CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 203634	Submission Date(s): 12/16/2011, 1/26/2012, 2/10/2012, 3/28/20112, 4/25/2012, 6/29/2012, 8/9/2012, 8/10/2012
Submission Type; Code	Original submission 505 (b)(2); Standard Review
Brand Name	Uceris
Generic Name	Budesonide
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	Santarus, Inc
Formulation; Strength(s)	Tablet, 9 mg
Proposed Indication	Induction of remission in patients with active, mild to moderate ulcerative colitis
Proposed Dosing Regiment	9 mg once daily for up to 8 weeks
PDUFA Goal Date:	01/16/2013

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1 Executive Summary

This is a 505(b)(2) application for Uceris (Budesonide MMX 9 mg) tablets referencing Entocort® EC capsule (NDA 21-324). Uceris is a new formulation of budesonide with proposed indication of induction of remission in adult patients with mild to moderate active ulcerative colitis (UC). Currently, there are various approved budesonide formulations available on the market for other indications including inhalation, nasal, and oral capsule formulations. Entocort EC capsule is the oral formulation of budesonide available on the market with indication for Crohn's disease. The proposed new formulation of budesonide in this application is designed to release budesonide in both delayed and extended release fashion to target the delivery of budesonide at the colon. The proposed dose for Uceris is 9 mg once daily up to 8 weeks for ulcerative colitis, which is the same recommended dose for Entocort EC for Crohn's disease. Hereinafter, Uceris may be referred to as Budesonide MMX 9 mg tablets or Budesonide MMX or Budesonide MMX extended release tablets.

In support of this application, the sponsor had submitted 3 Phase I studies in healthy subjects, 2 Phase II and 4 Phase III studies in patient population. Pharmacokinetics of budesonide was only characterized in healthy subjects during the phase I studies. In addition, the sponsor had also evaluated Uceris's potential to suppress HPA axis in the 1 phase II study and 3 phase III studies by evaluating the morning cortisol levels and conducting ACTH stimulation test.

List of Phase I studies:

- CRO-PK-06-178: BA study comparing Budesonide MMX 9 mg vs. 6 mg vs. Entocort EC
- CRO-PK-03-105: Food effect and multiple dose PK
- CRO-01-28: Scintigraphic and PK study

An optional intra-divisional level Clinical Pharmacology Briefing was held on December 13th, 2012 to discuss this NDA.

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached on the labeling languages.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose Selection Rationale:

The sponsor had evaluated the efficacy of Budesonide MMX 3 mg and 9 mg in 1 phase II dose-finding study and budesonide MMX 6 mg and 9 mg in 2 phase III studies. Theses studies have demonstrated that the 9 mg dose was more efficacious compared to 3 mg or 6 mg based on the numerical comparison of measured efficacy outcomes. However, those studies were not powered to detect a statistical difference between 3 mg vs. 9 mg or 6 mg vs. 9 mg.

In addition to the stated above, the sponsor selected budesonide MMX 9 mg dose as the phase 3 dose based on the followings: (1) 9 mg was the average dosage strength of oral budesonide (Entocort EC) that is being used as the standard of care in CD, and (2) published literature indicates that QD oral doses of budesonide 9 mg are more efficacious than multiple daily divided doses in patients with active distal UC.

Single-Dose PK (based on Study CRO-PK-06-178):
Following single oral dose administration of Budesonide MMX 9 mg under fasted condition in healthy subjects, C_{max} was 1348.8 ± 958.8 pg/ml, AUC_{0-t} was 13555.9 ± 7816.9 pg.h/ml, $AUC_{0-\infty}$ was 16431.2 ± 10519.8 pg.h/m, and T_{max} was 13.3 ± 5.9 hours. The pharmacokinetic parameters of Budesonide MMX 9 mg have high degree of variability among subjects with a CV ranging from 45% to 71%. In plasma concentration vs. time profile, there appears to be double peaks (based on both the mean profile and individual profiles) following single oral dose administration of Budesonide MMX 9 mg, occurring around 6 hours and 16 hours post-dose, respectively. Although the double peaks were observed in majority of the subjects, it was not always present in all of the subjects.

Multiple-Dose PK (based on Study CRO-PK-03-105):
Following 7 days of oral dosing of Budesonide MMX 9 mg, coefficient of accumulation was Css_{max}/C_{max} = 0.87 ± 0.51, AUC_{ss}/AUC_{inf} = 0.82 ± 0.47, and AUC_{ss}/AUC_{0-24} = 1.135 ± 0.6925, where AUC_{ss} was AUC_{0-tau} where 0-tau is 0-24 hours at steady state, indicating the absence of budesonide accumulation following multiple dose administration of Budesonide MMX 9 mg.

Relative Bioavailability (based on Study CRO-PK-06-178):
Relative bioavailability of Budesonide MMX 9 was compared with the reference product Entocort EC 3x3 mg. Budesonide MMX 9 mg has comparable exposure, but different PK profile compared to the reference product Entocort EC. AUC was 13555.9 ± 7816.9 and 13394.6 ± 5983.0, C_{max} was 1348.8 ± 958.8 and 1555.9 ± 588.0 for Budesonide MMX 9 mg and Entocort EC 3 x 3 mg, respectively. These two products are not statistically bioequivalent with respect to both rate (C_{max}) and extent (AUC) of budesonide absorption. In plasma concentration vs. time profile, Entocort EC appears to have one peak whereas the Budesonide MMX 9 mg appears to have double peaks, where the first peak is close to the T_{max} of the reference product Entocort EC.

Food Effect (based on Study CRO-PK-03-105):
The effect of food on absorption of budesonide in MMX formulation was studied following single dose administration of budesonide MMX 9 mg under fed and fasted states. The presence of food increased the absorption lag time (7.4 hr vs. 9.8 hr) and decreased the rate of absorption (4.7 hr increase in t_{max} and 27% decrease in C_{max}). However, effect of food on extent of absorption was small, only by 9% reduction in AUC_{0-t} and 5% reduction in $AUC_{0-\infty}$.

HPA Axis Suppression:
As budesonide is a glucocorticosteroid, the sponsor had evaluated HPA axis suppression potential of budesonide MMX in Phase2/3 studies by evaluating morning cortisol levels and conducting ACTH stimulation test. As ACTH stimulation test is a more reliable test to assess the HPA axis suppression compared to the morning cortisol levels, this review primarily focuses on the results of ACTH stimulation test. As expected, budesonide MMX 9 mg results in HPA axis suppression. 47% of patient who were treated with budesonide MMX 9 mg for 4 weeks and 79% of patients who were treated with budesonide MMX 9 mg for 8 consecutive weeks had abnormal response to ACTH stimulation test indicating HPA axis suppression. Compared to the reference product Entocort EC, the budesonide MMX 9 mg appears to have higher potential for HPA axis suppression, may be due to its prolonged exposure of budesonide in this new formulation compared to Entocort EC (Figure 1). The warning section of the label should include this information.

Pediatric Studies:
The sponsor has sought a waiver for pediatric population 0-4 years of age and a deferral for 5-17 years of age. Pediatric studies in children 5 to 17 years of age are under discussions as there are

concerns regarding HPA axis suppression. These studies, if required, should also include the PK component.

2 Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

Table 1. Summary of Clinical Pharmacology Studies

Study Ref	Study Objectives	Treatments	No Subjects
CRO-01-28	Single dose study to measure gastrointestinal transit, release and absorption of Budesonide MMX® in the colonic region and to characterize the single dose PK.	Budesonide MMX® 9mg with radiolabel to support scintigraphic analysis.	12
CRO-PK-06-178	Single-dose 3-way cross-over bioavailability study.	Budesonide MMX® 9mg Budesonide MMX® 6mg Entocort® EC 9 mg	12
CRO-PK-03-105	Part 1: Single-dose food effect study. Part 2: Multiple dose PK and tolerability study.	Budesonide 9mg	12

All three Phase I studies were conducted in Caucasian healthy volunteers in Europe. Since there is a no major polymorphism in budesonide metabolizing enzyme, CYP3A4, and there has been substantial human experiences with budesonide, the ethnic factor is not a major concern. Nonetheless, one of the phase 3 study (CB-01-02/01) did include various ethnic groups such as Caucasian (50%), African American (7.2%), Hispanic (7.4%) and Asians (34.4%) in the clinical trial whereas the other phase 3 study (study CB-01-02/02) conducted in Europe were in mostly Caucasian population (99.5%).

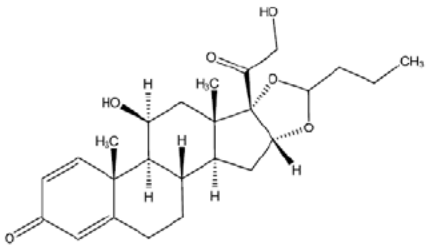
In addition to the above clinical pharmacology related phase 1 studies, the sponsor had also conducted two phase II clinical trials and four phase III clinical trials of Budesonide MMX extended-release tablets in patient population, in which plasma levels of budesonide were not measured.

2.2 General Attributes

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products?

Drug Substance:

- Name: Budesonide
- Chemical formula: $C_{25}H_{34}O_6$
- Molecular Weight: 430.5 g/mol
- Structural formula:



Formulation:

Budesonide tablets were formulated as both delayed and extended release formulation to target the delivery of budesonide drug substance at the colon (MMX formulation). The dosage form is designed as an ordered sequence of two types of matrix. The outer layer of each tablet is enterically coated to provide delayed release characteristics at the appropriate pH. The tablet core contains 9 mg of budesonide and a mixture of polymers that further control the extended release characteristics of the drug substance, along with other excipients.

Table 2. Budesonie MMX Extended Release Tablet, 9 mg, Composition

Components	Amount (mg)	Function	Reference to Standards
		(b) (4)	
Budesonide	9.0	Active Ingredient	USP
Stearic Acid	(b) (4)	(b) (4)	NF
Lecithin			NF
Microcrystalline cellulose			NF
Hydroxypropylcellulose			NF
Lactose (b) (4)			NF
Silicon Dioxide			NF
Magnesium Stearate			NF
(b) (4)			NF
		(b) (4)	
Methacrylic Acid Copolymer, Type A		(b) (4)	NF
Methacrylic Acid Copolymer, type B			NF
Talc			NF
Titanium Dioxide			NF
Triethylcitrate			NF
(b) (4)			NF
Tablet Weight:			

2.2.2 What is the proposed indication?

The proposed indication for Uceris is induction of remission in adult patients with mild to moderate active ulcerative colitis (UC).

2.2.3 What are the proposed mechanisms of actions?

The proposed mechanism of action of budesonide is that it has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to glucocorticosteroid receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.

2.2.4 What are the proposed dosage and route of administration?

The proposed dosage is one 9 mg tablet to be administered orally once daily in the morning for up to 8 weeks.

2.2.5 What is the regulatory background?

Capsule oral formulation of budesonide is currently marketed in the U.S under the name of Entocort® EC for treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon at 9 mg once daily dose and maintenance of clinical remission of mild to moderate Crohn's disease involving the ileum and/or the ascending colon at lower dose of 6 mg.

The sponsor had submitted this 505(b)(2) application for Budesonide MMX 9 mg tablet for ulcerative colitis indication referencing Entocort® EC capsules.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The budesonide MMX clinical development program is consisted of nine clinical studies: three Phase I studies, two Phase II studies, and four Phase III studies (including two adequate and well-controlled studies).

Phase I studies:

- Study CRO-PK-06-178 was an open-label, randomized, single-center, single-dose, three-way cross-over, exploratory study in 12 healthy male and female subjects under fasting condition to compare the bioavailability and PK profile of a new MMX 9 mg budesonide extended release tablets formulation vs. the market reference formulation, Entocort® EC 3 mg × 3 capsules and vs. MMX 6 mg budesonide extended release tablets.

- Study CRO-PK-03-105 was an open-label, randomized, single-center, cross-over study in 12 healthy male subjects to explore the effect of food (phase 1) and PK profile following multiple dosing (phase2) after 7 days of once daily dosing of MMX 9 mg budesonide extended release tablets formulation.

- Study CRO-01-28 was a single-center, single-dose, pilot study in 12 healthy male subjects under fasting condition to gain preliminary information on the gastrointestinal transit of a budesonide MMX 9 mg via scintigraphic data, on its systemic availability, and on overall safety profile.

Phase II studies:

- CB-01-02/05 was Phase II, dose-finding, double-blind, multi-center, comparative, pilot efficacy, and safety study in patients with active mild or modrate UC comparing budesonide MMX 3 mg , budesonide MMX 9 mg, and placebo over 8 weeks of treatment.

- CRO-03-53 was Phase II, randomized, placebo-controlled, parallel-group, pilot, multi-center efficacy study (double-blind during period 1 [4 weeks] and open-label during period 2 [4 weeks]) with two treatment arms in patients with active mild or moderate left-sided UC. Treatment A was budesonide MMX 9 mg QD for 8 week and treatment B was placebo tablet for 4 weeks during period 1 and budesonide MMX 9 mg QD for 4 weeks during period 2.
    - In this study, HPA axis suppression potential of budesonide MMX 9 mg was evaluated by conducting ACTH stimulation test at the end of 8 weeks of treatment in addition to measuring the morning cortisol levels before the treatment and end of the 4 and 8 weeks of treatment.

Phase III studies:

- CB-01-02/01 and CB-01-02/02: The sponsor conducted two adequate and well-controlled Phase III studies (CB-01-02/01 and CB-01-02/02) to demonstrate the efficacy of budesonide MMX 9 mg. Both of theses studies were multi-center, randomized, double-blind, placebo-controlled, double-dummy, parallel-group, comparative studies in patients with active mild or moderate UC. The doses evaluated in these studies were budesonide MMX 6 mg QD , budesonice MMX 9 mg QD, reference arm of Asacol 2x400 mg TID in Study CB-01-02/01 and Entocort EC 3x3 mg QD in CB-01-2/02 and placebo over 8 weeks of treatment.
    - In these studies, the sponsor had also measured morning cortisol levels at baseline and after 2, 4 and 8 weeks of treatment as a mean of evaluating HPA axis suppression potential of budesonide.

- CB-01-02/06: Patients who failed to achieve remission in studies CB-01-02/01 or CB-01-02/02 were eligible to enroll into Study CB-01-02/06, where all patients were administered open label budesonide MMX 9 mg for up to 8 weeks.

- CB-02-01/04: Patients who achieved UCDAI remission in CB-01-02/01, CB-01-02/02 or CB-01-02/06 were given the opportunity to enter into the extended safety study CB-02-01/04 without any interruption of treatment where subjects are randomized to receive budesonide MMX 6 mg or placebo for 12 month. Study drug was self-administered by the patient once daily, after breakfast, for up to 12 months or until the occurrence of clinical relapse (defined as the recurrence of rectal bleeding and/or an abnormal stool frequency).
    - In this study, HPA axis suppression potential of budesonide MMX 6 mg was evaluated by conducting ACTH stimulation test at the end of 12 month of treatment in addition to measuring the morning cortisol levels before the treatment and end of the 1, 3, 6, 9 and 12 month of treatment.

2.3.2 What were the results of phase 3 trials?

The sponsor claims that both of the main Phase III studies (CB-01-02/01 and CB-01-02/02) demonstrated that budesonide MMX 9 mg was statistically significantly superior to placebo in inducing clinical remission over 8-week treatment in patients with active, mild to moderate UC.

Medical Reviewer, Dr. Marjorie Dannis, also concluded that the efficacy of budesonide MMX 9 mg in inducing remission was established by demonstrating that budesonide MMX 9 mg was statistically significantly superior to placebo in inducing clinical remission, the primary endpoint of both studies. Thus, recommended for approval

However, according to the Statistical reviewer, Dr. Milton C. Fan, 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 abnormal histology at baseline, the budesonide MMX 9 mg was numerically better than placebo. But, subgroup of patients with abnormal histology was not pre-specified in the protocol.

2.3.3 What was the clinical endpoint in the Phase 3 trials?

- Primary efficacy endpoint in phase III studies (CB-01-02/01, CB-01-02/02 or CB-01-02/06) was percentage of patients achieving clinical remission after 8 weeks of treatment where clinical remission was defined as:

- Ulcerative Colitis Disease Activity Index (UCDAI) score ≤ 1 with score of 0 for rectal bleeding and stool frequency,
- A normal mucosa (no evidence of friability),
- ≥ 1 point reduction from baseline in endoscopy score

- In phase II dose-finding study (CB-01-02/05), the efficacy endpoints were UCDAI score, Clinical Activity Index (CAI) score, and Endoscopic Index (EI).

- In phase II study CRO-03-53, the efficacy endpoint was number of patients achieving an improvement from baseline CAI score of ≥ 50% and/or achieving remission (CAI score ≤ 4).

- The efficacy endpoint in phase III, 12-month extended safety study (CB-02-01/04) was proportion of patients in clinical remission (score of 0 for rectal bleeding and stool frequency) after 1, 3, 6, 9, and 12 months of treatment.

2.3.4 What is sponsor's dose selection rationale?

The sponsor had evaluated the efficacy of Budesonide MMX 3 mg and 9 mg in 1 phase II dose-finding study and budesonide MMX 6 mg and 9 mg in 2 phase III studies. The phase II dose-finding study (CB-01-02/05) was conducted in patients with active mild or moderate UC comparing budesonide MMX 9 mg, budesonide MMX 3 mg and placebo. In this study, budesonide MMX 9 mg appeared to have better measured efficacy outcomes (i.e., UCDAI, CAI, and EI scores) compared to budesonide MMX 3 mg or placebo. However, statistical difference was not observed due to the small size of the study.

In addition, the sponsor had also evaluated budesonide MMX 6 mg and budesonide MMX 9 mg in two phase 3 studies (CB-01-02/01 and CB-01-02/02) to identify the lowest effective dose in patients with active mild or moderate UC with 8 weeks of treatment. These studies were not powered to compare budesonide MMX 6 mg vs. budesonide MMX 9 mg. Nonetheless, according to sponsor's analysis, in both studies, there was a dose-dependent increase in the frequency of remission from placebo (7.4% and 4.5% CB-01-02/01 and CB-01-02/02, respectively) to budesonide MMX 6 mg (13.2% and 8.3%, respectively) to budesonide MMX 9 mg (17.9% and 17.4%, respectively). The differences between budesonide MMX 6 mg and placebo did not reach statistical significance in either study whereas budesonide MMX 9 mg was statistically superior to placebo in both studies, according to the sponsor's analysis.

In addition to the stated above, the sponsor selected budesonide MMX 9 mg dose as the phase 3 dose based on the followings: (1) 9 mg was the average dosage strength of oral budesonide (Entocort EC) that is being used as the standard of care in CD, and (2) published literature indicates that QD oral doses of budesonide 9 mg are more efficacious than multiple daily divided doses in patients with active distal UC.

2.3.5 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters?

Yes, the sponsor had used LC-MS/MS analytical method in Study CRO-PK-06-178 and GC-MS/NCI analytical method in Study CRO-PK-03-105 and Study CRO-PK-06-178 to measure the plasma concentration of budesonide with 50 pg/ml detection limits in both methods. Please refer to 2.6, Analytical Section for more detail.

2.3.6 What was the HPA axis suppression potential of the drug product?

As budesonide is a glucocorticosteroid, its potential to suppress HPA axis with this new MMX formulation was evaluated in a phase 2 study (CRO-3-53) and in a phase 3 extended safety study (CB-01-02/04) by evaluating the morning cortisol levels and conducting ACTH stimulation test. In addition, the sponsor had also evaluated the morning cortisol levels in two pivotal phase 3 studies (CB-01-02/01 and CB-01-02/02). As expected, budesonide MMX 9 mg does cause HPA axis suppression by reducing the morning plasma cortisol levels in dose depending manner and by causing abnormalities in ACTH stimulation test. Compared to the reference product Entocort EC, the new formulation MMX appears to have higher potential to suppress HPA axis, may be due to its prolonged exposure.

NOTE:

Currently in the United States, Cosyntropin is the diagnostic test for assessing HPA axis suppression (0.25 mg given as iv). However, in both Study CRO-3-53 and Study CB-01-02/04, the sponsor had used Synacthen test which uses stimulation with tetracosactide (0.25 mg given as im) for ACTH test to assess HPA axis suppression potential. According to the sponsor, Synacthen was the authorized product in Europe, where the study was conducted, for performing ACTH stimulation tests at the time when the phase 2 study (Study CRO-3-53) was being conducted. Synacthen was utilized again for the phase 3 study (Study CB-01-02/04) in order to maintain consistency across the budesonide MMX program.

Cosyntropin and Synacthen have same molecular entity (tetracosactide, which is composed of the first 24 of the 39 amino acids of natural ACTH) with the same amino acid sequence. Both products are administered at the same dosage strength of 250 μg/ml. The primary difference between these two products is their routes of administration, where Synacthen can be administered through intramuscular injection, and Cosyntropin is administered intravenously as a direct injection or as an infusion. These products also have similar criteria for a normal ACTH response, where normal response is defined as the plasma cortisol having an increment of at least 200 nanomoles/L (70 micrograms/L) above the basal level, and the plasma cortisol level attained 30 minutes after injection exceeds 500 nanomoles/L (180 micrograms/L). Therefore, Synacthen test used in these studies was considered to be an acceptable test to evaluate the HPA axis suppression.

Study CB-01-02/04

This was a phase 3 extended safety study with 6 mg of budesonide MMX over 12 month treatment where both morning plasma cortisol level and ACTH stimulation test were evaluated. Morning plasma cortisol level was measured at pre-treatment and after 1, 3, 6, 9, and 12 month of treatment with 6 mg of budesonide MMX. Plasma cortisol level increased from the baseline to the Final Visit in both placebo and treatment group (Table 6).

Table 3. Morning Plasma Cortisol (normal range 138 nmol/L – 690 nmol/L)

Mean ± SD (nmol/L)	Placebo N=61	MMX 6 mg N=62
Baseline	287.3 ± 153.49	244.6 ± 141.90
After 12 month treatment	359.7 ± 113.43	287.4 ± 160.87
Change from baseline	74.7 ± 194.99	50.4 ± 174.87

At baseline, both placebo and MMX 6 mg had similar percentage of patient with low cortisol level (16.9% vs. 20.0%). After 12-month of treatment with budesonide MMX 6 mg, more budesonide MMX patients (17.9%) had morning plasma cortisol levels below the normal range than placebo patients (0%). However, in the budesonide MMX 6 mg treatment arm, the percentage of patient with low cortisol level did not increase from the baseline to the end of 12-month treatment (20.0% vs.17.9%) (Table 4). Interesting to note in this study is that the actual morning cortisol level increased rather than decreased after treating the patients with MMX 6 mg for 6 month.

Table 4. Incidence of Low, Normal, and High Morning Plasma Cortisol Levels

Visit	Result	Placebo N=61 n (%)	MMX 6 mg N=62 n (%)
Visit 1 (Baseline)	Low	10 (16.9)	12 (20.0)
	Normal	49 (83.1)	48 (80.0)
	High	0	0
Final Visit/Completers (Month 12)	Low	0	1 (4.5)
	Normal	21 (100.0)	21 (95.5)
	High	0	0
Final Visit /All patients (Month 12 or early withdrawal)	Low	0	7 (17.9)
	Normal	41 (100.0)	32 (82.1)
	High	0	0

ACTH Stimulation Test (Synacthen test) was only performed at end of 12-month treatment, but not at baseline before the treatment. Greater percentage of patient in budesonide MMX 6 mg group had abnormal ACTH stimulation compared to the placebo group according to both sponsor's normal ACTH response criteria (30% vs. 18%) and Synacthen's label criteria (58% vs. 20%) (Table 5). It is important to point out that Study CB-01-02/04 had different dose and duration of treatment compared to what was proposed in this application (6 mg QD dose for 12 month vs. 9 mg QD dose 8 weeks).

Note:
Both Study CRO-3-53 and Study CB-01-02/04 had used different criteria for a normal ACTH response than the criteria in Synacthen label. Clinical criteria of interpretation of the ACTH test in theses studies were that the cortisolemia should be normal at pre-dose, i.e. it should fall in the interval 7.25-21.75 µg/dL. After adrenocorticotropic stimulation cortisolemia should be ≥15.95 µg/dL (440 nmol/L) and the increment should be of at least 6.16 µg/dL (170 nmol/L) in order to exclude axis impairment. Therefore, the results of ACTH stimulation test in these studies were re-analyzed with the criteria for normal ACTH response as specified in the Synacthen label.

Table 5. Patients on MMX 6 mg QD with Abnormal ACTH test at 12 months

	Placebo n (%)	MMX 6 mg n (%)
Based on Sponsor's Criteria	6/34 (18%)	10/33 (33%)
Based on Synacthen label Criteria	7/34 (20%)	19/33 (58%)

Study CRO-3-53:

Study CRO-03-53, which was a phase 2 study, had total of 8 weeks of treatment (which consist of 4 weeks of period 1 and another 4 week of period 2) with two treatment arms. Treatment A was budesonide MMX 9 mg QD in both period 1 and 2 for total of 8 weeks treatment, and treatment B was placebo tablet QD for 4 weeks during period 1 and budesonide MMX 9 mg QD for 4 weeks during period 2. The sponsor had measured morning plasma cortisol level before the treatment and at the end of 4 weeks and 8 weeks of treatment as a mean to assess the HPA axis suppression.

Table 6. Morning Plasma Cortisol level (normal range of 4.4-22.5 μg/dL)

	Mean ± SD (ug/dL)	Baseline	week 4	week 8
Treatment A N= 13	budesonide MMX 9 mg	11.2 ± 7.04	5.1 ± 3.31	3.59 ± 3.88
Treatment B N=14	Placebo	12.79 ± 7.74	19.34 ± 9.33	
	budesonide MMX 9 mg		19.34 ± 9.33 (baseline)	12.19 ± 6.02

Table 7. Number of Subjects with abnormally low cortisol values

		Baseline n (%)	week 4 n (%)	week 8 n (%)
Treatment A	budesonide MMX 9 mg	0/13 (0%)	6/12 (50%)	7/9 (78%)
Treatment B	Placebo	2/14 (14%)	0/14 (0%)	
	budesonide MMX 9 mg		0/14 (0%)	1/15 (6%)

The morning plasma corisol level appears to decrease with increased duration of budesonide MMX 9 mg treatment (Table 6). In parallel, the percentage of subject with abnormally low level of cortisol increases with increased duration of treatment with budesonide MMX9 mg (table 7).

In addition, the sponsor had also conducted ACTH stimulation test (short Synacthen® test) at the end of the 8-week treatment to assess the HPA axis suppression potential. At the end of treatment, 40% of patient who were treated with budesonide MMX 9 mg for last 4 weeks and 57% of patients who were treated with budesonide MMX 9 mg for 8 consecutive weeks had abnormal response according to the sponsor's normal ACTH response criteria. When ACTH stimulation test result was re-analyzed based on the criteria on Synacthen label, 47% of patient who were treated with budesonide MMX 9 mg for last 4 weeks and 79% of patients who were treated with budesonide MMX 9 mg for 8 consecutive weeks had abnormal ACTH response (Table 8).

Table 8. Patients on MMX 9 mg QD with Abnormal ACTH test

	4 weeks treatment n (%)	8 weeks treatment n (%)
Based on Sponsor's Criteria	6/15 (40%)	8/14 (57%)
Based on Synacthen label Criteria	7/15 (47%)	11/14 (79%)

It is important to point out that the ACTH stimulation test was not conducted as the baseline level before the start of treatment in both Study CRO-3-53 and Study CB-01-02/04. Therefore, the results of these studies are difficult to interpret as some patient in these studies could have entered the studies with some degree of adrenal insufficiency at the baseline. In addition, Study CRO-3-53 was a very small study with only 14-15 subjects without a proper placebo group, thus making it difficult to draw a general conclusion.

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

The sponsor had evaluated the morning plasma cortisol levels in pivotal two phase 3 studies where subjects were treated with either placebo, budesonide MMX 9 mg, budesonide MMX 6 mg, Asacol or Entocort 9 mg for 8 weeks. The morning plasma corisol levels were measured at baseline and after 2, 4 and 8 weeks of treatment. After 8 weeks of treatment, budesonide MMX 9 mg had the greatest decrease in the morning plasma level followed by MMX 6 mg where MMX 6 mg and Entocort had similar level of decrease (table 9). In parallel, budesonide MMX 9 mg has the greatest percentage of patient with abnormally low morning cortisol level after 8 weeks of treatment compared to other treatment groups (table 10).

Table 9. Morning Plasma Cortisol : Pooled analysis of CB-01-02/01 and CB-01-02/02: (normal limits 138 to 690 nmol/L).

Mean ± SD **(nmol/L)**	Placebo N= 258	MMX 9 mg N= 255	MMX 6 mg N= 254	Asacol N=127	Entocort N=126
Baseline	338.0 ± 135.20	341.1 ± 137.98	357.5 ± 124.53	357.1 ± 127.19	368.6 ± 145.61
After 8 weeks	347.5 ± 143.28	253.5 ± 172.94	299.4 ± 172.19	331.9 ± 133.94	322.9 ± 160.79
Change from baseline	14.9 ± 126.87	-101.0 ± 208.5	-50.7 ± 168.86	-25.3 ± 152.47	-47.0 ± 153.50
Mean % change	17.5 ± 101.67	-18.8 ± 66.06	-10.0 ± 56.34	0.9 ± 50.04	-8.2 ± 42.82

Table 10. Incidence of Low, Normal, and High Morning Plasma Cortisol Levels: Pooled analysis of CB-01-02/01 and CB-01-02/02

		Phase III Randomized, Double-blind				
Visit	**Result**	Placebo N=258 n (%)	MMX 9 mg N=255 n (%)	MMX 6 mg N=254 n (%)	Asacol N=127 n (%)	Entocort N=126 n (%)
Visit 2 (Baseline)	Low	9 (3.5)	11 (4.4)	6 (2.4)	3 (2.4)	3 (2.5)
	Normal	245 (96.5)	234 (93.6)	241 (96.8)	122 (96.8)	115 (94.3)
	High	0 (0.0)	5 (2.0)	2 (0.8)	1 (0.8)	4 (3.3)
Final Visit	Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
	Low	7 (3.0)	61 (25.8)	47 (19.3)	4 (3.4)	16 (13.3)
	Normal	226 (95.4)	173 (73.3)	191 (78.6)	114 (95.8)	100 (83.3)
	High	4 (1.7)	2 (0.8)	5 (2.1)	1 (0.8)	3 (2.5)

Note: The normal range for morning plasma cortisol is 138 – 690 nmol/L. A low morning plasma cortisol level was defined as <138 nmol/L; a normal value was defined as ≥138 nmol/L and ≤690 nmol/L; and a high value was defined as >690 nmol/L.

Comparison with Entocort:

Although budesonide MMX 9 mg and Entocort EC 3x3 mg have comparable exposures, they have different PK profiles. HPA axis suppression potential of budesonide MMX 9 mg appears to be slightly higher than that of Entorcort, may be due to the prolonged exposure of budesonide in MMX 9 mg formulation (Figure 1).

In respect to ACTH stimulation test, after 8 weeks of treatment, 79% of patient who were treated with budesonide MMX 9 mg had abnormal ACTH response where 54% patient who received Entocort had abnormal ACTH response (according to Medical Review for NDA 21324). However, this comparison with Entocort EC has several limitations. First of all, this study with budesonide MMX 9 mg was based on a very limited number of patients, n= 14. In addition, this comparison with Entocort EC is a cross-study comparison. Lastly, it is not clear that what kind of

criteria was used in Entocort EC to categorize a response as an abnormal ACTH response, and therefore, Entocort EC and budesonide MMX 9 mg may have different criteria for an abnormal ACTH response.

In respect to the morning cortisol level, based on the phase 3 studies results, budesonide MMX 9 mg had greater amount of decrease in the morning plasma cortisol levels compared to Entocort after 8 weeks of treatment, where the amount of decrease from the baseline level was -101 nmol/L in MMX 9 mg treatment group vs. -47.0 nmol/L in Entocort treatment group (table 9). In parallel, greater percentage of patients in budesonide MMX 9 mg group had abnormally low morning cortisol level compare to Entocort after 8 weeks of treatment (25.8% vs. 13.3%) (table 10).

Conclusion:
Regarding the morning cortisol level, the data from these 4 studies were hard to interpret as they had contradicting results. The morning cortisol level had increased in Study CB-01-02/04 where patients were treated with MMX 6 mg for 12 month, and it decreased in Studies CB-01-02/01, CB-01-02/02 and CRO-3-53 where patients were treated with MMX 9 mg for 8 weeks. In addition, morning cortisol levels generally are not used as diagnostic as it has low sensitivity.

Regarding the ACTH stimulation test, which is a more reliable method of measuring the HPA axis suppression compared to the morning cortisol level, both study CB-01-02/04 and CRO-03-53 have suggested that treatment with budesonide MMX causes abnormal response to ACTH stimulation test. In study CB-01-02/04, 58% of patient who were treated with 6 mg budesonide MMX for 12 month had abnormal response to ACTH stimulation test vs. 20% of patient who were treated with placebo. In study CRO-03-53, 47% of patient who were treated with budesonide MMX 9 mg for 4 weeks and 79% of patients who were treated with budesonide MMX 9 mg for 8 consecutive weeks had abnormal response to ACTH stimulation test. Nonetheless, both of these studies had their own limitations. Study CB-01-02/04 was conducted with different dose and duration of treatment compared to what is being proposed in this application (6 mg QD dose for 12 month in study CB-01-02/04 vs. 9 mg QD dose 8 weeks for the proposed indication). Study CRO-03-53 was a small study with only 14-15 subjects, without a proper placebo group. In addition, the ACTH stimulation test was not conducted as the baseline level before the start of treatment in both Study CRO-3-53 and Study CB-01-02/04 and, thus,some patient in these studies could have entered the studies with some degree of adrenal insufficiency at the baseline

2.3.7 Does this drug prolong QT/QTc Interval?

The sponsor had requested a waiver for TQT study. The QT-IRT team has reviewed the request and agrees that a TQT study is not needed for the following reason:

- Budesonide (capsules) is being marketed since 1997. The C_{max} with the approved formulation ENTOCORT EC is slightly higher than that expected with budesonide MMX (tablets).
- No AEs of concerns as per ICH E14 Guidance have been reported post-marketing.

2.4 PK Characteristics

2.4.1 How do the bioavailability profile of a new Budesonide MMX extended release (6, 9 mg tablets) formulation compare with reference product Entocort® 3 × 3 mg capsules?

The new test formulation Budesonide MMX extended release 9 mg tablet was not bioequivalent to the reference product Entocort® 3 x 3 mg capsules. However, they appear to have very similar level of exposure.

The sponsor has conducted one PK study (Study CRO-PK-06-178) to compare the bioavailability profile of new MMX Budesonide extended release (6, 9 mg tablets) formulation with reference product Entocort® 3 × 3 mg capsules.

Study CRO-PK-06-178 was an open-label, single center, single-dose, randomized, three-way cross-over exploratory study in 13 healthy Caucasian subjects (6 male and 7 female) under fasting condition to compare the bioavailability and the PK profile of a new MMX 9 mg budesonide extended release tablets formulation vs. the market reference formulation, Entocort® EC 3 mg × 3 capsules and vs. MMX 6 mg budesonide extended release tablets. This study consisted of three treatment periods, each of which included blood and urine sampling for 36 hours and a washout period of 5 calendar days between treatments. Subjects were instructed to swallow the whole tablet/capsules without chewing. No food was allowed for additional 5 hr. Standardized lunch and dinner were provided 5 and 12 hour pose-dose, respectively. 150 mL of mineral water was encouraged to take every 2 hour for 6 hours post dosing. PK blood samples were collected at pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 30, 36 hours post-dose.

This study was conducted in Switzerland. Of 13 enrolled subjects, 12 of them completed the study as planned receiving all 3 treatments. One subject withdrew from the study during Period III for personal reason. Safety population included all 13 subjects and PK population included 12 subjects who completed the study. One subject (subject N. 2) exhibited pre-dose values higher than LQL in the third period. Since pre-dose values were higher than 5% of C_{max}, PK analysis was conducted both including and excluding this subject.

Table 11. Concomitant Medications

Subject	Trade name	Active ingredients	Reason	Dose	Route	Related to AE(s)	Start	End	WHO Drug Dictionary code*
4	Tachipirina	Paracetamol 500 mg	Upper respiratory tract infection symptoms	OD	OS	1	14MAR07	15MAR07	000200-01-040
6	Dafalgan	Paracetamol 500 mg	Upper respiratory tract infection	OD	OS	1	20MAR07	21MAR07	000200-01-057
7	Fedra	Gestodene 75 ug + Ethinylestradiol 20 ug	Contraception	OD	OS		01JAN05	Ongoing	008616-01-029
9	Harmonet	Gestodene 75 ug + Ethinylestradiol 20 ug	Contraception	OD	OS		01JAN96	Ongoing	008616-01-019

***Reviewer's Comment*:**

- There is no major drug-drug interaction expected for Subjects 7 and 9 who took contraceptive that contain Ethinyl estradiol 20 ug. According to the Entocort EC label, oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide and budesonide does not affect the plasma concentration levels of oral contraceptives.
- For subject 4 and 6 who took Paracetamol (acetaminophen), no major drug-drug interaction is expected between the budesonide and co-medication paracetamol. Both of these subjects took acetaminophen during the washout periods, 2 days before the administration of budesonide in the next period. With a short half-life of 2-4 hours, acetaminophen is expected to be cleared from the plasma by the time that budesonide was administered during the next period.

- No obvious drug interaction/interference was noted from the visual inspection of individual concentration profiles for these subjects who had concomitant medications.

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

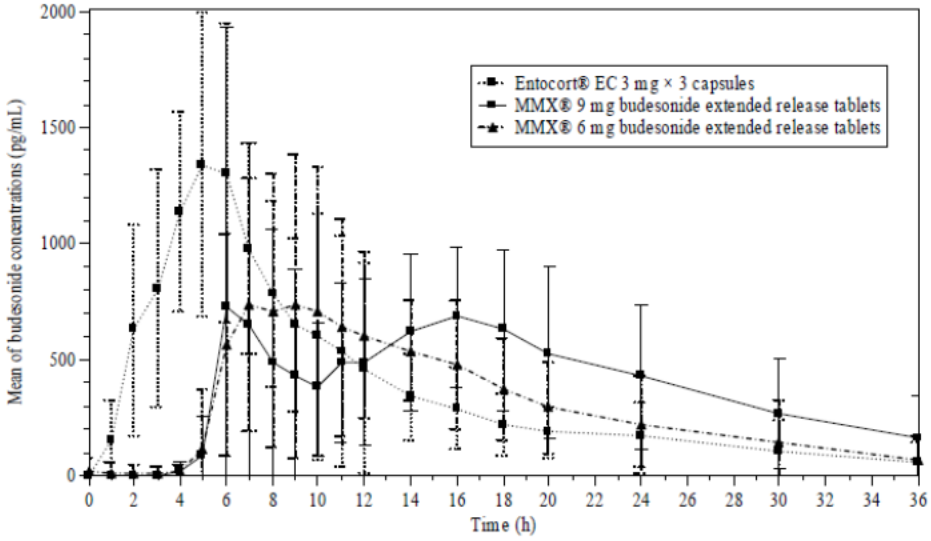


Table 12. Budesonide PK parameters

Plasma budesonide PK parameters - Mean ± SD (CV%)			
	MMX™ 9 mg (T1)	**MMX™ 6 mg (T2)**	**Entocort® EC 3 x 3 mg**
PP-population (N=12)			
T_{max}(h)	13.3 ± 5.9 (44.5)	11.4 ± 5.1 (44.4)	4.8 ± 1.4 (28.6)
C_{max} (pg/mL)	1348.8 ± 958.8 (71.1)	1158.5± 532.4 (46.0)	1555.9 ± 588.0 (37.8)
AUC_{0-t} (pg/mLxh)	13555.9 ± 7816.9 (57.7)	10818.3 ± 4401.6 (40.7)	13394.6 ± 5983.0 (44.7)
$AUC_{0-\infty}$ (pg/mL×h)	16431.2 ± 10519.8 (64.0)	11533.6 ± 4738.5 (41.1)	14057.0 ± 6378.7 (45.4)
C_{max} (pg/mL) / dose	149.9 ± 106.5 (71.1)	193.1 ± 88.7 (46.0)	172.9 ± 65.3 (37.8)
AUC_{0-t} (pg/mLxh) / dose	1506.2 ± 868.5 (57.7)	1803.0 ± 733.6 (40.7)	1488.3 ± 664.8 (44.7)
$t_{1/2}$(h)	8.2 ± 3.7 (44.7)	6.6 ± 2.4 (36.8)	7.7 ± 1.8 (23.1)
MRT (h)	21.4 ± 6.8 (31.5)	17.0 ± 5.7 (33.7)	11.6 ± 2.7 (23.1)
PP-control population (N=11)			
T_{max}(h)	12.8 ± 6.0 (46.7)	11.0 ± 5.1 (46.4)	4.6 ± 1.4 (29.4)
C_{max} (pg/mL)	1427.3 ± 964.3 (67.6)	1154.9 ± 558.2 (48.3)	1549.0 ± 616.2 (39.8)
AUC_{0-t} (pg/mLxh)	13963.7 ± 8063.4 (57.7)	10331.4 ± 4264.1 (41.3)	13741.1 ± 6147.5 (44.7)
$AUC_{0-\infty}$ (pg/mL×h)	17041.8 ± 10807.8 (63.4)	11533.6 ± 4738.5 (41.1)	14462.8 ± 6572.3 (45.4)
C_{max} (pg/mL) / dose	158.6 ± 107.1 (67.6)	192.5 ± 93.0 (48.3)	172.1 ± 68.5 (39.8)
AUC_{0-t} (pg/mLxh) / dose	1551.5 ± 895.9 (57.7)	1721.9 ± 710.7 (41.3)	1526.8 ± 683.1 (44.7)
$t_{1/2}$(h)	8.4 ± 3.7 (44.0)	6.6 ± 2.4 (36.8)	7.9 ± 1.7 (21.0)
MRT (h)	21.4 ± 7.1 (33.1)	17.0 ± 5.7 (33.7)	11.8 ± 2.7 (23.1)

***Reviewer's Comment*:**

- Although test formulation budesonide MMX 9 mg and the reference product Entocort EC have similar exposure regarding the AUC and Cmax, these two products have different PK profiles. Budesonide appears to have a more prolonged exposure in this new MMX formulation compared to Entocort EC.

- Budesonide plasma concentrations and its PK parameters exhibited a high inter-subject variability. The observed inter-subject variability is generally lower for Entocort® EC compared to the new formulation of budesonide MMX extended release 9 mg tablets.
- MRT was higher for test formulations (MMX 6 and 9 mg) compared to reference formulation (Entocort EC), which is consistent with the expected PK profiles of different formulations.
- There appears to be double peaks (based on the both mean profile and individual profiles) for the test formulation MMX extended release tablet (6 mg 9 mg), the first peak being close to the T_{max} of the reference product Entocort EC.
- 5 days of washout period was acceptable as the half –life of budesonide is 6-8 hours.

Table 13. Statistical analysis of Budesonide MMX 9 mg (T1) vs. Entocort® 3 x3 mg (R)

Budesonide MMX™ 9 mg (T1) vs Entocort® EC 3 x 3 mg (R)		
	PP-population (N=12)	PP-control population (N=11)
AUC_{0-t}		
Point estimate (ratio of geometric means) %	91%	91%
90% CI (ratio of the geometric means)	77 – 108%	77 – 108%
C_{max}		
Point estimate (ratio of geometric means)	79%	87%
90% CI (ratio of the geometric means)	63 - 100%	70 - 108%

Table 14. Statistical analysis of Budesonide MMX 9 mg (T1) vs. 6 mg (T2)

Budesonide MMX™ 9 mg (T1) vs 6 mg (T2)		
	PP-population (N=12)	PP-control population (N=11)
C_{max} / dose		
Point estimate (ratio of geometric means) %	75%	82%
90% CI (ratio of the geometric means)	59 – 95%	66 – 102%
AUC0-t / dose		
Point estimate (ratio of geometric means) %	80%	86%
90% CI (ratio of the geometric means)	67 – 94%	73 – 102%

***Reviewer's Comment*:**

- As expected, budesonide MMX extended release 9 mg tablet (T1) is not equivalent to the reference formulation Entocort® EC 3 x 3 mg capsule (R) regarding both rate and extent of budesonide absorption. The 90 % confidence interval (CI) for both AUC and C_{max} of budesonide were outside the limit of 80 - 125%. Budesonide MMX 9 mg tablet appears to has lower rate and but similar extent of budesonide absorption compared to Entocort® EC, administered at the same dose.
- High and low strength of test formulations T1 and T2 showed differences in the absorption profiles. The 90 % confidence intervals (CI) for both C_{max} and AUC_{0-t} budesonide were outside the limits of 80 to 125%, suggesting that the 6 mg formulation is more bioavailable than 9 mg formulation.

2.4.2 How do the exposure of Budesonide MMX 9 mg compared to other budesonide products in the market?

As budesonide is glucocorticoid that has growth suppression potential in addition to HPA axis suppression potential in pediatric population, for the purpose of proposed pediatric studies, the exposure of the proposed product budesonide MMX 9 mg was compared to other budesonide products on the market that has pediatric indications. Currently, the reference product Entocort EC does not any pediatric indication. The following exposure information was obtained the current labels or clinical pharmacology reviews for respective products from the Drugs@FDA.

Table 15. Comparison of Budesonide Exposure Across Different Budesonide Products

Budesonide Product /formulation/NDA #	Approved Dose	Cmax(nmol/L)/ dose	AUC (nmol.h/L)/ dose
Pulmicort Inhalation powder NDA 20441	Adults: 200-400 ug BID Ped (6 & up): 200 -400 ug BID	Not available	Not available
Pulmicort Flaxaler Inhalation powder NDA 21949	Adults: 180-360 ug BID Ped (6 & up): 180-360 ug BID	0.6 / 180 ug 1.6 /360 ug 3.32 /4*180 ug	9.5 /4 x 180 ug
Pulmicort Respules Inhalation suspension NDA 20929	Ped : (1-8 years): 0.5-1 QD 0.25-0.5 mg BID No adult indication	2.6 /1 mg (in ped)	10.9 / 1mg (in ped)
Rhinocort Aqua Nasal Spray NDA 20746	Adults: 64 ug QD (256 ug max) Ped (6 & up): 64 ug QD (128 ug max)	0.3 / 128 ug 1 / 400 ug	4.2 / 400 ug
Symbicort Aerosol Inhalation NDA 21929	Adults: 80-160 ug BID Ped (12 & up): 80-160 ug BID	1.36/ 4*160 ug (640) 3.9 / 8*160 ug (1280) 6.1/12*160 ug (1920) 1.8/ 12*40 ug (480) 3.2/ 12*80 ug (960) 5.4/12*160 ug (1920)	4.2/ 4*160 ug (640) 14.6 /8*160 ug (1280) 19.0 /12*160 ug (1920) 6.0/ 12*40 ug (480) 10.8/ 12*80 ug (960) 19.8/ 12*160 ug (1920)
Entocort EC Oral Capsule NDA 21324	Adults: 6-9 mg QD	5 / 9 mg (label) 3.6 /9 mg (in this submission)	30 / 9 mg (label) 31 /9 mg (in this submission)
Uceris	**Adults: 9 mg QD**	**3.1 /9 mg**	**38 /9 mg**

Based on the above comparison, the proposed product budesonide MMX 9 mg appears to have comparable exposure to Entocort EC oral capsule, but higher exposure compared to other inhalation or nasal spray budesonide products that have pediatric indication at the respective approved doses.

2.4.3 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single Dose PK:

The sponsor has evaluated single dose PK of Budesonide MMX 9 mg under fasted condition in healthy subjects in 3 separate studies, Study CRO-PK-06-178 (relative BA study), Study CRO-PK-03-105 (food effect study), and Study CRO-01-28 (scintigraphy study), with most extensive blood sampling in study CRO-PK-06-178. The mean values for PK parameters were fairly consistent across the studies (Tablet 18). The pharmacokinetic parameters have high degree of variability among subjects in all 3 studies with a CV ranging from 45% to 93%. In plasma concentration vs. time profile of study CRO-PK-06-178, there appears to be double peaks (based on the both mean profile and individual profiles) following single oral dose, occurring around 6

hours and 16 hours post-dose, respectively (Figure 1). The double peaks were not as obvious in the mean PK profiles in Study CRO-PK-03-105 and Study CRO-01-28 although they are observed in some individual profiles.

Table 16. Single Dose PK parameters of Budesonide MMX 9mg (mean ± SD)

	CRO-PK-01-28	CRO-PK-06-178	CRO-PK-03-105
C_{max} (pg/ml)	1768.7 ± 1499.8	1348.8 ± 958.8	1428.7 ± 1013.5
$AUC_{0-\infty}$ (pg.h/ml)	-	16431.2 ± 10519.8	15503 ± 11340
*AUC_{0-t} (pg.h/ml)	15607 ± 14549	13555.9 ± 7816.9	14814 ± 11254
T_{lag} (h)	6.97 ± 3.24	-	7.4 ± 4.2
T_{max} (h)	14.0 ± 7.7	13.3 ± 5.9	16.0 ± 3.4
$t_{½}$ (h)	-	8.2 ± 3.7	5.4 ± 2.0
MRT (h)	-	21.4 ± 6.8	19.9 ± 4.6

* Note that the time of the last PK sample varies between studies. $AUC_{0-\infty}$ is the better guide.

Multiple Dose PK:

The sponsor had conducted one multiple dose PK study (Study CRO-PK-03-105) that was open-label, randomized, single-center, cross-over study in 12 healthy Caucasian male subjects to explore the effect of food (phase 1) and PK profile following multiple dosing (phase2) of Budesonide MMX 9 mg extended release tablets. The two phases of the study were separated by 1 week of washout period. During the second phase of the study, Budesonide MMX 9 mg tablet was administered orally once daily after an overnight fasting of 12 hours, every morning for 7 consecutive days with 240 ml water. Blood samples were collected at pre-dose at day 1, 3, 5 and 6. On day 7, blood samples were collected pre-dose, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 h after last dose. Feces were collected daily until 48 h post dose of last dose on day 7. Standardized breakfasts, lunches and dinners were served at 2, 5 and 12 h after each drug administration. No one was taking any concomitant medication during the study and no one withdrew from the study.

Figure 2. Plasma Budesonide Concentrations after Single and Multiple Dose Administration in the Fasted State

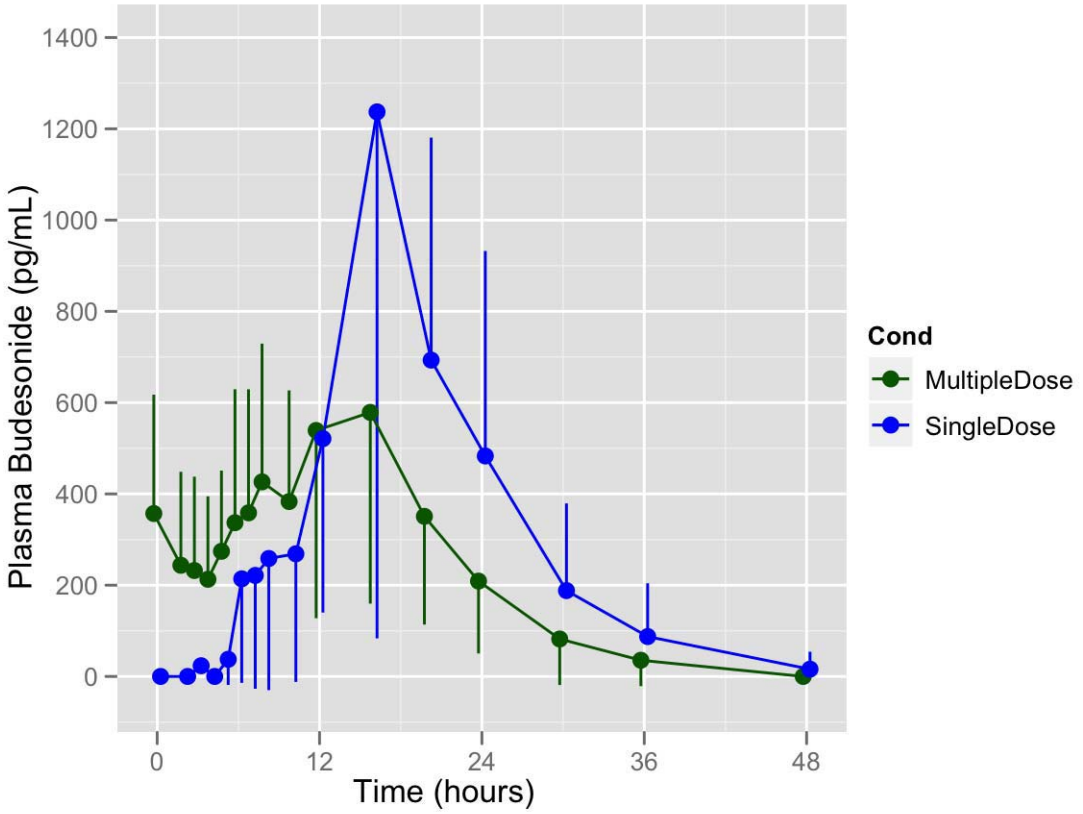


Table 17. PK parameters of budesonide at steady state

Css_{max}	maximum plasma concentration at steady state	pg/mL	891.3 ± 394.1
Css_{min}	minimum plasma concentration at steady state	pg/mL	109.9 ± 75.3
tss_{max}	time at which Css_{max} is achieved	h	11 ± 4.9
$C_{average}$	mean or average steady state drug concentration	pg/mL	387.3 ± 153.9
AUCss	AUC during the selected dosing interval, 0-tau (0-24 hr) at steady state calculated with trapezoidal method	pgxh/mL	9295.2 ± 3694.2
%PTF	peak-through-fluctuation percentage	%	205.9 ± 83.9

When PK parameters of multiples doses were compared with single dose under fasted state, both C_{max} and AUC appear to decrease following multiple dosing compared to single dosing. Coefficient of accumulation after multiple dosing was estimated as multiple/single dose ratio for C_{max} and AUC. Css_{max}/C_{max} was 0.87 ± 0.51, AUC_{ss}/AUC_{inf} was 0.82 ± 0.47, and $AUC_{ss}/AUC_{0\text{-}24}$ was 1.135 ± 0.6925 suggesting that there is no budesonide accumulation following multiple dose administration of Budesonide MMX 9 mg.

Reviewer's Comment:

- This observed lower AUC and Cmax of Budesonide MMX 9 mg after multiple dosing was also observed in the reference product Entocort EC after multiple dosing ($Css_{max}/C_{max} \approx 0.78$ and $AUC_{ss}/AUC \approx 0.74$, please refer to clinical pharmacology review of NDA 21324 for detail).

- According to the literature search (please see section 2.6.3), budesonide appears to be inducer of CYP3A4, which is the responsible drug enzyme for budesonide metabolism. Therefore, it might have self-induction of its own metabolism resulting in lower exposure of budesonide following multiple dosing.

2.4.4 Budesonide MMX was designed to have both delayed- and extended-release characteristics. What is the advantage of this design?

The sponsor conducted an exploratory pilot single-dose PK and scintigraphic study (Study CRO-01-28) of budesonide MMX 9 mg formulation in 12 healthy Caucasian male subjects under fasting condition to gain preliminary information on the gastrointestinal transit of a new MMX once daily budesonide formulation and its systemic availability. The formulation used in this study had incorporated ^{152}Sm oxide (5 mg/tablet), which was included as a tracing agent for pharmaco-scintigraphy. Inclusion of 5 mg of samarium oxide was compensated by minor adjustments to other noncritical excipients (microcrystalline cellulose and silicon dioxide). ^{152}Samarium was subsequently radio-labelled by neutron activation to ^{153}Sm.

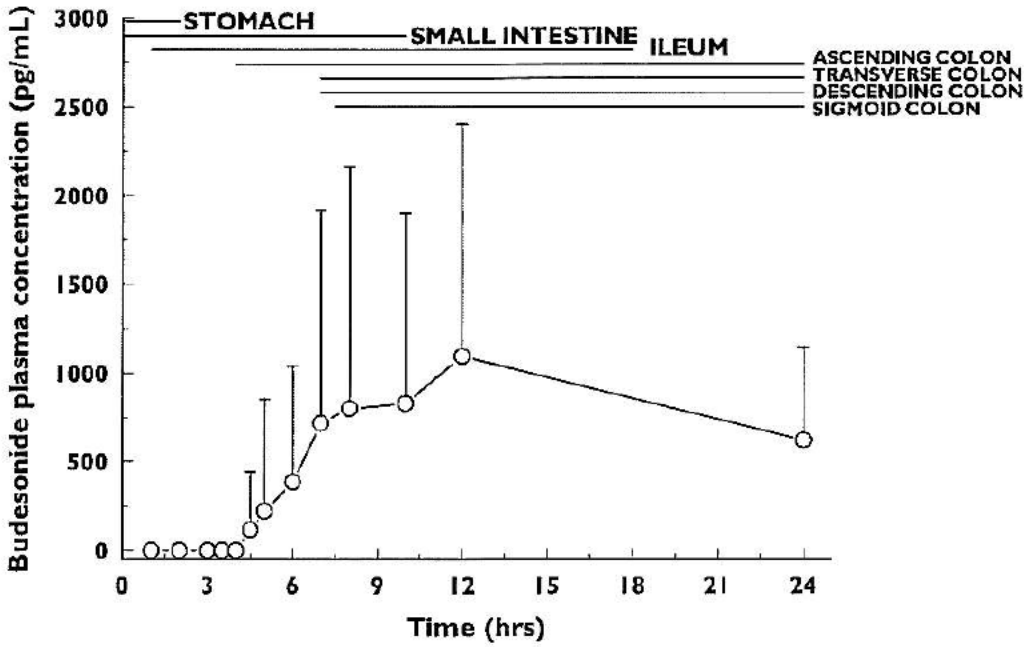
After the drug administration, scintigraphic scans, blood samples and urine samples were collected for 24 hours. Standardized breakfast, lunch and dinner were provided 2, 6 and 12 hours post-dose. All enrolled subject completed the study as planned, and there was no concomitant medication was taken during the study. PK blood samples to determine the plasma budesonide concentration were taken at pre-dose (0), 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12 and 24 h post-dose. To characterize the GI transit behavior of the study formulation, scintigraphic scans were recorded at approximately 20 min intervals up to 3 h post-dose, 30 min intervals up to 10 h and at 12 and 24 h post-dose.

Table 18. Budesonide MMX 9 mg tablet transit time throughout the whole GI tract. Time to arrive (min) and leave each GI segment

	STOMACH		SMALL INTESTINE		ILEUM		A. COLON		T. COLON		D. COLON		S. COLON	
	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT
MIN	3	20	3	40	60	240	240	450	420	600	420	1440	450	>1440
MAX	3	120	140	600	720	<1440	1440	>1440	1440	>1440	1440	>1440	1440	>1440

GI transit behavior of the tested formulation also has very high variability among subjects.

Figure 3. Plasma concentration vs. time profile (mean ± SD) of budesonide after single-dose administration of 153Sm-labeled budesonide MMX 9mg tablets in 12 healthy males



Lines depict periods between minimal time to arrive and maximal time to leave each gastrointestinal region.

Table 19. Budesonide mean Plasma PK parameters

N=12	C_{max} (pg/mL)	T_{max} (h)	AUC_t (pg*h/mL)	T_{lag} (h)	T_{max} - T_{lag} (h)
Mean	1768.7	14.00	15607	6.79	7.21
S.D.	1499.8	7.734	14549	3.24	5.49
CV	84.80	55.24	93.22	47.66	76.13
Min	337.3	5	2465	1	0
Max	4756.3	24	53163	12	17

***Reviewer's Comment*:**

- PK parameters of budesonide MMX 9 mg is highly variable among subject. In this study, plasma samples were not collected long enough to obtain plasma half-life of budesonide. Additionally, plasma sample was not collected between 12-24 hours, and therefore, the estimated T_{max} of 14 hour is not very reliable.
- Disintegration or visible erosion (ITD) of tablets was estimated by count spreading, after matrix erosion, and it started at 9.48± 5.11 hours on average after administration. It appears that disintegration takes place mostly in ileum (5 of 12 subjects, 42%), or ascending and traverse colon (4 of 12 subjects, 33%). However, it is important to note that disintegration was a subjective visual assessment as it was defined on the basis of appearance of scintigraphic image. It is unclear how the exactly the disintegration time was defined in the study.
- It is also unknown whether addition of samarium oxide to the formulations could alter their performance as there are no data to verify this.
- It was not clear what kind of external reference was used to determine the location of radioactivity in relation to the GI gut.
- Since this study was exploratory in nature and has many deficiencies as stated above, data from this scintigraphy study is not recommended to be included in the label.

2.4.5 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Sponsor had only measured the budesonide PK of the new formulation of MMX Budesonide extended release tablets in healthy subjects in phase 1 studies, but not in target patient population (patients with mild or moderate ulcerative colitis) in phase 2 or phase 3 studies.

2.4.6 What are the characteristics of drug metabolism?

The sponsor did not conduct any metabolism study in this submission. However, based on the reference product Entrocort EC label, budesonide is subject to high first pass metabolism (80-90%) where it is rapidly and extensively metabolsized, mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. The glucocorticoid activity of these metabolites is negligible (less than 1/100) in relation to that of the parent compound. Because of its metabolism via CYP3A4, potent inhibitors/inducers of CYP3A4 can increase the plasma level of budesonide by several folds.

2.5 General Biopharmaceutics

2.5.1 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

According to the sponsor, the formulation used in the phase 3 studies is the same as the to-be-marketed formulation.

2.5.2 What is the effect of food on the bioavailability of the drug when administered as drug product?

There appears to be a slight effect of food on the absorption of budesonide from the Budesonide MMX extended release tablets. Based on the arithmetic mean, AUC was decreased only by 5-10%, and C_{max} was decreased by approximately 27% in the presence of food. However, this small magnitude of difference in exposure in the present of food is not considered to be clinically significant. However, food does appear to delay the absorption.

The sponsor had evaluated the effect of food on absorption of budesonide from the MMX Budesonide extended release tablets in first phase of the Study CRO-PK-03-105.
Study CRO-PK-03-105, which consisted of two phases, was an open-label, randomized, single-center, cross-over study in 12 healthy Caucasian male subjects to explore the effect of food (phase 1) and PK profile following multiple dosing (phase2) of the a new MMX™ 9 mg budesonide extended release tablets formulation. The two phases of the study were separated by 1 week of washout period.
In the phase 1, which evaluated the effect of food, the subjects were randomized to either fasting (FA) group or fed (FE) group. In FE group, following overnight fasting, the subjects were given high fat, high calories breakfast. A single dose budesonide MMX 9 mg tablet was administered orally with 240 mL of water within 5 min after the breakfast. In the FA group, following at least 10 hr of overnight fasting, a single dose budesonide 9 mg tablet was given orally with 240 mL of water. Standardized meals were provided at 5 and 12 hour post-dose. For both groups, the blood samples were collected at pre-dose, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36 and 48 h post-dose. Following 1 week of washout period, the subjects were reassigned to the FA or FE treatment according to the cross-over study design. No one was taking any concomitant medication during the study. This study was conducted in Switzerland. All of the 12 enrolled subjects completed the study as planned.

Figure 4. Mean budesonide plasma concentration vs. time profiles after single administration of MMX-9 mg budesonide tablets under a Fed and a Fasted condition, N=12

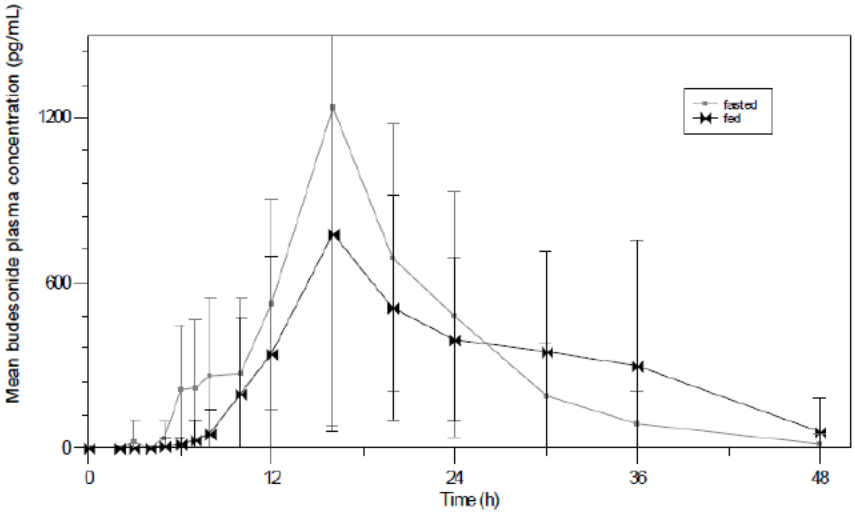


Table 20. Mean ± SD budesonide PK parameters under fed (FE) and fasted (FA) conditions, N=12

PK parameter	FA	FE
C_{max} (pg/mL)	1428.7 ± 1013.5	1039.9 ± 601.4
t_{lag} (h)	7.4 ± 4.2	9.8 ± 3.6
T_{max} (h)	16 ± 3.4	20.7 ± 8.7
AUC_{48} (pg×h/mL)	14814 ± 11254	13486 ± 9368.7
AUC_{∞} (pg×h/mL)	15503 ± 11340	14608 ± 9937.9
$t_{1/2}$ (h)	5.4 ± 2.0	5.6 ± 2.7
MRT (h)	19.9 ± 4.6	24.3 ± 7.1

90% CI for the ratio of geometric means between fed and fasted condition for C_{max} was 67.7-133.7% and for AUC for 66.9-130.87% and did not meet the limit of 80% to 125% to excluded the effect of food.

***Reviewer's Comment*:**

- There appears to be a delay in absorption (based on t_{lag}) under fed condition compared to fasted condition.
- For both AUC and C_{max}, 90% confidence interval for geometric mean ratio between fed and fasted states did not meet the pre-specified interval of 80-125% to exclude the effect of food on budesonide absorption. However, based on the arithmetic means, the extent of absorption, AUC, was decreased only by 5-10%, and C_{max} was decreased by approximately 27% in presence of food. The observed statistical difference between fed and fated stated could be due to the high variability in budesonide PK parameters. This small magnitude of difference in exposure in the presence of food is not considered to be clinically significant.

2.5.3 How the drug was administered in relation to meal in phase 3 studies?

To ensure consistent dosing conditions, in all Phase II and Phase III studies, patients were instructed to take all doses of budesonide MMX in the morning after breakfast with a glass of water.

2.6 Extrinsic factors

2.6.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The sponsor has not conducted any in-vitro study to evaluate budesonide's potential in-vivo drug-drug interaction. The following information is based on the current Entocort label and literature search.

2.6.2 Is the drug a substrate of CYP enzymes?

According to the current label of reference drug Entocort EC (revised on December 2011), based on *in vitro* experiments in human liver microsomes, budesonide is rapidly and extensively metabolized mainly by CYP3A4, to its 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone.

2.6.3 Is the drug an inhibitor and/or an inducer of enzymes?

The sponsor did not conduct any in-vitro study to evaluate whether budesonide is inhibitor and /or inducer of CYP enzyme. However, per FDA's request, the sponsor conducted a literature search to address whether budesonide is an inhibitor/inducer of CYP enzymes and found following two articles that are relevant to address this issue.

- Khan AA, Chow EC, van Loenen-Weemaes AM, Porte RJ, Pang KS, Groothuis GM. Comparison of effects of PXR, FXR and GR ligands on the regulation of CYP3A isozymes in rat and human intestine and liver. *Eur J Pharm Sci.* 2009 May 12; 37(2): 115-25.

  Khan and colleagues have evaluated if budesonide (BUD) induces CYP3A4 in human ileum tissue, but not in human liver tissue. When incubated for 8 and 24 hours, budesonide, at 10 nM concentration, induces CYP3A4 mRNA expression slightly in the ileum slices, but difference failed to reach statistical significance.

- Zimmermann C, van Waterschoot RA, Harmsen S, Maier A, Gutmann H, Schinkel AH. PXR mediated induction of human CYP3A4 and mouse Cyp3a11 by the glucocorticoid budesonide. *Eur J Pharm Sci.* 2009 Mar 2; 36(4-5): 565-71.

  In this study, budesonide did not inhibit CYP3A4 at concentrations from 0.025 to 25 uM when CYP3A4 activity was assessed by the metabolism of a luminogenic substrate (luciferin-benzylether) using recombinant human CYP3A4 protein. Poor solubility of the drug was observed at higher concentrations. In this study, ketaconazole (0.025-25uM) was used as the positive control as CYP3A4 inhibitor and exhibited a significant inhibition of CYP3A4 activity.

Fig. 1 – Determination of the effect of budesonide on CYP3A4 activity. CYP3A4-containing cell membranes were incubated with budesonide or ketoconazole (control inhibitor of CYP3A4). Luciferin-benzylether was applied as a CYP3A4 substrate and the metabolism to luciferin was analyzed after 60 min by measuring the resulting luminescence. Data points represent mean values ±SEM ($n = 4$). For ketoconazole a sigmoidal inhibition curve could be fitted.

This study also evaluated budesonide's potential to be an inducer of CYP3A4 utilizing LS180 human intestinal cells *in vitro*. When human LS180 colon carcinoma cells incubated with budesonide for 48 hr at 1 uM, 10 uM, and 25 uM, CYP3A4 mRNA expression were induced in a dose-dependent manner.

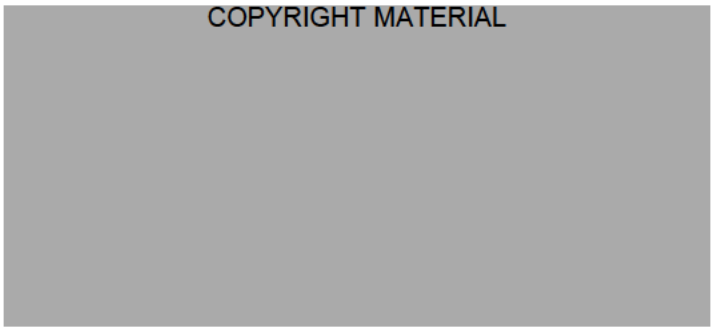


Fig. 2 – Effect of dexamethasone and budesonide on the expression of CYP3A4 mRNA in intestinal cells. LS180 cells were incubated with increasing concentrations (1, 10, and 25 μM) of dexamethasone and budesonide for 48 h. mRNA expression of CYP3A4 was measured by real-time PCR and normalized to the expression of glyceraldehyde-3-phosphate dehydrogenase (GAPDH). DMSO (control) and rifampicin (10 μM) were used as negative and positive controls, respectively. Results are mean values (±SD) pooled from 3 independent experiments (each $n = 3$). $^{*}p < 0.05$ vs control.

Reviewer's Comment:

The study had proper positive controls for both inhibition (ketoconazole) and induction (rifampin) components. The tested concentrations up to 25 uM for both inhibition and induction studies cover the expected human plasma Cmax of 3-4 nM and close to the expected intestinal concentration of budesonide 9 mg/430 mg/mmol/250mL= 84 uM. Based on the result of this study, budesonide appears not to inhibit CYP3A4. However, it has potential to induce CYP3A4.

2.6.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

The sponsor did not conduct any in-vitro study to evaluate whether budesonide is substrate/inhibitor/inducer of transporter. Per FDA's request, the sponsor conducted a literature to address this issue and found the following two articles that are relevant. The sponsor's search terms was only limited to ""Budesonide"[Mesh] AND ("Intestinal Absorption"[Mesh] OR "P-Glycoproteins"[Mesh]).

- Dilger K, Schwab M, Fromm MF. Identification of budesonide and prednisone as substrates of the intestinal drug efflux pump P-glycoprotein. *Inflammatory Bowel Dis* 2004;10:578-583.

  This study evaluated the bi-directional transport of [^{3}H]budesonide in monolayers of L-MDR1 cells (LLC-PK1 cells stably transfected with human MDR1 cDNA) and Caco-2 cells, both of which express P-glycoprotein (P-gp) in their apical membrane, as well as in non-transfected LLC-PK1 cells for 4 hours at substrate concentrations of 5 uM. Budesonide had greater basolateral to apical (B-A) transport compared to apical to basolateral (A-B) transport in L-MDR1 transfected cells whereas in non-transfected cell, budenoside B-A transport was similar to A-B transport. Similarly, budesonide had greater B-A transport compared to A-B transport in Caco-2 cell monolayers.

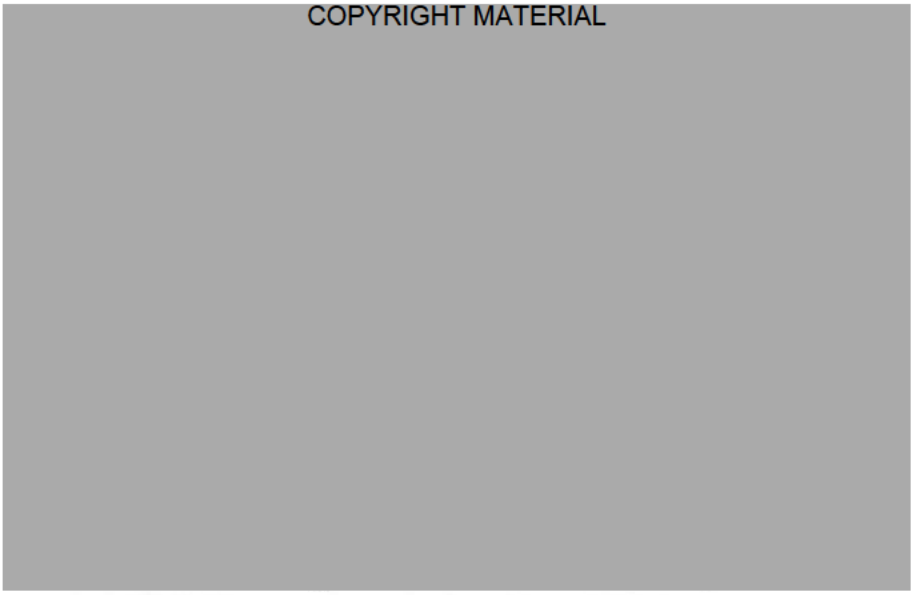
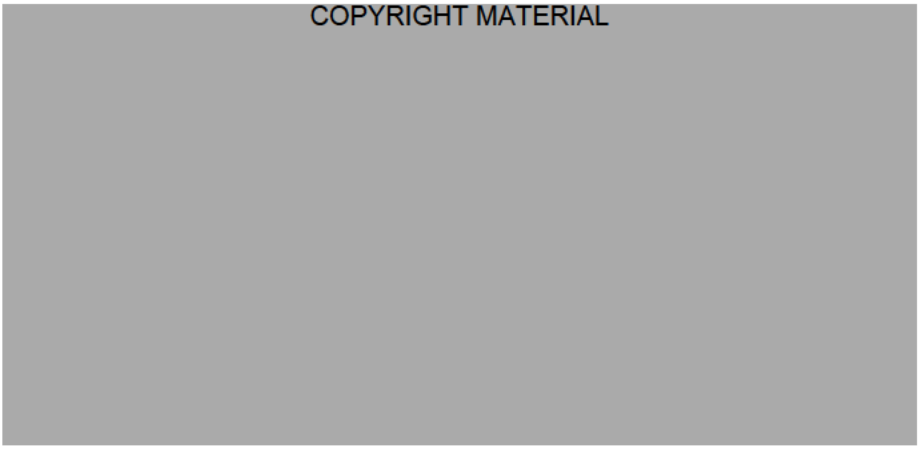


FIGURE 1. Transport of (A) budesonide and (B) prednisone from basal to apical compartments (squares and solid line) and from apical to basal compartments (triangles and dotted line). Data are mean ± SD from at least 6 experiments across L-MDR1 and LLC-PK1 monolayers.



Budesonide transport across Caco-2 cell monolayer was also evaluated in presence of P-gp inhibitor PSC-833 (1 uM).

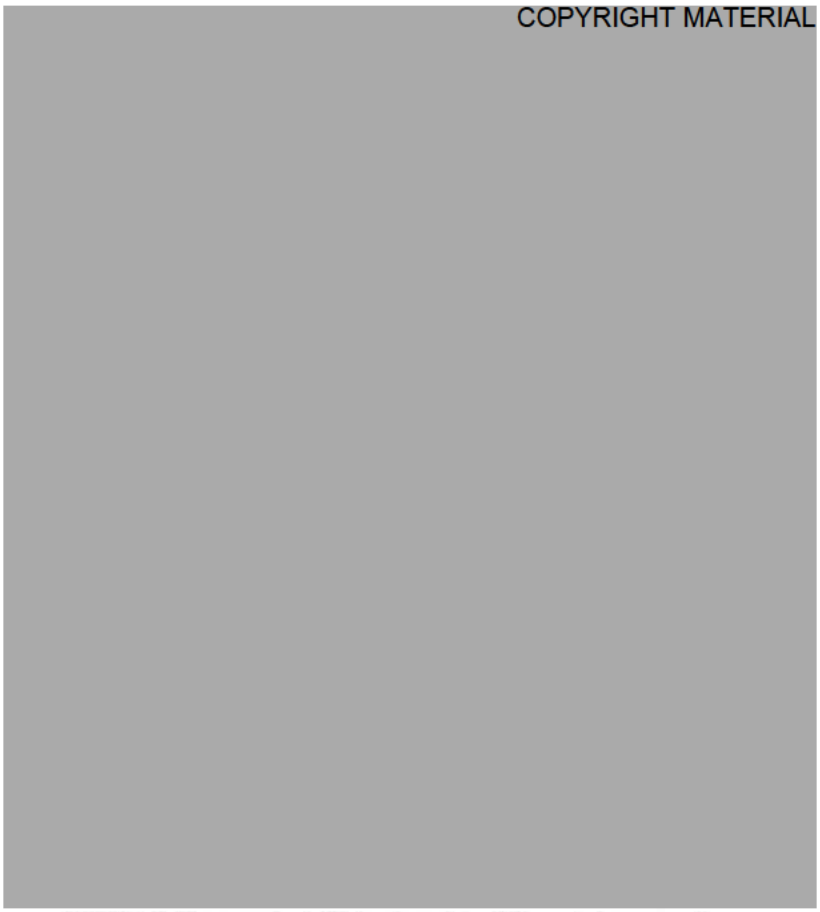
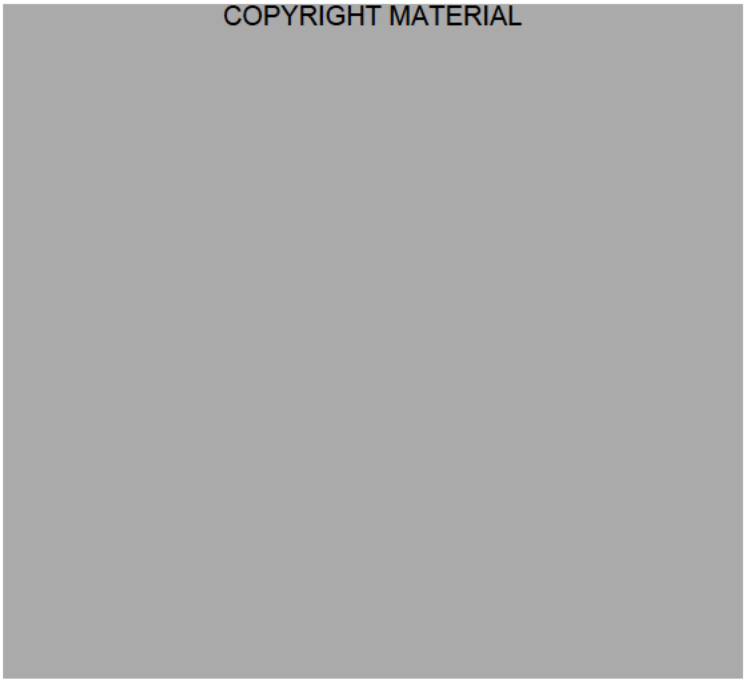


FIGURE 2. Transport of (A) budesonide, (B) prednisone, and (C) digoxin from basal to apical compartments (squares and solid line) and from apical to basal compartments (triangles and dotted line) in the absence or presence of PSC-833. Data are mean ± SD from at least 6 experiments across Caco-2 monolayers.



The investigator concluded that budesonide was identified as substrates of P-glycoprotein.

Reviewer's Comment:

Although this study result suggests that budesonide may be a substrate for P-gp transporter, the study result is not conclusive, and therefore, may not have a labeling implication. The study was only conducted at one concentration of 5 uM. Additionally, the results from MDR1 transfected LLC-PK1 cells and Caco-2 cells are not consistent.

- In Caco-2 cells, the net flux ratio R is estimated to be 1.45 based on $R = P_{B/A} / P_{A/B} = 13.5/9.3 = 1.45$. Based on net flux ratio >2 criteria, this study result suggest that budesonide is a poor or non P-gp transporter substrate.
- In MDR1 transfected LLC-PK1, the net flux ratio R can be estimated to be approximately 4 based on $(R) = (R_T) / (R_w) = (28.3/6.3) / (18.4/16.6) = 4.05$, where (R_T) and (R_W) are the permeability ratios for the transfected and the non-transfected cells. Therefore, based on net flux ratio >2 criteria, this study result suggest that budesonide is a substrate for P-gp transporter.

- Maier A, Zimmermann C, Beglinger C, Drewe J, Gutmann H. Effects of budesonide on P-glycoprotein expression in intestinal cell lines. *British Journal of Pharmacology* 2007; 150, 361-368

  The effect of budesonide on P-gp expression were evaluated by incubating budesonide in LS180 and Caco-2 cells and measuring the change in P-gp expression levels based on its mRNA, protein and functional levels. Theses two cell systems had contradictory results. Budesonide showed induction of P-gp in LS180 cells where it showed down-regulation of P-gp in Caco-2 cells.

Figure 1 Effect of budesonide on *MDR1* mRNA expression in LS180 (**a**) and Caco-2 (**b**) cell lines. Cells were incubated for 48 h and mRNA expression was determined by quantitative real-time PCR. Rifampicin was used as a positive control for *MDR1* induction in LS180 cells. Results are normalized to control cells and expressed as mean $\pm$ s.e.m. ($n=4$). *$P<0.05$, ***$P<0.001$ vs control cells.

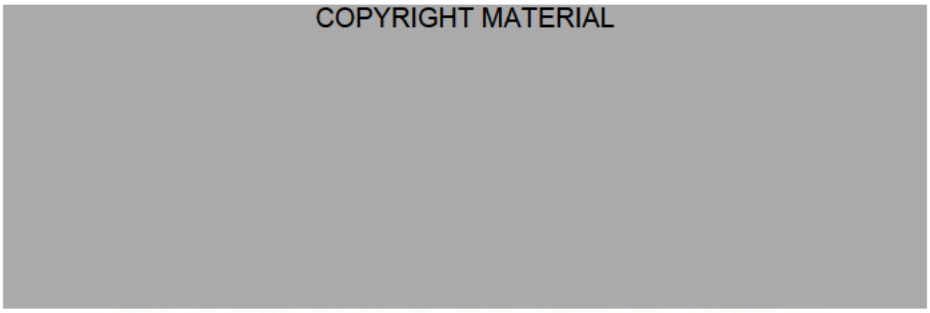


Figure 2 Effect of budesonide on *P*-gp protein expression. LS180 and Caco-2 cells were incubated for 72 h with 25 μM budesonide or vehicle. Rifampicin was used as a positive control for *MDR1* induction in LS180 cells. *P*-gp protein and β-actin were determined by Western blot analysis. β-Actin was used as loading control.

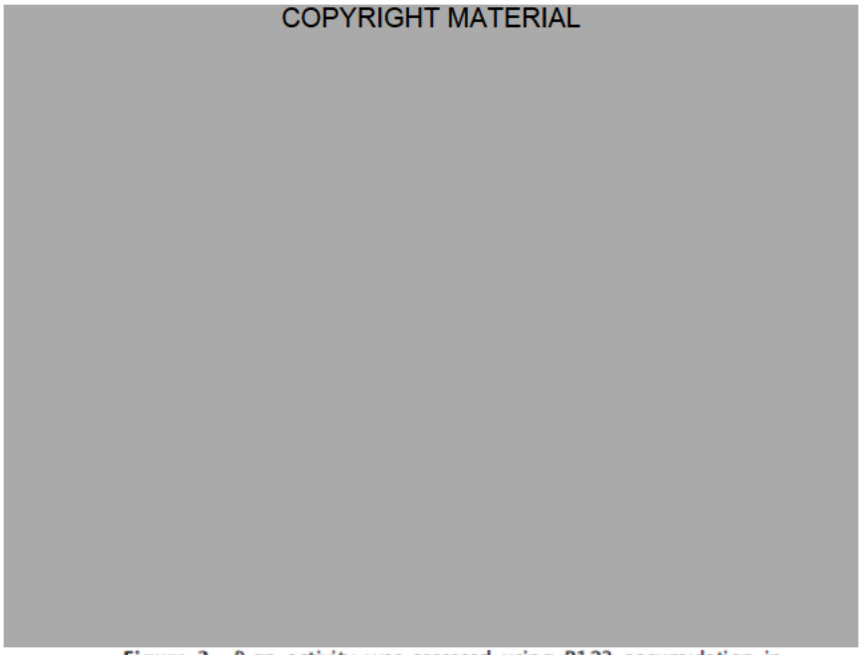


Figure 3 *P*-gp activity was assessed using R123 accumulation in LS180 and Caco-2 cells. Cells were pretreated with 20 μM budesonide or vehicle for 72 h. Rifampicin was used as a positive control for *P*-gp induction. Data represent R123 fluorescence normalized to verapamil-treated cells. A decrease in intracellular fluorescence is indicative of an increase in *P*-gp activity and *vice versa*. Results are expressed as mean$\pm$s.e.m. (n= 3–4). $^{**}P<0.01$, $^{***}P<0.001$ vs control cells.

Reviewer's Comment:

The study results from LS180 and Caco-2 cell systems were contradictory and the study in Caco-2 did not have a positive control. Therefore, this study result inconclusive and may not have labeling implication.

2.7 Analytical Section

2.7.1 What bioanalytical methods were used to assess the concentration?

The sponsor had used LC-MS/MS analytical method in Study CRO-PK-06-178 and GC-MS/NCI analytical method in Study CRO-PK-03-105 and Study CRO-PK-06-178 to measure the plasma concentration of budesonide.

- Plasma samples were stored frozen at $\leq$ -20°C until analysis in all 3 studies.
- Limit of Quantification was 50.0 pg/mL in all 3 studies.
- Linear regression equation of y = a + bx with 1/x weighting were used to calculated the concentration in all 3 studies.
- Calibration curve concentration ranged from ~ 50.0-5000 pg/ml (stored frozen <-20°C) in all 3 studies.

Study CRO-PK-06-178:
In Study CRO-PK-06-178, the sponsor had used LC-MS/MS method to measure the concentration of budesonide in plasma samples.

- The highest plasma budesonide concentration observed in this study was 4227.2 ng/mL, which was within the calibration standard range.

- R^2 ranged from 0.999561 to 0.99996.

Precision and accuracy of budesonide calibration standards:

l.Std Nominal nc (pg/mL)	50.0	100.0	250.0	499.9	999.9	2499.7	4999.4
cision CV (%)	0.74	1.71	1.06	0.5	0.37	0.54	0.37
curacy (%)	-2.6	2.95	-0.61	0.44	-0.41	0.40	-0.17

Precision and accuracy of budesonide quality controls:

Nominal QC Conc (pg/mL)		84	599.8	3998.8
Picosulfate	Precision (%)	5.11	3.17	2.98
	Accuracy (%)	-2.13	-0.17	0.70

- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of budesonide in plasma has been established.
    - Plasma samples were collected between 03/08/2007 through 04/19/2007.
    - Plasma samples for budesonide was analyzed between April 5th, 2007 to April 25th, 2007
    - Stability of budesonide in human plasma at -20 °C was established for at least for 706 days.

Study CRO-PK-03-105

Plasma budesonide concentrations were determined using validated GC-MS/NCI analytical method.

- The highest plasma budesonide concentration observed in this study was 3403.2 ng/mL, which was within the calibration standard range.

- R^2 ranged from 0.9993 to 1.0000.

Precision and accuracy of budesonide quality controls:

Nominal QC Conc (pg/mL)	64.2	401.0	4009.6
Precision (%)	2.31	3.15	3.76
Accuracy (%)	1.25	-3.31	-1.09

- Plasma samples, stored at approximately -20°C, were not analyzed within the time period for which the long-term stability of budesonide in plasma has been established in this study.
    - Plasma samples were collected between 06/05/2003 through 06/24/2003.
    - Plasma samples were received at the analytical site on 06/30/2003.
    - Plasma samples for budesonide was analyzed between 07/07/2003-08/12/2003
    - Stability of budesonide in human plasma at -20 °C was established for at least for 21 days.

Reviewer's Comment:

Although budesonide in plasma samples were not analyzed within the time frame in which stability was established (21 days) in this study, budesonide stability in human plasma was

established for at least 706 days at < -20 °C in study CRO-PK-06-178 using validated LC-MS/MS methods. Therefore, this will not be a review issue.

Study CRO-01-28
Plasma budesonide concentrations were analyzed using a validated GC/MS analytical method.

- The highest plasma budesonide concentration observed in this study were 4756.3 pg/mL, which was within the calibration standard range

- R^2 ranged from 0.9993 to 0.9998.

- The sponsor did not provide the stability data of budesonide in plasma at storage condition of at ≤ -20°C in this bioanalytical report. Therefore, it is not clear whether the plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of budesonide in plasma has been established.
    - Plasma samples were collected between 08/10/2002 through 08/19/2002.
    - Plasma samples for budesonide was analyzed between 11/28/2002 to 12/16/2002

Reviewer's Comment:
Although the sponsor did not provide the stability data at -20°C in this study report, since budesonide stability in human plasma was established for at least 706 days at < -20 °C in study CRO-PK-06-178 with using validated LC-MS/MS methods, and plasma samples were analyzed within this time frame in this study, this lack of data will not a review issue.

2.7.2 Were the analytical assay methods adequately validated?

Both of the bioanalytical methods, LC-MS/MS analytical method for Study CRO-PK-06-178 and GC-MS/NCI analytical method for Study CRO-PK-03-105 and Study CRO-01-28, in phase 1 pharmacokinetic studies were appropriated validate with adequate sensitivity, selectivity, linearity, accuracy, and precision. All of the bioanalytical work, including validation, was conducted at Pharmakin GmbH, Germany.

LC-MS/MS analytical method for Study CRO-PK-06-178:
The LC-MS/MS analytical method used in study CRO-PK-06-178 to determine the plasma concentration of budesonide is considered to be appropriately validated.

- Selectivity:
  Human plasma samples from 5 different sources were analyzed, and those blank plasma samples did not exhibit signal for budesonide.
  No significant interference was detected with CPD (citrate phosphate dextrose)-anticoagulated and Li-heparin-anticoagulated plasma.

- Sensitivity:
  The lower limit of quantification (LLOQ) for budesonide in human plasma was 50.0 pg/mL with acceptable accuracy and precisions (less than 15% each).

- Calibration Curve:
  The calibration (standard) curve for budesonide was in range of 50.0 – 4999.4 pg/mL.

Linear regression equation of y = ($-0.1867*10^{-1} \pm 0.6579*10^{-2}$) + ($0.1213*10^{-2} \pm 0.3202*10^{-5}$)*x with1/x weighting were used to calculated the concentration.

- Accuracy and Precision:
  The accuracy and precision for budesonide was within acceptable range, less than 15%.
  - The inter-run precision and accuracy for budesonide was less than 6.35 % and -2.05 %, respectively.
  - The intra-run precision and accuracy for budesonide was less than 4.88 % and 2.51 %, respectively.

- Stability:
  - Freeze-Thaw Stability: stable for at least 3 freeze-thaw cycles.
  - Long-Term Stability: stable for at least 706 days at < -20°C (storage condition).
  - Short-Term Stability: stable for at least 24 hr in room temperature and stable for at least 5 days at 4 °C (autosampler).
  - Stock Stability: Stock solutions for budesonide and its internal standard were found to be stable for at least 13 day at < -20°C (storage condition) and 6 hours storage at room temperature.

GC-MS/NCI analytical method for Study CRO-PK-03-105 and Study CRO-01-28

The GC-MS/NCI analytical method used in these studies to determine the plasma concentration of budesonide is considered to be appropriately validated.

- Selectivity:
  Human plasma samples from 6 different sources were analyzed, and those blank plasma samples did not exhibit signal for budesonide.

- Sensitivity:
  The lower limit of quantification (LLOQ) of budesonide in human plasma was 50.0 pg/mL with acceptable accuracy and precisions (less than 15% each).

- Calibration Curve:
  The calibration (standard) curve for budesonide was in range of 50.0-5001.7 pg/ml.
  Linear regression equation of y = ($-0.1298*10^{-2} \pm 0.1413*10^{-2}$) + ($0.4114*10^{-3} \pm 0.6871*10^{-6}$)*x with1/x weighting were used to calculated the concentration.

- Reproducibility:
  - Study CRO-PK-03-105

  Precision and accuracy of budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	50.0	100.0	250.1	500.2	1000.3	2500.9	5001.7
Precision CV (%)	5.36	0.86	8.10	4.17	0.53	0.29	0.58
Accuracy (%)	2.59	-1.55	1.47	-3.31	-0.68	0.08	0.10

  - Study report CRO-01-28

  Precision and accuracy of budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	50.0	100.0	250.	499.9	999.9	2499.7	4999.5
Precision CV (%)	7.08	1.59	2.17	3.23	2.34	1.66	0.83
Accuracy (%)	11.72	-1.13	-2.97	-5.61	-3.63	0.66	1.03

- Accuracy and Precision:
  The accuracy and precision for budesonide was within acceptable range, less than 15% in both studies.
  Study CRO-PK-03-105:
    - The within day precision and accuracy for budesonide was less than 2.71% and -4.1 %, respectively.
    - The between day precision and accuracy for budesonide was less than 5.14% and 4.2 %, respectively.

  Study report CRO-01-28
    - Precision and accuracy of QC sample for budesonide was less than 8.11 % and -14.29 %, respectively.

- Stability:
    - In Plasma:
        - Stable in plasma for at least 3 freeze-thaw cycles.
        - Stable in plasma for at least 21 days at < -20°C (storage condition).
        - stable in plasma for at least 24 hr in room temperature
        - stable in extract for at least 72 days at in autosampler at room temperature

    - Stock Stability: Stock solutions for budesonide and its internal standard were found to be stable for at least 18 day at < -20°C (storage condition)

    - Standard curve: Budesonide calibration standards curves are stable for at least 34 days at < -20°C

Reviewer's Comment:
In Study report CRO-01-28, stability of budesonide in human plasma in storage condition of < -20°C was not established. However, since budesonide stability in human plasma was established for at least 706 days at < -20 °C in study CRO-PK-06-178 with using validated LC-MS/MS methods, this lack of stability data will not be a review issue.

3 Detailed Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~.

2 DOSAGE AND ADMINISTRATION

Mild to Moderate Ulcerative Colitis

The recommended dosage for the induction of remission in adult patients with active, mild to moderate ulcerative colitis is 9 mg taken orally once daily in the morning for up to 8 weeks. Repeated 8 week courses of UCERIS can be given for active disease.

UCERIS should be swallowed whole and not chewed or broken.

2.2 CYP3A4 Inhibitors

If concomitant administration with ketoconazole, or any other CYP3A4 inhibitor, is indicated, patients should be closely monitored for increased signs and/or symptoms of hypercorticism. Grapefruit juice, which is known to inhibit CYP3A4, should also be avoided when taking UCERIS. In these cases, discontinuation of UCERIS or the CYP3A4 inhibitor should be considered [See *Drug Interactions* (7) *and Clinical Pharmacology* (12.3)].

7 DRUG INTERACTIONS

7.1 Interaction with CYP3A4 inhibitors

Concomitant oral administration of ketoconazole (a known inhibitor of CYP3A4 activity in the liver and in the intestinal mucosa) caused an eight-fold increase of the systemic exposure to oral budesonide. If treatment with inhibitors of CYP3A4 activity (such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin, etc.) is indicated, discontinuation of the UCERIS should be considered. After extensive intake of grapefruit juice (which inhibits CYP3A4 activity predominantly in the intestinal mucosa), the systemic exposure for oral budesonide increased about two times. Ingestion of grapefruit or grapefruit juice should be avoided in connection with UCERIS administration [*See Dosage and Administration (2) and Clinical Pharmacology*, (b) (4) (12.3)].

7.2 Inhibitors of Gastric Acid Secretion (this got removed in the new version of the label)

Since the dissolution of the coating of UCERIS is pH dependent, the release properties and uptake of the compound may be altered when UCERIS is used after treatment with gastric acid reducing agents (e.g., PPIs, H_2-blockers and antacids)

8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and effectiveness of UCERIS in pediatric patients have not been established. Glucocorticosteroids, such as UCERIS may cause a reduction of growth velocity in pediatric patients.

8.5 Geriatric Use

Clinical studies of did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, UCERIS should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Hepatic (b) (4) Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism. Discontinuing the use of UCERIS tablets should be considered in these patients [See *Warnings and Precautions* (5.4)].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Need CMC Input?

(b) (4)

[redacted]

12.2 Pharmacodynamics

Budesonide has a high glucocorticoid effect and a weak mineralocorticoid effect, and the affinity of budesonide to GCS receptors, which reflects the intrinsic potency of the drug, is about 200-fold that of cortisol and 15-fold that of prednisolone.
Treatment with systemically active GCS, including Uceris, is associated with a suppression of endogenous cortisol concentrations and an impairment of the hypothalamus-pituitary-adrenal (HPA) axis function. Markers, indirect and direct, of this are cortisol levels in plasma or urine and response to ACTH stimulation.

(b) (4)

[redacted]

In a study assessing the response to ACTH stimulation test in patients treated with Uceris 9 mg once daily, the proportion of patients with abnormal response was 47% at 4 weeks and 79% at 8 weeks.

(b) (4)

[redacted]

12.3 Pharmacokinetics
Absorption:

(b) (4)

(b) (4) Following single oral administration of UCERIS 9 mg in healthy subjects, peak plasma concentration (C_{max}) (b) (4) was 1.35 ± 0.96 ng/mL (b) (4) and ~~T~~the area under the plasma concentration time curve (AUC) ~~is~~ was approximately 16.43 ± 10.52 ng·hr/mL (b) (4) The time to peak concentration (T_{max}) varied across different individual patients, but on average was 13.3 ± 5.9 hours. The pharmacokinetic parameters of UCERIS 9 mg have high degree of variability among subjects.
There was no accumulation of budesonide in respect to both AUC and Cmax following 7 days of UCERIS 9 mg once daily dosing.

(b) (4)

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

Grapefruit juice approximately doubles the systemic exposure of oral budesonide.

Distribution
The mean volume of distribution (V_{SS}) of budesonide varies between 2.2 and 3.9 L/kg in healthy subjects and in patients. Plasma protein binding is estimated to be 85 to 90% in the concentration range 1 to 230 nmol/L, independent of gender. The erythrocyte/plasma partition ratio at clinically relevant concentrations is about 0.8.

Metabolism

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

In vivo investigations with intravenous doses in healthy subjects are in agreement with the in vitro findings and demonstrate that budesonide has a high plasma clearance, 0.9-1.8 L/min. [redacted] (b) (4) These high plasma clearance values approach the estimated liver blood flow, and, accordingly, suggest that budesonide is a high hepatic clearance drug.

The plasma elimination half-life, $t_{1/2}$, after administration of intravenous doses ranges between 2.0 and 3.6 hours, [redacted] (b) (4).

Excretion

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

Special Populations

[redacted] (b) (4)

NOTE: No PK comparison was conducted between genders for this formulation.

Hepatic [redacted] (b) (4) *Impairment*

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

Renal [redacted] (b) (4) *Impairment*

The pharmacokinetics of budesonide in patients with renal impairment has not been studied. Intact budesonide is not renally excreted, but metabolites are to a large extent, and might therefore reach higher levels in patients with impaired renal function. However, these metabolites have negligible corticosteroid activity as compared with budesonide (<1/100).

Drug-Drug Interactions

Budesonide is metabolized via CYP3A4. Potent inhibitors of CYP3A4 can increase the plasma levels of budesonide several-fold. Co-administration of ketoconazole results in an eight-fold increase in AUC of budesonide, compared to budesonide alone. Grapefruit juice, an inhibitor of gut mucosal CYP3A, approximately doubles the systemic exposure of oral budesonide. Conversely, induction of CYP3A4 can result in the lowering of budesonide plasma levels [See *Dosage and Administration (2)* *and Drug Interactions (7)*].

Oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide. Budesonide does not affect the plasma levels of oral contraceptives (ie, ethinyl estradiol) [redacted] (b) (4)


(b) (4)

4 Appendices

4.1 Individual Study Review

4.1.1 Study CRO-PK-06-178 - Sponsor code CB-01-02/03

TITLE: **Bioavailability Profile of a New MMX™ Budesonide Extended Release (6, 9 Mg Tablets) Formulation Compared vs. a Controlled Ileal Release Formulation, Entocort® 3 × 3 Mg Capsules, in Healthy Volunteers**

STUDY SITE:

Sponsor:	Cosmo Technologies Ltd, Ireland
Clinical Site:	Cross Research S.A. – Phase I Unit, Via F.A. Giorgioli, CH-6864 - Arzo, Switzerland.
Analytical Site:	Pharmakin GmbH Graf-Arco-Str. 3, 89079 Ulm, Germany.

PHASE OF STUDY: Phase 1 study

OBJECTIVE:
To compare the bioavailability and PK profile of a new MMX™ 9 mg budesonide extended release tablet formulation (Cosmo S.p.A. - Italy) vs. the market reference formulation, Entocort® EC 3 mg × 3 capsules (Astra-Zeneca) and vs. MMX™ 6 mg budesonide administered under fasting conditions.

END POINTS:

Primary end-point:

- To compare the bioavailability of plasma budesonide in terms of rate of absorption through the PK parameters Cmax and Tmax, between MMX™ 9 mg budesonide extended release tablets and Entocort® EC 3 mg × 3 capsules.

Secondary end-points:

- to compare the bioavailability in terms of extent of absorption through the PK parameter of AUC0-t between MMX™ 9 mg budesonide extended release tablets and Entocort® EC 3 mg × 3 capsules
- to compare the bioavailability in terms of extent of absorption through the PK parameter of AUC0-t between MMX™ 9 mg and 6 mg budesonide extended release tablets
- to evaluate the budesonide extent of absorption through measuring the urine excretion of the main budesonide metabolite (6β-hydroxy-budesonide)
- safety assessment of test and reference study formulations

STUDY DESIGN:

Reference Product:

Entocort® EC 3 x 3 mg (R) capsules (Astra-Zeneca, Sweden)

Test Products:

Budesonide MMXTM extended release tablets 9 mg (T1)
Budesonide MMXTM extended release tablets 6 mg (T2)

This study was an open-label, randomized, single-center, single-dose, three-way cross-over, exploratory study in 12 healthy male and female subjects under fasting condition to compare the bioavailability and PK profile of a new MMX™ 9 mg budesonide extended release tablets formulation vs. the market reference formulation, Entocort® EC 3 mg × 3 capsules and vs. MMX™ 6 mg budesonide extended release tablets. This study consisted of three treatment periods, each of which included blood and urine sampling for 36 hours, and a washout period of 5 calendar days between treatments. Subjects were assigned to treatment sequence according to the randomization schedule. Drugs were administered orally following at least 10 hrs of overnight fasting with 240 mL of water. Subjects were instructed to swallow the whole tablet/capsules without chewing. No food was allowed for additional 5 hr. Standardized lunch and dinner were provided 5 and 12 hour pose-dose. 150 mL of mineral water was encouraged to take every 2 hour for 6 hours post dosing.

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 18-55 with good health with a Body Mass Index between 18-29 kg/m2, were eligible to enroll.

Key exclusion criteria:

- *Diseases*: relevant history of renal, hepatic, cardiovascular, respiratory diseases, that might interfere with the aim of the study. In particular, no history of GI diseases such as ulcerative colitis, IBD, constipation, intolerance to lactose; no neoplasias.
- *Medications*: medications including OTC and CYP3A4 inducers/inhibitors, during 2 weeks before the start of the study. Grapefruit and grapefruit juice were forbidden from 24 h before first drug administration until the end of the study.
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered might affect the outcome of the study

Study Population:

This study had 13 healthy volunteers (6 males and 7 females) enrolled and 12 of them completed the study as planned receiving all 3 treatments. One subject withdrew from the study during Period III for personal reason. Safety population included all 13 subjects and PK population included 12 subjects who completed the study.

All subjects were Caucasian.

Summary of Demographic

Parameters	**Category/statistics**	**All subject (N= 13)**
Gender	Male	6
	Female	7

Age (years)	Mean	36.8
	SD	9.2
	Range	22-51
Height (cm)	Mean	171.2
	SD	10.2
	Range	154-189
Weight (kg)	Mean	67.7
	SD	14.6
	Range	46.5-98
BMI (kg/m2)	Mean	22.9
	SD	3.0
	Range	18.2-27.4

Pharmacokinetic Measurements:
PK blood samples (10 mL) to determine the plasma budesonide were taken at pre-dose (0), 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 30, 36 h after the administration of dose (21 blood samples).

Urine samples were collected at interval of pre-dose (0), 0-12, 12-24, 24-36 h post-dose to determine budesonide main metabolite (6β-hydroxy-budesonide).

The pharmacokinetic parameters $AUC_{0\text{-}t_{last}}$, $AUC_{0\text{-}\infty}$, C_{max}, T_{max}, $t_{½}$, $\%AUC_{extrap}$, MRT, and Xut (cumulative urinary excretion) were determined for budesonide and budesonide main metabolite, using non-compartmental analysis.

Analysis of variance (ANOVA) was performed on log-transformed data for C_{max} and $AUC_{0\text{-}t}$. T_{max} was compared using the non-parametric sign test (and the Shapiro-Wilk test to show the normal distribution of data). C_{max} and $AUC_{0\text{-}t}$ and $Xu_{0\text{-}36h}$ were compared based on an ANOVA for a 3 ways crossover design and bioequivalence concluded if the 90% CI for the ratio of the geometric means of both the two parameters C_{max} and $AUC_{0\text{-}t}$ fell within the acceptance range of 80-125%. This comparison was performed for T1 vs. R and for dose-normalised T1 vs. T2. The assessment of the 90% CI corresponded to the two one-sided t-tests of Schuirmann at the level of significance of 5%. Treatment sequence, treatment, random subject within treatment sequence and period were analysed as sources of variability.

All Plasma concentrations that were below the quantification limit (BQL) were treated as zero for descriptive statistics and estimation of PK parameters.

Concomitant Medications

Subject	Trade name	Active ingredients	Reason	Dose	Route	Related to AE(s)	Start	End	WHO Drug Dictionary code*
4	Tachipirina	Paracetamol 500 mg	Upper respiratory tract infection symptoms	OD	OS	1	14MAR07	15MAR07	000200-01-040
6	Dafalgan	Paracetamol 500 mg	Upper respiratory tract infection	OD	OS	1	20MAR07	21MAR07	000200-01-057
7	Fedra	Gestodene 75 ug + Ethinylestradiol 20 ug	Contraception	OD	OS		01JAN05	Ongoing	008616-01-029
9	Harmonet	Gestodene 75 ug + Ethinylestradiol 20 ug	Contraception	OD	OS		01JAN96	Ongoing	008616-01-019

Bioanalytical Analysis:

- The concentration of both budesonide in plasma and 6β-hydroxy-budesonide in urine samples were determined using validated LC-MS/MS methods.
- Plasma and urine samples were stored frozen at ≤ -20°C until analysis

Plasma budesonide Concentration:

- Calibration curve concentration ranged from 50.0-4999.4 pg/ml. (stored frozen <-20°C).
  - Calibration standard solutions and QC samples were used within the time period in which stability was established.
  - Calibration curve was prepared on 02/21/2007 and 04/24/2007(stored frozen <-20°C).
  - QC samples were prepared on 02/21/2007 (stored frozen <-20°C).

- The highest plasma budesonide concentration observed in this study were 4227.2 ng/mL, which was within the calibration standard range.
- Lower limit of quantification is 50.0 pg/mL
- Linear regression equation of y = a + bx with 1/x weighting were used to calculated the concentration. R^2 ranged from 0.999561 to 0.99996.

Precision and accuracy of budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	50.0	100.0	250.0	499.9	999.9	2499.7	4999.4
Precision CV (%)	0.74	1.71	1.06	0.5	0.37	0.54	0.37
Accuracy (%)	-2.6	2.95	-0.61	0.44	-0.41	0.40	-0.17

Precision and accuracy of budesonide quality controls:

Nominal QC Conc (pg/mL)		84	599.8	3998.8
Picosulfate	Precision (%)	5.11	3.17	2.98
	Accuracy (%)	-2.13	-0.17	0.70

- The analytical method used for this study is considered to be appropriately validated.

- Plasma samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability of plasma budesonide has been established.
  - Plasma samples were collected between 03/08/2007 through 04/19/2007.
  - Plasma samples for budesonide was analyzed between April 5th, 2007 to April 25th, 2007
  - Stability of budesonide in human plasma at -20 °C was established for at least for 706 days.

Urine 6β-hydroxy-budesonide Concentration:

- During each interval, the containers were kept refrigerated at 4°C. After all urine samples were collected, they were kept at ≤ -20°C until analysis.
- Calibration curve concentration ranged from 50.0-1000.4 ng/ml.
  - Calibration standard solutions and QC samples were used within the time period in which stability was established.
  - Calibration curve was prepared on 03/07/2007(stored frozen <-20°C).
  - QC samples were prepared on 03/08/2007 (stored frozen <-20°C).

- Lower limit of quantification is 5.00 ng/ml.
- Linear regression equation of y = a + bx with1/x weighting were used to calculated the concentration. R^2 ranged from 0.999504 to 0.999853.

Precision and accuracy of urine 6β-hydroxy-budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	5.00	10.00	25.01	50.02	100.04	250.1	500.2	1000.4
Precision CV (%)	5.93	5.76	2.62	5.45	5.72	1.24	0.92	0.24
Accuracy (%)	-0.25	-8.56	5.90	-0.59	-0.36	4.83	0.48	-1.44

Precision and accuracy of urine 6β-hydroxy-budesonide quality controls:

Nominal QC Conc (ng/mL)		8.00	80.01	800.1
Picosulfate	Precision (%)	6.08	5.86	3.46
	Accuracy (%)	2.79	4.69	1.00

- The analytical method used for above study is considered to be appropriately validated.
- Urine samples, stored at approximately -20°C, were analyzed within the time period for which the long-term stability 6β-hydroxy-budesonide has been established.
    - Plasma samples were collected between 03/08/2007 through 04/19/2007
    - urine samples were analyzed between April 17th, 2007 to April 23th, 2007
    - Stability of *6β-hydroxy-budesonide* in human urine at -20 °C was established for at least for 42 days.

Bioanalytical Method Validation:

Plasma Concentration:

The LC-MS/MS analytical method used in this study to determined the plasma concentration of budesonide are considered to be appropriately validated.

- Selectivity:
  Human plasma samples from 5 different sources were analyzed and those blank plasma samples did not exhibit signal budesonide.
  No significant interference was detected with CPD (citrate phosphate dextrose)-anticoagulated and Li-heparin-anticoagulated plasma.
- Sensitivity:
  The lower limit of quantification (LLOQ) for human plasma budesonide was 50.0 pg/mL, with acceptable accuracy and precisions (less than 15% each).
- Calibration Curve:
  The calibration (standard) curve for budesonide was in range of 50.0 – 4999.4 pg/mL.
  Linear regression equation of $y = (-0.1867*10^{-1} \pm 0.6579*10^{-2}) + (0.1213*10^{-2} \pm 0.3202*10^{-5})*x$ with1/x weighting were used to calculated the concentration.
- Accuracy and Precision:
  The accuracy and precision for budesonide was within acceptable range, less than 15%.
    - The inter-run precision and accuracy for budesonide was less than 6.35 % and -2.05 %, respectively.

- The intra-run precision and accuracy for budesonide was less than 4.88 % and 2.51 %, respectively.

- Stability:
  - Freeze-Thaw Stability: stable for at least 3 freeze-thaw cycles.
  - Long-Term Stability: stable for at least 706 days at < -20°C (storage condition).
  - Short-Term Stability: stable for at least 24 hr in room temperature and stable for at least 5 days at 4 °C (autosampler).
  - Stock Stability:
    Stock solutions for budesonide and its internal standard were found to be stable for at least 13 day at < -20°C (storage condition) and 6 hours storage at room temperature.

Urine 6β-hydroxy-budesonide Concentration:
The LC-MS/MS analytical method used for above study to determined the urine concentration of 6β-hydroxy-budesonide is considered to be appropriately validated.

- Selectivity:
  Human urine samples from six different sources were analyzed and those blank plasma samples did not exhibit signal for 6β-hydroxy-budesonide.
- Sensitivity:
  The lower limit of quantification (LLOQ) for human urine 6β-hydroxy-budesonide was 5.00 ng/, with acceptable accuracy and precisions (less than 15% each).
- Calibration Curve:
  The calibration (standard) curve for was in range of 5.0-100.40 ng/mL. Linear regression equation of $y = (-0.1461*10^{-2} \pm 0.1124*10^{-1}) + (0.4777*10^{-2} \pm 0.2842*10^{-4})*x$ with1/x weighting were used to calculated the concentration.
- Accuracy and Precision:
  The accuracy and precision for both picosulfate and BMPH in urine were within acceptable range, less than 15%.
  - The inter-run precision and accuracy for urine 6β-hydroxy-budesonide was less than 9.32 % and 5.94 % respectively.
  - The intra-run precision and accuracy 6β-hydroxy-budesonide was less than 5.44 % and -7.73 % respectively.
- Stability:
  - Freeze-Thaw Stability: stable for at least 3 freeze-thaw cycles.
  - Long-Term stability: stable for at least 42 days at < -20°C.
  - Short-Term Stability: stable for at least 24 hr in room temperature and stable for at least 5 days at 4°C.
  - Stock Stability:
    Stock solutions for 6β-hydroxy-budesonide and its internal standard were found to be stable for at least 47 day at < -20°C (storage condition) and 6 hours storage at room temperature

RESULTS:
Of 13 enrolled healthy subjects, 12 subjects completed study as planned receiving all three different treatments. One subject (subject N. 2) exhibited pre-dose values higher than LQL in the

third period. Since pre-dose values were higher than 5% of C_{max}, PK analysis was conducted both including and excluding this subject.

Definision of Population:

Population	N	Definition
ITT	13	All subjects who took at least a dose of study medication
PP	12	All subjects who completed the study according to the protocol
PP-control	11	All subjects who completed the study according to the protocol and did not show pre-dose values

Figure 1. Mean Budesonide plasma profiles following administration of Budesonide MMX™ 9 mg tablets (T1), Budesonide MMX™ 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules (R) – PP population, N=12

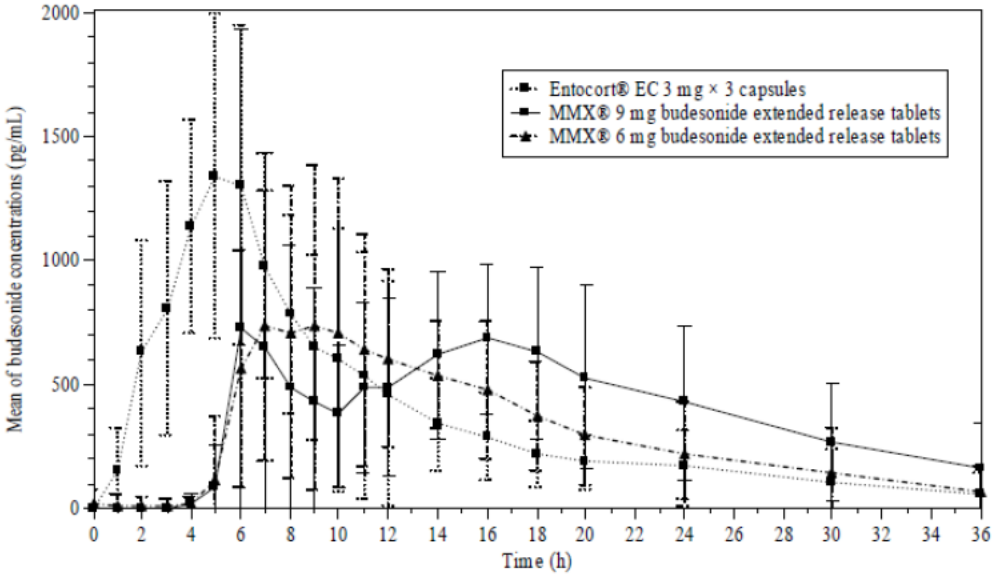


Figure 11.4.1 Budesonide plasma profiles following administration of Budesonide MMX™ 9 mg tablets (T1), Budesonide MMX™ 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules (R) – PP population, N=12

Mean ± SD budesonide PK parameters after administration of T1, T2 and R – PP population, N=12, and PP-control population,N=11

Table 11.4.1 **Mean ± SD budesonide PK parameters after administration of T1, T2 and R – PP population, N=12, and PP-control population, N=11**

Plasma budesonide PK parameters - Mean ± SD (CV%)			
	MMX™ 9 mg (T1)	**MMX™ 6 mg (T2)**	**Entocort® EC 3 x 3 mg**
PP-population (N=12)			
T_{max}(h)	13.3 ± 5.9 (44.5)	11.4 ± 5.1 (44.4)	4.8 ± 1.4 (28.6)
C_{max} (pg/mL)	1348.8 ± 958.8 (71.1)	1158.5± 532.4 (46.0)	1555.9 ± 588.0 (37.8)
AUC_{0-t} (pg/mLxh)	13555.9 ± 7816.9 (57.7)	10818.3 ± 4401.6 (40.7)	13394.6 ± 5983.0 (44.7)
$AUC_{0-\infty}$ (pg/mL×h)	16431.2 ± 10519.8 (64.0)	11533.6 ± 4738.5 (41.1)	14057.0 ± 6378.7 (45.4)
C_{max} (pg/mL) / dose	149.9 ± 106.5 (71.1)	193.1 ± 88.7 (46.0)	172.9 ± 65.3 (37.8)
AUC_{0-t} (pg/mLxh) / dose	1506.2 ± 868.5 (57.7)	1803.0 ± 733.6 (40.7)	1488.3 ± 664.8 (44.7)
$t_{1/2}$(h)	8.2 ± 3.7 (44.7)	6.6 ± 2.4 (36.8)	7.7 ± 1.8 (23.1)
MRT (h)	21.4 ± 6.8 (31.5)	17.0 ± 5.7 (33.7)	11.6 ± 2.7 (23.1)
PP-control population (N=11)			
T_{max}(h)	12.8 ± 6.0 (46.7)	11.0 ± 5.1 (46.4)	4.6 ± 1.4 (29.4)
C_{max} (pg/mL)	1427.3 ± 964.3 (67.6)	1154.9 ± 558.2 (48.3)	1549.0 ± 616.2 (39.8)
AUC_{0-t} (pg/mLxh)	13963.7 ± 8063.4 (57.7)	10331.4 ± 4264.1 (41.3)	13741.1 ± 6147.5 (44.7)
$AUC_{0-\infty}$ (pg/mL×h)	17041.8 ± 10807.8 (63.4)	11533.6 ± 4738.5 (41.1)	14462.8 ± 6572.3 (45.4)
C_{max} (pg/mL) / dose	158.6 ± 107.1 (67.6)	192.5 ± 93.0 (48.3)	172.1 ± 68.5 (39.8)
AUC_{0-t} (pg/mLxh) / dose	1551.5 ± 895.9 (57.7)	1721.9 ± 710.7 (41.3)	1526.8 ± 683.1 (44.7)
$t_{1/2}$(h)	8.4 ± 3.7 (44.0)	6.6 ± 2.4 (36.8)	7.9 ± 1.7 (21.0)
MRT (h)	21.4 ± 7.1 (33.1)	17.0 ± 5.7 (33.7)	11.8 ± 2.7 (23.1)

Reviewer's Comment:

- Although test formulation budesonide MMX 9 mg and the reference product Entocort EC have similar exposure regarding the AUC and Cmax, these two products have different PK profiles.
- Budesonide plasma concentrations and the its PK parameters have a high inter-subject variability (based on CV%)
    - The observed inter-subject variability is generally lower for Entocort® EC whose absorption occurs earlier and it is faster.
- Extent of absorption based on AUC is similar among different formulations.
- High and low strength of test formulations T1 and T2 showed differences in the absorption profile. The sponsor attributes this difference to the high inter-subject variability in the absorption process throughout the whole colon and the sigmoid.
- MRT was higher for test formulations (MMX 6 and 9 mg) compared to reference formulation (Entocort EC), consistent with the expected PK profiles of different formulations.
- There appears to be double peaks (based on the both mean profile and individual profiles) for the test formulations (MMX 6 and 9 mg), the first peak being close to the Tmax of the reference product Entocort EC.

Budesonide MMXTM 9 mg (T1) vs Entocort® 3 x3 mg (R)

Budesonide MMX™ 9 mg (T1) vs Entocort® EC 3 x 3 mg (R)		
	PP-population (N=12)	**PP-control population (N=11)**
AUC_{0-t}		
Point estimate (ratio of geometric means) %	91%	91%
90% CI (ratio of the geometric means)	77 – 108%	77 – 108%
C_{max}		
Point estimate (ratio of geometric means)	79%	87%
90% CI (ratio of the geometric means)	63 - 100%	70 - 108%

Reviewer's Comment:

The 90 % confidence interval (CI) for both AUC and C_{max} of budesonide were outside the limit of 80 - 125% indicating that Budesonide MMX™ 9 mg tablets (T1) and Entocort® EC 3 x 3 mg capsules (R) have different release characteristic, and Budesonide MMX™ 9 mg tablets have

lower rate and but similar extent of budesonide absorption compared to Entocort® EC administered at the same dose.

Budesonide MMXTM 9 mg (T1) vs. 6 mg (T2)

Table 11.4.4 Statistical analysis of secondary variables (T_{max} and dose-normalised C_{max} and AUC_{0-t}) between T1 and T2

Budesonide MMX™ 9 mg (T1) vs 6 mg (T2)		
	PP-population (N=12)	**PP-control population (N=11)**
C_{max} / dose		
Point estimate (ratio of geometric means) %	75%	82%
90% CI (ratio of the geometric means)	59 – 95%	66 – 102%
AUC0-t / dose		
Point estimate (ratio of geometric means) %	80%	86%
90% CI (ratio of the geometric means)	67 – 94%	73 – 102%

Reviewer's Comment:

The 90 % confidence intervals (CI) for both C_{max} and AUC_{0-t} budesonide were outside the limits of 80 to 125%. This result, together with the corresponding Point Estimate values (75% and 80% for C_{max} and AUC_{0-t}, respectively), indicated that the 6 mg formulation is more bioavailable compared to the 9 mg formulation.

Cumulative urinary excretion of 6-β-hydroxy-budesonide in the 0-36 h pot-dose collection interval after administration of Budesonide MMX™ 9 mg tablets (T1), Budesonide MMX™ 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules (R) – PP population, N=12

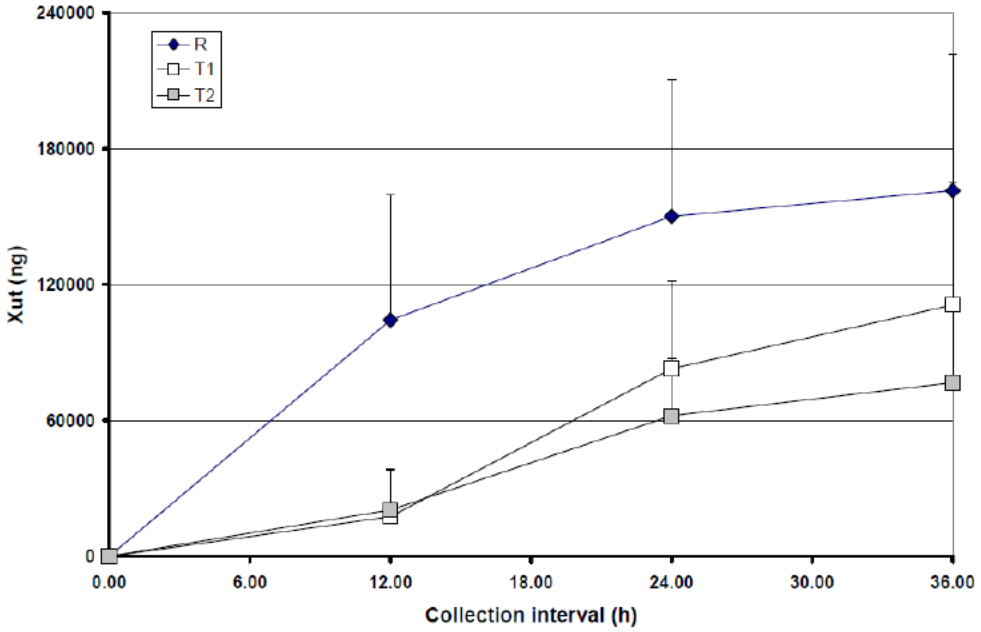


Figure 11.4.2 Cumulative urinary excretion of 6-β-hydroxy-budesonide in the 0-36 h pot-dose collection interval after administration of Budesonide MMX™ 9 mg tablets (T1), Budesonide MMX™ 6 mg tablets (T2) and Entocort® EC 3 x 3 mg capsules (R) – PP population, N=12

Mean (± SD) cumulative 6-β-hydroxy-budesonide urinary excretion (Xu0-36h and Xu0-36h / dose) PK parameters _ PP population, N=12, and PP-control population, N=11

Table 11.4.2 Mean (± SD) cumulative 6-β-hydroxy-budesonide urinary excretion (Xu_{0-36h} and Xu_{0-36h} / dose) PK parameters _ PP population, N=12, and PP-control population, N=11

Cumulative 6-β-hydroxy-budesonide urinary excretion – Mean ± SD (CV%)			
	MMX™ 9 mg (T1)	MMX™ 6 mg (T2)	Entocort® EC 3 x 3 mg
PP population (N=12)			
Xu_{0-36h} (ng)	111061.9 ± 53992.6 (48.6)	76683.4 ± 31879.4 (41.6)	161535.4 ± 60309.8 (37.3)
Xu_{0-36h} (ng) /dose	12340.2 ± 5999.2 (48.6)	12780.6 ± 5313.2 (41.6)	17948.4 ± 6701.1 (37.3)
PP-control population (N=11)			
Xu_{0-36h} (ng)	114449.9 ± 55273.9 (48.3)	74729.9 ± 32673.4 (43.7)	164572.0 ± 62283.9 (37.8)
Xu_{0-36h} (ng) /dose	12716.6 ± 6141.5 (48.3)	12455.0 ± 5445.6 (43.7)	18285.8 ± 6920.4 (37.8)

Table 11.4.5 Statistical analysis of secondary variables (Xu_{0-36h}) between T1 and R and between (dose normalised) T1 and T2

Budesonide MMX™ 9 mg (T1) vs Entocort® EC 3 x 3 mg (R)		
Xu_{0-36h}	PP-population (N=12)	PP-control population (N=11)
Point estimate (ratio of geometric means) %	66%	67%
90% CI (ratio of the geometric means)	54 – 81%	54 – 83%
Budesonide MMX™ 9 mg (T1) vs 6 mg (T2)		
Xu_{0-36h}		
Point estimate (ratio of geometric means) %	96%	102%
90% CI (ratio of the geometric means)	79 – 117%	82 – 126%

Reviewer's Comment:

The sponsor only measured the metabolite 6β-hydroxy-budesonide in the urine although budesonide supposed to have 2 major metabolites, 6β-hydroxy budesonide and 16α-hydroxy prednisolone. Analysis of 6β-hydroxy-budesonide urinary excretion (Xu_{0-36h}) demonstrated a different rate and extent of elimination among formulations (T1 vs. R). Urinary elimination of 6β-hydroxy-budesonide appears to be faster and higher in reference product Entocort EC compared to the test formulations of MMX 6 or 9 mg tablets. However, the results of the comparison of the 6 and 9 mg doses when dose normalized (T1 vs. T2) of MMX formulations were borderline. Since the sponsor only measured one metabolite, result of this study is difficult to interpret in respect to overall elimination of budesonide.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, haemotology, clinical chemistry, urinalysis, pregnancy test for female subjects, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no deaths, or serious adverse event (SAE) during the study. Overall, 3 subjects reported experiencing AEs during the study. 1 with T2 formulation consisted of upper respiratory tract infection and 2 with R formulation and consisted of headache and upper respiratory tract infection. Of these 3 AEs, only 1 AE reported with R formulation (i.e. headache) was judged as possibly related to treatment. All the AEs were considered to be mild to moderate intensity.

Table 14.3.11 Display of AEs – ITT population, N=13

Treatment	Subject	MedDRA Description*	Type	MedDRA LLT code*	Time from administration	Duration	Intensity	Relationship	Action taken**
T2	4	Upper respiratory tract infection viral NOS	Single episode	10046308	1 day and 12:51 h	3 days and 11:00 h	Moderate	Unlikely/none	STC(Tachipirina;OD;OS)
R	3	Headache	Single episode	10019211	1 day and 6:54 h	4:00 h	Mild	Possible	None
	6	Upper respiratory tract infection viral NOS	Single episode	10046308	23:45 h	6 days and 23:00 h	Moderate	Unlikely/none	STC(Dafalgan;OD;OS)

*MedDRA dictionary version 10.0 was used for coding
** STC Specific Therapeutic Countermeasures

REVIEWER'S COMMENTS:

- *As expected, budesonide MMX™ extended release 9 mg tablets (T1) is not equivalent to the reference formulation Entocort® EC 3 x 3 mg capsules (R) regarding both rate and extent of absorption.*
- *Including or excluding one subject* with pre-dose level higher than 5% of C_{max} did not change the result of PK analysis.
- *5 days of washout period was acceptable as the half –life of budesonide is 6-8 hours.*
- *The study was conducted only in Caucasian subjects. Since there is not major polymorphism in budesonide metabolizing enzyme CYP3A4, the ethnic invariability in this study is not a major concern.*
- *Co-Medication*
    - *There is no major drug-drug interaction is expected for Subjects 7 and 9 who took contraceptive that contain Ethinyl estradiol 20 ug. According to the Entocort EC label, oral contraceptives containing ethinyl estradiol, which are also metabolized by CYP3A4, do not affect the pharmacokinetics of budesonide and budesonide does not affect the plasma levels of oral contraceptives.*
    - *For subject 4 and 6 who took Paracetamol (acetaminophen), there is no major drug-drug interaction is expected between the budesonide and co-medication paracetamol (acetaminophen). Both of these subjects took acetaminophen during the washout periods, 2 days before the administration of budesonide in the next period. With short half-life of 2-4 hours, acetaminophen is expected to be cleared from the plasma by the time that budesonide was administered during the next period.*
    - *No obvious drug interaction/interference was noted from the visual inspection of individual concentration profiles for these subjects who had concomitant medication.*

4.1.2 Study CRO-PK-03-105 - Sponsor code Bud 1001

TITLE: **Multiple Dose Pharmacokinetics and Food Effect Study of a New Budesonide 9 mg Extended Release Oral Formulation in Male Healthy Volunteers**

STUDY SITE:

Sponsor: (b) (4)

Clinical Site: Cross Research S.A. – Phase I Unit, Via F.A. Giorgioli, CH-6864 - Arzo, Switzerland.

Analytical Site: Pharmakin GmbH
P.O.B. 1780, D- 89079 Ulm, Germany.

PHASE OF STUDY: Phase 1 study

OBJECTIVE:
Aim of the present study was to assess the extent, if any, of food on the budesonide absorption rate and to determine the steady-state PK profile (under fast state) of the steroid when administered as MMX-9 mg budesonide tablets.

END POINTS:
- 1st study period (food effect): to evaluate the food-effect on PK of budesonide in plasma after single oral administration of budesonide, C_{max}, T_{max}, AUC_t, AUC_{inf} were analysed
- 2nd study period (steady state PK): to evaluate the steady state PK of budesonide after multiple dose administration, Css_{max}, Css_{min}, tss_{max}, $C_{average}$, AUCss were analyzed.

STUDY DESIGN:

Reference Product: N/A

Test Products: Budesonide MMX™ extended release tablets 9 mg

This study was an open-label, randomized, single-center, balanced , cross-over, study in 12 healthy male subjects to explore the effect of food (phase 1) and PK profile following multiple dosing (phase2) of the a new MMX™ 9 mg budesonide extended release tablets formulation. This study consisted of two phases separated by 1 week of washout period.

In the phase 1 (food effect), following overnight fasting, the subjects were randomized to either fasting (FA) group or fed (FE) group. In FE group, the subjects were given high fat, high calories breakfast. A single dose budesonide 9 mg tablet was administered orally with 240 mL of water within 5 min after the breakfast. In the FA group, following at least 10 hr of overnight fasting, a single dose budesonide 9 mg tablet was given orally with 240 mL of water. Standardized meals were provided at 5 and 12 hour post-dose. For both groups, the blood samples were collected up to 48 hours. Following 1 week of washout period, the subjects were reassigned to the FA or FE treatment according to the cross-over study design.

The phase 2 (multiple dose PK) part of the study started after another 7 days of washout period following the phase 1 study. the test medication, budesonide 9 mg tablet, was administered orally

once daily after an overnight fasting of 12 hours, every morning for 7 days with 240 ml water. Blood samples were collected at pre-dose at day 1, 3, 5 and 6. On day 7, blood samples were collected pre-dose, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 h after last dose. Feces were collected daily until 48 h post dose of last dose on day 7. Standardized breakfasts, lunches and dinners, based on the normal caloric need of a male adult with normal weight and moderate physical activity were served at 2, 5 and 12 h after each morning drug administration.

Key inclusion criteria:

- Healthy males subjects ages between 18-45 with good health with a Body Mass Index between 18-30 kg/m^2, were eligible to enroll.

Key exclusion criteria:

- *Diseases*: relevant history of renal, hepatic, gastrointestinal, cardiovascular, haemotological, respiratory, endocrine or neurologic diseases, that might interfere with the aim of the study. In particular, no history of GI diseases, IBD, intolerance to lactose; no neoplasias
- *Medications*: medications during 2 weeks before the start of study, in particular, drug affecting GI physiology.
- *Allergy*: ascertained or presumptive hypersensitivity to the active principle and/or formulations' ingredients; history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered might affect the outcome of the study
- Grapefruit consumption was not allowed since 24 h before the 1st drug administration until the end of the study.

Study Population:

This study had 12 healthy male volunteers enrolled and all of them completed the study as planned. No subject withdrew from the study.

All subjects were Caucasian male.

Summary of Demographic

Parameters	**Category/statistics**	**All subject (N= 12)**
Gender	Male	12
	Female	0
Age (years)	Mean	22.3
	SD	4.0
	Range	18-30
Height (cm)	Mean	177.4
	SD	7.6
	Range	167-189
Weight (kg)	Mean	74.3
	SD	8.9
	Range	64-89
BMI (kg/m2)	Mean	23.5
	SD	2.6
	Range	20.1-29.1

Pharmacokinetic Measurements:

Phase 1:
For both FE (fed) and FA (fasted) group, PK Blood samples (10 mL) were collected at pre-dose, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 30, 36 and 48 h after the administration of dose (16 blood samples).

Phase 2:
Pre-dose PK blood samples were collected on days 1, 3, 5 and 6.
On day 7, PK blood samples were collected at pre-dose and 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 36 and 48 h after last dose.
Feces were collected daily until 48 h post dose of last dose on day 7.

The following pharmacokinetic parameters were determined for budesonide using KINETICA™ 2003 version software with non-compartmental model.
Phase 1(food effect): $AUC_{(0\text{-}t_{last})}$, $AUC_{(0\text{-}\infty)}$, $C_{max,}$, $T_{max,}$,t_{lag}, $t_{½\ z}$, , MRT,
Phase2 (steady state PK): $Css_{max,}$ $Css_{min,}$ $tss_{max,}$ $C_{average}$, AUCss, %PTF (peak-through-fluctuation percentage)

For C_{max} and $AUC_{0\text{-}t}$, analysis of variance (ANOVA) was performed on log-transformed data at the level of significance $p<0.05$. The 90% CI for the ratio of the values obtained for the FE and FA condition was calculated; A two one-sided t-test was carried out as a confirmation. Absence of a food effect was concluded when the 90% CI for the ratio of means (geometric means based on log transformed data) between FE and FA treatment met the interval 80%-125% for both AUC and C_{max}.

Concomitant Medications
No one was taking concomitant medication.

Bioanalytical Analysis:

- The concentration of budesonide in plasma samples were determined using validated GC-MS/NCI with SIM-detection methods.
- Human Plasma samples were stored frozen at $\leq$ -20°C until analysis
- Calibration curve concentration ranged from 50.0-5001.7 pg/ml. (stored frozen <-20°C).
    - Calibration standard solutions and QC samples were used within the time period in which stability was established.
        - Calibration curve and QC samples were prepared on 07/07/2003 (stored frozen <-20°C).
        - Calibration curve and QC samples were used between 07/16/2003 and 08/12/2003 (stored frozen <-20°C).
        - Budesonide calibration standards are stable for at least 34 days at < -20°C
- Lower limit of quantification is 50.0 pg/mL
- Linear regression equation of y = a + bx with1/x weighting were used to calculated the concentration. R^2 ranged from 0.9993 to 1.0000.

Precision and accuracy of budesonide quality controls:

Nominal QC Conc (pg/mL)	64.2	401.0	4009.6
Precision (%)	2.31	3.15	3.76
Accuracy (%)	1.25	-3.31	-1.09

- The analytical method used for above study is considered to be appropriately validated.
- The highest plasma budesonide concentration observed in this study was 3403.2 ng/mL, which was within the calibration standard range.
- Plasma samples, stored at approximately -20°C, were NOT analyzed within the time period for which the long-term stability of plasma budesonide has been established.
  - Plasma samples were collected between 06/05/2003 through 06/24/2003.
  - Plasma samples were received at the analytical site on 06/30/2003.
  - Plasma samples for budesonide was analyzed between 07/07/2003-08/12/2003
  - Stability of budesonide in human plasma at -20 °C was established for at least for 21 days.

Reviewer Comment:
Although budesonide in plasma samples were not analyzed within the time frame in which stability was established (21 days) in this study, budesonide stability in human plasma was established for at least 706 days at < -20 °C in study CRO-PK-06-178 - Sponsor code CB-01-02/03 (single dose PK study) with using validated LC-MS/MS methods.

Bioanalytical Method Validation:
The GC-MS/NCI analytical method used in this study to determine the plasma concentration of budesonide is considered to be appropriately validated.

- Selectivity:
  Human plasma samples from 6 different sources were analyzed and those blank plasma samples did not exhibit signal budesonide.
- Sensitivity:
  The lower limit of quantification (LLOQ) for human plasma budesonide was 50.0 pg/mL, with acceptable accuracy and precisions (less than 15% each).
- Calibration Curve:
  The calibration (standard) curve for budesonide was in range of 50.0-5001.7 pg/ml. Linear regression equation of $y = (-0.1298*10^{-2} \pm 0.1413*10^{-2}) + (0.4114*10^{-3} \pm 0.6871*10^{-6})*x$ with1/x weighting were used to calculated the concentration.
- Reproducibility
  Precision and accuracy of budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	50.0	100.0	250.1	500.2	1000.3	2500.9	5001.7
Precision CV (%)	5.36	0.86	8.10	4.17	0.53	0.29	0.58
Accuracy (%)	2.59	-1.55	1.47	-3.31	-0.68	0.08	0.10

- Accuracy and Precision:
  The accuracy and precision for budesonide was within acceptable range, less than 15%.
  - The within day precision and accuracy for budesonide was less than 2.71% and -4.1 %, respectively.
  - The between day precision and accuracy for budesonide was less than 5.14% and 4.2 %, respectively.
- Stability:
  - In Plasma:
    - Stable in plasma for at least 3 freeze-thaw cycles.
    - Stable in plasma for at least 21 days at < -20°C (storage condition).
    - stable in plasma for at least 24 hr in room temperature

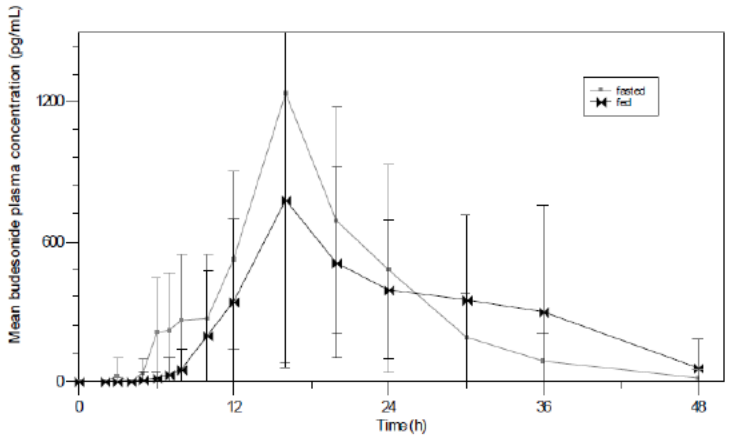
- stable in extract for at least 72 days at in autosampler at room temperature
- Stock Stability: Stock solutions for budesonide and its internal standard were found to be stable for at least 18 day at < -20°C (storage condition)
- Standard curve: Budesonide calibration standards curves are stable for at least 34 days at < -20°C

RESULTS:

All of enrolled 12 subjects completed study as planned.

Phase 1: Food Effect:

Figure 1. Mean (N=12) budesonide plasma concentration (pg/mL) vs. time profiles after single administration of MMX®-9 mg budesonide tablets under a Fed (black plot) and a Fasted condition (grey plot). N=12



Mean ± SD budesonide PK parameters under fed (FE) and fasted (FA) conditions, N=12

PK parameter	FA	FE
C_{max} (pg/mL)	1428.7 ± 1013.5	1039.9 ± 601.4
t_{lag} (h)	7.4 ± 4.2	9.8 ± 3.6
T_{max} (h)	16 ± 3.4	20.7 ± 8.7
AUC_{48} (pg×h/mL)	14814 ± 11254	13486 ± 9368.7
AUC_{∞} (pg×h/mL)	15503 ± 11340	14608 ± 9937.9
$t_{1/2}$ (h)	5.4 ± 2.0	5.6 ± 2.7
MRT (h)	19.9 ± 4.6	24.3 ± 7.1

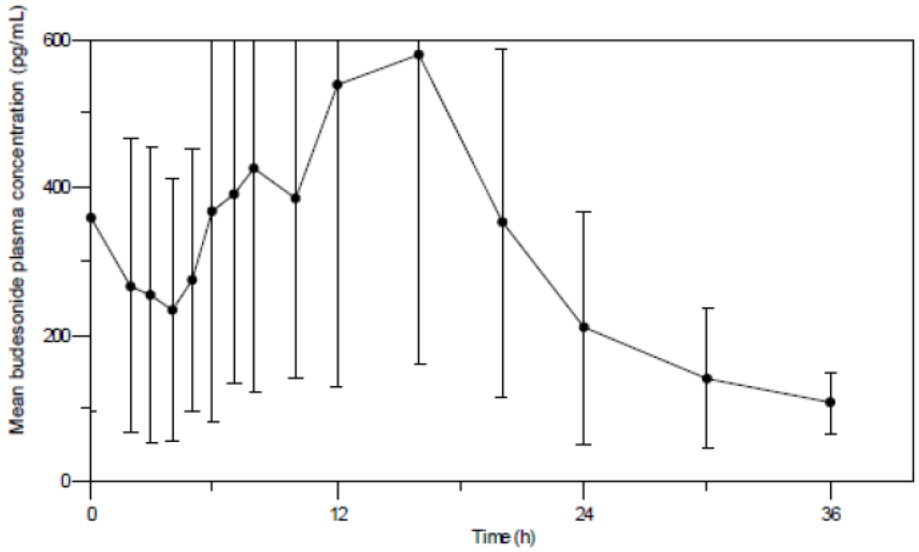
90% CI for the ration of geometric mean between fed and fasted condition for Cmax was 67.7-133.7% and for AUC for 66.9-130.87% and did not meet the limit of 80% to 125% to excluded the effect of food.

Reviewer's Comment:

- There appears to be a delay in absorption (based on t_{lag}) under fed condition compared to fasted condition.
- For both AUC and Cmax, 90% confidence interval for geometric mean ratio between fed and fasted states did not meet the pre-specified interval of 80-125% to exclude the effect of food on budesonide absorption. From on the numerical comparison based on the

arithmetic means, while the extent of absorption, AUC, was decreased only by 5-10%, Cmax appears to decrease by approximately 27% in presence of food. The observed statistical difference between fed and fated stated could be due to the high variability in budesonide PK parameters. However, this small magnitude of difference in exposure in present of food is not considered to be clinically significant.

Mean plasma budesonide concentration vs. time profile, obtained at steady state after 7 days of treatment with MMX®-9mg budesonide tablets

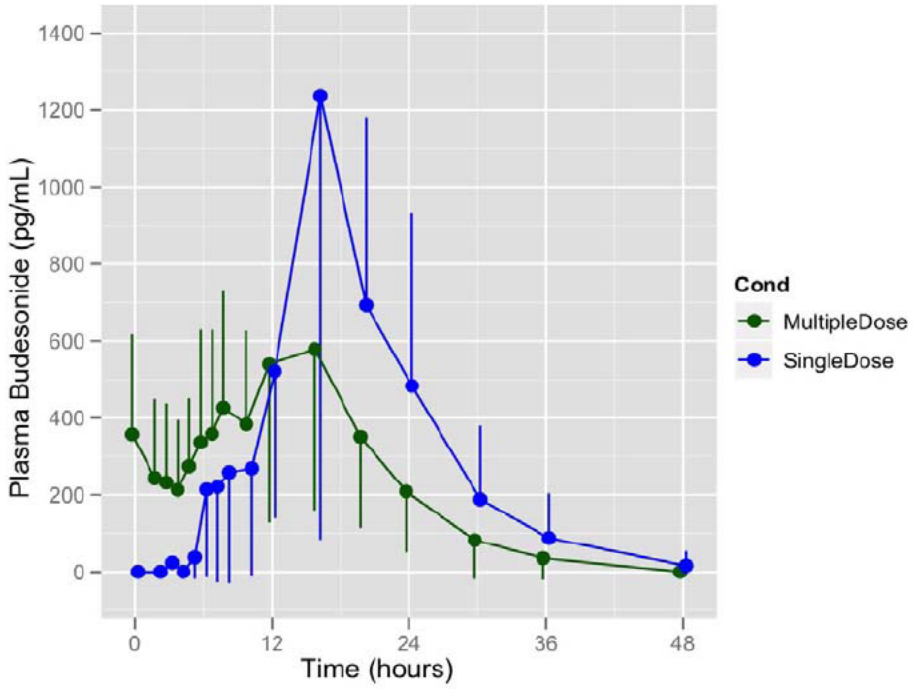


PK parameters of budesonide at steady state

Cssmax	maximum plasma concentration at steady state	pg/mL	891.3 ± 394.1
Cssmin	minimum plasma concentration at steady state	pg/mL	109.9 ± 75.3
tssmax	time at which Cssmax is achieved	h	11 ± 4.9
Caverage	mean or average steady state drug concentration	pg/mL	387.3 ± 153.9
AUCss	AUC during the selected dosing interval, 0-tau (0-24 hr) at steady state calculated with trapezoidal method	pgxh/mL	9295.2 ± 3694.2
%PTF	peak-through-fluctuation percentage	%	205.9 ± 83.9

Css_{max} and AUC_{ss} after multiple dosing were compared with C_{max} and AUC of single dose under fasted state.

Plasma Budesonide Concentrations after Single and Multiple Dose Administration under the Fasted State



When PK parameters of multiples doses were compared with single dose under fasted state, both C_{max} and AUC appear to decrease following multiple dosing compared to single dosing. Coefficient of accumulation after multiple dosing was estimated as multiple/single dose ratio for C_{max} and AUC. Css_{max}/C_{max} was 0.87 ± 0.51, AUC_{ss}/AUC_{inf} was 0.82 ± 0.47, and AUC_{ss}/AUC_{0-24} was 1.135 ± 0.6925 suggesting that there is no budesonide accumulation following multiple dose administration.

Reviewer's Comment:

- According to the literature search, budesonide appears to be inducer of CYP3A4, which is the responsible drug enzyme for budesonide metabolism. Therefore, it might have self-induction of its own metabolism resulting in lower exposure of budesonide following multiple dosing.

SAFETY:

The safety endpoints evaluated in this study included physical examinations, vital signs, haemotology, clinical chemistry, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there was no death or serious adverse event (SAE) during the study. Overall, one subject reported a single episode of mild nausea (AE) and it was judged not related to the treatment and resulted in complete recovery.

REVIEWER'S CONCLUSION:

- *Food only has slight effect on extent of absorption and reduces the rate of absorption, Cmax, by approximately 27%. There was a delay in absorption under fed condition compared to fasted condition.*
- *There was no budesonide accumulation after multiple dose administration.*
- *The study was conducted only in Caucasian subjects. Since there is not major polymorphism in budesonide metabolizing enzyme CYP3A4, the ethnic invariability in this study is not a major concern.*

4.1.3 Study CRO-01-28 - Sponsor code CB-01-02

TITLE: **Single Dose, Pharmaco-Scintigraphic and Kinetic Study of the Gastrointestinal Transit and Release of a 152Sm-Labelled Controlled Release Formulation of Budesonide in Fasting Male Healthy Volunteers**

STUDY SITE:

Sponsor: Cosmo S.p.A.
Via C. Colombo, 1
20020 Lainate (MI) - Italy

Clinical Site: Departments of Clinical Pharmacology and Nuclear Medicine, Vienna University Medical School,
Allgemeines Krankenhaus (AKH), Währinger Gürtel 18-20, 1090 Vienna, Austria

Analytical Site: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:
Aim of this study is to evaluate the drug release and absorption from a new extended release tablets formulation containing 9 mg budesonide in the GI tract by pharmacoscintigraphic and PK determinations and to demonstrate that the active ingredient is highly and progressively released in the colon (target region).

Test Products:
Budesonide MMX™ extended release tablets 9 mg
^{152}Sm-labelled budesonide extended release oral tablets, 9 mg (^{152}Sm-oxide 5 mg/tablet).

The formulation in this study had incorporated ^{152}Sm oxide (5 mg/tablet), which is included was a tracing agent for pharmaco-scintigraphy. Inclusion of 5 mg of samarium oxide was compensated by minor adjustments to other noncritical excipients (microcrystalline cellulose and silicon dioxide). ^{152}Samarium was subsequently radio-labelled by neutron activation to ^{153}Sm ($^{152}Sm_2O_3 \uparrow\uparrow {}^{153}Sm_2O_3$). This compound is not absorbed from the GI tract and has the advantage to be activated in a comparatively short irradiation time, to be more readily available, and to retain a suitable decay life (46.7 h), for its use in clinical studies

STUDY DESIGN:
This study was single-center, single-dose, phase 1 pilot study in 12 healthy male subjects under fasting condition to gain preliminary information on the gastrointestinal transit of a new MMX once daily budesonide formulation, on its systemic availability and overall safety profile. Drugs were administered orally following at least 10 hrs of overnight fasting with 200 mL of water. Subjects were instructed to swallow the whole tablet/capsules without chewing. After the drug

administration, scintigraphic scans, blood samples and urine samples were collected for 24 hours. Standardized breakfast, lunch and dinner were provided 2, 6 and 12 hours post-dose.

Key inclusion criteria:

- Healthy males subjects ages between 18-45 with good health with a Body Mass Index between 19.1-31.9 kg/m2, were eligible to enroll.

Key exclusion criteria:

- *Diseases*: relevant history of renal, hepatic, cardiovascular, GI, haematological, respiratory, endocrine or neurologic diseases, that might interfere with the aim of the study.
- *Medications*: no drug treatment with any CYP-P450 3A inhibitor (e.g., ketoconazole, erythromicin, ranitidine) or inductor (e.g., phenotiazines, rifampicin) during 1 month before the start of the study
- *Allergy*: no history of anaphylaxis to drugs or allergic reactions in general, which the Investigator considered might affect the outcome of the study. no history of hypersensitivity to corticosteroids
- no alcohol or grapefruit juice intake within 24 h before drug administration and during the whole study
- **Radiations:** no diagnostic examinations with radiation burden (e.g. thyroid scanning, pulmonary roentgen, computerised tomography, dental radiography, etc.) during 3 months before the start of the study

Study Population:

This study had 12 healthy male volunteers enrolled and all of them completed the study as planned. No one withdrew from the study.

All subjects were Caucasian male.

Summary of Demographic

Parameters	**Category/statistics**	**All subject (N= 12)**
Gender	Male	12
	Female	0
Age (years)	Mean	31.75
	SD	5.12
	Range	26-40
Height (cm)	Mean	178.2
	SD	5.47
	Range	169-189
Weight (kg)	Mean	81.11
	SD	12.48
	Range	66-107.3
BMI (kg/m2)	Mean	25.48
	SD	3.1
	Range	21.7-31.1

Pharmacokinetic Measurements:
PK blood samples (15 mL) to determine the plasma budesonide were taken at pre-dose (0), 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12 and 24 h post-dose (14 blood samples).

Urine samples were collected at pre-dose and at following collection intervals: 0-6, 6-12 and 12-24 h post-dose.

The following PK parameters were determined for budesonide, using the KINETICA^{TM} version 4.0 software: $C_{max,}$ $T_{max,}$ t_{lag}, AUC_t, AUC_{colon} using non-compartmental analysis.

Pharmaco-scintigraphy
To characterize the GI transit behavior of the study formulation, images were recorded at approximately 20 min intervals up to 3 h post-dose, 30 min intervals up to 10 h and at 12 and 24 h post-dose. The following Regions of Interest (ROIs) were defined: stomach, small intestine, terminal ileum, ileo-caecal junction and caecum, ascending, transverse, descending and sigmoid colon. Quantification of the distribution were achieved by measuring the count rates recorded from the ROIs. The geometric means of the corresponding anterior and posterior count rates were calculated, corrected for ^{153}Sm decay and expressed as % of the dose.

Concomitant Medications
No concomitant medication was taken during the study.

Bioanalytical Analysis:
Plasma budesonide Concentration:

- Plasma budesonide concentrations were analyzed using a validated GC/MS method.
- Plasma samples were stored frozen at $\leq$ -20^{o}C until analysis
- Calibration curve concentration ranged from 50.0-4999.4 pg/ml. (stored frozen <-20^{o}C).
    - It is not clear, based on this analytical report, whether calibration standard solutions and QC samples were used within the time period in which stability was established.
    - Stock solution for calibration curve and QC samples were prepared on 11/28/2002 (stored frozen <-20^{o}C).
    - Plasma samples for budesonide was analyzed between 11/28/2002 to 12/16/2002
    - However, in Study CRO-PK-03-105 - Sponsor code Bud 1001 (food effect study), Budesonide calibration standards curve stability was established for at least 34 days using validated GC-MS/NCI analytical method (same method as this study). Therefore, lack of data does not cause a significant concern.

- Lower limit of quantification is 50.0 pg/mL
- Linear regression equation of y = a + bx with 1/x weighting were used to calculated the concentration. R^2 ranged from 0.9993 to 0.9998.
- The highest plasma budesonide concentration observed in this study were 4756.3 pg/mL, which was within the calibration standard range.
- Based on analytical report for this study, it is not clear whether the plasma samples, stored at approximately -20^{o}C, were analyzed within the time period for which the long-term stability of plasma budesonide has been established.
    - Plasma samples were collected between 08/10/2002 through 08/19/2002.
    - Plasma samples for budesonide was analyzed between 11/28/2002 to 12/16/2002

- However, budesonide stability in human plasma was established for at least 706 days at < -20 °C in study CRO-PK-06-178 - Sponsor code CB-01-02/03 (single dose PK study) with using validated LC-MS/MS methods

Bioanalytical Method Validation:
The GC-MS/NCI analytical method used for above study to determine the plasma concentration of budesonide are NOT considered to be appropriately validated in this study as budesonide long term stability and standard curved stability in storage condition were not established.

- Selectivity:
  Human plasma samples from 6 different sources were analyzed and those blank plasma samples did not exhibit signal budesonide.
- Sensitivity:
  The lower limit of quantification (LLOQ) for human plasma budesonide was 50.0 pg/mL.
- Calibration Curve:
  The calibration (standard) curve for budesonide was in range of 50.0 – 4999.5 pg/mL.
  Linear regression equation of $y = (-0.3218*10^{-2} \pm 0.4008*10^{-2}) + (0.5177*10^{-3} \pm 0.1950*10^{-5})*x$ with1/x weighting were used to calculated the concentration.
- Reproducibility
  Precision and accuracy of budesonide calibration standards:

Cal.Std Nominal Conc (pg/mL)	50.0	100.0	250.	499.9	999.9	2499.7	4999.5
Precision CV (%)	7.08	1.59	2.17	3.23	2.34	1.66	0.83
Accuracy (%)	11.72	-1.13	-2.97	-5.61	-3.63	0.66	1.03

- Accuracy and Precision:
  The accuracy and precision for budesonide was within acceptable range, less than 15%.
  - Precision and accuracy of QC sample for budesonide was less than 8.11 % and -14.29 %, respectively.
- Stability:
  - In Plasma:
    - Stable in plasma for at least 3 freeze-thaw cycles.
    - stable in plasma for at least 24 hr in room temperature
    - stable in extract for at least 72 days at in autosampler at room temperature
  - Stock Stability: Stock solutions for budesonide and its internal standard were found to be stable for at least 18 day at < -20^{o}C (storage condition)

Reviewer Comment:
Stability of budesonide in human plasma and standard curve in storage condition of < -20^{o}C were not established. However, since budesonide stability in human plasma was established for at least 706 days at < -20 °C in study CRO-PK-06-178 - Sponsor code CB-01-02/03 (single dose PK study) with using validated LC-MS/MS methods, and budesonide calibration standards curve stability was established for at least 34 days in Study CRO-PK-03-105 - Sponsor code Bud 1001 (food effect study) using validated GC-MS/NCI analytical method (same method as this study), this lack of stability data will not be a review issue.

RESULTS:

12 subjects were enrolled and completed study as planned. No one withdrew from the study.

Scintigraphy Analysis

MMX 9 mg budesonide tablet transit time throughout the whole GI tract. Time to arrive (min) and leave each GI segment.

	STOMACH		SMALL INTESTINE		ILEUM		A. COLON		T. COLON		D. COLON		S. COLON	
	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT	IN	OUT
MIN	3	20	3	40	60	240	240	450	420	600	420	1440	450	>1440
MAX	3	120	140	600	720	<1440	1440	>1440	1440	>1440	1440	>1440	1440	>1440

The average permanence of the radioactive tablets in the 7 different ROIs were also obtained after normalization of ^{153}Sm counts according to the administered radioactivity dose.

Figure 11.4.1 Mean (+ SD) ^{153}Sm permanence in the stomach (N=12)

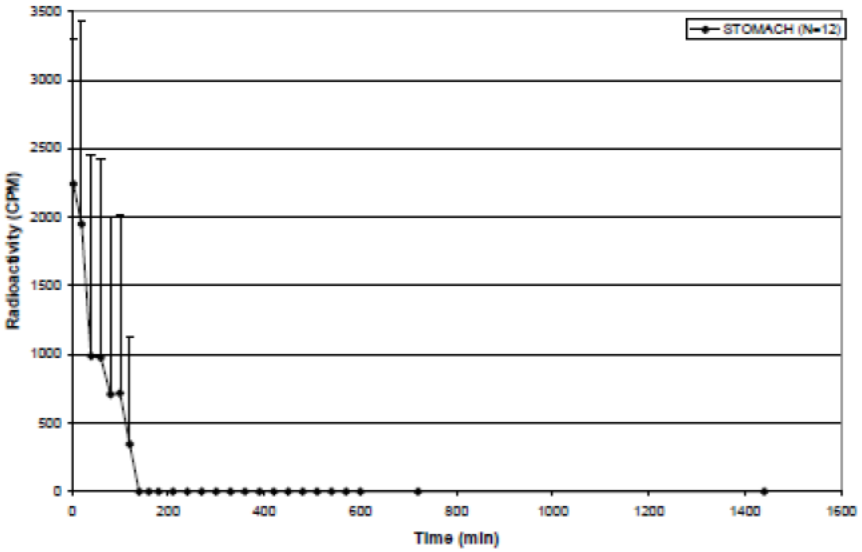


Figure 11.4.2 Mean (+ SD) ^{153}Sm permanence in the Small intestine(N=12)

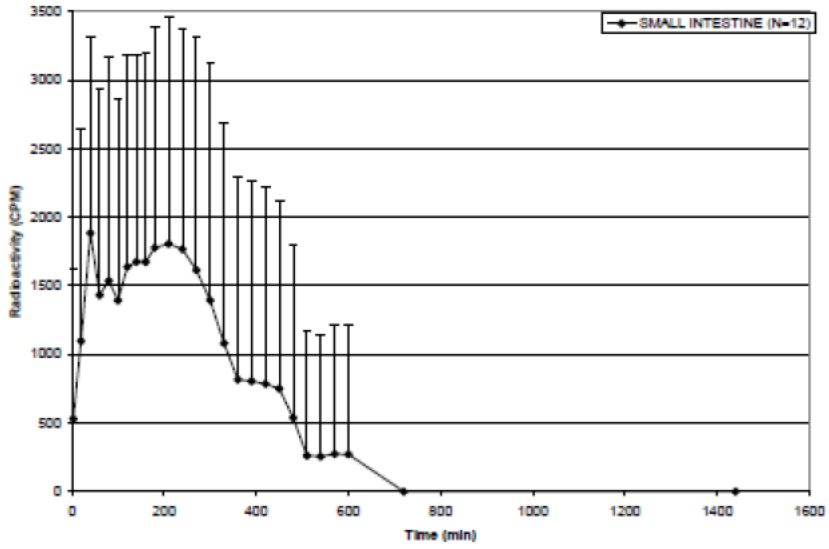


Figure 11.4.3 Mean (+ SD) ^{153}Sm permanence in the Ileum (N=12)

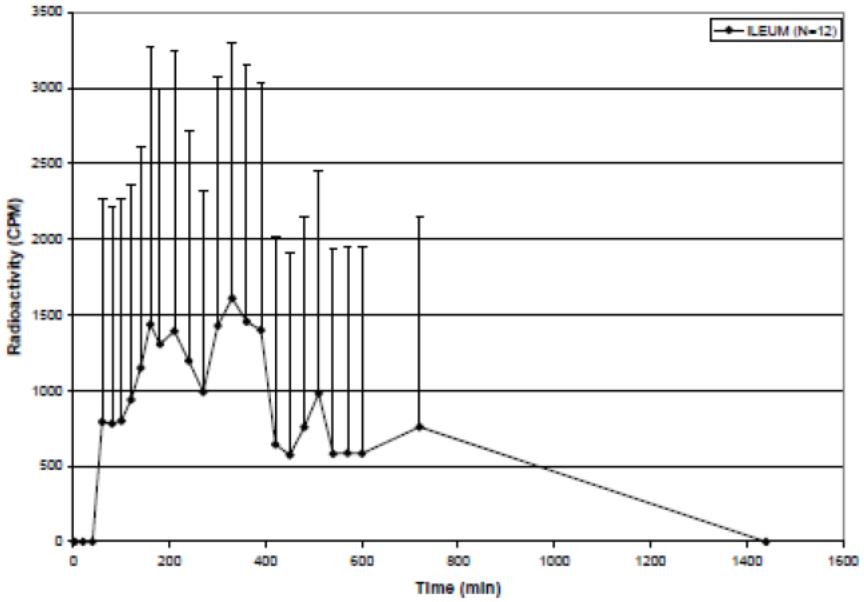


Figure 11.4.4 Mean (+ SD) ^{153}Sm permanence in the Ascending colon (N=12)

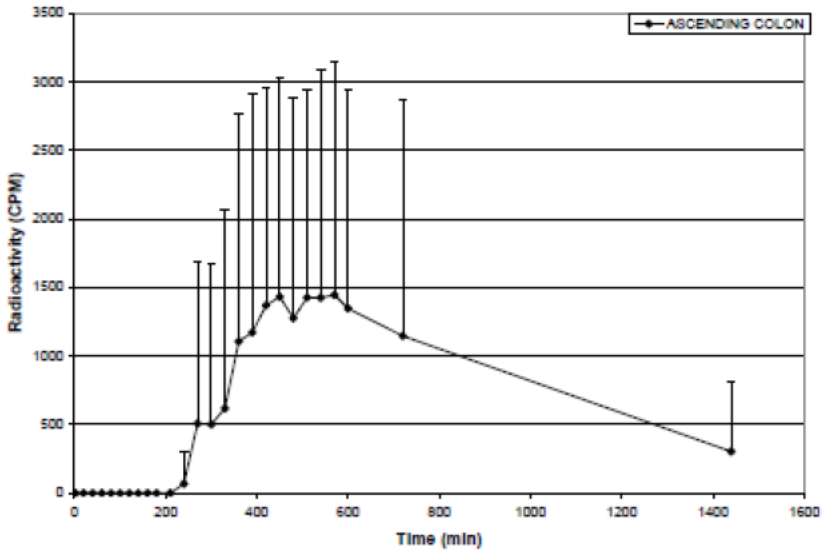


Figure 11.4.5 Mean (+ SD)^{163}Sm permanence in the Transverse colon (N=12)

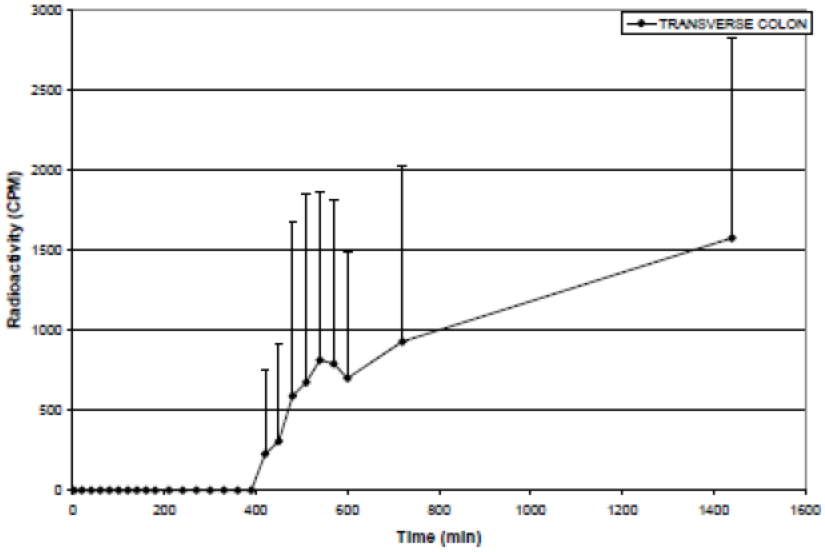


Figure 11.4.6 Mean (+ SD)^{163}Sm permanence in the Descending colon (N=12)

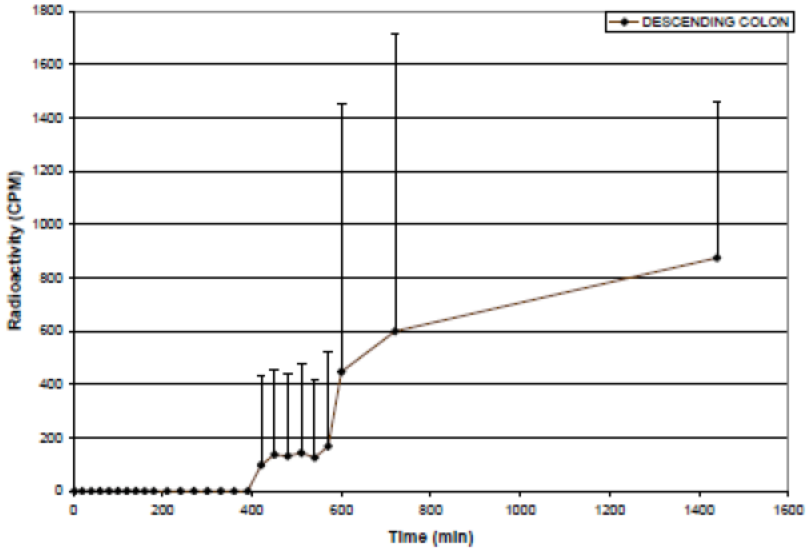
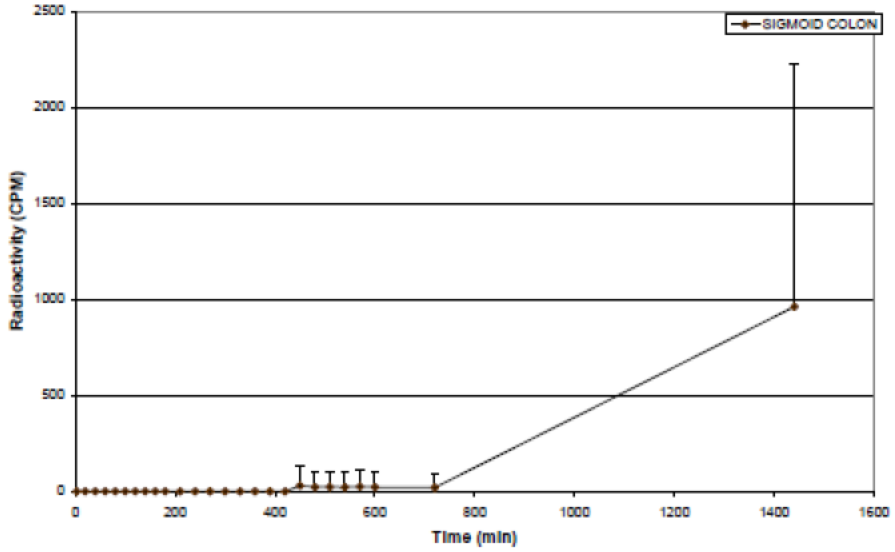


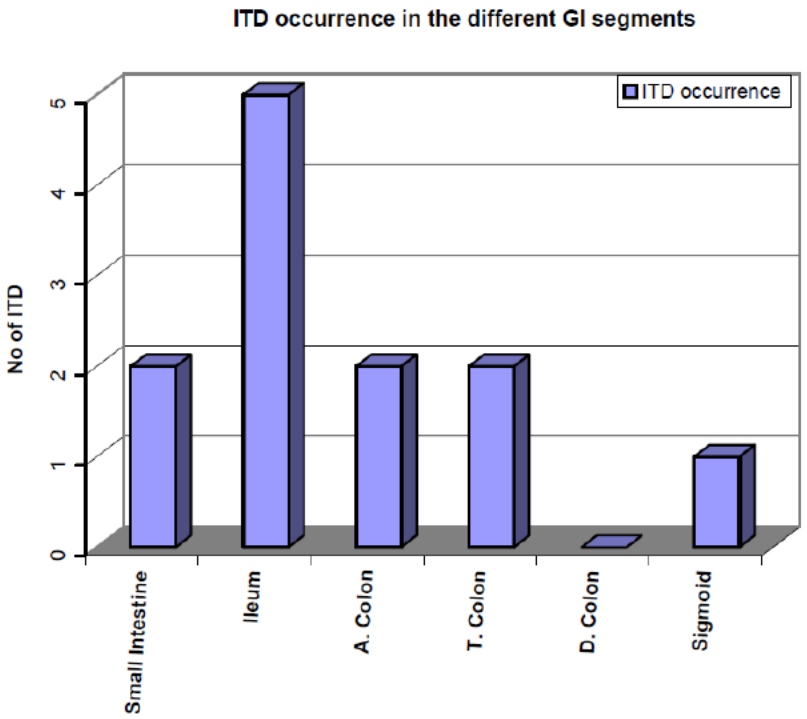
Figure 11.4.7 Mean (+ SD)^{168}Sm permanence in the Sigmoid colon (N=12)



Disintegration or visible erosion (ITD) of tablets were estimated by count spreading, after matrix erosion.

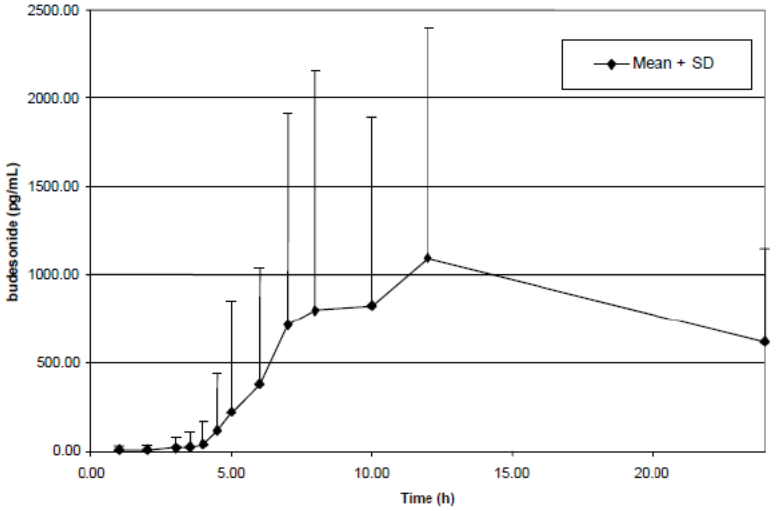
Disintegration time and location of the MMX-budesonide tablets (pg/mL)

Subject No	ITD (h)	Location in the GI tract
01	(b) (4)	(b) (4)
02		
03		
04		
05		
06		
07		
08		
09		
10		
11		
12		
MEAN	9.478	SI 2 subjects IL 5 subjects AC 2 subjects TC 2 subjects DC any subject SC 1 subject
SD	5.111	
CV%	53.93	
MIN	4.25	
MAX	>24	



Pharmacokinetic Analysis

Figure 11.4.8 Plasma concentration of budesonide in male healthy volunteers administered MMX- budesonide 9 mg tablets. Mean + SD (N=12)



N=12	C_{max} (pg/mL)	T_{max} (h)	AUC_t (pg*h/mL)	T_{lag} (h)	T_{max} - T_{lag} (h)
Mean	1768.7	14.00	15607	6.79	7.21
S.D.	1499.8	7.734	14549	3.24	5.49
CV	84.80	55.24	93.22	47.66	76.13
Min	337.3	5	2465	1	0
Max	4756.3	24	53163	12	17

SAFETY:
The safety endpoints evaluated in this study included physical examinations, vital signs, haemotology, clinical chemistry, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no deaths, or serious adverse event (SAE) during the study. Overall, 3 subjects reported experiencing AEs during the study. 1 Subject (01), reported headache lasting 8.20 h after administration, 1 subject (06) showed high leucocytes value (1 day after administration) that retuned normal 3 days later, and 1 subject (07) had CRP out of normal limit (1 day after administration) that returned normal 3 days later. These AEs were judged unlikely (subjects 01 and 06) and not related to treatment (subject 07).

SPONSOR'S CONCLUSION:
1. t_{lag}, i.e. appearance of the drug in the bloodstream, occurred in 6.79 ± 3.24 h;
2. ITD started in 9.48 ± 5.11 h when tablets were mostly in the IL, AC and TC, even if the appearance of plasma levels is faster 6.79 ± 3.24h;;
3. tablets arrival in the AC occurred in 7-10 h post-dosing;
4. budesonide plasma concentration peak was achieved in 14.00 ± 7.73 h (tmax);
5. absorption of the drug occurred mostly in the colon, 95.88 ± 4.19 % of total absorption.

It can be concluded that MMX-budesonide 9 mg tablet formulation is a suitable delivery system targeting the whole colon where it release the glucocorticoid for a topical pharmacological action. The transit and disintegration properties, shown together with the drug release profile, suggest its use in the therapy of ulcerative colitis and distal Chron's disease rather than ileal localization of proximal Chron's disease.

REVIEWER'S COMMENTS:
- *There is a very high inter-subject variability regarding GI transit behaviors of the tested formulation.*
- *Plasma samples were not collected long enough to obtain plasma half-life of budesonide.*
- *Plasma samples were not collected between 12-24 hours. Therefore, the estimated Tmax of 14 hours in not very reliable.*
- *The obtained PK profile and PK parameters are fairly consistent with result of Study CRO-PK-06-178 - Sponsor code CB-01-02/03 (single dose BA study).*
- *It appears that disintegration takes place mostly in ileum (5 of 12 subjects, 42%), or ascending and traverse colon (4 of 12 subjects, 33%). However, it is important to note that disintegration was a subjective visual assessment as it was defined on the basis of appearance of scintigraphic image. It is unclear how the exactly the disintegration time was defined in the study.*

4.2 Cover sheet and OCP Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**203634**	**Brand Name**	**UCERIS**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Budesonide MMX**
Medical Division	**Gastroenterology and Inborn Errors of Metabolism Products**	**Drug Class**	**Corticosteroid, antinflammatory agent**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**Induction of remission in patients with active, mild to moderate ulcerative colitis.**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Extended Release Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**9 mg tablet taken once daily**
Date of Submission	**12-14-2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**09/11/2012**	**Sponsor**	**Santarus, Inc.**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**10/16/2012**	**Application Type**	**505 (b)(2)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		pharmaco-scintigraphic study
multiple dose:	**X**	**1**		This study had two parts: Part 1: food effect study. Part 2: multiple dose PK study
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				

Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		This study had two parts: Part 1: food effect study. Part 2: multiple dose PK study
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**0**	**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	According to the sponsor, the formulation did NOT change between TBM product and phase 3 studies.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Metabolism information is described in Entocort label. Need more information for its potential being inhibitor/inducer or substrate of transporter.
3	Has the sponsor submitted bioavailability	X			

	data satisfying the CFR requirements?				
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			The sponsor has conducted a dose finding study (in phase II) in patient population with 3 mg and 9 mg of budesonide MMX vs. placebo. In phase III, the sponsor has also explored 9 mg and 6 mg doses.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate			X	The sponsor is requesting (b) (4) (b) (4) for pediatr

	effectiveness, if the drug is indeed effective?				assessment.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

The NDA is **Filelable** from clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Dilara Jappar — Feb 10th, 2012

Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee

Team Leader/Supervisor — Date

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

/s/

DILARA JAPPAR
12/19/2012

SUE CHIH H LEE
12/19/2012

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 203634	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	December 16, 2011		
Division:	Division of Gastroenterology Products	**Team Leader:** Angelica Dorantes, PhD	
Applicant:	Santarus Inc.	**Acting Supervisor:** Richard Lostritto, PhD	
Trade Name:	UCERIS (budesonide) Extended Release Tablet	**Date Assigned:**	December 21, 2011
Generic Name:	Budesonide	**Date of Review:**	December 12, 2012
Indication:	Induction of remission in patients with active mild to moderate ulcerative colitis	**Type of Submission:** 505(b)(2) Original New Drug Application	
Formulation/ strengths	Oral enteric coated-extended release tablet/ 9 mg		
Route of Administration	Oral		

SYNOPSIS:

Submission: This 505(b)(2) New Drug Application is for an enteric coated (delayed release) and extended release budesonide tablet indicated for the induction of remission in adult patients with mild to moderate active ulcerative colitis. Budesonide is a corticosteroid with high affinity for the glucocorticoid receptor. The reference listed drug is Entocort® EC 3 mg capsules (NDA 21-324).

The drug product was formulated as a delayed and extended release drug product that is intended to deliver budesonide directly into the colon (site of action) and then slowly disperses the drug over time. The tablet is coated with a pH dependent polymer film, which is designed to break down at or above pH 7.0, normally in the terminal ileum where budesonide is supposed to be released from the tablet core. The tablet core is formulated to contain budesonide and controlled release polymers and is designed to provide for extended release of budesonide throughout the colon.

The proposed formulation includes an enteric coating, a hydrophilic matrix, and (b) (4) The enteric coating contributes to the delayed release functionality, the hydrophilic matrix provides hydrodynamic controlled release (swelling), (b) (4) controlled release of the active ingredient.

(b) (4)

The tablets are coated with pH-resistant acrylic copolymers, which are supposed to delay the release until the tablet reaches an environment where the pH is greater than 7. The Applicant claims that the hydrophilic matrix polymers (b) (4) Whether these design features are actually performing (in vivo) as proposed is beyond the scope of this review, and can not be predicted from the in vitro tests that are the subject of this review. An in vitro dissolution study was performed to evaluate the effect of alcohol dose dumping on Budesonide tablets.

Review:

The Biopharmaceutics review for this NDA is focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) the dissolution acceptance criteria, 3) the alcohol dose dumping method and data, and 4) the extended release claim.

Communications with the Applicant:

As outlined in the Biopharmaceutics filing review (dated 1/31/12), the Applicant was asked to provide a detailed dissolution method development report and complete dissolution profile data (individual, mean, SD, profiles) for the biobatches and the primary stability batches (at each tested stability time point). The Applicant responded in an amendment dated 2/10/12. Additional dissolution data and a revision of the drug product dissolution acceptance criteria were requested in an information request on 6/8/12. The applicant responded in an amendment dated 8/17/12. A telephone conference was held between FDA and the Applicant on 11/21/12. As a result of the telephone conference, additional dissolution data, justifications, revised drug product specifications and a proposed post-approval commitment were submitted in an amendment dated 11/30/12. Another information request to tighten the 4 hour buffer stage dissolution acceptance range was sent to the Applicant on 12/10/12. The Applicant responded on 12/12/12 with the final agreed upon drug product specifications.

RECOMMENDATION:

ONDQA-Biopharmaceutics has evaluated the information provided in NDA 203-634 and has the following comments:

1. The following dissolution method and acceptance criteria are acceptable:

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

2. The results of the in vitro alcohol dose dumping study indicate that dose dumping does not occur in vitro.

3. The extended release claim is acceptable.

4. The following post-action commitment have been agreed upon with the Applicant:
   - (b) (4)

From the Biopharmaceutics perspective, NDA 203634 for Budesonide Extended Release Tablets, 9 mg is recommended for APPROVAL.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

BIOPHARMACEUTICS EVALUATION

DISSOLUTION METHOD:

Proposed dissolution method:
The proposed dissolution method utilizes a two stage approach:
Acid stage (first 2 hours):

Parameter	Criteria
Apparatus	USP Apparatus 2 (Paddle)
Temperature	37 (b) (4)
Speed	100 rpm
Volume	500 mL
Dissolution Media	0.1M HCl (b) (4) and (b) (4) Macrogol Cetostearyl Ether
Sampling Time Points	2 hours

Followed by a buffer stage:

Parameter	Criteria
Apparatus	USP Apparatus 2 (Paddle)
Temperature	37 (b) (4)
Speed	100 rpm
Volume	1000 mL
Dissolution Media	pH 7.2 phosphate buffer and (b) (4) Macrogol Cetostearyl Ether
Sampling Time Points	(b) (4) 4, 8 hours

The dissolution method development report was submitted in an amendment dated 2/10/12. The following parameters were evaluated during the development of the method.

1. Selection of surfactant:

The Applicant evaluated (b) (4) as surfactants. The Applicant chose (b) (4) based on ease of handling and lack of interference during detection. Using (b) (4), the following surfactant concentrations were evaluated in the buffer stage medium:

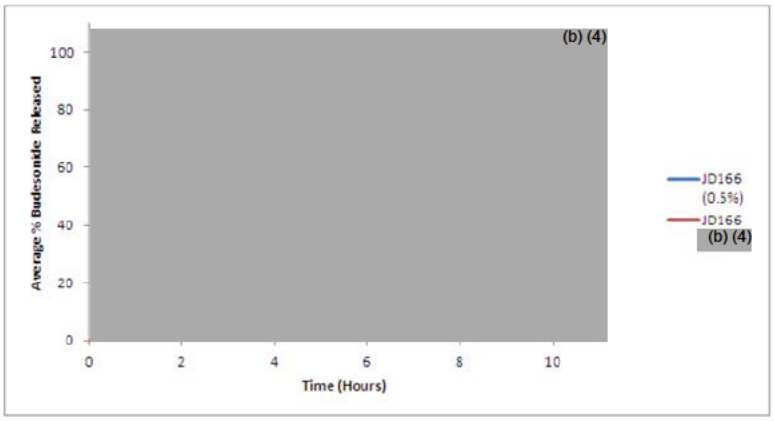
Surfactant concentration	% Budesonide recovery at pH 7.2
No surfactant	(b) (4)
Surfactant (b) (4)	
Surfactant	
Surfactant	

The Applicant proposed to use (b) (4) % surfactant; however, based on the above data, the use of 0.5% surfactant was recommended in an information request dated 6/8/12. The following comment was sent in the IR Letter:

"Based on the provided data, it is recommended that the surfactant concentration in the dissolution medium be changed from (b) (4) to 0.5%"

Applicant's Response dated 8/17/12: The evaluation of the surfactant concentration change from (b) (4)% to 0.5% in pH 7.2 dissolution medium was performed. Based on the results and as shown in Figure 1, the change in surfactant levels did not appear to have any significant change in the performance of the dissolution of the Budesonide MMX Tablets. Therefore, either surfactant level could be considered appropriate to evaluate the Budesonide MMX Tablets for dissolution. Considering that all the historical data has been generated using the (b) (4) surfactant level, it would be Santarus' preference to continue with the (b) (4) surfactant buffer concentration.

Figure 1. Budesonide MMX Tablet Dissolution Profile Comparison of Between (b) (4) versus 0.5% Surfactant in pH 7.2 Dissolution Medium (Lot JD166)[1]



[1] Data from Report R12-0005

Reviewer Comments:

- ***Evaluation of Response:*** *Since both the 0.5% and the (b) (4) surfactant provided the same dissolution profiles, the lower surfactant concentration of 0.5% should be used. This was discussed during the telephone conference on 11/21/12, when the FDA and the Applicant agreed that the dissolution method using 0.5% surfactant will be validated and implemented* (b) (4)

- ***Evaluation of the Applicant's commitment: Acceptable***
  As agreed in the teleconference, the validation and implementation of the method change will (b) (4)

2. The selection of pH

The selection of pH 7.2 for the buffer medium is (b) (4). To justify the medium pH for the buffer stage, additional dissolution data were requested in an information request dated 6/8/12: The following comment was sent in the IR Letter.

"To justify your selection of the medium pH for the buffer stage and specification sample time points, provide complete dissolution profiles (e.g. 1, 2, 4, 6, 8 and 10 hours) and the individual data in media with pH between 6-7.5 (e.g. pH 6, 6.5, 6.8, 7 and 7.2)."

Applicant's Response dated 8/17/12: Subsequent to the request by the Agency dated June 8, 2012, a protocol was prepared and executed to collect Budesonide MMX Tablets dissolution profiles at multiple pH conditions (i.e. 6.0, 6.4, 6.8, 7.0, and 7.2) and sampling time points (i.e. 1, 2, 4, 6, 8, and 10 hrs). The data generated from this study were assessed and determined to support the current selection of pH 7.2 medium for the buffer stage and sampling time points (1, 4, and 8 hrs), which are the basis for the quality control method used for evaluating both the drug product release and stability.

Figure 2. Budesonide MMX Tablets Dissolution Profiles Across Multiple pH

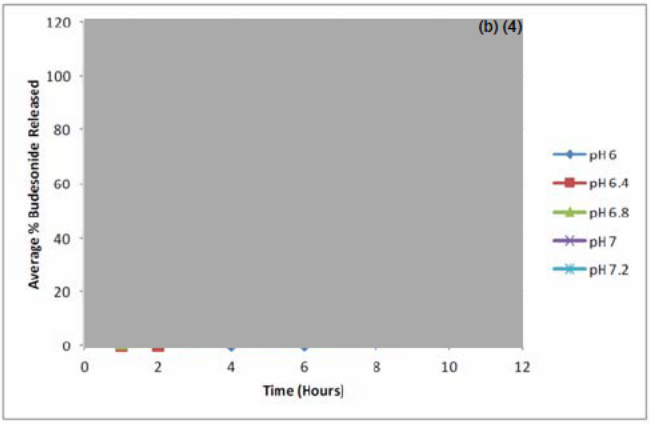


Table 1. Budesonide MMX Tablet Dissolution Profile Summaries across Multiple pH and Sampling Time points

	Average % Budesonide Released					
pH	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr
[a]6.0	(b) (4)					
[b]6.4						
[c]6.8						
[c]7.0						
[d]7.2						
	% Budesonide Release Range (%RSD)					
pH	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr
[a]6.0	(b) (4)					
[b]6.4						
[c]6.8						
[c]7.0						
[c]7.2						
[d]7.2						

[a] :Lots 159517 (n=6 Tablets per lot)
[b] :Lots 159517, 159518, and 159519 (n=6 Tablets per lot)
[c] :Lots 159517, 159518, and 159519 (n=12 Tablets per lot)
[d]: Lots 159517, 159518, 159519. AA062/1, AA063/1, AA064/1, and JD166 (n=12 Tablets per lot)
Data from Report R12-0005

As the pH is increased to pH 7.0 and above, the enteric coating is no longer controlling the release of the active but instead the tablet's polymer matrix core is controlling the release. When comparing the dissolution data between pH 7.0 and 7.2, from the same lots, the results were similar, showing only a slight decrease in variability at pH 7.2. For a quality control method, the dissolution data from pH 7.2 appears to be best suited for characterizing the drug's solubilization of the tablet's enteric coating and the drug's extended release profile as controlled by the multi-polymer matrix tablet core. Based on these reasons, Santarus feels that selecting the pH 7.2 dissolution medium would ensure a more consistent quality control dissolution method for evaluating the initial drug product testing and stability performance. Therefore, a pH of 7.2 would be recommended as the preferred dissolution medium pH for the buffer phase.

Full dissolution profiles were generated using the multiple sampling time points requested by the Agency, refer to Figure 2 and Table 1. When utilizing the preferred dissolution buffer at pH of 7.2 the results showed that 1, 4, and 8 hours are the ideal time points to characterize the extended release profile of the drug product. The one hour time point demonstrated that the polymer matrices are effective in controlling the release of the drug product by consistently showing less than (b) (4) drug product release demonstrating a time dependent release of the drug substance from the tablet. The intermediate four hour time point defined the mid-point of the drug product release. The 4 hour time point results also showed that the product is consistently releasing within the linear part of the curve; whereas, the 6 hour time point, at least one tablet per lot, and in some cases up 4 tablets, showed an (b) (4) or more released. The full release of the active ingredient was achieved by the 8 hour time point, showing consistently greater than (b) (4) release and confirming that the drug is completely released *in vitro.*

In summary, the pH medium at 7.2 and sampling time points 1, 4, and 8 hours were confirmed and justified for several reasons: 1) the pH provides an optimum condition for proper dissolution of the enteric coating, allowing for reduced drug release variability, 2) the sampling time points characterize the extended release profile of the Budesonide MMX Tablets, and 3) the release and stability data collected to date were generated using these current dissolution conditions. Therefore, the selected pH of 7.2 for the buffer stage and specification sampling time points of 1, 4, and 8 hours are supported by the data as appropriate dissolution parameters for characterizing the extended release profile of the Budesonide MMX Tablets in assessing the consistency of the finished drug product for release and stability.

Reviewer Comments

- ***Evaluation of Response:*** *During the telephone conference on 11/21/12, the Applicant was told that the use of pH 7.0 is preferred and recommended but that the use of pH 7.2 is acceptable. The Applicant decided to keep the pH 7.2 for the dissolution medium.*

- *Note: it is reported in the literature (Gut 2001; 48:571-577) that patients with Ulcerative Colitis may have a pH below 7 in the colon. Therefore, this drug may not be released in the colon in some patients.*

3. ***Selection of apparatus and rotation speed:***

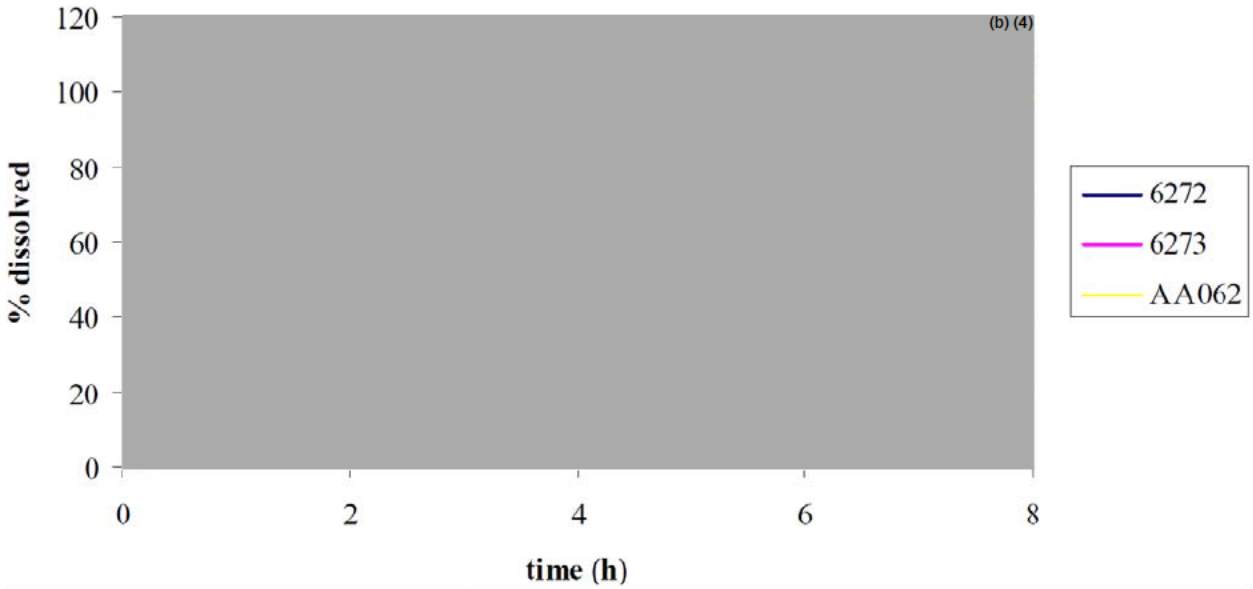
Apparatus	Sampling time	Budesonide dissolved after 8 hours at pH 7.2 (%)		
		(b) (4) rpm	(b) (4) rpm	100 rpm
I (baskets)	1h			(b) (4)
	4h			
	8h			
II (paddles)	1h			
	4h			
	8h			

Reviewer's Evaluation: Acceptable

The Applicant proposes to use Apparatus II at 100 rpm. This speed is acceptable.

4. ***Discriminating Power:***

The following figure includes the comparative dissolution profiles of 3 batches with different amounts of lactose (b) (4) and hydroxypropylcellulose (in buffer stage).



Excipient	*Lot AA062	Lot 6272	Lot 6273
Hydroxypropylcellulose	(b) (4)		
Lactose			

*Same lot used for Process Validation, NDA Registration, and Phase III Clinical Study

Reviewer's Evaluation: Acceptable

The selected dissolution method was able to differentiate the 3 batches made with different amounts of lactose (b) (4) and hydroxypropylcellulose.

DISSOLUTION DATA AND PROPOSED ACCEPTANCE CRITERIA:

The originally proposed dissolution acceptance criteria are listed in the table below:

USP Apparatus	Spindle Rotation	Media Volume	Medium	Time	Acceptance criteria
II	100 rpm	500 mL	**Acid stage:** (0.1 M HCl pH 1 and (b) (4) Macrogol Cetostearyl Ether)	2 hours	NMT (b) (4)
II	100 rpm	1000 mL	**Buffer stage:** (Phosphate buffer pH 7.2 and (b) (4) Macrogol Cetostearyl Ether)	1 hour 4 hours 8 hours	NMT (b) (4) (b) (4) - (b) (4) NLT (b) (4)

Reviewer's Comment:

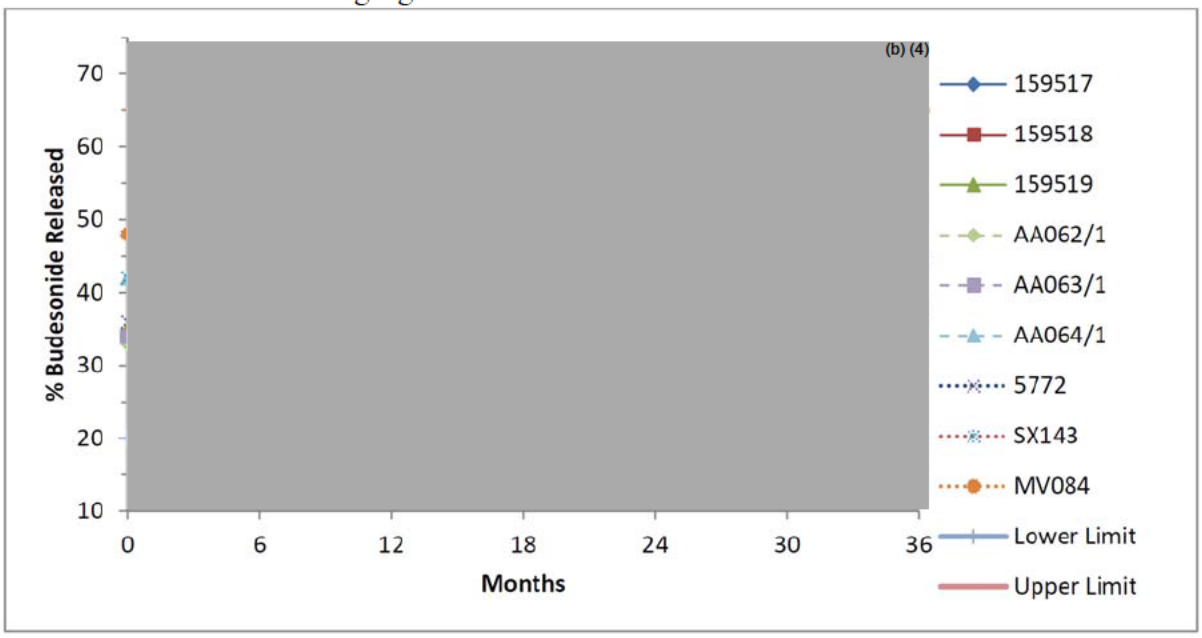
The proposed acceptance criteria for the Buffer stage were revised during the review process and the final agreed upon drug product dissolution criteria are stated in the conclusion of this review.

Upon request, individual dissolution data collected during stability studies for the following phase 3 and registration batches were provided:

Product Lot Packaging Configuration	Use of Batch	Stability Condition	Time Points
159517 Trade Bottles	Mfg Process Validation NDA Registration Batch	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
159518 Trade Bottles	Mfg Process Validation NDA Registration Batch	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
159519 Trade Bottles	Mfg Process Validation NDA Registration Batch	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
AA062/1 Physician Samples - Blisterpack	Mfg Process Validation NDA Registration Batch *Clinical Phase III	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
AA063/1 Physician Samples - Blisterpack	Mfg Process Validation NDA Registration Batch	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
AA064/1 Physician Samples - Blisterpack	Mfg Process Validation NDA Registration Batch	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
SX143-1	*Clinical Phase III	25°C/ 60%RH	0, 3, 6, 9, 12, 18 and 24 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months
SX143-2	*Clinical Phase III	25°C/ 60%RH	0, 3, 6, 9, 12, 18, 24 and 36 months
		40°C/ 75%RH	1, 3, and 6 months
		30°C/ 65%RH	3, 6, 9, and 12 months

* Same bulk tablet lots as used in the clinical trials

The stability dissolution mean data (25°C/60% RH) for the 4 hour time point at pH 7.2, can be summarized in the following figure:



*Batch MV084 was used in the bioavailability study CRO-PK-06-178.
*Batch 5772 was used in clinical study CRO-03-53.
For the 1 hour time point pH 7.2 (stored at 25 °C/60% RH): All data indicate that NMT (b) (4) budesonide is released.
For the 8 hour time point pH 7.2 (stored at 25 °C/60% RH): All data indicated that NLT (b) (4) budesonide is released.

Reviewer's Evaluation of the proposed dissolution acceptance criteria:

- *Based on the provided data, the proposed revised acceptance criterion for the acid phase (NMT (b) (4) at 2 hours) is acceptable.*
- *Based on the provided data, and with the goal to set the acceptance criteria in a way to ensure consistent drug product performance from lot to lot and to prevent release of any drug product lot with dissolution profiles outside those that were clinically tested, it is recommended that the acceptance criteria for the buffer phase be tightened as follows: 1 hour: NMT (b) (4) 4 hour: (b) (4) - (b) (4) and 8 hour: NLT (b) (4)*

The above recommendation was sent to the Applicant in an information request dated 6/8/12. The following comment was conveyed:

Based on the mean in-vitro dissolution profiles at release and under long term stability studies the following dissolution acceptance criteria for the "Buffer Phase" are recommended:

- **1 hr: NMT (b) (4)**
- **4 hrs: (b) (4) - (b) (4)**
- **8 hrs: NLT (b) (4)**

Applicant's Response dated 8/17/12: The dissolution data provided in Table 2, which includes the three Budesonide MMX Tablet registration batches that were manufactured in April 2009 and

one recent manufactured lot in June 2012, provide a more representative view of the dissolution variability for the four hour time point as typically seen at release and/or stability than just the overall mean data that was provided in the original NDA submission. Table 2 summarizes the overall dissolution variability, which shows that at the 4 hour time point, the variability was (b) (4) with a range of (b) (4)% for individual values. Santarus' assessment of the data would indicate that the Agency's proposed specification of (b) (4)% would result in a high failure rate of not meeting USP Dissolution <711> Stage 1 testing, which requires that no individual value can be outside this range and no value is less than the stated amount at the final test time. Therefore, USP Dissolution Stage 2 testing would be required at a high frequency (i.e. > (b) (4) during normal product release and stability testing.

Table 2. Budesonide MMX Tablet Dissolution Profiles at pH 7.2 Dissolution Medium

Average % Budesonide Released		
1 hr	4 hr	8 hr
(b) (4)		
% Budesonide Release Range (RSD)		
1 hr	4 hr	8 hr
(b) (4)		

Three registration lots packaged in trade bottles (Pkg. Lots 159517, 159518, 159519) and blister packs (Pkg lots. AA062/1, AA063/1, AA064/1), and new bulk tablet lot JD166 (n=12 Tablets per lot)

Based on the limited of number of manufactured lots and dissolution data collected to date, Santarus is recommending the following interim specification, which would be performed with pH 7.2 dissolution medium for the buffer stage and (b) (4) surfactant:

Table 3. Santarus Proposed Dissolution Specification

Time Points	Current Specification	Agency Proposed	Interim Proposed
1 hour	NMT (b) (4)%	NMT (b) (4)%	NMT (b) (4)%
4 hour	(b) (4)%	(b) (4)%	(b) (4)%
8 hour	NLT (b) (4)%	NLT (b) (4)%	NLT (b) (4)%

(b) (4)

The root cause of the high variability in the dissolution at the 4 hour time point and the appropriate acceptance criteria were discussed with the Applicant in a telephone-conference dated 11/21/12. The applicant was unable to identify a root cause for the variability. The buffer stage dissolution acceptance criteria were discussed as described in the Applicant's amendment dated 11/30/12:

Santarus confirmed agreement with the acceptance criterion of NMT (b) (4) release at the 1-hour time point as stated in Quality Information Amendment – Section 1.3 (Sequence 0035).

With respect to the 4-hour time point, FDA stated that current practice is a ± (b) (4) range for dissolution acceptance criteria, and that additional justification is needed to accept ranges outside of the ± (b) (4) target. As discussed in the teleconference, the acceptance criteria for the dissolution 4-hour time point could have a range greater than ± (b) (4) as long as the range is supported by clinical use. At this time, Santarus proposes tightened acceptance criteria with a range of ± (b) (4) ((b) (4)) vs. the ± (b) (4) (b) (4)% proposed in Sequence 0035 (amendment dated 8/17/12). To

support this range, Table 1, along with Figure 1 and Figure 2, detail the release and stability data associated with the 4-hour time point of the lots of Budesonide MMX that were utilized in the Phase 3 clinical trials. The bulk lots utilized for the Phase 3 clinical trials were SX143 and AA062.

Table 1. 4- Hour Dissolution Data for Budesonide MMX Phase 3 Clinical Lots

Lot	Package		Stability Interval (months)							
			0	3	6	9	12	18	24	36
SX143	HDPE Bottle	Avg % Released	(b) (4)							
		Range								
	Blister	Avg % Released								
		Range								
AA062	HDPE Bottle	Avg % Released								
		Range								
	Blister	Avg % Released								
		Range								

* Values associated with 12 tablets

The following figures detail the 4-hour dissolution data along with the USP <711> Stage Requirements (stages 1, 2, and 3) associated with the proposed acceptance criteria of (b) (4) %, highlighting the clinical trial utilization phase over the entire proposed 36 months expiry period:

Figure 1. Lot SX143 4-Hour Dissolution Data (individual data points)

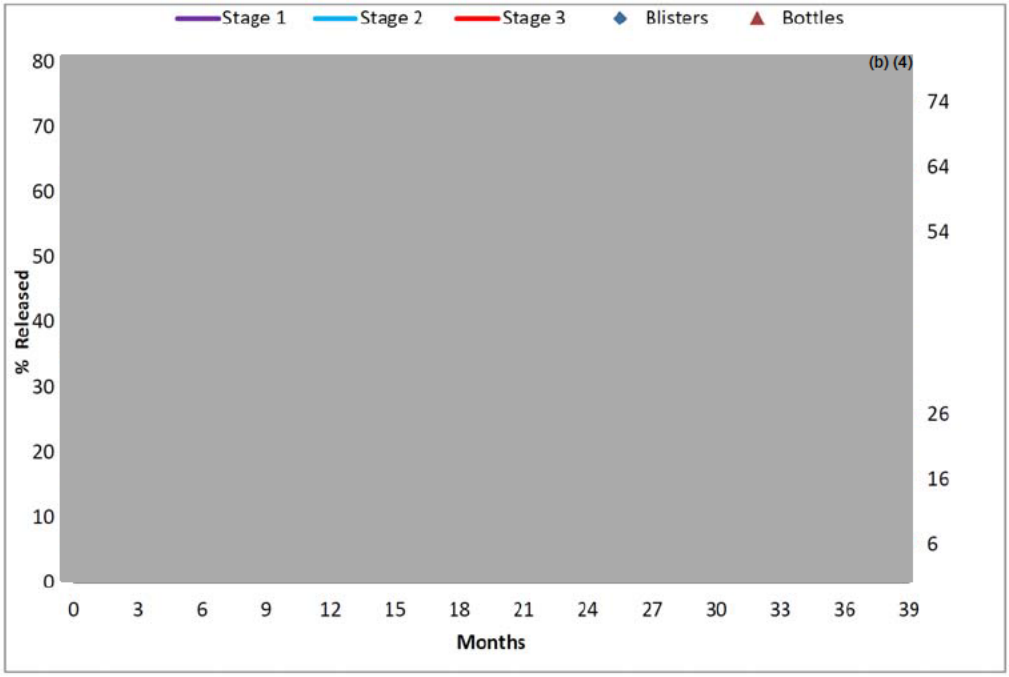
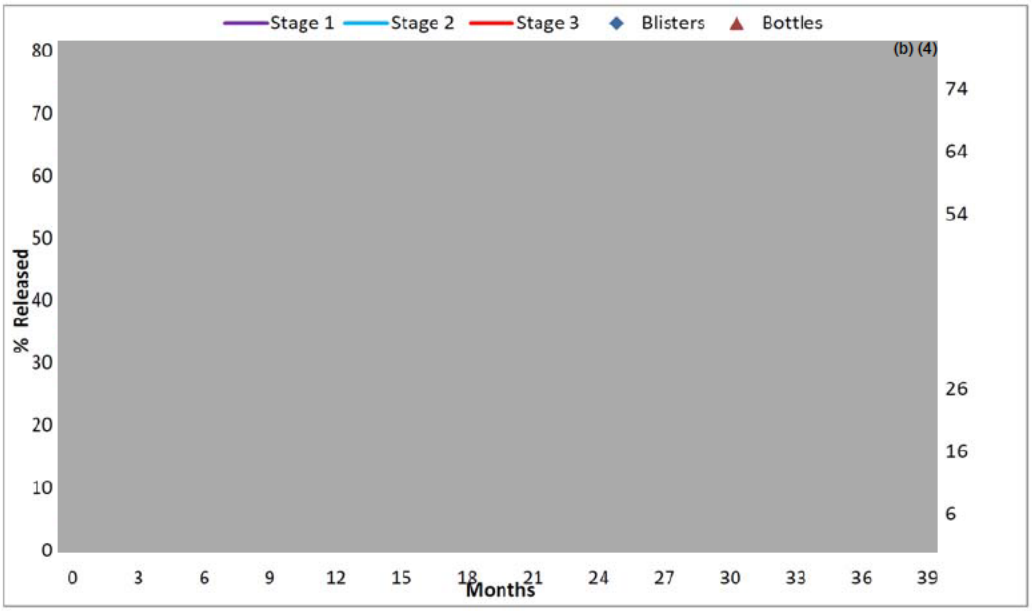


Figure 2. Lot AA062 4-Hour Dissolution Data (individual data points)



The rationale for the acceptance criteria of (b) (4) is based upon a combination of the actual data collected from the clinical lots and the Stage 2 acceptance criteria defined in USP <711>. The USP <711> Stage 2 requirement is two-fold:

- the average value must be within the stated range ((b) (4)
- no individual data point can be more than (b) (4) out of the stated range ((b) (4))

The proposed acceptance criteria of (b) (4) for the 4-hour dissolution time point is based on clinical lot data and appropriate application of USP <711> Stage 2 requirements. In addition, the non-clinical drug product lot dissolution data further supports this specification (Quality Information Amendment Summarized Dissolution Data Collected during Stability for Phase III and Registration Batches (Sequence 0004), submitted February 10, 2012). However, based on the limited number of manufactured lots and data collected to date, Santarus proposes a (b) (4) .

Reviewer's Comments

Evaluation of Response: *The proposed interim 4 hr buffer stage dissolution acceptance range of (b) (4)% is inadequate. The range is too wide to assure consistent lot to lot drug product performance as well as to prevent release of drug product lots with dissolution profiles outside those that were tested in clinical trials. The recommended acceptance range is (b) (4), which will require stage 2 and possible stage 3 testing due to the observed variability in the drug product dissolution. This following comments were sent to the Applicant in an IR dated 12/10/12:*

- *Your proposed interim four (4) hr buffer stage dissolution acceptance range of ± (b) (4) from target is inadequate. This range is too wide to assure consistent lot to lot drug product performance as well as to prevent release of drug product lots with dissolution profiles outside those that were tested in clinical trials.*

- *Based on the provided data from the clinical batches, our recommendation for the acceptance range for the four (4) hour time point is ± (b) (4) from target as communicated to you on 08-JUN-2012 and discussed on 21-NOV-2012. This situation persists as an approvability deficiency.*

Applicant's Response dated 12/12/12: Santarus revised the (4) hour dissolution time point in accordance with the FDA's recommendation to (b) (4) Please find the revised commercial specifications for Budesonide MMX 9 mg tablets attached as Appendix 1.

Reviewer's Comments:

<u>Evaluation of Response:</u> Acceptable

- *The revised 4 hour buffer stage dissolution acceptance criterion of (b) (4) is acceptable and consistent with the provided dissolution data of the clinical trial batches. The provided drug product stability data were collected using the originally proposed very wide acceptance range of (b) (4) for the 4 hour time point, and therefore only included n= 6 dissolution data (stage (b) (4) and occasionally n=12 testing (stage (b) (4). As a result of the revised 4 hour buffer stage dissolution acceptance range of (b) (4) stage (b) (4) testing would have been required for several batches and stability time points.*
- *It should be noted that Biopharmaceutics is of the opinion that based on the provided data, it can be expected that the stability batches would have passed stage (b) (4) esting and occasionally stage (b) (4) testing using the newly agreed upon 4 hour buffer stage acceptance range of (b) (4) to (b) (4)*

On 12/12/12, the Applicant submitted the following revised drug product specification table for the drug product.

Appendix 1 Specifications for Budesonide MMX 9 mg tablets

Test	Reference Method	Specification
[a] Appearance	Visual	White to off-white, round, biconvex film coated tablets debossed on one side with MX9
Identification - Budesonide	HPLC	Positive (The retention time of the main peaks in the sample chromatogram corresponds to that of the peaks in the standard chromatogram)
	UV	Positive (The UV spectrum of the sample corresponds to that of the standard)
Content Uniformity	USP<905>	Conforms to USP<905>
[a] Budesonide Assay	HPLC	(b) (4) % of the labeled claim (b) (4) mg/tab)
[a] Related substances	HPLC	Individual Specified Degradants: (b) (4) NMT (b) (4) NMT NMT NMT (b) (4)
		Individual Unspecified Degradants: NMT (b) (4) %
		Total Degradants: NMT (b) (4)
[a] Dissolution	Dissolution<711> (pH 1)	After 2 hours: NMT (b) (4)
	Dissolution<711> (pH 7.2)	After 1 hour: NMT (b) (4)
		After 4 hours: Between (b) (4)
		After 8 hours: NLT (b) (4) %
(b) (4)		(b) (4)
[a c] Microbiological Analysis Total Aerobic Microbial Count (TAMC) Total Yeasts and Molds Count (TYMC)	USP<61>	NMT (b) (4) CFU/g NMT CFU/g
[a c] Escherichia coli	USP<61>	Absent from (b) (4) g
[b] (b) (4)	GC	(b) (4) NMT (b) (4) ppm

[a] Indicates test is used for both release and stability.
[b] The (b) (4) test will be done on every (b) (4) batch, or (b) (4) per year, whichever comes first.
[c] The microbial limit test will be done on every (b) (4) batch, or (b) (4) per 6 months, whichever comes first.

The drug product's dissolution acceptance criteria as show above are acceptable. Evaluation of the other specifications for the proposed drug product is discussed in the CMC review by Ray Frankewich, Ph.D.

ALCOHOL DOSE DUMPING METHOD AND DATA:

A dissolution medium containing 0.1N HCl and 40% ethanol was used. For comparison purposes, control samples were also run utilizing acidic dissolution media containing no alcohol. After 2 hours, samples were removed to evaluate the amount of budesonide released from the tablets. Then the acidic dissolution media was removed and replaced with pH 7.2 phosphate buffer. No alcohol was used for this stage to reflect in-vivo conditions. That is, in the in-vivo environment the alcohol would have been considered absorbed by the stomach and would not have passed through into the intestine. Samples were taken at 1, 4, and 8 hours. The results are summarized in the next table as follows:

Samples (Batch AA063)	**Budesonide dissolved amount (%)**			
	pH 1	*pH 7.2*		
	2h	*1h*	*4h*	*8h*
Reference(without ethanol)				
Average value	**<1**	**2**	**31**	**96**
RSD%	---	11.6	10.9	3.2
Minimum value	---	2	27	92
Maximum value	---	3	36	100
Sample(with ethanol)				
Average value	**<1**	**3**	**41**	**97**
RSD%	---	29.6	26.0	2.3
Minimum value	---	2	26	92
Maximum value	---	4	64	99

***Reviewer's Evaluation:* Acceptable**
The presence of 40% ethanol did not significantly alter the release of the drug from the drug product. No in vivo alcohol dose dumping is expected based on these in vitro results.

EXTENDED RELEASE CLAIM:

In order to be claim "extended release", the drug product must fulfill the requirements of 21 CFR 320.25*(f). (1) The purpose of an in vivo bioavailability study involving a drug product for which an extended release claim is made is to determine if all of the following conditions are met:*
(i) The drug product meets the extended release claims made for it.
(ii) The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.
(iii) The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.
(iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

Input from OCP was requested and the response was: "OCP does not have any objections to the extended release claim." (Dr. Sue Chih Lee, OCP team leader on phone during NDA team meeting on 11/14/12).

***Reviewer's Evaluation:* Acceptable**

The provided dissolution data support the extended release claim. Therefore, the "extended release" claim is acceptable.

RECOMMENDATION:

The applicant's dissolution methodology, as summarized below is acceptable:

Acid stage (first 2 hours):
USP Apparatus II (paddle)
Volume: 500 mL
Dissolution medium: 0.1 M HCl containing 0.5% Macrogol Cetostearyl Ether
Temperature: 37 °C
Rotation speed: 100 rpm

Buffer stage (after 2 hours):
USP Apparatus II (paddle)
Volume: 1000 mL
Dissolution medium: Phosphate buffer pH 7.2 containing 0.5% Macrogol Cetostearyl Ether
Temperature: 37 °C
Rotation speed: 100 rpm

- The following drug product dissolution acceptance criteria are acceptable:

Test	Method	Time	Acceptance criteria
Dissolution	USP<711> Acid stage: pH 1	2 hours	NMT (b) (4)
	USP<711> Buffer stage: pH 7.2	1 hour 4 hours 8 hours	NMT (b) (4) (b) (4) NLT (b) (4)

- Alcohol dose dumping does not occur in vitro.
- The extended release claim is acceptable.
- The following post-approval commitments have been agreed upon with the Applicant:

(b) (4)

From the Biopharmaceutics perspective, NDA 203634 for Budesonide Extended Release Tablets, 9 mg is recommended for APPROVAL.

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

/s/

ELSBETH G CHIKHALE
12/12/2012

ANGELICA DORANTES
12/12/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**203634**	**Brand Name**	**UCERIS**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**Budesonide MMX**
Medical Division	**Gastroenterology and Inborn Errors of Metabolism Products**	**Drug Class**	**Corticosteroid, antinflammatory agent**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**Induction of remission in patients with active, mild to moderate ulcerative colitis.**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Extended Release Tablet**
Pharmacometrics Reviewer		**Dosing Regimen**	**9 mg tablet taken once daily**
Date of Submission	**12-14-2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**09/11/2012**	**Sponsor**	**Santarus, Inc.**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**10/16/2012**	**Application Type**	**505 (b)(2)**

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		pharmaco-scintigraphic study
multiple dose:	**X**	**1**		This study had two parts: Part 1: food effect study. Part 2: multiple dose PK study
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		This study had two parts: Part 1: food effect study. Part 2: multiple dose PK study
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**0**	**3**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	According to the sponsor, the formulation did NOT change between TBM product and phase 3 studies.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Metabolism information is described in Entocort label. Need more information for its potential being inhibitor/inducer or substrate of transporter.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			The sponsor has conducted a dose finding study (in phase II) in patient population with 3 mg and 9 mg of budesonide MMX vs. placebo. In phase III, the sponsor has also explored 9 mg and 6 mg doses.
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The sponsor is requesting (b) (4) (b) (4) for pediatric assessment.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	clinical pharmacology section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

The NDA is **Filelable** from clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

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

Dilara Jappar — Feb 10th, 2012

Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee

Team Leader/Supervisor — Date

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

/s/

DILARA JAPPAR
02/10/2012

SUE CHIH H LEE
02/10/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203-634	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	December 16, 2011		
Division:	Division of Gastroenterology Products	**Team Lead:** Angelica Dorantes, PhD	
Applicant:	Santarus Inc.	**Acting Supervisor:** Angelica Dorantes, PhD	
Trade Name:	UCERIS (budesonide)	**Date Assigned:**	December 21, 2011
Generic Name:	Budesonide	**Date of Review:**	January 31, 2012
Indication:	Induction of remission in patients with active mild to moderate ulcerative colitis	**Type of Submission:** Original New Drug Application 505(b)(2)	
Formulation/ strengths	Oral enteric coated-extended release tablet/ 9 mg		
Route of Administration	Oral		

SUBMISSION:

This 505(b)(2) New Drug Application is for an enteric coated, extended release budesonide tablet indicated for the induction of remission in adult patients with mild to moderate active ulcerative colitis. Budesonide is a corticosteroid with high affinity for the glucocorticoid receptor. The reference listed drug is Entocort® EC 3 mg capsules (NDA 21-324).

UCERIS was formulated as a delayed and extended release drug product that delivers budesonide, directly into the colon and then slowly disperses the drug over time. The tablet is coated with a pH dependent polymer film, which breaks down at or above pH 7.0, normally in the terminal ileum where budesonide then begins to be released from the tablet core. The tablet core contains budesonide with controlled release polymers and provides for extended release of budesonide throughout the colon.

The proposed formulation includes an enteric coating, a hydrophilic matrix, and (b) (4) The enteric coating contributes delayed release functionality, the hydrophilic matrix provides hydrodynamic controlled release (swelling), and (b) (4) controlled release of the active ingredient.

(b) (4)

The tablets are coated with pH-resistant acrylic copolymers, which are supposed to delay the release until the tablet reaches an environment where the pH is greater than 7. The applicant claims that the hydrophilic matrix polymers (b) (4)

An in vitro dissolution study was performed to evaluate the effect of alcohol dose dumping on Budesonide tablets. Budesonide tablets were exposed to an alcohol acidic medium and followed by the standard dissolution test at pH 7.2 utilized to evaluate the dissolution profile of the finished product at release.

BIOPHARMACEUTICS:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of 1) the proposed dissolution methodology, 2) dissolution acceptance criteria, and 3) the alcohol dose dumping method and data. This submission does not include a detailed dissolution method development report, which will be requested.

Proposed dissolution method: The proposed dissolution method is a USP Type 2 apparatus operated at 100 rpm with a volume of 500 mL. The method utilizes a two stage approach to first test the integrity of the tablet enteric coating in 0.1N HCl dissolution media (acid stage), and then evaluate the extended release profile of the product in phosphate buffer at pH 7.2 (buffer stage).

Proposed dissolution acceptance criteria:

Test	Reference Method	Specification
[a] Dissolution	Dissolution<711> (pH 1)	After 2 hours: NMT (b) (4)%
	Dissolution<711> (pH 7.2)	After 1 hour: NMT (b) (4)%
		After 4 hours: Between (b) (4)%
		After 8 hours: NLT (b) (4)%

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 203-634 for filing purposes. The applicant has submitted a reviewable submission and we found this NDA filable from a biopharmaceutics perspective. However, some information is lacking and the following comment should be sent to the Applicant in the 74-day letter.

Reviewer Comments:

1. Provide the detailed dissolution method development report, including the following information/data;
   - The complete dissolution profile data collected during the development and validation of the proposed dissolution method.
   - A detailed description of the optimal in vitro dissolution methodology and the developmental parameters (i.e., solubility data for the drug substance across the pH range, selection of the equipment/apparatus, in vitro dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify this method as most appropriate should be included in the report. The dissolution profile should be complete and cover at least (b) (4) of drug dissolved or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend using at least twelve samples per testing variable.
   - The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim). The testing conditions used for each test should be clearly specified.
   - Also, include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).
   - The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance.
2. Provide complete dissolution profile data (individual, mean, SD, profiles) for the biobatches and the primary stability batches (at each tested stability time point).

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc. R. Frankewich, M. Kowblansky

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/s/

ELSBETH G CHIKHALE
01/31/2012

ANGELICA DORANTES
01/31/2012