%, 30.5%)
Latvia	0/2 (0.0%)	0/2 (0.0%)		
Lithuania	3/17 (17.6%)	0/14 (0.0%)	17.6%	(-0.5%, 35.8%)
Poland	3/15 (20.0%)	2/13 (15.4%)	4.6%	(-23.6%, 32.8%)
Romania	2/6 (33.3%)	0/3 (0.0%)	33.3%	(-4.4%, 71.1%)
Russia	8/40 (20.0%)	10/37 (27.0%)	-7.0%	(-26.0%, 11.9%)
Slovakia	3/12 (25.0%)	7/23 (30.4%)	-5.4%	(-36.3%, 25.5%)
Sweden	0/1 (0.0%)	0/2 (0.0%)		
UK		0/4 (0.0%)		
Ukraine	1/7 (14.3%)	0/9 (0.0%)	14.3%	(-11.6%, 40.2%)
<b>Baseline UCDAI Score</b>				
4	5/14 (35.7%)	7/23 (30.4%)	5.3%	(-26.1%, 36.6%)
5	6/15 (40.0%)	2/18 (11.1%)	28.9%	(0.2%, 57.6%)
6	4/19 (21.1%)	3/21 (14.3%)	6.8%	(-16.9%, 30.4%)
7	4/26 (15.4%)	3/24 (12.5%)	2.9%	(-16.3%, 22.1%)
8	2/23 (8.7%)	3/15 (20.0%)	-11.3%	(-34.6%, 12.0%)
9	1/17 (5.9%)	0/11 (0.0%)	5.9%	(-5.3%, 17.1%)
10	0/3 (0.0%)	0/5 (0.00%)		
< 4 or > 10	0/10 (0.0%)	1/12 (8.3%)	-8.3%	(-24.0%, 7.3%)
<b>Baseline CRP</b>				
< 10 mg/L	20/107 (18.7%)	18/103 (17.5%)	1.2%	(-9.2%, 11.6%)
≥ 10 mg/L	2/20 (10.0%)	1/25 (4.0%)	6.0%	(-9.2%, 21.2%)

Copied from Tables 79 to 110, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were numerically higher for budesonide MMX 9 mg for male, Italy, Lithuania, Romania, Ukraine, and baseline UCDAI score 5 for all randomized patients analysis.

Remission rates were numerically lower for budesonide MMX 9 mg for Russia, Slovakia, baseline UCDAI score 8.

Summary of results for subgroup analyses for all randomized patients with positive histology at baseline is given Table 28.

**Table 28 Analysis of Remission  
Study CB-01-02/02**

**All Randomized Patients with Positive Histology at Baseline**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	12/66 (18.2%)	3/60 (5.0%)	13.2%	(2.4%, 24.0%)
Female	7/48 (14.6%)	2/36 (5.6%)	9.0%	(-3.5%, 21.5%)
<b>Age</b>				
<65	19/111 (17.1%)	5/84 (6.0%)	11.2%	(2.5%, 19.8%)
≥65	0/4 (0.00%)	1/12 (8.3%)	-8.3%	(-24.0%, 7.3%)
<b>Race</b>				
White	19/113 (16.8%)	6/96 (6.3%)	10.6%	(2.1%, 19.0%)
Asian	0/1 (0.0%)			
Other	0/1 (0.0%)			
<b>Country</b>				
Australia	0/1 (0.0%)	0/2 (0.0%)		
Estonia	0/6 (0.0%)	0/5 (0.0%)		
France	0/1 (0.0%)	0/1 (0.0%)		
Italy	2/14 (14.3%)	0/16 (0.0%)	14.3%	(-4.0%, 32.6%)
Latvia	0/2 (0.0%)	0/2 (0.0%)		
Lithuania	3/17 (17.6%)	0/12 (0.0%)	17.6%	(-0.5%, 35.8%)
Poland	3/15 (20.0%)	2/9 (11.1%)	8.9%	(-19.9%, 37.7%)
Romania	2/5 (40.0%)	0/3 (0.0%)	40.0%	(-2.9%, 82.9%)
Russia	8/37 (21.6%)	4/28 (14.3%)	7.3%	(-11.2%, 25.9%)
Slovakia	1/6 (18.7%)	1/11 (9.1%)	7.6%	(-26.7%, 41.9%)
Sweden	0/1 (0.0%)	0/2 (0.0%)		
UK		0/4 (0.0%)		
Ukraine	0/6 (0.0%)	0/5 (0.0%)		
<b>Baseline UCDAI Score</b>				
4	2/11 (18.2%)	1/12 (8.3%)	9.8%	(-17.8%, 37.5%)
5	6/12 (50.0%)	2/10 (10.0%)	40.0%	(6.1%, 73.9%)
6	4/19 (21.1%)	2/17 (11.8%)	9.3%	(-14.6%, 33.2%)
7	4/25 (16.0%)	0/19 (0.0%)	16.0%	(1.6%, 30.4%)
8	2/22 (9.1%)	2/14 (14.3%)	-5.2%	(-27.1%, 16.7%)
9	1/17 (5.9%)	0/10 (0.0%)	5.9%	(-5.3%, 17.1%)
10	0/3 (0.0%)	0/5 (0.0%)		
< 4 or > 10	0/6 (0.0%)	0/9 (0.0%)		
<b>Baseline CRP</b>				
< 10 mg/L	17/95 (17.9%)	5/75 (6.7%)	11.2%	(1.7%, 20.8%)
≥ 10 mg/L	2/20 (10.0%)	1/21 (4.8%)	5.2%	(-10.8%, 21.2%)

Copied from Tables 111 to 142, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were statistically significantly higher at 5% significance level for budesonide MMX 9 mg for male, age <65, white, baseline UCDAI scores 5 and 7 for all randomized patients with positive histology at baseline.

However, number of patients in budesonide NMX 9 mg group was higher than that in placebo in all randomized patients with positive histology at baseline (115 vs. 96; P<0.001). Results from subgroup analyses might be difficult to be interpreted statistically.

Summary of results for subgroup analyses for all randomized patients with normal histology at baseline is given Table 29.

**Table 29 Analysis of Remission  
Study CB-01-02/02**

<b>All Randomized Patients with Normal Histology at Baseline</b>				
	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Gender</b>				
Male	2/4 (50.0%)	6/16 (37.5%)	12.5%	(-4.2%, 66.9%)
Female	1/8 (12.5%)	7/17 (41.2%)	-28.7%	(-61.4%, 4.1%)
<b>Age</b>				
<65	3/12 (25.0%)	12/31 (38.7%)	-13.7%	(-43.6%, 16.2%)
≥65		1/2 (50.0%)		
<b>Race</b>				
White	3/12 (25.0%)	13/33 (39.4%)	-14.4%	(-44.0%, 15.2%)
<b>Country</b>				
Estonia		0/1 (0.0%)		
Italy	0/1 (0.0%)	0/1 (0.0%)		
Lithuania		0/2 (0.0%)		
Poland		1/4 (25.0%)		
Romania	0/1 (0.0%)			
Russia	0/3 (0.0%)	6/9 (66.7%)	-66.7%	(-97.5%, -35.9%)
Slovakia	2/6 (33.3%)	6/12 (50.0%)	-16.7%	(-63.8, 30.5%)
Ukraine	1/1 (100.0%)	0/4 (0.0%)	100.0%	(100.0%, 100.0%)
<b>Baseline UCDAI Score</b>				
4	3/3 (100.0%)	6/11 (54.5%)	45.5%	(16.0%, 74.9%)
5	0/3 (0.0%)	1/8 (12.5%)	-12.5%	(-35.4%, 10.4%)
6		1/4 (25.0%)		
7	0/1 (0.0%)	3/5 (60.0%)	-60.0%	(-100.0%, -17.1%)
8	0/1 (0.0%)	1/1 (100.0%)	-100.0%	(-100.0%, -100.0%)
9		0/1 (0.0%)		
< 4 or > 10	0/4 (0.0%)	1/3 (33.3%)	-33.3%	(-86.7%, 20.0%)
<b>Baseline CRP</b>				
< 10 mg/L	3/12 (25.0%)	13/28 (46.4%)	-21.4%	(-52.1%, 9.3%)
≥ 10 mg/L		0/4 (0.0%)		

Copied from Tables 143 to 174, Efficacy Information Amendment 1.11.3 dated 09 May 2012.

As seen from the table above, remission rates were numerically higher for budesonide MMX 9 mg for male and baseline UCDAI score 4 for all randomized patients with normal histology at baseline.

Remission rates were numerically lower for budesonide MMX 9 mg for female, age < 65, white, Russia, Slovakia, and baseline CRP < 10 mg/L.

However, number of patients in budesonide NMX 9 mg group was higher than that in placebo in all randomized patients with positive histology at baseline (12 vs. 33; P<0.001). Results from subgroup analyses might be difficult to be interpreted statistically

### 3.1.3 Study CB-01-02/04

#### 3.1.3.1 Study Design

Additionally, a 12-month, double-blind, placebo-controlled Phase III study enrolling patients achieving remission in any of the previous three Phase III studies followed 123 patients for up to 12 months with the objective of assessing long-term safety and maintenance of remission with budesonide MMX 6 mg.

#### 3.1.3.2 Sponsor's Analysis

A total of 153 patients were screened for study entry, and 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 Table 30.

**Table 30 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

Source: CSR CB-01-02/04 Table 14.1-1

#### 3.1.3.2.1 Planned Analysis

The SAP stated that this study was an exploratory in nature and such there was no formal sample size calculation. It is planned that approximately 150 patients will be randomized, giving 75 patients per treatment group.

The SAP also stated that this study is not powered to show statistically significant differences between budesonide MMX and placebo. So, this study should be considered as exploratory study.

### 3.1.3.2.2 Treatment Group Comparability

In general, demographic and baseline characteristics were similar in the placebo and budesonide MMX treatment groups.

### 3.1.3.2.3 Sponsor's Analysis of Primary Efficacy Variable

In the ITT population, 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 Table 31.

**Table 31 Patients in Clinical Remission by Study Visit (ITT Population)**

Patients in Clinical Remission at:	Placebo N = 61 x/n (%)	MMX 6 mg N = 61 x/n (%)	P-Value
1 Month	36/47 (76.6%)	40/46 (87.0%)	0.1962
3 Months	38/41 (92.7%)	37/41 (90.2%)	0.6927
6 Months	28/35 (80.0%)	27/34 (79.4%)	0.9516
9 Months	23/27 (85.2%)	26/28 (92.9%)	0.3616
12 Months	18/23 (78.3%)	19/22 (86.4%)	0.4773
End of Study/Early Withdrawal Visit	22/44 (50.0%)	22/36 (61.1%)	0.3203

Source: CSR CB-01-02/04 Table 14.2-2.2

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.

As seen in the table above, the numbers of patients that remained in clinical remission decreased over the 12-month period in both treatment groups. No statistically significant differences in the percentages of patients in clinical remission were observed between budesonide MMX and placebo.

**Table 32 Patients in Clinical Remission by Study Visit (EE Population)**

Patients in Clinical Remission at:	Placebo N = 32 x/n (%)	MMX 6 mg N = 39 x/n (%)	P-Value
1 Month	23/30 (76.7%)	30/34 (88.2%)	0.2209
3 Months	23/25 (92.0%)	30/31 (96.8%)	0.4303
6 Months	16/21 (76.2%)	20/25 (80.0%)	0.7550
9 Months	13/15 (86.7%)	19/20 (95.0%)	0.3835
12 Months	11/13 (84.6%)	14/15 (93.3%)	0.4570
End of Study/Early Withdrawal Visit	12/28 (42.9%)	15/26 (57.7%)	0.2760

Source: CSR CB-01-02/04 Table 14.2-1.2

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.

### 3.1.3.2.4 Sponsor's Analyses of Secondary Variables

#### 3.1.3.2.4.1 Time to Clinical Relapse

In the ITT population, time to clinical relapse is summarized by treatment group in Table 33.

**Table 33 Time to Clinical Relapse (ITT Population)**

	Placebo N = 61	MMX 6 mg N = 61	Total N = 122
Patients Experiencing Clinical Relapse (n [%])	34 (55.7%)	18 (29.5%)	52 (42.6%)
Censored Patients (n [%])	27 (44.3%)	43 (70.5%)	70 (57.4%)
K-M Percentile Estimates (95% CI) (days)			
25 <sup>th</sup> Percentile	27 (1, 38)	165 (32, 315)	30 (28, 105)
50 <sup>th</sup> Percentile	181 (38, 374)	NC (NC, NC)	315 (178, NC)
75 <sup>th</sup> Percentile	374 (366, NC)	NC (NC, NC)	374 (374, NC)
Log Rank Test p-value (Budesonide MMX versus placebo)	0.0224		
K-M Estimates of Relapse Probability (95% CIs)			
1 Month	0.350 (0.225, 0.474)	0.144 (0.051, 0.237)	0.250 (0.169, 0.331)
3 Months	0.424 (0.294, 0.554)	0.188 (0.081, 0.295)	0.312 (0.224, 0.400)
6 Months	0.486 (0.352, 0.619)	0.319 (0.181, 0.457)	0.405 (0.308, 0.502)
9 Months	0.572 (0.437, 0.707)	0.374 (0.228, 0.521)	0.479 (0.377, 0.580)
12 Months	0.597 (0.461, 0.733)	0.409 (0.255, 0.563)	0.508 (0.405, 0.612)
> 12 Months	0.827 (0.576, 1.000)	0.409 (0.255, 0.563)	0.772 (0.450, 1.000)

Source: CSR CB-01-02/04 Table 14.2-2.3

Note: K-M = Kaplan-Meier.

CI = Confidence interval (based on Greenwood's formula).

NC = Not calculable.

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

Maximum time on study: placebo group = 382 days, budesonide MMX group = 373 days.

As seen from the table above, a statistically significant difference was observed in the distributions of time to clinical relapse between budesonide MMX and placebo ( $p = 0.0224$ ). The median time to relapse was shorter in the placebo group (181 days) than in the budesonide MMX group (> 1 year, the median was never reached).

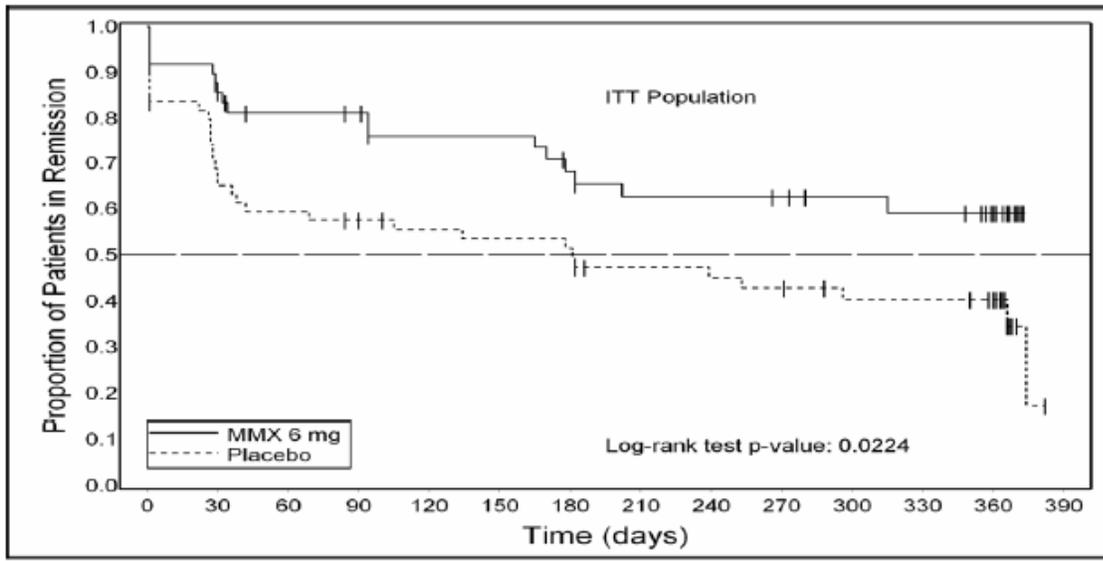
Additionally, the probability of experiencing clinical relapse was numerically higher in the placebo group at all time points evaluated. At 12 months, the estimated probability of relapse was 59.7% in the placebo group and 40.9% in the budesonide MMX group.

A number of patients in both treatment groups remained on study for more than 12 months; the maximum time on study was 382 days for placebo patients and 373 days for budesonide MMX patients.

When all patients had completed the study, the estimated probability of relapse was 82.7% in the placebo group and 40.9% in the budesonide MMX group.

The Kaplan-Meier distributions of time to clinical relapse for the placebo and the budesonide MMX treatment groups are presented in Figure 1.

**Figure 1 Time to Clinical Relapse (ITT Population)**



In the EE population, time to clinical relapse is summarized by treatment group in table 34.

**Table 34 Time to Clinical Relapse (EE Population)**

	Placebo N = 32	MMX 6 mg N = 39	Total N = 122
Patients Experiencing Clinical Relapse (n [%])	19 (59.4%)	12 (30.8%)	31 (43.7%)
Censored Patients (n [%])	13 (40.6%)	27 (69.2%)	40 (56.3%)
K-M Percentile Estimates (95% CI) (days)			
25 <sup>th</sup> Percentile	33 (27, 178)	178 (34, NC)	94 (30, 181)
50 <sup>th</sup> Percentile	182 (69, NC)	NC (NC, NC)	315 (181, NC)
75 <sup>th</sup> Percentile	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)
Log Rank Test p-value (Budesonide MMX versus placebo)	0.0546		
K-M Estimates of Relapse Probability (95% CIs)			
1 Month	0.250 (0.100, 0.400)	0.087 (0.000, 0.180)	0.165 (0.076, 0.254)
3 Months	0.344 (0.179, 0.508)	0.147 (0.028, 0.267)	0.242 (0.139, 0.345)
6 Months	0.447 (0.272, 0.623)	0.284 (0.126, 0.443)	0.363 (0.244, 0.483)
9 Months	0.557 (0.377, 0.736)	0.358 (0.186, 0.530)	0.455 (0.328, 0.582)
12 Months	0.601 (0.420, 0.783)	0.404 (0.222, 0.586)	0.501 (0.370, 0.632)
> 12 Months	0.681 (0.479, 0.882)	0.404 (0.222, 0.586)	0.556 (0.401, 0.711)

Source: CSR CB-01-02/04 Table 14.2-1.3

Note: K-M = Kaplan-Meier.

CI = Confidence interval (based on Greenwood's formula).

NC = Not calculable.

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

Maximum time on study: placebo group = 382 days, budesonide MMX group = 373 days.

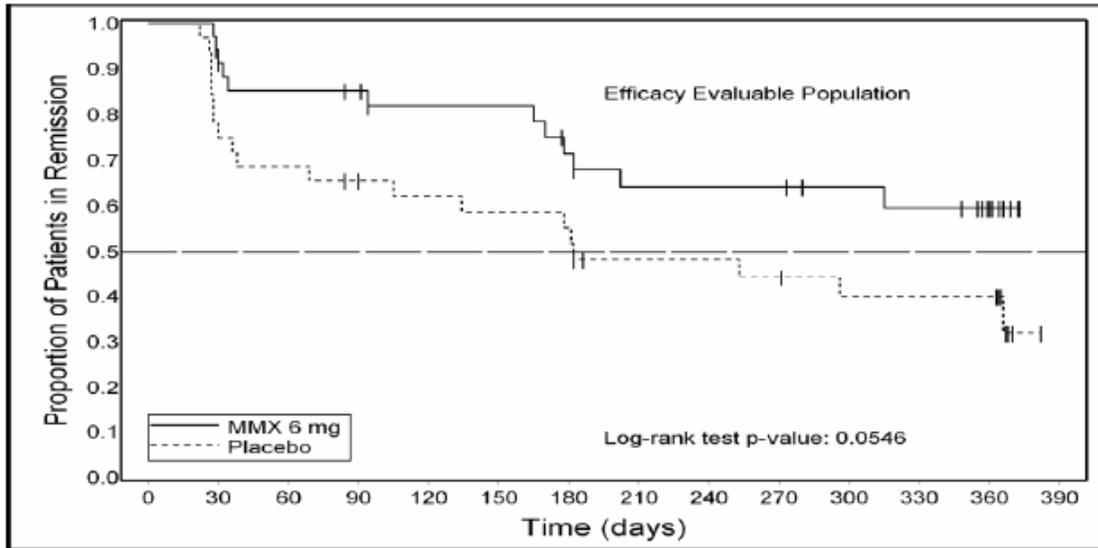
As seen from the table above, a comparison of the distributions of time to clinical relapse between budesonide MMX and placebo just missed reaching statistical significance ( $p = 0.0546$ ). The median time to relapse was shorter in the placebo group (182 days) than in the budesonide MMX group (> 1 year, the median was never reached).

The probability of experiencing clinical relapse was numerically higher in the placebo group at all time points evaluated. At 12 months, the estimated probability of relapse was 60.1% in the placebo group and 40.4% in the budesonide MMX group.

A number of patients in both treatment groups remained on study for more than 12 months; the maximum time on study was 382 days for placebo patients and 373 days for budesonide MMX patients.

The Kaplan-Meier distributions of time to clinical relapse for the placebo and the budesonide MMX treatment groups are presented in the Figure 2.

**Figure 2 Time to Clinical Relapse (EE Population)**



### 3.1.3.2.4.2 Endoscopic Relapse

In the ITT population, the percentages of patients in endoscopic relapse in the placebo and the budesonide MMX groups are summarized in Table 35.

**Table 35 Patients in Endoscopic Relapse (ITT Population)**

	Placebo N = 61	MMX 6 mg N = 61	Total N = 122
Patients Experiencing Endoscopic Relapse (n [%])	39 (63.9%)	42 (68.9%)	81 (66.4%)
(95% Confidence Interval)	(51.9, 76.0)	(57.2, 80.5)	(58.0, 74.8)
Difference Between Placebo and Budesonide MMX	4.9		
(95% Confidence Interval)	(-13.5, 23.3)		
P-Value	0.5653		

Source: CSR CB-01-02/04 Table 14.2-2.4

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.

As seen in the table above, in the ITT population, the percentages of patients in the budesonide MMX and placebo groups that were in endoscopic relapse at the End of study/Early Withdrawal Visit were similar.

In the EE population, the percentages of patients in endoscopic relapse in the placebo and the budesonide MMX groups are summarized in Table 36.

**Table 36 Patients in Endoscopic Relapse (EE Population)**

	Placebo N = 61	MMX 6 mg N = 61	Total N = 122
Patients Experiencing Endoscopic Relapse (n [%])	16 (50.0%)	27 (69.2%)	43 (60.6%)
(95% Confidence Interval)	(32.7, 67.3)	(54.7, 83.7)	(49.2, 71.9)
Difference Between Placebo and Budesonide MMX	19.2		
(95% Confidence Interval)	(-6.2, 44.7)		
P-Value	0.0990		

Source: CSR CB-01-02/04 Table 14.2-1.4

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.

As seen in Table above, no statistically significant differences in the percentages of patients in endoscopic remission between budesonide MMX and placebo were observed.

### 3.1.3.3 Reviewer's Comments and Evaluation

The SAP stated that this study was an exploratory in nature and such there was no formal sample size calculation. It is planned that approximately 150 patients will be randomized, giving 75 patients per treatment group.

The SAP also stated that this study is not powered to show statistically significant differences between budesonide MMX and placebo. So, this study should be considered as exploratory study.

Furthermore, the SAP stated that the primary efficacy endpoints are clinical remission at 1, 3, 6, 9 months and at the End of Study/Early Withdrawal Visit.

If no multiplicity adjustments were to be applied to primary efficacy endpoints, results for primary efficacy endpoints should be considered exploratory.

So, Study CB-01-02/04 should be considered as exploratory.

## **3.2 Evaluation of Safety**

### **3.2.1 Study CB-01-02/01**

The overall percentages of patients with any AE were similar for the two budesonide MMX groups (9 mg, 57.5% and 6 mg, 58.7%) and slightly higher in the placebo (62.8%) and Asacol (63.0%) groups. Most patients had AEs that were mild or moderate in severity. The percentage of patients with severe AEs was highest for placebo (12.4%). Overall 13.9% (71/509) of patients experienced AEs leading to study discontinuation, with the highest percentage in the placebo group (18.6%). SAEs were infrequent and occurred in similar percentages of patients across all treatment groups. There were no deaths in the study. There was no evidence of a dose trend for budesonide MMX with respect to the overall percentages of patients with AEs or SAEs.

### **3.2.2 Study CB-01-02/02**

Among all 511 treated patients, 277 (54.2%) experienced one or more AE; 23.7% of patients experienced one or more treatment-related AE, with similar percentages across all treatment groups. Thus, a majority of patients had AEs that were considered to be not related to study treatment. The overall percentages of patients with any AE were similar for budesonide MMX 9 mg and Entocort EC (55.5% and 54.8%, respectively); the percentage was 62.5% for budesonide MMX 6 mg and 44.2% for placebo. Most patients had events that were mild or moderate in severity. The frequency of patients with severe AEs was highest for budesonide MMX 9 mg (9.4%). Overall 18.6% (95/511) of patients experienced AEs leading to study discontinuation, with the highest percentage in the budesonide MMX 6 mg group (23.4%). SAEs were infrequent, but the percentage of patients with SAEs was slightly higher in the placebo group (3.9%) compared with the other groups (0.8% to 3.1%).

### **3.2.3 Study CB-01-02/04**

Overall, TEAEs occurred in a higher percentage of patients in the placebo group (72.1%) than in the budesonide MMX group (64.5%). Treatment-related TEAEs occurred in a similar percentage of patients in both treatment groups (21.3% and 21.0% in the placebo and budesonide MMX groups, respectively). The majority of patients in both treatment groups reported events that were mild to moderate in severity, and not considered to be treatment related. A higher percentage of placebo patients (27.9%) withdrew from the study due to a TEAE than budesonide MMX patients (16.1%). SAEs were reported infrequently (one patient each in the placebo and budesonide MMX 6 mg groups).

There were no deaths or life-threatening events in this study. Both SAEs were judged by the Investigator not to be related to study drug.

## **4. FINDINGS IN SPECIAL/SUBGROUP POPULATION**

This reviewer performed subgroup analyses of remission rates for gender, age (<65 vs. ≥65), and race for sponsor's ITT analysis.

## 4.1 Gender, Race and Age

### 4.1.1 Study CB-01-02/01

The summary of results of subgroup analyses of remission rates for Study CB-01-02/01 is given below.

<b>Analysis of Remission Study CB-01-02/01 Sponsor's ITT Analysis</b>				
	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
Gender				
Male	13/77 (16.9%)	6/68 (8.8%)	8.1%	(-2.7%, 18.8%)
Female	9/46 (19.6%)	3/53 (5.7%)	13.9%	(0.9%, 27.0%)
Age				
<65	21/119 (17.7%)	9/114 (7.9%)	9.8%	(1.3%, 18.2%)
≥65	1/4 (25.0%)	0/7 (0%)	25.0%	(-17.4%, 67.4%)
Race				
White	10/60 (16.7%)	4/64 (6.3%)	10.4%	(-0.7%, 21.6%)
Black	2/9 (22.2%)	0/7 (0.0%)	22.2%	(-4.9%, 49.4%)
Asian	10/44 (22.7%)	5/39 (12.8%)	9.9%	(-6.3%, 26.1%)
Other	0/10 (0.0%)	0/11 (0.0%)		

Obtained by this reviewer.

As seen from table above, remission rates were statistically significantly higher at 5% significance level for budesonide MMX 9 mg for female and age <65 for the sponsor's ITT analysis.

### 4.1.2 Study CB-01-01/02

The summary of results of subgroup analyses of remission rates for Study CB-01-02/02 is given below.

<b>Analysis of Remission Study CB-01-02/02 Sponsor's ITT Analysis</b>				
	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
Gender				
Male	12/64 (18.8%)	3/57 (5.3%)	13.5%	(2.3%, 24.7%)
Female	7/45 (15.6%)	1/32 (3.1%)	12.5%	(0.3%, 24.6%)
Age				
<65	19/105 (18.1%)	3/79 (3.8%)	14.3%	(5.8%, 22.8%)
≥65	0/4 (0.0%)	1/10 (10.0%)	-10.0%	(-28.6%, 8.6%)
Race				
White	19/107 (17.8%)	4/89 (4.5%)	13.3%	(4.8%, 21.7%)
Asian	0/1 (0.0%)			
Other	0/1 (0%)			

Obtained by this reviewer.

As seen from table above, remission rates were statistically significantly higher for budesonide MMX 9 mg for female and male, age <65, and white for the sponsor's ITT analysis.

#### 4.2 Other Special/Subgroup Population

This reviewer performed subgroup analyses of remission rates for country, and baseline UCDAI score for sponsor's ITT analysis.

##### 4.2.1 Study CB-01-02/01

The summary of results of subgroup analyses of remission rates for Study CB-01-02/01 is given below.

<b>Analysis of Remission Study CB-01-02/01 Sponsor's ITT Analysis</b>				
	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Country</b>				
Canada	0/7 (0.0%)	0/5 (0.0%)		
India	10/40 (25.0%)	5/39 (12.8%)	12.2%	(-4.9%, 29.2%)
US	12/76 (15.8%)	4/77 (5.2%)	10.6%	(0.1%, 20.2%)
<b>Baseline UCDAI Score</b>				
1		0/1 (0.0%)		
2	1/3 (33.3%)	0/1 (0.0%)	33.3%	(-20.0%, 86.7%)
3	0/11 (0.0%)	1/5 (20.0%)	-20.0%	(-55.1%, 15.1%)
4	4/14(28.6%)	3/11(27.3%)	1.6%	(-34.1%, 36.7%)
5	6/13 (46.2%)	1/17 (5.9%)	40.3%	(11.0%, 69.6%)
6	3/15 (20.0%)	0/16 (0.0%)	20.0%	(-0.2%, 40.2%)
7	4/19 (21.1%)	2/20 (10.0%)	11.1%	(-11.5%, 33.6%)
8	3/19 (15.8%)	1/17 (5.9%)	9.9%	(-9.9%, 29.8%)
9	0/16 (0.0%)	0/11 (0.0%)	0.0%	
10	1/4 (25.0%)	1/8 (11.1%)	13.9%	(-35.7%, 60.7%)
11		0/1 (0.0%)		

Obtained by this reviewer.

As seen from table above, for the sponsor's ITT analysis, remission rates were statistically significantly higher for budesonide MMX 9 mg for US. Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of scores 3, 4, and 9.

##### 4.2.2 Study CB-01-01/02

The summary of results of subgroup analyses of remission rates for Study CB-01-02/02 is given below.

**Analysis of Remission  
Study CB-01-02/02  
Sponsor's ITT Analysis**

	MMX 9 mg	Placebo	Diff (MMX-PLA)	95% CI
<b>Country</b>				
Australia	0/1 (0.0%)	0/2 (0.0%)		
Estonia	0/6 (0.0%)	0/5 (0.0%)		
France	0/1 (0.0%)	0/1 (0.0%)		
Great Britain	0/4 (0.0%)			
Italy	2/12 (16.7%)	0/13 (0.0%)	16.7%	(-4.4%, 37.8%)
Latvia	0/2 (0.0%)	0/2 (0.0%)		
Lithuania	3/17 (17.6%)	0/12 (0.0%)	17.6%	(-0.5%, 35.8%)
Poland	3/14 (21.4%)	1/9 (11.1%)	10.3%	(-19.4%, 40.0%)
Romania	2/5 (40.0%)	0/3 (0.0%)	40.0%	(-2.9%, 82.9%)
Russia	8/35 (22.9%)	3/28 (10.7%)	12.2%	(-5.9%, 30.2%)
Slovakia	1/4 (25.0%)	0/7 (0.0%)	25.0%	(-17.4%, 67.4%)
Sweden	0/1 (0.0%)	0/2 (0.0%)		
Ukraine	0/6 (0.0%)	0/5 (0.0%)		
<b>Baseline UCDAI Score</b>				
2		0/1 (0.0%)		
3	0/3 (0.0%)	0/1 (0.0%)		
4	2/10 (20.0%)	0/9 (0.0%)	20.0%	(-4.8%, 44.8%)
5	6/12 (50.0%)	1/8 (12.5%)	37.5%	(1.1%, 73.9%)
6	4/19 (21.1%)	2/16 (12.5%)	8.6%	(-15.9%, 33.0%)
7	4/23 (17.4%)	0/19 (0.0%)	17.4%	(1.9%, 32.9%)
8	2/21 (9.5%)	1/14 (7.1%)	2.4%	(-16.1%, 20.8%)
9	1/17 (5.9%)	0/10 (0.0%)	5.9%	(-5.3%, 17.1%)
10	0/3 (0.0%)	0/5 (0.00%)		

Obtained by this reviewer.

As seen from table above, for the sponsor's ITT analysis, remission rates were numerically higher for budesonide MMX 9 mg across countries in Europe. Remission rates were numerically higher for budesonide MMX 9 mg across all baseline UCDAI scores with exception of score 8.

## 5. SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues and Collective Evidence

The sponsor submitted two induction trials (Study CB-01-02/01 and CB-01-02/02) and one maintenance trial (Study CB-01-02/04).

Study CB-01-02/01 showed that in the sponsor's ITT population, the percentage of patients achieving clinical remission at Week 8 in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group. Remission rates for budesonide MMX 6 mg was numerically greater than placebo, but the difference did not reach statistical significance.

Result of subgroup analysis of rate of clinical remission at Week 8 was inconsistent between  $\leq 42$  years vs.  $> 42$  years (1.2% vs. 21.0%).

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

Study CB-01-02/02 conducted in Europe was problematic with regard to the sponsor's ITT population. The sponsor's ITT population excluded four sites with significant GCP violations, and significantly more patients were excluded from the placebo group compared to the budesonide MMX 9 mg group (31.0% vs. 13.5%) mainly due to normal histology at baseline.

Results for this study in sponsor's ITT population tended to be biased against placebo and might not be interpretable with placebo.

Study CB-01-02/02 showed that in the sponsor's ITT population, the percentage of patients in clinical remission at Week 8 was significantly higher for patients receiving budesonide MMX 9 mg than for patients receiving placebo.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

The sponsor's ITT population was not pre-specified in the protocol but was pre-specified in the protocol. But, proposed SAP excluding patients with normal histology at baseline and critical GCP violations was submitted FDA just 17 days before the last patient out. The SAP was finalized about 5 months after last patient out. The SAP did not state clearly which analysis (randomized or ITT) was to be the primary efficacy analysis. In the Teleconference dated April 13, 2010, the agency clearly stated that "true" ITT analysis should be considered as the primary efficacy analysis. The agency assumed the primary analysis was to be based on the as-randomized and recommended the sponsor's ITT analysis would be a sensitivity analysis to support the primary analysis.

In the pre-NDA meeting on May 31, 2011, the Agency restated that the "true" ITT population should be used as the primary analysis population.

This reviewer performed "true" ITT analyses including all randomized patients for both studies (CB-01-02/01 and CB-01-02/02). Results showed that remission rates for budesonide MMX 9 mg were numerically greater than placebo for both studies, but differences did not reach statistical significance for this "true" ITT population. The treatment differences between budesonide MMX

9 and placebo were 6.3% with 95% CI (-2%, 15.0%) and 3.2% with 95% CI (-5.6%, 12.1%) for Study CB-01-02/01 and Study CB-01-02/02, respectively.

In Study CB-01-02/01, the number of patients with normal histology at baseline was comparable among treatment groups. Rate of clinical remission for budesonide MMX9 mg group was numerically higher than for placebo for patients with positive baseline histology (18.5% vs. 8.2%) with nominal p-value of 0.0238 (Fisher's exact test).

In Study CB-01-02/01, 5 of 6 placebo patients with normal histology at baseline had clinical remission. None of the 3 budesonide MMX 9 mg patients with normal histology at baseline had clinical remission. The p-value changed from 0.0238 in "positive histology" population to 0.1365 in the reviewer's "true" ITT population. So, the p-value for the sponsor's ITT analysis was at best at borderline significant compared to the pre-specified threshold of 0.025.

In Study CB-01-02/02, statistically significant more placebo patients with normal histology at baseline were observed as compared to other treatment groups. So, results from the sponsor's ITT analysis excluding patients with normal histology might not be statistically interpretable. The rate of clinical remission for the budesonide MMX 9 mg group was numerically higher than that for placebo for patients with positive baseline histology (16.7% vs. 6.3%) with nominal p-value of 0.0308 (Fisher's exact test). The p-value changed from 0.0308 in "positive histology" population to 0.4746 in "true" ITT population. Results from the sponsor's ITT analysis might not be considered robust.

Furthermore, since the sponsor's ITT analysis excluded all patients with normal histology at baseline, the sponsor's ITT analysis should not be considered as a modified ITT analysis but a subgroup analysis for patients with abnormal histology at baseline. Basing the primary analysis on the subgroup of patients with abnormal histology was not pre-specified in the original protocols but was introduced in the SAP after study enrollment but before database lock. Without clear pre-specification, this subgroup analysis should be considered as exploratory and hypothesis generating in nature.

For the maintenance trial (Study CB-01-02/04), the SAP stated that this study was an exploratory in nature with no formal sample size calculation. This study was not powered to show statistically significant differences between budesonide MMX 6 mg and placebo. So, this study should be considered as an exploratory study.

In conclusion, for induction, both studies (Study CB-01-02/01 and Study CB-01/02/02) did not provide substantially statistical evidence demonstrating superiority of the budesonide MMX 9 mg over placebo for all randomized population. For patients with positive histology at baseline, the budesonide MMX 9 mg was numerically better than placebo. But, subgroup of patients with positive histology was not pre-specified in the protocol. Without clear pre-specification, this subgroup analysis should be considered exploratory and hypothesis generating in nature.

For the maintenance, Study CB-01-02/04 was designed as exploratory in nature. Results cannot be statistically interpretable.

## 5.2 Conclusions and Recommendations

The sponsor submitted two induction trials (Study CB-01-02/01 and CB-01-02/02) and one maintenance trial (Study CB-01-02/04).

Study CB-01-02/01 showed that in the sponsor's ITT population, the percentage of patients achieving clinical remission at Week 8 in the budesonide MMX 9 mg group was significantly greater than the percentage of patients in the placebo group. Remission rates for budesonide MMX 6 mg was numerically greater than placebo, but the difference did not reach statistical significance.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

Study CB-01-02/02 conducted in Europe was problematic with regard to the sponsor's ITT population. The sponsor's ITT population excluded four sites with significant GCP violations, and significantly more patients were excluded from the placebo group compared to the budesonide MMX 9 mg group (31.0% vs. 13.5%) mainly due to normal histology at baseline.

Results for this study in sponsor's ITT population tended to be biased against placebo and might not be interpretable statistically with placebo.

Study CB-01-02/02 showed that in the sponsor's ITT population, the percentage of patients in clinical remission at Week 8 was significantly higher for patients receiving budesonide MMX 9 mg than for patients receiving placebo.

For both secondary endpoints (rate of clinical improvement and rate of endoscopic improvement), the rates were numerically higher in the budesonide MMX 9 mg group than in the placebo group, but the differences failed to reach statistical significance.

The sponsor's ITT population did not include all randomized patients. It included all randomized patients who received at least one dose of study drug, had no major entry criteria (e.g., a *C. difficile* infection during screening) or GCP violations, and had mucosal histology consistent with active UC at baseline.

This reviewer performed "true" ITT analyses including all randomized patients for both studies (CB-01-02/01 and CB-01-02/02). Results showed that remission rates for budesonide MMX 9 mg was numerically greater than placebo for both studies, but differences did not reach statistical significance for the "true" ITT population. The treatment differences between budesonide MMX 9 and placebo were 6.3% with 95% CI (-2%, 15.0%) and 3.2% with 95% CI (-5.6%, 12.1%) for Study CB-01-02/01 and Study CB-01-02/02, respectively.

In Study CB-01-02/01, the number of patients with normal histology at baseline was comparable among treatment groups. Rate of clinical remission for budesonide MMX 9 mg group was numerically higher than for placebo for patients with positive baseline histology (18.5% vs. 8.2%) with nominal p-value of 0.0238 (Fisher's exact test).

In Study CB-01-02/01, 5 of 6 placebo patients with normal histology at baseline had clinical remission. None of the 3 budesonide MMX 9 mg patients with normal histology at baseline had clinical remission. The p-value changed from 0.0238 in “positive histology” population to 0.1365 in the reviewer’s “true” ITT population. So, the p-value for the sponsor’s ITT analysis was at best at borderline significant compared to the pre-specified threshold of 0.025.

In Study CB-01-02/02, statistically significant more placebo patients with normal histology at baseline were observed as compared to other treatment groups. So, results from the sponsor’s ITT analysis excluding patients with normal histology might not be statistically interpretable. The rate of clinical remission for the budesonide MMX 9 mg group was numerically higher than that for placebo for patients with positive baseline histology (16.7% vs. 6.3%) with nominal p-value of 0.0308 (Fisher’s exact test). The p-value changed from 0.0308 in “positive histology” population to 0.4746 in “true” ITT population. Results from the sponsor’s ITT analysis might not be considered robust.

Furthermore, since the sponsor’s ITT analysis excluded all patients with normal histology at baseline, the sponsor’s ITT analysis should not be considered as a modified ITT analysis but a subgroup analysis for patients with abnormal histology at baseline. Basing the primary analysis on the subgroup of patients with abnormal histology was not pre-specified in the original protocols but was introduced in the SAP after study enrollment but before database lock. Without clear pre-specification, this subgroup analysis should be considered as exploratory and hypothesis generating in nature.

For the maintenance trial (Study CB-01-02/04), the SAP stated that this study was an exploratory in nature with no formal sample size calculation. This study was not powered to show statistically significant differences between budesonide MMX 6 mg and placebo. So, this study should be considered as an exploratory study.

In conclusion, for induction, both studies (Study CB-01-02/01 and Study CB-01/02/02) did not provide substantially statistical evidence demonstrating superiority of the budesonide MMX 9 mg over placebo for the all randomized population. For patients with positive histology at baseline, the budesonide MMX 9 mg was numerically better than placebo. But, subgroup of patients with positive histology was not pre-specified in the protocol. Without clear pre-specification, this subgroup analysis should be considered exploratory and hypothesis generating in nature.

For maintenance, Study CB-01-02/04 was designed as exploratory in nature. Results cannot be statistically interpretable.

## 6. Appendix

**Table 1 Summary of Demographic and Baseline Characteristics --- Protocol CB-01-02/01**  
Sponsor's ITT Population

Characteristics	Placebo (N=121)	MMX 9 mg (N=123)	MMX 6 mg (N=121)	Asacol (N=124)	Among Treatment p-value
Sex					0.1912
Male	68 (56.2%)	77 (62.6%)	59 (48.8%)	69 (55.6%)	
Female	53 (43.8%)	46 (37.4%)	62 (51.2%)	55 (44.4%)	
Race					0.9511
Caucasian	64 (52.9%)	60 (48.8%)	60 (49.6%)	61 (49.2%)	
Black	7 (5.8%)	9 (7.3%)	11 (9.1%)	8 (6.5%)	
Hispanic or Latino	9 (7.4%)	8 (6.5%)	7 (5.8%)	12 (9.7%)	
Asian/	39 (32.2%)	44 (35.8%)	42 (34.7%)	43 (34.7%)	
Other Races	2 (1.7%)	2 (1.6%)	1 (0.8%)	0 (0.0%)	
Age (yr)					
Mean (SD)	41.0 (13.4)	41.5 (12.4)	43.7 (13.2)	43.8 (12.3)	0.1986
Age					0.7850
<65	114 (94.2%)	119 (96.7%)	115 (95.0%)	117 (94.4%)	
≥65	7 (5.8%)	4 (3.3%)	6 (5.0%)	7 (5.6%)	
Height (cm)					0.3987
Mean (SD)	166.8 (10.5)	168.2 (11.7)	166.0 (10.0)	167.8 (10.9)	
Weight (kg)					0.4328
Mean (SD)	72.0 (21.4)	73.5 (20.2)	72.2 (19.6)	75.9 (21.4)	
Baseline CRP					0.0325
N	120	123	121	124	
< 10 mg/L	93 (77.5%)	92 (74.8%)	95 (78.5%)	79 (63.7%)	
≥ 10 mg/L	27 (22.5%)	31 (25.2%)	26 (21.5%)	45 (36.3%)	
Baseline UCDAI score					0.3613
N	120	123	121	124	
Mean (SD)	6.7 (1.9)	6.4 (1.8)	6.5 (1.8)	6.8 (2.0)	
Baseline Endoscopic index score					0.5604
Mean (SD)	7.5	7.7 (1.9)	7.7 (2.0)	7.9 (2.2)	
Disease duration					0.1772
Mean (SD)	5.6 (7.4)	5.8 (7.3)	7.1 (8.5)	7.5 (9.3)	
Number of flares in Last 2 years					0.9799
N	121	122	121	121	
Mean (SD)	4.0 (4.7)	4.0 (9.5)	3.7 (4.5)	3.9 (7.8)	

Copied from Table 12.

P-values were computed by this reviewer.

**Table 2 Sponsor’s Analysis of Remission Rates –“true” ITT Analysis – Protocol CB-01-02/01**

**Table 20. Primary Endpoint (Remission) in the “true” ITT Population: Study CB-01-02/01**

	Placebo N=128 n (%)	MMX 9 mg N=127 n (%)	MMX 6 mg N=128 n (%)	Asacol N=127 n (%)	Total N=510 n (%)
Remission Status					
Yes	15 (11.7)	23 (18.1)	20 (15.6)	17 (13.4)	75 (14.7)
No	113 (88.3)	104 (81.9)	108 (84.4)	110 (86.6)	435 (85.3)
95% CI for Remission Rate (%)	(6.1, 17.3)	(11.4, 24.8)	(9.3, 21.9)	(7.5, 19.3)	(11.6, 17.8)
Difference between Active & Placebo		6.4	3.9	1.7	
95% CI for the Difference in Rates		(-2.3, 15.1)	(-4.5, 12.3)	(-6.5, 9.8)	
P-value		0.1518*	0.3630*	0.6878*	

Abbreviations: MMX = UCERIS™ (budesonide)

Remission is defined as a UCDAI score ≤1 with a score of 0 for rectal bleeding and stool frequency, a ≥ 1-point reduction in the Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

The “true” Intent-to-treat (ITT) population includes all patients who were randomized.

\* P-values are based on the Chi-square test.

**Table 3 Sponsor’s Analysis of Remission Rates – All Randomized Patients with Positive Histology at Baseline – Protocol CB-01-02/01**

	Placebo N=122 n (%)	MMX 9 mg N=124 n (%)	MMX 6 mg N=123 n (%)	Asacol N=124 n (%)	Total N=493 n (%)
Remission Status					
Yes	10 (8.2)	23 (18.5)	17 (13.8)	15 (12.1)	65 (13.2)
No	112 (91.8)	101 (81.5)	106 (86.2)	109 (87.9)	428 (86.8)
95% CI for Remission Rate (%)	(3.3,13.1)	(11.7,25.4)	(7.7,19.9)	(6.4,17.8)	(10.2,16.2)
Difference between Active and Placebo		10.4	5.6	3.9	
95% CI for the Difference in Rates		(2.0,18.7)	(-2.2,13.4)	(-3.6,11.4)	
P-value		0.0172*	0.1598*	0.3114*	

Note: Remission is defined as a UCDAI score of  $\leq 1$  with a score of 0 for both rectal bleeding and stool frequency, a  $\geq 1$ -point reduction in Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

One patient was randomized to MMX 6 mg, but was not dosed; this patient was included in the analysis as not having achieved remission.

All patients for whom remission status could not be calculated because of missing data were considered as not having achieved remission.

\* P-values are based on the Chi-square test.

The denominators for calculating percentages are the numbers of randomized patients with positive histology at baseline in each treatment group or the total number of patients.

All confidence intervals are computed based on the normal approximation.

Program: FDA Requests\trc-itt-30apr2012-01.sas (04MAY2012)

**Table 4 Sponsor’s Analysis of Remission Rates – All Randomized Patients with Normal Histology at Baseline – Protocol CB-01-02/01**

	Placebo N=6 n (%)	MMX 9 mg N=3 n (%)	MMX 6 mg N=5 n (%)	Asacol N=3 n (%)	Total N=17 n (%)
Remission Status					
Yes	5 (83.3)	0 (0.0)	3 (60.0)	2 (66.7)	10 (58.8)
No	1 (16.7)	3 (100.0)	2 (40.0)	1 (33.3)	7 (41.2)
95% CI for Remission Rate (%)	(53.5,100.0)	(0.0,0.0)	(17.1,100.0)	(13.3,100.0)	(35.4,82.2)
Difference between Active and Placebo		-83.3	-23.3	-16.7	
95% CI for the Difference in Rates		(-113,-53.5)	(-75.6,28.9)	(-77.8,44.4)	
P-value		0.0476**	0.5455**	1.0000**	

Note: Remission is defined as a UCDAI score of <= 1 with a score of 0 for both rectal bleeding and stool frequency, a >= 1-point reduction in Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

All patients for whom remission status could not be calculated because of missing data were considered as not having achieved remission.

\*\* P-values are based on the Fisher's Exact test.

The denominators for calculating percentages are the numbers of randomized patients with normal histology at baseline in each treatment group or the total number of patients.

All confidence intervals are computed based on the normal approximation.

Program: FDA Requests\lcr-itt-30apr2012-01.sas (04MAY2012)

**Table 5 Summary of Demographic and Baseline Characteristics --- Protocol CB-01-02/02  
Sponsor's ITT Population**

Characteristics	Placebo (N=89)	MMX 9 mg (N=109)	MMX 6 mg (N=109)	Entocort EC (N=103)	Among Treatment p-value
Sex					0.3266
Male	57 (64.0%)	64 (58.7%)	57 (52.3%)	55 (53.4%)	
Female	32 (36.0%)	45 (41.3%)	52 (47.7%)	48 (46.6%)	
Race					
White	89 (100.0%)	107 (98.2%)	109 (100.0%)	103 (100.0%)	
Asian/ Other Races	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	
Other Races	0 (0.0%)	1 (0.9%)	0 (0.0%)	0 (0.0%)	
Age (yr)					0.7735
Mean (SD)	44.8 (13.4)	42.8 (13.9)	44.8 (13.0)	43.8 (14.0)	
Age					0.2045
<65	77 (88.8%)	105 (96.3%)	102 (93.6%)	94 (91.3%)	
≥65	10 (11.2%)	4 (3.7%)	7 (6.4%)	9 (8.7%)	
Height (cm)					0.1028
N	89	109	109	102	
Mean (SD)	173.9 (8.0)	172.5 (9.7)	172.0 (9.3)	170.7 (9.0)	
Weight (kg)					0.4210
Mean (SD)	76.7 (15.1)	75.3 (14.5)	74.3 (15.8)	73.2 (13.8)	
Baseline CRP					
N	120	123	121	124	
< 10 mg/L	93 (77.5%)	92 (74.8%)	95 (78.5%)	79 (63.7%)	
≥ 10 mg/L	27 (22.5%)	31 (25.2%)	26 (21.5%)	45 (36.3%)	
Baseline UCDAI score					0.9482
Mean (SD)	6.7 (1.8)	6.8 (1.7)	6.8 (1.6)	6.8 (1.8)	
Baseline Endoscopic index score					0.0051
Mean (SD)	7.0 (1.9)	6.8 (1.7)	7.4 (1.7)	6.7 (1.7)	
Disease duration					0.7048
Mean (SD)	6.7 (7.6)	5.8 (7.0)	5.7 (5.5)	6.0 (5.9)	
Number of flares in Last 2 years					0.6537
N	88	109	109	101	
Mean (SD)	2.8 (2.1)	2.7 (1.4)	2.6 (1.4)	2.9 (2.2)	

Copied from Table 13.

P-values were computed by this reviewer.

**Table 6 Sponsor’s Analysis of Remission Rates –“true” ITT Analysis – Protocol CB-01-02/02**

**Table 21. Primary Endpoint (Remission) in the “true” ITT Population: Study CB-01-02/02**

	Placebo N=129 n (%)	MMX 9 mg N=127 n (%)	MMX 6 mg N=128 n (%)	Entocort N=128 n (%)	Total N=512 n (%)
Remission Status					
Yes	19 (14.7)	22 (17.3)	16 (12.5)	21 (16.4)	78 (15.2)
No	110 (85.3)	105 (82.7)	112 (87.5)	107 (83.6)	434 (84.8)
95% CI for Remission Rate (%)	(8.6, 20.8)	(10.7, 23.9)	(6.8, 18.2)	(10.0, 22.8)	(12.1, 18.3)
Difference between Active & Placebo		2.6	-2.2	1.7	
95% CI for the Difference in Rates		(-6.4, 11.6)	(-10.6, 6.2)	(-7.2, 10.5)	
P-value		0.5715*	0.6025*	0.7107*	

Abbreviations: MMX = UCERIS<sup>TM</sup> (budesonide)

Remission is defined as a UCDAI score ≤1 with a score of 0 for rectal bleeding and stool frequency, a ≥ 1-point reduction in the Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

The “true” Intent-to-treat (ITT) population includes all patients who were randomized.

\* P-values are based on the Chi-square test.

**Table 7 Sponsor’s Analysis of Remission Rates – All Randomized Patients with Positive Histology at Baseline – Protocol CB-01-02/02**

	Placebo N=96 n (%)	MMX 9 mg N=115 n (%)	MMX 6 mg N=112 n (%)	Entocort N=112 n (%)	Total N=435 n (%)
Remission Status					
Yes	6 (6.3)	19 (16.5)	9 (8.0)	16 (14.3)	50 (11.5)
No	90 (93.8)	96 (83.5)	103 (92.0)	96 (85.7)	385 (88.5)
95% CI for Remission Rate (%)	(1.4, 11.1)	(9.7, 23.3)	(3.0, 13.1)	(7.8, 20.8)	(8.5, 14.5)
Difference between Active and Placebo		10.3	1.8	8.0	
95% CI for the Difference in Rates		(1.9, 18.6)	(-5.2, 8.8)	(-0.1, 16.1)	
P-value		0.0215*	0.6197*	0.0603*	

Note: Remission is defined as a UCDAI score of  $\leq 1$  with a score of 0 for both rectal bleeding and stool frequency, a  $\geq 1$ -point reduction in Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

Three patients were randomized (one to MMX 9 mg and two to Entocort), but were not dosed; these patients were included in the analysis as not having achieved remission.

Two patients were dosed (one to Placebo and one to MMX 9 mg), but were not randomized; these patients were not included in the analysis.

All patients for whom remission status could not be calculated because of missing data were considered as not having achieved remission.

\* P-values are based on the Chi-square test.

The denominators for calculating percentages are the numbers of randomized patients with positive histology at baseline in each treatment group or the total number of patients.

All confidence intervals are computed based on the normal approximation.

Program: FDA Requests\trc-itt-30apr2012-02.sas (04MAY2012)

**Table 8 Sponsor’s Analysis of Remission Rates – All Randomized Patients with Normal Histology at Baseline – Protocol CB-01-02/02**

	Placebo N=33 n (%)	MMX 9 mg N=12 n (%)	MMX 6 mg N=16 n (%)	Entocort N=16 n (%)	Total N=77 n (%)
Remission Status					
Yes	13 (39.4)	3 (25.0)	7 (43.8)	5 (31.3)	28 (36.4)
No	20 (60.6)	9 (75.0)	9 (56.3)	11 (68.8)	49 (63.6)
95% CI for Remission Rate (%)	(22.7,56.1)	(0.5,49.5)	(19.4,68.1)	(8.5,54.0)	(25.6,47.1)
Difference between Active and Placebo		-14.4	4.4	-8.1	
95% CI for the Difference in Rates		(-44.0,15.2)	(-25.1,33.8)	(-36.3,20.0)	
P-value		0.3724*	0.7711*	0.5792*	

Note: Remission is defined as a UCDAI score of  $\leq 1$  with a score of 0 for both rectal bleeding and stool frequency, a  $\geq 1$ -point reduction in Endoscopic Index score and no evidence of mucosal friability as determined by endoscopy.

All patients for whom remission status could not be calculated because of missing data were considered as not having achieved remission.

\* P-values are based on the Chi-square test.

The denominators for calculating percentages are the numbers of randomized patients with normal histology at baseline in each treatment group or the total number of patients.

All confidence intervals are computed based on the normal approximation.

Program: FDA Requests\lcr-itt-30apr2012-02.sas (04MAY2012)

**Table 9 Rate of Clinical Remission for All Randomized Patients with GCP violations by Baseline Histology Status by Site**

**Rate of Clinical Remission for All Randomized Patients with GCP Violations  
by Baseline Histology Status by Site  
Study CB-01-02/02**

Site	Country	Baseline Histology	MMX 9 mg	Placebo	MMX 9 mg vs. Placebo p-value
1040	Italy	abnormal	0/2 (0.0%)	0/3 (0.0%)	
		normal	0/1 (0.0%)	0/1 (0.0%)	
		Total	0/3 (0.0%)	0/4 (0.0%)	
1082	Slovakia	abnormal		0/1 (0.0%)	
		normal	1/1 (100.0%)	1/2 (50.0%)	
		Total	1/1 (100.0%)	1/3 (33.0%)	
1106	Russia	abnormal	0/1 (0.0%)		
		normal		4/4 (100.0%)	
		Total	0/1 (0.0%)	4/4 (100.0%)	
1122	Slovakia	abnormal	1/2 (50.0%)	1/3 (33.3%)	
		normal	1/3 (33.3%)	3/6 (50.0%)	
		Total	1/5 (20.0%)	4/9 (44.4%)	
Total		abnormal	0/5 (0.0%)	1/7 (14.3%)	1.0000
		normal	2/5 (40.0%)	8/13 (61.5%)	0.6078
		Total	2/10 (20.0%)	9/20 (45.0%)	0.2465

p-value was obtained by Fisher's exact test

All randomized patients who received at least one dose a study drug were included.

**Appendix A Meeting Minutes for teleconference 4/13/10**



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type C  
**Meeting Category:** Other

**Meeting Date and Time:** April 13, 2010; 4:00 to 5:00 p.m. EDT  
**Meeting Location:** Teleconference

**Application Number:** IND 074882  
**Product Name:** Budesonide MMX Extended Release Tablets  
**Indication:** Induction of remission in patients with mild to moderate ulcerative colitis and prevention of relapse

**Sponsor/Applicant Name:** Santarus, Inc.

**Meeting Chair:** John Hyde, Ph.D., M.D., Medical Team Leader  
**Meeting Recorder:** Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager

**FDA ATTENDEES**

Donna Griebel, M.D., Director, Division of Gastroenterology Products (DGP)  
John Hyde, Ph.D., M.D., Medical Team Leader, DGP  
Zana Marks, M.D., M.P.H., Medical Reviewer, DGP  
Mike Welch, Ph.D., Deputy Director, Division of Biometrics III  
Milton Fan, Ph.D., Statistical Reviewer, Division of Biometrics III  
Roland Girardet, M.H.S., M.S., M.B.A., Regulatory Project Manager, DGP

**SPONSOR ATTENDEES**

**Santarus, Inc.**

Gerald Proehl, Chief Executive Officer  
E. David Ballard II, M.D., Sr. V.P., Clinical Research and Medical Affairs  
Maria Bedoya-Toro, Ph.D., M.B.A., V.P., Regulatory Affairs and Quality Assurance  
Robert Bagin, Ph.D., Sr. Director, Biostatistics and Data Management  
Kristin Koch, M.D., Sr. Medical Director, Clinical Research  
Joanne Peake, Sr. Director, Clinical Development  
Theres Gautille, R.N., Sr. Manager, Clinical Development  
Arley David Mundt, Sr. Manager, Statistical Programming and Data Management  
Giles Hulley, Sr. Manager, Regulatory Affairs

## 1. BACKGROUND

On February 17, 2010, Santarus requested a Type A meeting to discuss the statistical analysis plans (SAPs) for U.S. study protocol CB-01-02/01 and E.U. study protocol CB-01-02/02 submitted to IND 074882 on January 27, 2010. After reviewing the meeting request, it was determined that the statement of purpose, objectives, and proposed agenda outlined in the meeting request were more consistent with the criteria for a Type C meeting. Therefore on March 3, 2010 a Type C meeting was granted. Santarus submitted a briefing package on March 5, 2010, which was received by the FDA on March 8, 2010.

On April 2, 2010, the FDA requested an update on the status of enrollment of both Phase 3 studies. On April 6, 2010, and April 8, 2010, Santarus provided updated information on study enrollment, which indicated that enrollment in the U.S. study (CB-01-02/01) was anticipated to be complete by June, 2010, and that enrollment in the European study (CB-01-02/02) was completed in February, 2010.

The FDA communicated preliminary comments to Santarus on April 9, 2010.

In response to the Additional FDA Comments located at the end of the FDA preliminary comments, Santarus sent via email on April 12, 2010, a copy of a protocol titled, "*Randomized, Double-Blind, Multi-Centre, 12 Month Extension Study to Evaluate the Safety and Efficacy of Daily Budesonide MMX 6 mg vs. Placebo in the Maintenance or Remission in Subjects with Ulcerative Colitis,*" which had previously been submitted to IND 074882 on August 12, 2009.

On April 13, 2010, Santarus sent via email a PowerPoint presentation (Attachment 1) and a one page excerpt from the Clinical Review of Lialda (Attachment 2).

The teleconference took place on April 13, 2010.

## 2. DISCUSSION

(Questions in the briefing package are shown in plain font. The FDA's preliminary responses are shown in **boldface**. Discussion at the meeting is show in ***bold italics.***)

1. Does FDA agree with the statistical methodologies proposed within the SAPs for U.S. Study Protocol CB-01-02/01 and E.U. Study Protocol CB-01-02/02? The two SAPs are identical regarding the statistical methodology.

### FDA Response:

**We strongly discourage any changes in the primary endpoint analysis once the study is underway. 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. Your newly proposed primary endpoint analysis will be viewed as supportive only.**

**We have the following additional concerns about your proposed analysis population and hierarchical testing approach.**

- A. Your Full Analysis Set (FAS) population is not a “true” Intent-to-Treat (ITT) population, which is defined as including all randomized subjects. The FAS population is commonly defined as a modified ITT (mITT) population.**

**Analysis based on the “true” ITT population should be considered as the primary analysis. Analysis based on the mITT population should be considered as sensitivity analysis.**

**Meeting Discussion**

*Santarus stated that after reviewing the FDA’s preliminary comments they would use the original primary endpoint.*

*Santarus stated that they are committed to maintaining the blinding of the data until the data lock date and that they have measures in place to ensure the data clean-up activities do not influence the clinical results. Further, Santarus stated they would include documentation in their NDA submission of the measures used to maintain blinding.*

*Santarus stated that they understood the definition of the ITT as described in the FDA’s preliminary comments.*

*Santarus proposed to exclude non-GPC compliant patients from the FAS and to include them in a sensitivity analysis as non-responders.*

*The FDA disagreed with Santarus’s proposal to exclude non-GCP compliant patients from the ITT and stated that all randomized patients should be included in the primary analysis. The FDA further stated that the issue of non-GCP compliance would be taken into account during the review of the NDA. The FDA commented that it was not prepared to commit to having any particular alternative analysis serve as the basis for a regulatory action without fully reviewing the data. The FDA stated that Santarus may include alternative analyses, along with rationale to support them, with their NDA submission, and these would be taken into consideration during the review process.*

*Santarus noted that in the Lialda Clinical Review, a group of non-GCP compliant subjects was removed from the primary analysis. The FDA stated that it was not able to provide comment on the excerpt from the Lialda review without a full understanding of the context in which the non-GCP compliant patients were removed. Since the full Lialda review had not been submitted as part of the original background package, the*

*FDA was not able to comment on the applicability of this portion of the review to Santarus's proposal.*

*Santarus stated that they understood the FDA's position of not excluding non-GCP compliant patients from the ITT population and that they would include justification for any alternative analyses presented in their NDA submission.*

- B. In your proposed hierarchical testing model, the 6 mg dose will be compared with placebo with respect to the primary endpoint only if the 9 mg dose is statistically significant at the  $p = 0.05$  level of significance for the primary endpoint and the secondary endpoints, clinical improvement and endoscopic improvement. Using this procedure might limit your opportunity to show the efficacy of the 6 mg dose.**

*A more appropriate approach for regulatory purposes would be to first test the primary endpoint for each dose. For your primary analysis, you should use your originally planned procedure to test the primary endpoint for each dose (9 mg and 6 mg) against placebo first. If at least one dose shows efficacy for the primary endpoint, the secondary endpoints can then be tested.*

#### *Meeting Discussion*

*Santarus proposed to use a sequential testing procedure in which the 9 mg strength would first be tested against placebo at an alpha of .05 for the primary endpoint. If the results from this test were found to be statistically significant in favor of the drug, then the 6 mg strength would be tested against placebo at an alpha of .05. If the results from both strengths were found to be statistically significant, the secondary efficacy endpoints would then be tested.*

*The FDA stated that when changes of this nature are proposed so late in the study enrollment, it raises concerns of introducing bias, even when the blind is maintained. As a result, the FDA strongly recommended that Santarus revert to the originally proposed testing method. The FDA further stated that if alternative testing methods are presented with the NDA submission, this information would be taken into account; however, any new testing methods presented would be a review issue. The FDA stated that documentation of the procedures used to maintain blinding should also be submitted along with any new analyses.*

*The FDA asked why Santarus was proposing to change their testing procedure. Santarus explained that early in development, they thought the 9 mg was likely to be the most effective dose; however, they had added the 6 mg dose based on feedback they had received from the FDA, which had been communicated in the form of a response to a special protocol assessment request. Since Santarus believed the 9 mg was the most effective dose, they wanted to use a testing method that was the most likely to detect a difference in the 9 mg dose.*

*Santarus stated that they understood the FDA's request to use the original testing procedure and would submit justification for any additional procedures used in their NDA submission.*

2. Does FDA agree that the Fisher's Exact Test and exact confidence intervals (and not the Pearson Chi-Square Test) should be used when comparing remission rates between active and placebo?

**FDA Response:**

**The Fisher's Exact Test and exact confidence intervals are appropriate methods for analyzing binary data.**

**Meeting Discussion**

*No discussion.*

3. Does FDA agree with the proposed method for defining the Full Analysis Set (FAS) as described in Section 4.2.2?

[Redacted] (b) (4)

**FDA Response:**

**No, we do not agree. Please see our response to Question 1 regarding your FAS analysis.**

**Patients**

[Redacted] (b) (4). **Otherwise, study bias might occur due to potential baseline imbalance. Your proposed FAS can be presented as exploratory analyses.**

**Meeting Discussion**

*Santarus stated that there were some discrepancies between patient diaries and investigator assessments in the values for rectal bleeding and stool frequency. In order to reconcile these differences, Santarus proposed* [Redacted] (b) (4)

*The FDA requested that Santarus include analyses using both sets of values as well as the reasons for the differences in their NDA submission. In addition, Santarus should include justification for what they thought was the appropriate analysis.*

*Santarus asked if they could submit the proposed analyses for FDA comment before the data lock date. The FDA stated that it could not commit to reviewing this information before the data lock date but that it would make a good faith effort to do so.*

**ADDITIONAL FDA COMMENTS:**

**As discussed during the meeting held on March 7, 2008, we request that your initial NDA include information regarding the chronic treatment of ulcerative colitis (UC) using your product. UC is a chronic disease. Clinical data evaluating the safety and efficacy of the use of the product as intended for the chronic management of this disease is needed to support writing adequate instructions for use. As we clarified at that meeting, this does not mean that continuous therapy needs to be studied; episodic re-treatment for flairs might be the appropriate use of the drug. We strongly recommended that your development program include an evaluation of the use of your product in the chronic management of UC. Please clarify your plans for obtaining such information.**

**Meeting Discussion:**  
***No discussion***

**3. ATTACHMENTS AND HANDOUTS**

Attachment 1 - PowerPoint Slides  
Attachment 2 - Excerpt from the Lialda Clinical Review

**Appendix B Meeting Minutes for Pre-NDA Meeting 5/31/11**

APPEARS THIS WAY ON ORIGINAL

### MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** May 31, 2011  
**Meeting Location:** 10903 New Hampshire Avenue, White Oak Building 22,  
Conference Room 1315, Silver Spring, MD 20903

**Application Number:** IND 074882  
**Product Name:** Budesonide MMX Extended Release Tablets  
**Indication:** Treatment of, and induction of remission in, patients with active mild to moderate ulcerative colitis  
**Sponsor/Applicant Name:** Santarus, Inc

**Meeting Chair:** Donna Griebel, M.D.  
**Meeting Recorder:** Kevin Bugin, M.S., R.A.C.

#### FDA ATTENDEES

Donna Griebel, M.D. Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)  
Joyce Korvick, M.D., M.P.H. Deputy Director, DGIEP  
Anil Rajpal, M.D., Medical Team Leader, DGIEP  
Aisha Peterson Johnson, M.D., MPH, MBA, Medical Officer, DGIEP  
Sue Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Office of Translational Sciences  
Dilara Jappal, Ph.D., Clinical Pharmacology Reviewer, OTS  
Sushanta Chakder, Ph.D., Nonclinical Team Leader, DGIEP  
Sruthi King, Ph.D., Nonclinical Reviewer, DGIEP  
Mike Welch, Ph.D., Biometrics Team Leader, Office of Translational Sciences  
Wen Jen Chen, Ph.D., Biometrics Reviewer, Office of Translational Sciences  
Kevin Bugin, M.S., R.A.C., Regulatory Health Project Manager, DGIEP  
Valerie Gooding, Division of Regulatory Review Support, electronic Submission Support Team

#### SPONSOR ATTENDEES

Bob Bagin, Ph.D., Senior Director, Biostatistics and Data Management, Santarus, Inc.  
Maria Bedoya-Toro, Ph.D., M.B.A., Senior Vice President, RA & QA, Santarus, Inc.  
E. David Ballard II, M.D., Senior Vice President, Med. Affairs & Pharmacovig., Santarus, Inc.  
(b) (4) Regulatory Consultant

(b) (4)

Michael Huang, M.D., Medical Director, Clinical Research, Santarus, Inc.

(b) (4) Drug Development Consultant

(b) (4) Clinical and Regulatory Consultant, (b) (4)

Matthew Moran, Senior Director, Regulatory Affairs, Santarus, Inc.

(b) (4) Chief Scientific Officer and R&D Director, (b) (4)

Gerald Proehl, President & Chief Executive Officer, Santarus, Inc.

(b) (4) Clinical Consultant, (b) (4)

(b) (4) Clinical Consultant, (b) (4)

## 1.0 BACKGROUND

On March 28, 2011, Santarus, Inc requested a meeting with the Agency to discuss the submission of a new NDA to the Division of Gastroenterology and Inborn Errors Products for Budesonide MMX extended release tablets for the treatment of, and induction of remission in, patients with active mild to moderate ulcerative colitis.

The key objectives of the meeting were to reach and capture agreements related to the results from the two Phase III, Multicentre, Randomized, Double-Blind, Double Dummy, Placebo-Controlled, Studies (U.S. Study CB-01-02/01 and E.U. Study CB-0102/02) and the companion study CB-01-02/06; the analysis plans for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS); and Santarus's proposal to submit the data from Study CB-01-02/04 (12 month extension study evaluating safety and efficacy of maintenance therapy with budesonide MMX 6 mg) (b) (4) the Original NDA submission.

The meeting took place as scheduled on May 31, 2011 and the following minutes reflect the agreements and discussion of that meeting.

## 2. DISCUSSION

[The Sponsor's original questions are in plain font. The Division's preliminary comments is in **Bold** font and discussion from the meeting is in ***Bold italics***. Where available, the Sponsor's response to Agency preliminary comments is also in ***Bold italics***.]

### *Medical*

Question 1: It is Santarus' opinion that the two Phase III, Multicentre, Randomized, Double-Blind, Double Dummy, Placebo-Controlled, Studies (U.S. Study CB-01-02/01 and E.U. Study CB-01-02/02) provide substantial evidence for the safety, efficacy and clinical benefit of budesonide MMX in the induction of remission in patients with active mild to moderate ulcerative colitis. Santarus believes that the results from these studies are adequate for filing and review in a NDA. Does the agency agree?

### **FDA Response:**

**The final determination on the adequacy of an NDA for filing will be determined at the time of filing. Whether the two studies (U.S. Study CB-01-02/01 and E.U. Study CB-01-02/02) provide substantial evidence for the safety, efficacy, and clinical benefit of**

**budesonide MMX in the induction of remission in patients with active mild to moderate ulcerative colitis will be determined during the review period.**

**Discussion:**

*No further discussion.*

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Question 1a: The analyses of efficacy for the two pivotal studies were conducted in the prospectively defined ITT population according to the SAPs dated July 15, 2010. Additional post hoc sensitivity analyses included all randomized patients who received at least one dose of study drug, but those who had major entry criteria violations, GCP violations, or normal histology at baseline were analyzed as non-remitters. Analyses of efficacy in the ITT population as defined in the SAP dated July 15, 2010 and the supportive sensitivity analyses will be presented in the clinical study reports (CSRs) and ISE. Does the agency agree?

**FDA Response:**

**We understand that you are planning to exclude 50 patients from your ITT analysis due to GCP violations and have read your rationale. Be advised that this is a review issue and as discussed in the April 13, 2010 meeting, we will consider the true ITT population as the primary analysis population. Furthermore, at this time we can not commit to having any alternative analysis serve as the basis for regulatory action without fully reviewing all the data.**

**Also, see additional comments below.**

**Santarus Response:**

*Santarus understands FDA's response regarding patients with GCP violations. However, FDA was silent on the issue of excluding patients with normal histology. Santarus would like to briefly present the medical rationale behind the exclusion of patients with normal histology and gain an understanding of FDA's thinking with regard to this issue.*

*Could the Agency clarify its position on the exclusion of patients with normal histology at baseline?*

**Discussion:**

*The Agency will review all of the data and will consider the proposed population (excluding patients with normal histology) in its determination of efficacy. This remains a review issue. The primary analysis population will remain the true ITT population.*

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*Medical/Biometrics*

Question 2: The ISE will include efficacy data from all patients from completed Phase II and III studies in the budesonide MMX clinical development program. Specifically, data from the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) will be combined and analyzed. Data

from the Companion Study (CB-01-02/06) and the two Phase II studies (CB-01-02/05 and CRO-03-53) will be also be summarized and discussed in the ISE. Does the agency agree?

**FDA Response:**

**Your proposed ISE analysis plan appears to be acceptable and will be assessed during the review process. However, the data from the individual studies as analyzed in the clinical study reports are the main focus of review as these provide the basis for demonstration of efficacy. Results based on the ISE analyses are largely exploratory and not supportive for labeling purposes.**

**Discussion:**

***No further discussion.***

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Question 3: For the ISS, the following three analyses are planned:

First, a combined analysis of the data from the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02) will follow the analyses of all safety endpoints as specified in the SAP for both studies. Second, a combined analysis of the data from all completed Phase II and III studies from the budesonide MMX clinical development studies including the two pivotal Phase III studies (CB-01-02/01 and CB-01-02/02), the Companion study (CB-01-02/06), and the two Phase II studies (CB-01-02/05 and Cro-03-53) will evaluate safety by dosage strength and by duration of treatment. Third, a combined analysis of the three Phase I studies (CR-01-28, CROPK-06-178 and CROPK03105) will evaluate AEs, SAEs, physical examination results and laboratory results. Does the agency agree?

**FDA Response:**

**Your proposal for the ISS appears reasonable.**

**Discussion:**

***No further discussion.***

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Question 4: Santarus proposes to submit the data from the currently ongoing Extension Study CB-01-02/04 as part of [REDACTED] <sup>(b) (4)</sup> the Original NDA submission. Does the agency agree?

**FDA Response:**

**All efficacy and safety data for labeling consideration must be submitted at the time of original NDA submission.**

**Santarus Response:**

***Santarus is currently seeking an induction of remission label claim for the 9 mg dose***

- ***Santarus*** [REDACTED] <sup>(b) (4)</sup>

- *The emphasis of the data from the 12 month extension study will be on safety*

*Therefore, we would like to understand the rationale for the request to submit the data from the extension study at the time of the original NDA, [REDACTED] (b) (4), [REDACTED]. Can the Agency please clarify?*

**Discussion:**

*The Agency reiterated that we need to have any efficacy data with the original NDA submission for consideration of efficacy. The Agency also requests that the results of the 12-month extension study be included in the original NDA submission.*

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Question 5: Because the programming for the study reports for all studies and for the integrated summaries were conducted using SAS 99 compliant datasets, it is our intention to submit the CRF data and all analysis datasets in SAS 99 compliant format. It is also our intention to submit SDTM datasets for the four Phase III studies. Does the Agency agree?

**FDA Response:**

**It is not clear what you mean by “SAS 99 compliant.” Data sets must be submitted in the SAS XPORT Transport Format which is an open (non proprietary) format. Refer to the Study Data Specifications document for additional information provided at: <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>.**

**We recommend that you provide the following full case report tabulation (CRT) for each adequate and well-controlled clinical study (per 21 CFR 314.126) you plan to include in your NDA/BLA submission:**

- 1. All clean/locked clinical data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, along with the annotated case report form (aCRF) and a thorough data definition file. We recommend that the electronic datasets, aCRF, and data definition file fully comply with the latest CDISC/SDTM, CDISC/CDASH, and CDISC/Define.XML standards respectively.**

**Discussion:**

*No further discussion.*

- 2. All corresponding analysis data presented in electronic datasets, submitted utilizing SAS Version 5 Transport, should be submitted along with a thorough data definition file. We recommend that these electronic datasets fully incorporate the modeling approaches described by both the latest CDISC/ADaM standard and the FDA Study Data Specifications document, cited above. We recommend that the data definition file fully comply with the latest CDISC/Define.XML standard.**

**Discussion:**

*No further discussion.*

3. A well commented and organized software program written for each analysis dataset and efficacy table created.

**Discussion:**

*No further discussion.*

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**Additional FDA Comments:**

1. Please refer to our statistics comments from the April 13, 2010 meeting. The issues discussed during that meeting are considered review issues and will be assessed.

**Discussion:**

*No further discussion.*

2. Your proposed Type I error control stated in section 9.5 (“Efficacy Analysis”) of the protocol for the two pivotal studies (CB-01-02/01 and CB-01-02/02) is not clear. We recommend the significance level of 2.5% for the primary and secondary endpoints analyses be applied as a two-sided testing procedure because for each endpoint there are two study drug doses being compared with placebo.

**Discussion:**

*No further discussion.*

3. We recommend that you conduct an *in-vitro* study to evaluate whether budesonide is a substrate, inhibitor, or inducer of transporters. [Please refer to Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling, *DRAFT GUIDANCE*.]

**Santarus Response:**

*The effects of budesonide on p-gp transporters has already been investigated in-vitro in the literature. Santarus intends to submit the NDA as a 505(b)(2) application, referencing this budesonide literature. Based on this filing strategy, and the safety profile of budesonide, Santarus believes this additional study is unnecessary. Does the Agency concur?*

**Discussion:**

*Acceptability of literature to support the lack of an in vitro study to evaluate the effects of budesonide as a substrate, inhibitor or inducer of transporters will be a review issue.*

4. Please evaluate the effect of alcohol dose dumping on Budesonide MMX Extended Release Tablets.

*Santarus Response:*

*The budesonide MMX technology is similar to the technology utilized in Lialda® for UC. Unlike other delayed-release steroid formulations, which have only a pH-sensitive coating as a rate-limiting step for drug release, budesonide MMX also has the multi-matrix structure which is responsible for the extended release profile of the tablet. Even upon sudden dissolution of the coating, the multi-matrix structure ensures a slow, homogeneous release of drug over time. We are unaware of any safety signals related to this technology. Santarus would like to understand the Agency's rationale behind this request.*

*Discussion:*

*Alcohol dose dumping studies are required for all delayed release products. Santarus will provide dissolution data in the CMC sections of the NDA submission to support a justification for lack of dose dumping studies. Depending on the results of the in vitro studies, an in vivo study may be necessary*

5. We note that two of the Phase-1 studies (CRO-01-28 and CRO-PK-03-105) were conducted with only male healthy subjects, and only one Phase 1 study with single dose (CRP-PK-06-178) included both male and female healthy subjects in the study. If we observe PK differences due to gender in this single-dose study, we may ask for additional data (e.g., multiple dose and food effect studies) that include both male and female subjects.

*Discussion:*

*No further discussion.*

6. CDER's preferred electronic format for submitting a new application is eCTD format. Please refer to Guidance for Industry, Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. If this is your first eCTD submission, it is recommended that a sample eCTD be completed prior to submitting an actual submission, please refer to the eCTD Sample Web page or contact ESUB (esub@fda.hhs.gov) for more information."

*Discussion:*

*No further discussion.*

7. We note you refer to the Special Protocol Assessments (SPAs) for protocols CB-01-02/01 and CB-01-02/02; we remind you that no formal agreement was reached on these protocols following the Agency's comments sent on January 28, 2008. Please

refer to **Guidance for Industry-Special Protocol Assessment for further information** (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080571.pdf>).

**Santarus Response:**

*To address FDA's comments from January 28, 2008, the Sponsor requested a Type A Meeting which was held on March 7, 2008. Please see memorandum of meeting minutes dated April 4, 2008 (included in the pre-NDA meeting briefing package).*

**Discussion:**

*There were agreements in response to specific questions throughout the SPA review process and the April 04, 2008 meeting. These agreements are still valid. The Agency simply points out that no SPA agreement on the Protocol as a whole was reached.*

**3. ATTACHMENTS AND HANDOUTS**

Santarus, Inc slide presentation attached.

## Appendix C: Timeline for Change of Sponsor's ITT Population

11/30/07 IND 74,882 S/N 0001 Special Protocol Assessment for 02/01 and 02/02

- ITT – include all randomized patients with at least one dose administered and with at least a post-baseline efficacy assessment

4/13/10 IND 74,882 Teleconference Minutes to seek agreement on the proposed UCDAI calculation and the proposed Full Analysis Set

- Use original definition as specified in the protocol
  - Proposed to exclude from the FAS patients that were not compliant with Good Clinical Practice; these patients will be included in a sensitivity analysis as responders
  - Observed that 3 of Eastern European Sites had reported unusually high Remission Rate (67%-73% vs. 9.2% for Western Europe)
  - Expand the histological evaluation to all patients enrolled in the studies.
  - Proposed to remove these patients from the FAS
1. Does FDA agree with the statistical methodologies proposed within the SAPs for U.S. Study Protocol CB-01-02/01 and E.U. Study Protocol CB-01-02/02? The two SAPs are identical regarding the statistical methodology.

### **FDA Response:**

**We strongly discourage any changes in the primary endpoint analysis once the study is underway. 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. Your newly proposed primary endpoint analysis will be viewed as supportive only.**

**We have the following additional concerns about your proposed analysis population and hierarchical testing approach.**

- A. Your Full Analysis Set (FAS) population is not a “true” Intent-to-Treat (ITT) population, which is defined as including all randomized subjects. The FAS population is commonly defined as a modified ITT (mITT) population.**

**Analysis based on the “true” ITT population should be considered as the primary analysis. Analysis based on the mITT population should be considered as sensitivity analysis.**

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Analysis based on the “true” ITT population should be considered as the primary analysis. Analysis based on the mITT population should be considered as sensitivity analysis.

Meeting Discussion

*Santarus stated that after reviewing the FDA’s preliminary comments they would use the original primary endpoint.*

*Santarus stated that they are committed to maintaining the blinding of the data until the data lock date and that they have measures in place to ensure the data clean-up activities do not influence the clinical results. Further, Santarus stated they would include documentation in their NDA submission of the measures used to maintain blinding.*

*Santarus stated that they understood the definition of the ITT as described in the FDA’s preliminary comments.*

Meeting Discussion

*Santarus stated that after reviewing the FDA's preliminary comments they would use the original primary endpoint.*

*Santarus stated that they are committed to maintaining the blinding of the data until the data lock date and that they have measures in place to ensure the data clean-up activities do not influence the clinical results. Further, Santarus stated they would include documentation in their NDA submission of the measures used to maintain blinding.*

*Santarus stated that they understood the definition of the ITT as described in the FDA's preliminary comments.*

*Santarus proposed to exclude non-GPC compliant patients from the FAS and to include them in a sensitivity analysis as non-responders.*

*The FDA disagreed with Santarus's proposal to exclude non-GCP compliant patients from the ITT and stated that all randomized patients should be included in the primary analysis. The FDA further stated that the issue of non-GCP compliance would be taken into account during the review of the NDA. The FDA commented that it was not prepared to commit to having any particular alternative analysis serve as the basis for a regulatory action without fully reviewing the data. The FDA stated that Santarus may include alternative analyses, along with rationale to support them, with their NDA submission, and these would be taken into consideration during the review process.*

*Santarus stated that they understood the FDA's position of not excluding non-GCP compliant patients from the ITT population and that they would include justification for any alternative analyses presented in their NDA submission.*

7/15/10 IND 74,882 Revised Statistical Analysis Plan (SAP) for Studies 02/01 and 02/02

7/19/10 IND 74,882 S/N 0055 Revised SAP for 02/01 and 02/02 dated July 15, 2010

- It stated that

#### **4.2 Analysis Populations**

The following analysis populations are defined.

##### **4.2.1 Randomized Set**

The Randomized Set (RS) is defined as all patients who are randomized into the study.

##### **4.2.2 Intent-to-Treat Population**

The Intent-to-Treat (ITT) population is the primary population for the analysis of all efficacy endpoints. The ITT population is defined as all randomized patients who received at least one dose of a study drug and who had no GCP or major entry criteria violations (e.g., a *C. difficile* infection during Screening) or normal histology at Baseline as determined by biopsy. These exclusions are consistent with ICH E9 and the Statistical and Medical reviews for Lialda, Attachments 1 – 3).

##### **4.8.2 Primary Endpoint**

The percentage of patients achieving clinical remission in both the 9 mg and 6 mg Budesonide-MMX groups will be compared with the percentage of placebo patients achieving clinical remission using the Chi-square test at the  $\alpha=0.025$  level of significance.

If at least one of the primary endpoint comparisons is statistically significant, an exploratory analysis will be conducted in the ITT population comparing remission rates between Budesonide-MMX and placebo, adjusting for region: Canada, United States (and Mexico) and India, using the Cochran Mantel-Haenszel test. Additional exploratory analyses for the ITT population will investigate the effects of the following variables on the primary endpoint using the Cochran Mantel-Haenszel test:

- Age ( $\leq$  median age at randomization,  $>$  median age at randomization)
- Sex
- In the telecom dated 4/13/10, it was stated that the "true" ITT analysis should be considered as the primary efficacy analysis.
- The SAP did not state which analysis (randomized or ITT) is the primary efficacy analysis. At the time I reviewed the revised SAP, I assumed that the primary analysis should be based on randomized population. So, this reviewer did not make comments on the study population.

5/7/11 IND 74,882 Slide Presentation for 02/02 Study Results

- Modified ITT excluded 101 patients (50 for GCP violation, 48 for normal histology at baseline, 1 for major entry criteria violation and 2 not randomized through IVRS)

5/31/11 IND 74,882 Discuss the submission of a new NDA for Budesonide

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Question 1a: The analyses of efficacy for the two pivotal studies were conducted in the prospectively defined ITT population according to the SAPs dated July 15, 2010. Additional post hoc sensitivity analyses included all randomized patients who received at least one dose of study drug, but those who had major entry criteria violations, GCP violations, or normal histology at baseline were analyzed as non-remitters. Analyses of efficacy in the ITT population as defined in the SAP dated July 15, 2010 and the supportive sensitivity analyses will be presented in the clinical study reports (CSRs) and ISE. Does the agency agree?

**FDA Response:**

**We understand that you are planning to exclude 50 patients from your ITT analysis due to GCP violations and have read your rationale. Be advised that this is a review issue and as discussed in the April 13, 2010 meeting, we will consider the true ITT population as the primary analysis population. Furthermore, at this time we can not commit to having any alternative analysis serve as the basis for regulatory action without fully reviewing all the data.**

**Also, see additional comments below.**

**Santarus Response:**

***Santarus understands FDA's response regarding patients with GCP violations. However, FDA was silent on the issue of excluding patients with normal histology. Santarus would like to briefly present the medical rationale behind the exclusion of patients with normal histology and gain an understanding of FDA's thinking with regard to this issue.***

***Could the Agency clarify its position on the exclusion of patients with normal histology at baseline?***

**Discussion:**

***The Agency will review all of the data and will consider the proposed population (excluding patients with normal histology) in its determination of efficacy. This remains a review issue. The primary analysis population will remain the true ITT population.***

## Appendix D: Sponsor's Timeline for Studies CB-01-02/01 and CB-01-02/02

	CB-01-02-01	CB-01-02-02
Protocol		
Original Protocol	18 Mar 2008	18 Mar 2008
Amendment 1	27 May 2009	
Statistical Analysis Plan	18 Jan 2010 (version) 22 Jan 2010 (signed) 15 Jul 2010 (version) 16 Jul 2010 (signed)	18 Jan 2010 (version) 22 Jan 2010 (signed) 15 Jul 2010 (version) 16 Jul 2010 (signed)
Date of First Patient Enrollment	20 Aug 2008	24 Jul 2008
Date of Last Patient Enrollment	23 Mar 2010	24 Nov 2009
Date of Database Lock	23 Sep 2010	04 Nov 2010

## Appendix E: Timeline of Activities Leading to Revision of the Statistical Analysis Plan (SAP)

Date	Event
November 29, 2007	Original IND 74,882 submitted by Cosmo Technologies Ltd. (Cosmo)
March 7, 2008	Type A Meeting between Cosmo and FDA regarding Special Protocol Assessment (SPA)
March 18, 2008	Study protocol finalized
July 24, 2008	First patient in (FPI) for CB-01-02/02
August 1, 2008	European Medicines Agency (EMA) released Guideline on the development of new medicinal products for the treatment of ulcerative colitis
February 6, 2009	Transfer of IND sponsorship from Cosmo to Santarus, Inc. (Santarus)
November 24, 2009	Last patient in (LPI)
December 1, 2009	<p>Cosmo/Santarus review mucosal biopsy results in blinded fashion after approximately half of specimens have been analyzed. Number of mucosal biopsies analyzed: 292 (56.8% of randomized patients).</p> <ul style="list-style-type: none"> <li>• Typical turnaround time from randomization to biopsy report: 3.5 to 6 months. (specimens were reviewed in batches by blinded, central laboratory)</li> <li>• A few sites were noted to have unusually large number of patients with normal histology (i.e., no histological evidence of active ulcerative colitis [UC])</li> </ul>
December 2, 2009	Cosmo/Santarus present concerns regarding normal histology results from blinded database to Lead Investigator of CB-01-02/02, Simon Travis <sup>1</sup> . Dr. Travis recommended using biopsy results from screening to ascertain active UC status, a position supported by EMA guidelines. Dr. Travis, in conjunction with EMA guidelines, recommended removal of patients with no histological evidence of active UC from efficacy analysis population.
January 27, 2010	Proposed Statistical Analysis Plan (SAP) excluding patients with normal histology at screening and critical GCP violations submitted to FDA
February 13, 2010	Last patient out (LPO)
February 17, 2010	Santarus requested Type A Meeting to discuss proposed SAP
April 13, 2010	Type C Meeting Teleconference with FDA to discuss revised SAP to exclude patients with normal histology at screening and patients with critical GCP violations
May-June 2010	Seven GCP audits conducted at various sites in Europe
July 28, 2010	Meeting held between Sponsor and ICON and decision made to exclude efficacy data primary analysis population from three sites (1082, 1122, and 1106) for critical GCP violations
June-October 2010	Twenty-eight assessment and/or re-monitoring visits conducted at various sites in Europe
July 16, 2010	Finalized SAP submitted to FDA
October 26, 2010	Classification meeting held and decision made to also exclude the efficacy data from primary analysis population from site 1040 (in addition to sites 1082, 1122, and 1106) for critical GCP violations
October 28, 2010	Database lock

Date	Event
October 29, 2010	Un-blinding of the data
November 3, 2010	Database un-locked to make a single correction to a randomization number and to add the treatment group for two subjects randomized outside the IVRS
November 4, 2010	Second Database Lock
<p><sup>1</sup> Simon Travis, MD, was the lead investigator for Study CB-01-02/02, and a (b) (4) (b) (4) He is President of the European Crohn's and Colitis Organisation (ECCO) for 2012-14, is an elected Member of International Organisation of Inflammatory Bowel Disease, and author of 11 peer-reviewed international guidelines.</p>	

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/s/  
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MILTON C FAN  
12/21/2012

MICHAEL E WELCH  
12/21/2012

Do not concur with reviewer's overall conclusion.  
See TL review memo.

# STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

**NDA/BLA Number:**203-634     **Applicant:** Santarus, Inc  
**Drug Name:**Uceris                     **NDA/BLA Type:** Efficacy

**Stamp Date:** 12/14/11  
**Indication:** induction of remission in patients with active, mild to moderate ulcerative colitis

On **initial** overview of the NDA/BLA application for RTF:

	<b>Content Parameter for RTF</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comments</b>
1A	Paper Submission: Index is sufficient to locate necessary reports, tables, data, etc.			<b>X</b>	Electronic submission
1B	Electronic Submission: Indexing and reference links within the electronic submission are sufficient to permit navigation through the submission, including access to reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Efficacy was investigated for gender, racial, and geriatric subgroups investigated.	X			Pooled analyses ≤60 vs. >60, no racial No subgroup analyses for CB-01-02/04
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			No index of data definition tables

**IS THE STATISTICAL SECTION OF THE APPLICATION IS FILEABLE ?** Yes

<b>Content Parameter (possible review concerns for 74-day letter)</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No efficacy interim analysis planned.
Appropriate references for novel statistical methodology (if present) are included.		X		
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			Included OC

## Background

Santarus, Inc. submitted this original NDA for budesonide 9 mg tablet as an orally administered treatment for induction of remission in patients with active, mild to moderate ulcerative colitis pursuant to the requirement of section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 CFR 314 and supporting FDA guidelines.

Budesonide MMX 9 mg tablets is an enteric coated, extended release, oral dosage formulation designed for the induction of remission in adult patients with active, mild to moderate ulcerative colitis (UC). UC is a chronic, relapsing/remitting inflammatory bowel disease (IBD) involving the colorectal mucosa. To provide an enhanced standard of treatment for UC, budesonide, a topically-active glucocorticosteroid, was selected as the active ingredient and combined with the novel, patented multimatrix (MMX) delivery technology.

The sponsor has submitted four Phase III studies, CB-01-02/06, CB-01-02/04, CB-01-02/01 and CB-01-02/02. Studies CB-01-02/01 and CB-01-02/02 were two adequate well-controlled studies (CB-01-02/01 and CB-01-02/02) in patients with active, mild to moderate UC. CB-01-02/01 was conducted in the US, Canada, Mexico and India and CB-01-02/02 was conducted in Europe, Russia, Israel, and Austria. With the exception of the reference comparator arm (Asacol in CB-01-02/01 and Entocort in CB-01-02/02), these studies were identical in design.

CB-01-02/06 was a open-label efficacy and safety study in patients with mild to moderate, active ulcerative colitis. CB-01-02/04 was a 12 month, double-blind, placebo-controlled Phase III extension study in maintenance of remission in subjects with ulcerative colitis..

This review will focus three studies (CB-01-02/01, CB-01-02/02, and CB-01-02/04).

All ADaM analysis datasets and study reports for this submission have been submitted in electronic Common Technical Document (eCTD) format to the EDR at:

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MILTON C FAN  
01/26/2012

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