**OXFORD**

Original Article

# Budesonide MMX for the Induction of Remission of Mild to Moderate Ulcerative Colitis: A Pooled Safety Analysis

**JCC**
JOURNAL of CROHN'S and COLITIS

**Gary R. Lichtenstein,[a] Simon Travis,[b] Silvio Danese,[c] Geert D'Haens,[d] Luigi Moro,[e] Richard Jones,[e] Michael Huang,[f] E. David Ballard,[f] Robert Bagin,[f] Yun Hardiman,[f] Raul Collazo,[f] William J. Sandborn[g]**

[a]Division of Gastroenterology, Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA [b]Translational Gastroenterology Unit, Oxford University Hospitals, Oxford, UK [c]Instituto Clinico Humanitas, Milan, Italy [d]Academic Medical Center, Amsterdam, The Netherlands [e]Cosmo Technologies Ltd, Dublin, Ireland [f]Santarus, Inc., San Diego, CA, USA [g]University of California San Diego, La Jolla, CA, USA

Corresponding author: Department of Medicine, Division of Gastroenterology GI Administration Offices, 9th Floor Penn Tower, One Convention Avenue, Philadelphia, PA 19104-4283, USA. Tel.: +1-215-349-8222. Email: grl@uphs.upenn.edu

## Abstract

**Background and aims:** Cumulative safety and tolerability of budesonide MMX, a once-daily oral corticosteroid for inducing mild to moderate ulcerative colitis remission, was examined.
**Methods:** Data from three randomized, double-blind, placebo-controlled, phase II or III studies [budesonide MMX 9 mg, 6 mg, or 3 mg for 8 weeks]; one phase II study [randomisation to budesonide MMX 9 mg or placebo for 4 weeks, then open-label budesonide MMX 9 mg for 4 weeks]; and one open-label study [budesonide MMX 9 mg for 8 weeks] were pooled.
**Results:** Patients randomised to budesonide MMX 9 mg [$n = 288$], 6 mg [$n = 254$], or placebo [$n = 293$] had similar rates of adverse events [AEs] [27.1%, 24.8%, and 23.9%, respectively] and serious AEs [2.4%, 2.0%, and 2.7%, respectively]; treatment-related AEs and serious AEs were reported by 11.8% and 13.5%, and 5.9% and 2.2%, respectively, of patients receiving budesonide MMX 3 mg [$n = 17$] or open-label budesonide MMX 9 mg [$n = 89$]. Mean morning plasma cortisol concentrations were normal from baseline to final visit across randomised groups; in patients receiving open-label budesonide, mean cortisol concentration was 129.9 nmol/l after 4 weeks, returning to normal concentrations at final visit. Budesonide MMX was not associated with an overall increased risk for glucocorticoid-related adverse effects.
**Conclusions:** Budesonide MMX 9 mg was associated with normal mean cortisol concentrations at final visit and an AE incidence comparable to placebo. Overall, budesonide MMX was safe and well tolerated for inducing remission of patients with mild to moderate ulcerative colitis.

**Keywords:** Budesonide MMX; ulcerative colitis; safety; tolerability

## 1. Introduction

The prevalence of ulcerative colitis [UC] has been noted to be up to 0.51% of the population in Europe, 0.17% in Asia and the Middle East, and up to 0.25% in North America.[1] UC is associated with a high degree of healthcare utilisation and burden of disease. From 1998 to 2004, there was a 3% annual increase in hospitalisation

rates for UC,[2] and direct medical costs were estimated to be > US $2 billion in 2004.[3] Current treatment guidelines, edited by the professional bodies or associations up to 2012, recommend 5-aminosalicylic acid [5-ASA] as first-line therapy for the induction of remission in patients with mild to moderate UC.[4,5] Systemic corticosteroids are usually required as the disease progresses, but are associated with safety concerns, including adrenal suppression, infections, ophthalmic effects [eg cataracts, glaucoma], and mood changes.[4,6]

The potent, second-generation corticosteroid budesonide may have an improved safety profile over conventional corticosteroids because of its low [10–15%] systemic bioavailability, attributable to its extensive presystemic elimination in the gastrointestinal tract and liver.[7] The affinity of budesonide for the glucocorticoid receptor is approximately 8.5 times higher than that of dexamethasone[8] and 15 times higher than that of prednisolone.[9] Because of its rapid elimination, a form of extended-release budesonide with delayed elimination was developed that uses multi-matrix [MMX®] technology [budesonide MMX].[10,11] In this formulation, the active drug is embedded in an inner lipophilic [stearic acid] matrix with an overlying amphiphilic [lecithin] matrix and surrounded by a hydrophilic [hydroxypropylcellulose] matrix-forming polymer. The entire tablet is coated with gastro-resistant methacrylic acid copolymers that dissolve at a pH ≥ 7,[7,11] thus targeting release of > 95% of active budesonide throughout the entire colon.[7] The efficacy and safety of budesonide MMX has been reported in two phase III, randomised, placebo-controlled studies. In the CORE I[12] and CORE II[13] studies, budesonide MMX 9 mg was significantly more efficacious than placebo for the induction of clinical and endoscopic remission and symptom resolution [ie achievement of Ulcerative Colitis Disease Activity Index [UCDAI] rectal bleeding and stool frequency subscale scores of 0] in patients with mild to moderate UC. Given the potential safety concerns associated with the use of corticosteroids, the objective of the current analysis was to conduct a safety and tolerability assessment of budesonide MMX for the induction of remission in patients with mild to moderate UC, by pooling data from five clinical studies.

## 2. Materials and Methods

### 2.1. Patients and study design

The safety data from five clinical trials were pooled for analysis: two phase III, randomised, double-blind, placebo-controlled studies (CORE I [NCT00679432] and CORE II [NCT00679380]),[12,13] two phase II, randomised, double-blind, placebo-controlled studies [CB-01-02/05 and CRO-03-53], and one phase III open-label study [CB-01-02/06; NCT01100112]. Analyses were conducted with regard to short-term induction of remission of mild to moderate UC in patients aged ≥ 18 years [study NCT01100112 enrolled patients aged ≥ 26 years] [Table 1]. All patients receiving ≥ 1 dose of budesonide MMX in the five studies were included in the analysis.

The two phase III, randomised, double-blind studies for induction of UC remission [ie CORE I and CORE II] were identical in study design with the exception of the active reference arms (Asacol® [Warner Chilcott, Rockaway, NJ, USA] in CORE I and Entocort® EC [AstraZeneca LP, Wilmington, DE, USA] in CORE II).[12,13] Briefly, patients with a UCDAI score of ≥ 4 and ≤ 10 and histological evidence of active UC received budesonide MMX 9 mg, budesonide MMX 6 mg, placebo, or reference medication once daily for 8 weeks.[12,13] Remission, the primary endpoint, was strictly defined as a total UCDAI score ≤ 1, with a rectal bleeding score of 0, stool frequency score of 0, mucosal appearance score of 0 on full colonoscopy

**Table 1.** Clinical studies of budesonide MMX included in pooled safety analysis.

| Study | Phase | Duration of treatment, weeks | Randomised, double-blind studies, n [%] | | | | Open-label studies, n [%] |
|---|---|---|---|---|---|---|---|
| | | | Budesonide MMX 9 mg/d [n = 288] | Budesonide MMX 6 mg/d [n = 254] | Budesonide MMX 3 mg/d [n = 17] | Placebo [n = 293] | Budesonide MMX 9 mg/d [n = 89] |
| CORE I[a,12] | III | 8 | 127 [44.1] | 126 [49.6] | 0 | 129 [44.0] | |
| CORE II[b,13] | III | 8 | 128 [44.4] | 128 [50.4] | 0 | 129 [44.0] | |
| CB-01-02/05 | II | 8 | 15 [5.2] | 0 | 17 [100.0] | 17 [5.8] | |
| CB-01-02/06[c,d] | III | 8 | | | | | 60 [67.4] |
| CRO-03-53 | II | | | | | | |
| Period 1 | | 4 | 18 [6.3] | | | 18 [6.1] | |
| Period 2 | | 4 | | | | | 29 [32.6] |

d, day.
[a]NCT00679432.
[b]NCT00679380.
[c]Patients may have received budesonide MMX in the CORE I study.
[d]NCT01100112.

[no sign of mucosal friability], and a ≥ 1-point reduction in baseline endoscopic index score at Week 8.

One of the phase II, randomised, double-blind studies [CB-01-02/05] was a pilot study in which patients with mild to moderate UC [UCDAI score of ≥ 4 and ≤ 10], received budesonide MMX 9 mg, budesonide MMX 3 mg, or placebo once daily for 8 weeks. A second phase II study [CRO-03-53] consisted of two periods: a randomised, double-blind phase in which patients with mild to moderate left-sided UC [Clinical Activity Index < 14] received budesonide MMX 9 mg or placebo once daily for 4 weeks [period 1], followed by an open-label phase of budesonide MMX 9 mg once daily for 4 weeks [period 2]. Lastly, patients who failed to achieve remission in the CORE I study were eligible to enrol in the phase III, open-label study of budesonide MMX 9 mg once daily for 8 weeks.

Adherence to ethical principles was confirmed via approval of clinical protocols by institutional review boards or ethics committees, and study conduct complied with principles of the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and national and/or local regulations relevant to research in humans at participating research sites. All patients provided written informed consent.

## 2.2. Safety assessments

Safety parameters assessed in the studies included overall adverse events [AEs], AEs resulting in study discontinuation, serious AEs [SAEs], mean morning plasma cortisol concentrations, and systemic glucocorticoid-related adverse effects. Blood samples for determination of cortisol concentrations were collected at screening, Day 1, Day 14, Day 28, and final visit [Day 56 or early withdrawal] for the CORE I and II studies; at screening, Day 0, Day 28, and final visit [Day 56 or early withdrawal] for study CB-01-02/05; at screening, Day 1, Day 28, and final visit [Day 56 or early withdrawal for study CB-01-02/06; and at screening, Day 28, and Day 56 for study CRO-03-53. AEs potentially related to the use of glucocorticoids were prespecified [ie acne, insomnia, hirsutism, flushing, fluid retention, mood changes, moon face, sleep changes, and striae rubrae] in four studies and were evaluated by investigators at screening, Day 28, final visit, and at follow-up [2 weeks after final visit] for studies CORE I and II; at screening, Day 28, Day 56, and at follow-up [~ 2 weeks after final visit] in study 01-02/05; and on Day 1, Day 28, and final visit [Day 56 or early withdrawal] in study CB-01-02/06.

## 2.3. Statistical analyses

The safety population included all patients who received ≥ 1 dose of study drug. Descriptive statistics were used to summarise demographic and baseline disease characteristics of the safety population and safety variables. Qualitative variables were presented as category counts and percentages. Statistical comparisons of safety endpoints were performed using a Fisher's exact test, and comparisons of mean morning cortisol concentrations were performed using a t-test. Compliance was evaluated by tablet counts and calculated using the following formula:

$$\% \text{ compliance} = \frac{\left(\begin{array}{c}\text{number of tablets dispensed} -\\ \text{number of tablets returned}\end{array}\right)}{\left(\begin{array}{c}\text{study drug return day} -\\ \text{study drug dispense day}\end{array}\right)} \times 100$$

Patients were considered compliant if they took > 80% of study drug. To maintain consistency with data analysis, data collected during the last visit for patients who discontinued the study early were mapped to the final visit time point.

# 3. Results

## 3.1. Patients

Overall, 648 patients received budesonide MMX 9 mg, budesonide MMX 6 mg, or budesonide MMX 3 mg, with 58.2% receiving budesonide MMX 9 mg [Table 1]; 293 patients received placebo. Demographic and baseline disease characteristics were generally comparable across treatment groups for the randomised, controlled trials [Table 2]. The percentage of patients with proctosigmoiditis, left-sided colitis, and extensive UC were comparable within each group and among groups, except for patients in the budesonide MMX 3 mg group, for whom these data were not collected. The majority of patients had moderate disease [UCDAI score 6–10] at baseline.

Overall exposure to the study drug was similar among treatment groups in the randomised, double-blind studies [Table 3]. The median duration of study drug exposure for patients receiving budesonide MMX 9 mg, 6 mg, 3 mg, or placebo was 56.0 days for each group in the randomised, double-blind studies, and 55.0 days for patients receiving open-label budesonide MMX 9 mg in the open-label studies. Patients receiving budesonide MMX 9 mg in the open-label study had previously completed 8 weeks of treatment with budesonide MMX 9 mg, budesonide MMX 6 mg, 5-ASA 2.4 g/day, or placebo, in the CORE I study. Thus, patients who received budesonide MMX 9 mg in the CORE I study had 16 weeks of consecutive exposure to budesonide MMX.

Compliance [ie ≥ 80% of doses taken] with tablets was 87.2%, 92.9%, and 85.3% for patients receiving budesonide MMX 9 mg, budesonide MMX 6 mg, or placebo, respectively, in the randomized, double-blind studies, and 92.1% for patients receiving budesonide MMX 9 mg in the open-label studies. The majority of patients receiving budesonide MMX 9 mg, 6 mg, 3 mg, or placebo completed the randomised, controlled studies [72.6%, 68.9%, 88.2%, and 71.7%, respectively]; 87.6% of patients receiving budesonide MMX 9 mg completed the open-label studies.

The most common reason for study discontinuation in the randomised, controlled studies was treatment failure. Study discontinuation due to AEs occurred in 3.1%, 3.1%, 0%, and 3.8% of patients receiving budesonide MMX 9 mg, 6 mg, 3 mg, and placebo, respectively, in the, double-blind studies; 2.2% of patients receiving budesonide MMX 9 mg in the open-label studies discontinued on account of AEs.

## 3.2. Adverse events

The percentage of patients with any AE was generally similar among the budesonide MMX 9 mg and 6 mg groups [54.5% vs 60.6%, respectively] and placebo [50.5%] in the randomised, double-blind studies, and in the budesonide MMX 9 mg group of the open-label studies [50.6%; Table 4]. Patients receiving budesonide MMX 3 mg reported the fewest AEs [35.3%]. The frequency of drug-related AEs was similar among the budesonide MMX 9 mg, 6 mg, and placebo groups in the randomised, double-blind studies; patients receiving budesonide MMX 3 mg or budesonide MMX 9 mg in the open-label studies had the fewest drug-related AEs. The most frequently reported AEs were UC, headache, and nausea in patients receiving budesonide MMX 9 mg, 6 mg, or placebo in the randomised, double-blind studies, whereas decreased blood cortisol concentrations and urinary tract infection were the most commonly reported AEs in the open-label studies of budesonide MMX 9 mg. The percentage of patients with infections was generally similar among the budesonide MMX 9 mg, 6 mg, and placebo groups [12.7%, 12.2%, and 8.5%, respectively] across randomised and open-label studies, with

5.9% of patients receiving budesonide MMX 3 mg developing an infection.

Most AEs were mild [24%] or moderate [24%] in intensity; 7% of AEs were considered by investigators to be severe. In the randomised, double-blind studies, UC was the most commonly reported SAE in patients receiving budesonide MMX 9 mg, 6 mg, or placebo [3.1%, 3.9%, or 3.1%, respectively]. No SAEs were reported by patients receiving budesonide MMX 3 mg. In the open-label studies, SAEs were reported by 3.4% of patients, and included defaecation urgency, oral abscess, and endometrial hyperplasia.

Overall, SAEs were reported by 2.4% of patients across all treatment groups; the percentage of patients with SAEs was similar across groups [Table 4]. Serious AEs led to study discontinuation in 1.9%, 1.6%, and 1.4% of patients receiving budesonide MMX 9 mg, 6 mg, or placebo, respectively, across randomised and open-label studies. No patient receiving budesonide MMX 3 mg experienced an SAE leading to study discontinuation. UC-related events [eg worsening of UC] were the most common SAE leading to withdrawal in patients receiving budesonide MMX 9 mg, 6 mg, or placebo. No deaths were reported.

## 3.3. Plasma cortisol concentrations

In the randomised, double-blind studies, mean morning plasma cortisol concentrations decreased in a dose-dependent manner from

**Table 2**. Demographics and baseline characteristics.

| Characteristic | Randomised, double-blind studies | | | | Open-label studies |
|---|---|---|---|---|---|
| | Budesonide MMX 9 mg/d[a] [*n* = 288] | Budesonide MMX 6 mg/d [*n* = 254] | Budesonide MMX 3 mg/d [*n* = 17] | Placebo[a] [*n* = 293] | Budesonide MMX 9 mg/d[a] [*n* = 89] |
| Age, years, mean [SD, range] | 42.7 [13.0, 18–69] | 43.5 [13.5, 18–75] | 44.6 [14.8, 26–66] | 44.0 [13.4, 18–77] | 41.6 [11.6, 19–65] |
| Sex, *n* [%] | | | | | |
|   Male | 167 [58.0] | 130 [51.2] | 8 [47.1] | 170 [58.0] | 58 [65.2] |
|   Female | 121 [42.0] | 124 [48.8] | 9 [52.9] | 31 [34.8] | 31 [65.2] |
| Race, *n* [%] | | | | | |
|   White | 221 [76.7] | 190 [74.8] | 17 [100] | 229 [78.2] | 29 [32.6] |
|   Asian | 47 [16.3] | 46 [18.1] | 0 | 44 [15.0] | 60 [67.4] |
|   Black | 9 [3.1] | 10 [3.9] | 0 | 8 [2.7] | 0 |
|   Hispanic or Latino | 8 [2.8] | 7 [2.8] | 0 | 10 [3.4] | 0 |
|   Other | 3 [1.0] | 1 [0.4] | 0 | 2 [0.7] | 0 |
| Duration of disease, years, mean [SD] | 5.6 [6.8] | 6.3 [7.3] | 5.3 [7.5] | 6.0 [7.2] | 2.5 [2.5] |
| Extent of disease, *n* [%] | | | | | |
|   Proctosigmoiditis | 93 [36.5] | 88 [34.6] | 0 | 109 [42.2] | 15 [25.0] |
|   Left-sided UC | 71 [27.8] | 83 [32.7] | 0 | 79 [30.6] | 23 [38.3] |
|   Extensive/pancolitis | 88 [34.5] | 80 [31.5] | 0 | 63 [24.4] | 22 [36.7] |
|   Missing | 3 [1.2] | 3 [1.2] | 17 [100] | 7 [2.7] | 0 |
| Severity of disease,[b] *n* [%] | | | | | |
|   Mild [UCDAI 4–5] | 68 [25.2] | 69 [27.2] | 6 [35.3] | 82 [29.8] | 18 [30.0] |
|   Moderate [UCDAI 6–10] | 169 [62.6] | 164 [64.6] | 11 [64.7] | 158 [57.5] | 36 [60.0] |
|   UCDAI < 4 or > 10 | 22 [8.1] | 10 [3.9] | 0 | 14 [5.1] | 2 [3.3] |
|   Missing | 11 [4.1] | 11 [4.3] | 0 | 21 [7.6] | 4 [6.7] |
| UCDAI score, mean [SD, range] | 6.3 [2.0, 2–10] | 6.5 [1.9, 2–11] | 6.1 [1.3, 4–8] | 6.3 [2.0, 1–11] | 6.4 [1.8, 3–10] |
| Endoscopic Index score, mean [SD, range] | 7.1 [1.9, 1–12] | 7.4 [1.9, 1–12] | 6.2 [1.3, 3–7] | 7.0 [2.0, 0–12] | 7.2 [1.6, 3–10] |
| Concomitant 5-ASA use, *n* [%] | 55 [19.1] | 37 [14.6] | 2 [11.8] | 43 [14.7] | 37 [41.6] |

SD, standard deviation; d, day; UC, ulcerative colitis; UCDAI, Ulcerative Colitis Disease Activity Index.

[a]Baseline disease characteristics were not collected for patients in studies CB-01-02/05 [*n* = 32] and CRO-03-53 open-label period [period 2] [*n* = 29].

[b]Severity of disease based on UCDAI diary score in CORE I and II studies, and on investigator UCDAI score in study CB-01-02/05.

**Table 3**. Summary of study drug exposure.

| Duration of exposure,[a] *n* [%] | Randomised, double-blind studies | | | | Open-label studies |
|---|---|---|---|---|---|
| | Budesonide MMX 9 mg/d [*n* = 288] | Budesonide MMX 6 mg/d [*n* = 254] | Budesonide MMX 3 mg/d [*n* = 17] | Placebo [*n* = 293] | Budesonide MMX 9 mg/d[b] [*n* = 89] |
| Mean [SD] | 48.6 [15.9] | 47.0 [18.0] | 53.1 [9.5] | 48.0 [28.3] | 45.3 [15.7] |
| Median [range] | 56.0 [1–106] | 56.0 [3–89] | 56.0 [28–59] | 56.0 [3–421] | 55.0 [8–62] |
| Missing | 16 | 9 | 0 | 16 | 4 |

SD, standard deviation; d, day.

[a]Duration of exposure calculated by: [day study drug returned] – [day study drug dispensed].

[b]Patients receiving budesonide MMX 9 mg in the open-label study had previously completed 8 weeks of treatment with budesonide MMX 9 mg, budesonide 6 mg, 5-ASA 2.4 g/day, or placebo, in the CORE I study. Thus, patients who received budesonide MMX 9 mg in the CORE I study had 16 weeks of consecutive exposure to budesonide MMX.

**Table 4**. Summary of adverse events.

| AE, *n* [%] | Randomised, double-blind studies | | | | Open-label studies |
|---|---|---|---|---|---|
| | Budesonide MMX 9 mg/d [*n* = 288] | Budesonide MMX 6 mg/d [*n* = 254] | Budesonide MMX 3 mg/d [*n* = 17] | Placebo [*n* = 293] | Budesonide MMX 9 mg/d [*n* = 89] |
| Any AE | 157 [54.5] | 154 [60.6] | 6 [35.3] | 148 [50.5] | 45 [50.6] |
|   Leading to discontinuation | 41 [14.2] | 48 [18.9] | 2 [11.8] | 48 [16.4] | 3 [3.4] |
| Treatment-related AEs[a] | 78 [27.1] | 63 [24.8] | 2 [11.8] | 70 [23.9] | 12 [13.5] |
| Any SAE[b] | 7 [2.4] | 5 [2.0] | 1 [5.9] | 8 [2.7] | 2 [2.2] |
|   Leading to discontinuation[c] | 6 [2.1] | 4 [1.6] | 0 | 4 [1.4] | 1 [1.1] |
| AE severity | | | | | |
|   Mild | 62 [21.5] | 69 [27.2] | 3 [17.6] | 53 [18.1] | 35 [39.3] |
|   Moderate | 74 [25.7] | 67 [26.4] | 3 [17.6] | 71 [24.2] | 7 [7.9] |
|   Severe | 21 [7.3] | 17 [6.7] | 0 | 22 [7.5] | 3 [3.4] |
| AEs reported in ≥ 4% of patients in any group[d] | | | | | |
|   Ulcerative colitis | 36 [12.5] | 42 [16.5] | 1 [5.9] | 38 [13.0] | 1 [1.1] |
|   Headache | 34 [11.8] | 37 [14.6] | 1 [5.9] | 28 [9.6] | 0 |
|   Nausea | 13 [4.5] | 12 [4.7] | 0 | 12 [4.1] | 1 [1.1] |
|   Decreased blood cortisol concentrations | 12 [4.2] | 6 [2.4] | 0 | 1 [0.3] | 9 [10.1] |
|   Abdominal pain | 10 [3.5] | 7 [2.8] | 1 [5.9] | 18 [6.1] | 1 [1.1] |
|   Insomnia | 7 [2.4] | 9 [3.5] | 0 | 12 [4.1] | 0 |
|   Pyrexia | 6 [2.1] | 6 [2.4] | 0 | 12 [4.1] | 0 |
|   Urinary tract infection | 6 [2.1] | 1 [0.4] | 0 | 1 [0.3] | 7 [7.9] |
|   Anaemia | 5 [1.7] | 4 [1.6] | 1 [5.9] | 5 [1.7] | 0 |
|   Diarrhoea | 4 [1.4] | 7 [2.8] | 0 | 11 [3.8] | 4 [4.5] |
|   Nasopharyngitis | 4 [1.4] | 13 [5.1] | 0 | 6 [2.0] | 3 [3.4] |
|   Asthenia | 2 [0.7] | 5 [2.0] | 1 [5.9] | 1 [0.3] | 0 |
|   Haematochezia | 1 [0.3] | 0 | 1 [5.9] | 4 [1.4] | 1 [1.1] |
|   Nephrolithiasis | 1 [0.3] | 0 | 1 [5.9] | 0 | 0 |
|   Acute tonsillitis | 0 | 0 | 1 [5.9] | 2 [0.7] | 0 |
|   Fluid retention | 0 | 2 [0.8] | 1 [5.9] | 3 [1.0] | 1 [1.1] |

AE, adverse event; SAE, severe adverse event; d, day.

[a]*p* = 0.26 for budesonide MMX 9 mg vs budesonide MMX 3 mg and *p* = 0.56 for budesonide MMX 9 mg vs budesonide MMX 6 mg [randomised, double-blind studies].

[b]*p* = 0.37 for budesonide MMX 9 mg vs budesonide MMX 3 mg and *p* = 0.78 for budesonide MMX 9 mg vs budesonide MMX 6 mg [randomised, double-blind studies].

[c]*p* > 0.99 for budesonide MMX 9 mg vs budesonide MMX 3 mg and *p* = 0.76 for budesonide MMX 9 mg vs budesonide MMX 6 mg [randomised, double-blind studies].

[d]AEs presented in descending order of frequency for budesonide MMX 9 mg group, then alphabetically for AEs with equal frequency.

baseline to final visit for budesonide MMX 9 mg, 6 mg, and 3 mg [19.4%, 10.0%, and 1.0%, respectively] and generally remained within normal limits [ie 138–690 nmol/l] during the study [Figure 1]. Mean morning plasma cortisol concentrations at baseline decreased in patients receiving budesonide MMX 9 mg in the open-label studies compared with patients in the randomised, controlled studies. Further, patients receiving budesonide MMX 9 mg had mean morning plasma cortisol concentrations of 129.9 nmol/l at Week 4; this was below normal concentrations, but mean cortisol concentrations returned to normal concentrations at the final visit. The changes from baseline to final visit were statistically significant for placebo [increase from baseline] and all budesonide MMX groups [decrease from baseline] except budesonide MMX 3 mg.

### 3.4. Potential glucocorticoid-related adverse effects

The incidence of potential glucocorticoid-related adverse effects was < 10% across all treatment groups [Table 5]. There was no apparent dose-related increase in potential glucocorticoid-related adverse effects following treatment with budesonide MMX. Further, the incidence of potential glucocorticoid-related adverse effects was similar when mean morning cortisol concentrations at final visit

were distributed across quartiles. When patients with low morning plasma cortisol concentrations [< 138 nmol/l] at the final visit were selectively examined, mood and sleep changes were the most frequently reported potential glucocorticoid-related adverse effects among patients who received budesonide MMX 9 mg, 6 mg, or placebo [Table 6]. In the budesonide MMX 3 mg group, one patient reported fluid retention.

### 4. Discussion

Budesonide MMX is a second-generation oral corticosteroid indicated for the induction of remission in patients with active, mild to moderate UC.[10] In a pooled safety analysis of five clinical studies, budesonide MMX administered for up to 8 weeks demonstrated a favourable safety and tolerability profile for the induction of remission in patients with active, mild to moderate UC. The overall AE profile in patients taking budesonide MMX was comparable to that of those taking placebo. Pooling of safety data for 648 patients receiving budesonide MMX 9 mg, 6 mg, or 3 mg provided a more robust evaluation of the safety of budesonide MMX and allowed for greater accuracy in estimating the incidence of drug-related AEs,
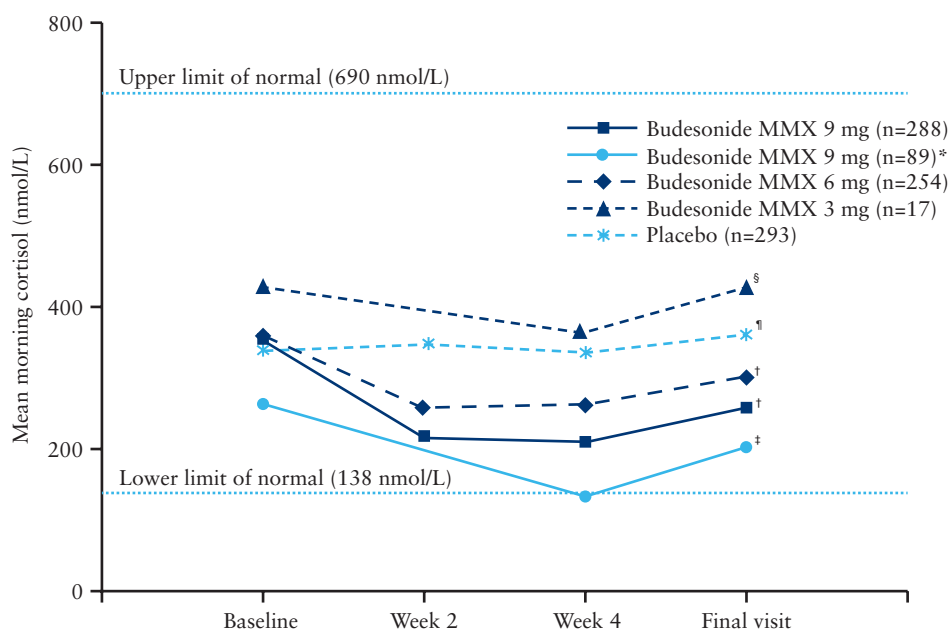
**Figure 1.** Mean morning plasma cortisol concentrations. *Of the 89 patients who received open-label budesonide MMX 9 mg, several had previously completed 8 weeks of treatment with budesonide MMX 9 mg [*n* = 12] or budesonide MMX 6 mg [*n* = 16] in CORE 1, and thus had 16 weeks of consecutive exposure to budesonide MMX. [†]$p < 0.0001$; [‡]$p = 0.03$; [§]$p = 0.93$; [¶]$p = 0.01$, for changes from baseline to final visit.

**Table 5**. Summary of potential glucocorticoid-related adverse effects.

| Effect, *n* [%] | Randomised, double-blind studies | | | | Open-label studies |
|---|---|---|---|---|---|
| | Budesonide MMX 9 mg/d [*n* = 270][a] | Budesonide MMX 6 mg/d [*n* = 254] | Budesonide MMX 3 mg/d [*n* = 17] | Placebo [*n* = 293] | Budesonide MMX 9 mg/d [*n* = 60][a] |
| Any potential glucocorticoid-related adverse effect[b,c] | 26 [9.6] | 19 [7.5] | 1 [5.9] | 27 [9.8] | 5 [8.3] |
| Mood changes | 9 [3.3] | 10 [3.9] | 0 | 11 [4.0] | 0 |
| Sleep changes | 7 [2.6] | 10 [3.9] | 0 | 12 [4.4] | 0 |
| Acne | 6 [2.2] | 2 [0.8] | 0 | 5 [1.8] | 1 [1.7] |
| Insomnia | 6 [2.2] | 6 [2.4] | 0 | 8 [2.9] | 1 [1.7] |
| Moon face | 3 [1.1] | 3 [1.2] | 0 | 4 [1.5] | 3 [5.0] |
| Fluid retention | 2 [0.7] | 3 [1.2] | 1 [5.9] | 3 [1.1] | 1 [1.7] |
| Hirsutism | 1 [0.4] | 0 | 0 | 0 | 0 |
| Flushing | 0 | 1 [0.4] | 0 | 3 [1.1] | 0 |
| Striae rubrae | 0 | 0 | 0 | 2 [0.7] | 0 |

d, day.

[a]Adverse events potentially related to the use of glucocorticoids were not prespecified in study CRO-03-53 and thus this population was not included in the analysis.

[b]Potential glucocorticoid-related adverse effects presented in descending order of frequency for budesonide MMX 9 mg group, then alphabetically for AEs with equal frequency.

[c]$p > 1.0$ for budesonide MMX 9 mg vs budesonide MMX 3 mg [randomised, double-blind studies].

especially when compared with assessments of the studies individually. The findings of this pooled analysis support the short-term safety and tolerability of budesonide MMX for the induction of remission in patients with mild to moderate UC.

The frequency and intensity of AEs were generally comparable across treatment groups, with the fewest AEs reported in the budesonide MMX 3 mg group; however, this treatment group also included the fewest patients [*n* = 17]. Suppression of the immune system may occur during treatment with systemic corticosteroids,[6] thus increasing the risk of infection in patients. However, this analysis suggested no apparent dose-related increase in the incidence of infections. Further, patients receiving budesonide MMX 9 mg or 6 mg had a

rate of infection similar to that of patients receiving placebo, and patients receiving budesonide MMX 3 mg had the lowest incidence of infection. The occurrence of SAEs during treatment with budesonide MMX was infrequent, with patients in randomised, double-blind studies in the budesonide MMX 9 mg group reporting the greatest frequency of SAEs [2.4%]. The AE profile of patients in this pooled safety analysis is comparable to previous reports of patients with left-sided UC or Crohn's disease who received once-daily oral budesonide 9 mg for 8 to 16 weeks.[14–16]

Decreased plasma cortisol concentrations and glucocorticoid-related adverse effects [e.g. moon face, striae rubrae, mood changes, sleep changes] are associated with treatment with systemic

**Table 6**. Summary of potential glucocorticoid-related adverse effects in patients with low cortisol morning plasma concentrations [< 138 nmol/l] at final visit.[a]

| Effect, n [%] | Budesonide MMX 9 mg/d [n = 63] | Budesonide MMX 6 mg/d [n = 47] | Budesonide MMX 3 mg/d [n = 2] | Placebo [n = 8] |
|---|---|---|---|---|
| Any glucocorticoid-related adverse effect[b] | 9 [14.3] | 2 [4.3] | 1 [50.0] | 2 [25.0] |
| Mood changes | 4 [6.3] | 2 [4.3] | 0 | 1 [12.5] |
| Acne | 2 [3.2] | 0 | 0 | 0 |
| Fluid retention | 1 [1.6] | 0 | 1 [50.0] | 0 |
| Hirsutism | 1 [1.6] | 0 | 0 | 0 |
| Insomnia | 1 [1.6] | 1 [2.1] | 0 | 0 |
| Moon face | 1 [1.6] | 0 | 0 | 0 |
| Sleep changes | 1 [1.6] | 1 [2.1] | 0 | 2 [25.0] |
| Flushing | 0 | 0 | 0 | 0 |
| Striae rubrae | 0 | 0 | 0 | 0 |

d, day.

[a]Patients in randomised, double-blind, phase II and III studies.

[b]Potential glucocorticoid-related adverse effects presented in descending order of frequency for budesonide MMX 9 mg group, then alphabetically for AEs with equal frequency.

corticosteroids.[17–19] However, in the current study, although the changes from baseline to final visit were statistically significant for placebo and all budesonide MMX groups except budesonide MMX 3 mg, morning plasma cortisol concentrations remained within normal concentrations [ie 138–690 nmol/l] for the majority of patients. Mean cortisol concentrations decreased to 129.9 nmol/l after 4 weeks in patients receiving open-label treatment with budesonide MMX 9 mg, but recovered to normal concentrations [ie 200.1 nmol/l] by the final visit. This finding was consistent with results of a previous study of once-daily oral budesonide 15 mg, 9 mg, or 3 mg in patients with Crohn's disease,[20] which showed that patients receiving oral budesonide 9 mg had a decrease in median morning cortisol concentrations to 135.2 nmol/l after 4 weeks, that returned to normal after 8 weeks. Mean cortisol concentrations after 4 weeks following treatment with budesonide MMX 9 mg in the open-label studies were decreased compared with those for patients who received budesonide MMX 9 mg in the randomised, controlled studies; this finding may be due to the number of patients who had previously completed 8 weeks of treatment with budesonide MMX 9 mg or 6 mg in the CORE I study. Results of this analysis suggest that short-term [up to 8 weeks] treatment with budesonide MMX had a minimal effect on the hypothalamic-pituitary-adrenal axis, a finding that is consistent with the pharmacodynamic activity of budesonide. The minimal systemic exposure of budesonide is due to its > 90% first-pass hepatic metabolism.[21] Glucocorticoid-related adverse effects occurred in < 10% of patients in each treatment group. Patients with low [< 138 nmol/l] plasma cortisol concentrations at final visit did not appear to be at increased risk for potential glucocorticoid-related adverse effects compared with placebo. However, it is difficult to draw firm conclusions given the small number of patients in the budesonide MMX 3 mg and placebo groups.

Several limitations of this analysis should be noted, including differences in study design among the clinical trials analysed [eg randomised, controlled studies; open-label studies] and the wide variation in the number of patients across budesonide MMX treatment groups [eg budesonide MMX 3 mg, n = 17; budesonide MMX 6 mg, n = 254; vs budesonide MMX 9 mg, n = 377]. Further, the studies were not designed, and thus not sufficiently powered, to specifically evaluate safety outcomes. Although the studies included did not contribute equally to the analysis, it is reassuring that a low incidence of AEs were reported in the two large, randomised, controlled trials.

In conclusion, the findings of this pooled safety analysis demonstrate that short-term treatment with budesonide MMX for the induction of remission in patients with mild to moderate UC was well tolerated, with an AE profile comparable to placebo. Although 5-ASAs are currently the most frequently prescribed treatment for the induction of remission of mild to moderate UC,[4,5] budesonide MMX is a second-generation glucocorticosteroid indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis and may be an alternative to conventional corticosteroid in such patients.

## Conflicts of Interest

G D'Haens has served as a speaker, consultant, and/or principal investigator for AbbVie, AM-Pharma BV, Amgen, AstraZeneca, Boehringer Ingelheim, Centocor Ortho Biotech, Cosmo Pharmaceuticals S.p.A, Dr Falk Pharma GmbH, Elan Pharmaceuticals, Ferring Pharmaceuticals, Galapagos NV, Giuliani S.p.A, Given Imaging, GlaxoSmithKline, Janssen, Millennium Pharmaceuticals, MSD, Norgine, Novo Nordisk A/S, Otsuka Pharmaceutical, PDL BioPharma, Pfizer, PhotoPill Medical Ltd, Shire, Takeda Pharmaceutical Co., Ltd, Teva Pharmaceutical Industries, Ltd, Tillotts Pharma AG, UCB, Versant Ventures, and Vifor Pharma.

L Moro is an employee of Cosmo Technologies Ltd, a subsidiary of Cosmo Pharmaceuticals S.p.A., and owns stock in Cosmo Pharmaceuticals S.p.A.

R Jones is an employee of Cosmo Technologies Ltd, a subsidiary of Cosmo Pharmaceuticals S.p.A., and owns stock in Cosmo Pharmaceuticals S.p.A.

M Huang is a former employee of Santarus, Inc.

E D Ballard is a former employee of Santarus, Inc.

R Bagin is a former employee of Santarus, Inc.

Y Hardiman is a former employee of Santarus, Inc.

R Harris-Collazo is a former employee of Santarus, Inc.

W Sandborn has served as a consultant for AbbVie, ActoGeniX NV, AGI Therapeutics, plc, Alba Therapeutics Corp., Albireo, Alfa Wassermann, AM-Pharma BV, Amgen, Anaphore, Aptalis, Astellas, Athersys, Inc., Atlantic Healthcare plc., BioBalance Corp., Boehringer-Ingelheim, Bristol-Myers Squibb, Celek Pharmaceuticals, Celgene, Cellerix SA, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Coronado Biosciences, Cosmo Technologies Ltd, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research Inc., Elan Pharmaceuticals, Eli Lilly, EnGene, Inc., Enteromedics, Exagen Diagnostics, Inc., Ferring Pharmaceuticals, Flexion Therapeutics, Inc., Funxional Therapeutics Ltd., Genentech, Genzyme Corp., Gilead Sciences, Given Imaging, GlaxoSmithKline, Human Genome Sciences, Ironwood Pharmaceuticals, Janssen, KaloBios Pharmaceuticals, Inc., Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals, Merck & Co., Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceutical Co., Ltd, Novo Nordisk A/S, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, Inc., PDL BioPharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies, Inc., Receptos, Relypsa, Inc., S.L.A. Pharma [UK] Ltd, Salient Pharmaceuticals, Salix, Santarus, Inc., Shire, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, Inc., Targacept, Teva Pharmaceutical Industries, Ltd, Therakos, Tillotts Pharma AG, TxCell SA, UCB, Vascular Biogenics Ltd, Viamet Pharmaceuticals, and Warner Chilcott UK Ltd. he has received speakers' bureau fees for AbbVie, Bristol-Myers Squibb, and Janssen; and he has received financial support for research from AbbVie, Bristol-Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Millennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire, and UCB.

## Funding

## Acknowledgments

## Author Contributions

## References

1. Molodecky NA, Soon IS, Rabi DM, *et al.* Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;**142**:46–54.

2. Nguyen GC, Tuskey A, Dassopoulos T, Harris ML, Brant SR. Rising hospitalization rates for inflammatory bowel disease in the United States between 1998 and 2004. *Inflamm Bowel Dis* 2007;**13**:1529–35.

3. Kappelman MD, Rifas-Shiman SL, Porter CQ, *et al.* Direct health care costs of Crohn's disease and ulcerative colitis in United States children and adults. *Gastroenterology* 2008;**135**:1907–13.

4. Kornbluth A, Sachar DB; the Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;**105**:501–23.

5. Dignass A, Lindsay JO, Sturm A, *et al.* Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 2: current management. *J Crohns Colitis* 2012;**6**:991–1030.

6. Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. *Drug Saf* 2000;**23**:429–48.

7. Brunner M, Ziegler S, Di Stefano AF, *et al.* Gastrointestinal transit, release and plasma pharmacokinetics of a new oral budesonide formulation. *Br J Clin Pharmacol* 2006;**61**:31–8.

8. Esmailpour N, Högger P, Rohdewald P. Binding kinetics of budesonide to the human glucocorticoid receptor. *Eur J Pharm Sci* 1998;**6**:219–23.

9. Rutgeerts P, Löfberg R, Malchow H, *et al.* A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* 1994;**331**:842–5.

10. *Uceris [budesonide] extended release tablets, for oral use. [Package insert.]* Raleigh, NC: Salix Pharmaceuticals, Inc.; 2014.

11. Fiorino G, Fries W, De La Rue SA, Malesci AC, Repici A, Danese S. New drug delivery systems in inflammatory bowel disease: MMX™ and tailored delivery to the gut. *Curr Med Chem* 2010;**17**:1851–7.

12. Sandborn WJ, Travis S, Moro L, *et al.* Once-daily budesonide MMX® extended-release tablets induce remission in patients with mild to moderate ulcerative colitis: results from the CORE I study. *Gastroenterology* 2012;**143**:1218–26.

13. Travis SP, Danese S, Kupcinskas L, *et al*. Once-daily budesonide MMX in active, mild-to-moderate ulcerative colitis: results from the randomised CORE II study. *Gut* 2014;**63**:433–41.

14. D'Haens GR, Kovács A, Vergauwe P, *et al*. Clinical trial: preliminary efficacy and safety study of a new Budesonide-MMX® 9 mg extended-release tablets in patients with active left-sided ulcerative colitis. *J Crohns Colitis* 2010;**4**:153–60.

15. Thomsen OO, Cortot A, Jewell D, *et al*. A comparison of budesonide and mesalamine for active Crohn's disease. International Budesonide-Mesalamine Study Group. *N Engl J Med* 1998;**339**:370–4.

16. Dignass A, Stoynov S, Dorofeyev AE, *et al*. Once versus three times daily dosing of oral budesonide for active Crohn's disease: A double-blind, double-dummy, randomised trial. *J Crohns Colitis* 2014;**8**:970–80.

17. Rhodes JM, Robinson R, Beales I, *et al*. Clinical trial: oral prednisolone metasulfobenzoate [Predocol] vs. oral prednisolone for active ulcerative colitis. *Aliment Pharmacol Ther* 2008;**27**:228–40.

18. *Entocort EC [budesonide] capsules. [Package insert.]* Wilmington, DE: AstraZeneca LP; 2012.

19. Desramé J, Sabaté JM, Agher R, *et al*. Assessment of hypothalamic-pituitary-adrenal axis function after corticosteroid therapy in inflammatory bowel disease. *Am J Gastroenterol* 2002;**97**:1785–91.

20. Greenberg GR, Feagan BG, Martin F, *et al*; Canadian Inflammatory Bowel Disease Study Group. Oral budesonide for active Crohn's disease. *N Engl J Med* 1994;**331**:836–41.

21. Iborra M, Álvarez-Sotomayor D, Nos P. Long-term safety and efficacy of budesonide in the treatment of ulcerative colitis. *Clin Exp Gastroenterol* 2014;**7**:39–46.