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Induction of clinical and colonoscopic remission of mild-to-moderate ulcerative colitis with budesonide MMX 9 mg: pooled analysis of two phase 3 studies

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SUMMARY

Background
Conventional oral corticosteroids are effective at reducing inflammation associated with ulcerative colitis (UC); however, systemic adverse effects limit their use. Budesonide MMX is an extended-release, second-generation corticosteroid that targets delivery of budesonide to the entire colon.

Aim
To analyse efficacy and safety outcomes from two phase 3 studies of budesonide MMX in patients with mild-to-moderate active UC.

Methods
Patients were assigned to budesonide MMX 9 mg, budesonide MMX 6 mg, or placebo once daily in two randomised, double-blind, placebo-controlled, 8-week studies (CORE I and II). Pooled data were analysed for pre-defined primary (combined clinical and colonoscopic remission), secondary and exploratory endpoints. Primary endpoint data were analysed to evaluate the potential influence of demographical and baseline disease characteristics on remission.

Results
Modified intent-to-treat population (histological evidence of baseline inflammation) had 232, 230 and 210 patients in budesonide MMX 9 mg, budesonide MMX 6 mg and placebo groups respectively. Combined clinical and colonoscopic remission rates were significantly greater than placebo (6.2%) for the budesonide MMX 9 mg group (17.7%; $P = 0.0002$), but not the budesonide MMX 6 mg group (10.9%). The primary endpoint of remission with budesonide MMX 9 mg was significantly greater than placebo in most subgroups analysed. Symptom resolution and colonoscopic improvement rates were significantly greater with budesonide MMX 9 mg vs. placebo. Budesonide MMX was safe and well tolerated.

Conclusion
This pooled analysis showed that budesonide MMX 9 mg is efficacious, safe and well tolerated for inducing remission of mild-to-moderate UC.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colonic mucosal surface related to a dysregulated immune response to commensal gut flora.[1, 2] Inflammation typically starts in the rectum and extends proximally through the colon. Orally administered, conventional corticosteroids are effective at reducing inflammation associated with UC, but serious systemic adverse effects limit their use to patients with severe disease or to those who are refractory to first-line therapy with an oral 5-aminosalicylic acid (5-ASA) in combination with rectal therapy.[3–5] Budesonide is a second-generation corticosteroid with low systemic availability after oral administration.[6] Some gut-specific formulations of budesonide use a pH-mediated delivery method to release drug into the distal ileum and proximal colon; however, these formulations are not optimised for delivery to the more distal sites of disease associated with UC.[3, 7]

Budesonide MMX [Cosmo Technologies, Ltd., Dublin, Ireland; licensed as Uceris (Salix Pharmaceuticals, Inc., Raleigh, NC, USA) in the USA and Cortiment (Ferring Pharmaceuticals, St. Prex, Switzerland) outside the USA] is an extended-release, oral tablet with a gastro-resistant outer layer that dissolves as the gastrointestinal luminal pH increases over 7.0.[7, 8] Inner hydrophilic and inert polymer matrices encase the drug to provide a controlled, homogeneous and progressive release of budesonide throughout the colon. In a pilot study in patients with left-sided colitis, budesonide MMX 9 mg demonstrated rapid clinical improvement after 4 weeks of treatment.[9] In addition, in two phase three clinical studies (CORE I and II) in patients with mild-to-moderate active UC, budesonide MMX 9 mg was associated with a significantly greater percentage of patients achieving combined clinical and colonoscopic remission and symptom resolution compared with placebo.[10, 11] We present pooled efficacy and safety results from the CORE I and II studies, which had the same eligibility criteria and the same primary, secondary and exploratory endpoints.

MATERIALS AND METHODS

Study design

Detailed methodology for the CORE I and II studies have been published previously (ClinicalTrials.gov identifiers NCT00679432 and NCT00679380).[10, 11] The CORE I and II studies were 8-week, randomised, double-blind, double-dummy, placebo-controlled and multicenter studies. Before randomisation, patients underwent a ≥2-day washout period, during which they received no treatment for UC. In CORE I, patients were randomly assigned to once-daily oral budesonide MMX 9 mg, budesonide MMX 6 mg, mesalazine (mesalamine) 2400 mg (two 400-mg tablets three times a day; Asacol, owned at the time of the study by Procter & Gamble Pharmaceuticals, Cincinnati, OH, USA), or placebo. In CORE II, patients were randomly assigned to receive once-daily oral budesonide MMX 9 mg, budesonide MMX 6 mg, controlled ileal-release budesonide (three 3-mg capsules; Entocort EC, AstraZeneca LP, Wilmington, DE, USA), or placebo. Local institutional review boards approved the clinical protocols, and study conduct complied with principles of International Conference on Harmonisation Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and national and local regulations relevant to research in humans at participating research sites. All patients provided written consent before participation.

Patients

Eligible participants were adults 18–75 years of age with mild-to-moderate active UC for ≥6 months and a UC Disease Activity Index (UCDAI) score between 4 and 10 (inclusive). Key exclusion criteria were proctitis (from anal verge up to 15 cm), severe UC (UCDAI score >10), infectious colitis, history of toxic megacolon, severe anaemia, leukopenia or granulocytopenia, or severe diseases in other organs and systems. Concomitant use of oral 5-ASA was not permitted; patients receiving oral 5-ASA at screening underwent a washout period of ≥2 days. Orally or rectally administered corticosteroids, immunosuppressive agents and antitumor necrosis factor alpha agents were not allowed for 4 weeks, 8 weeks and 3 months, respectively, before screening. Concurrent use of any rectal preparations, antibiotics or known cytochrome P450 3A4 inducers or inhibitors was not permitted during the study. Although not part of the inclusion criteria, to be included in the efficacy analyses (see below), patients had to have baseline histological evidence of active UC, identified by mucosal biopsy (according to Saverymuttu criteria[12] and evaluated at a central laboratory).

Assessments

The primary endpoint was combined clinical and colonoscopic remission at week 8, which was defined as a UCDAI score of ≤1, with no rectal bleeding (UCDAI subscore = 0), normal stool frequency (UCDAI subscore = 0), normal mucosa with no evidence of friability at full colonoscopy and an endoscopic index score ≥1 point lower than baseline. Secondary endpoints were

clinical improvement (≥3-point improvement in UCDAI from baseline to week 8) and colonoscopic improvement (≥1-point improvement in the endoscopic mucosal appearance subscore of the UCDAI from baseline to week 8). Exploratory endpoints included symptom resolution (UCDAI subscores of 0 for both stool frequency and rectal bleeding at week 8), histological healing (total histological score of ≤1, according to Saverymuttu criteria[12] for all biopsy specimens at week 8) and mucosal healing (UCDAI mucosal appearance score of 0 at week 8). Safety assessments included adverse event (AE) reporting throughout the study and potential glucocorticoid-related AEs.

Analysis

Integrated efficacy analyses were conducted in a pre-defined modified intent-to-treat (mITT) population in the placebo, budesonide MMX 9 mg and budesonide MMX 6 mg study arms, which included all randomised patients who received ≥1 dose of study drug, had histological evidence of active disease at baseline (according to Saverymuttu criteria[12]) and were not enrolled at sites with major violations of entry criteria or GCP guidelines. Patients receiving systemic corticosteroids during the study were categorised as having not met any endpoint. Subgroup analyses were conducted to determine the potential effects of sex, age (≤60 years, >60 years), prior 5-ASA use, baseline disease severity (i.e. mild or moderate), baseline disease extent (i.e. proctosigmoiditis, left-sided colitis or extensive disease/pancolitis) and disease duration (≤1 year, >1 year to ≤5 years, >5 years).

The Cochran–Mantel–Haenszel test was used for binomial proportions, stratified by study. Continuous variables were analysed by the Cochran–Mantel–Haenszel Mean Score test, stratified by study. For the primary endpoint, percentages of patients achieving clinical and colonoscopic remission were compared at the $\alpha = 0.025$ level of significance. Hierarchical testing was performed for secondary endpoints, such that if the primary endpoint comparison met statistical significance for ≥1 budesonide MMX dosage strength, secondary endpoints were tested for dosage strength(s) at the $\alpha = 0.025$ level. All other endpoints were tested at the $\alpha = 0.05$ level. Missing data were handled by the worst-case imputation method; any patient with missing data for any endpoint was categorised as having not met that nor any other endpoint. Odds ratios (ORs) to achieve primary, secondary and exploratory endpoints were calculated for budesonide MMX 9 mg and budesonide MMX 6 mg compared with placebo. The safety population included all patients who received at least one dose of the study drug.

RESULTS

Patients

The mITT population consisted of 672 patients (placebo, $n = 210$; budesonide MMX 9 mg, $n = 232$; budesonide MMX 6 mg, $n = 230$; Figure 1). In the mITT population, 68.2% of the 672 patients completed either CORE I or II. Across the three groups, mean exposure to study drug was 46–50 days. A majority of patients were male (56.8%), and most were white (72.8%). Across study groups, data were similar with respect to mean age, disease duration, disease extent, baseline endoscopic index and UCDAI scores and prior 5-ASA use (Table 1). Most patients (66.7%) had moderate UC at baseline, with a UCDAI score in the range of 6–10, and the majority of patients (69.6%) reported prior use of 5-ASAs.

Efficacy

A larger percentage of patients had combined clinical and colonoscopic remission (the primary endpoint) with budesonide MMX 9 mg (17.7%) and budesonide MMX 6 mg (10.9%) treatment compared with placebo (6.2%). These differences were statistically significant for the budesonide MMX 9 mg group ($P = 0.0002$), but not for the budesonide MMX 6 mg group ($P = 0.0692$; Figure 2). Compared to patients receiving placebo, patients who received budesonide MMX 9 mg were >3 times more likely to achieve combined clinical and colonoscopic remission [OR, 3.3 (95% CI: 1.7–6.4)]. In addition, both male and female patients receiving budesonide MMX 9 mg had a significantly ($P \leq 0.01$) higher combined clinical and colonoscopic remission rate than those receiving placebo (17.7% vs. 7.2% for males, respectively, and 17.6% vs. 4.7% for females respectively). Patients ≤60 years of age receiving budesonide MMX 9 mg had a significantly greater rate of combined clinical and colonoscopic remission compared with placebo (17.1% vs. 6.5%, $P = 0.001$); a greater percentage of patients >60 years of age receiving budesonide MMX 9 mg achieved combined clinical and colonoscopic remission compared with placebo, but this comparison was not statistically significant (25.0% vs. 4.2%, $P = 0.0594$).

Budesonide MMX 9 mg-treated patients with mild disease (36.7% vs. 11.1%, $P = 0.0039$) and moderate disease (14.1% vs. 5.1%, $P = 0.0098$), and those with left-sided colitis (20.3% vs. 3.2%, $P = 0.0018$) and proctosigmoiditis (23.5% vs. 11.0%, $P = 0.0349$), had a

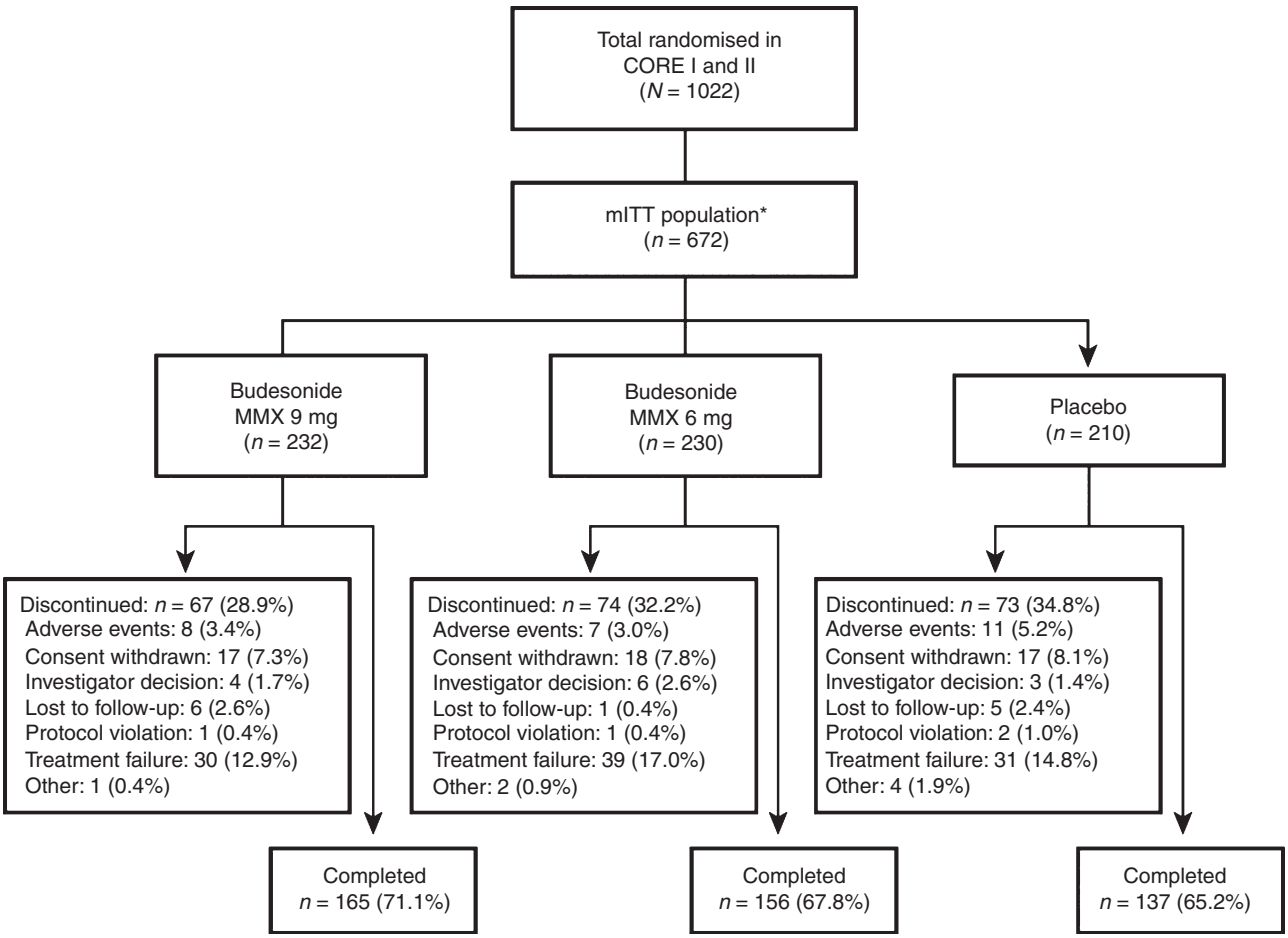

Figure 1 | Patient disposition. mITT, modified intent-to-treat population. *Includes budesonide MMX 9 mg, budesonide MMX 6 mg and placebo groups. Data from study data and Sandborn *et al.*[10] and Travis *et al.*[11]

significantly higher rate of combined clinical and colonoscopic remission compared with placebo (Figure 2). No significant treatment effect was observed for patients with extensive/pancolitis UC (9.4% vs. 3.3%, $P = 0.1585$). A significantly greater percentage of patients receiving budesonide MMX 9 mg, relative to placebo, who had a disease duration of >1 to ≤5 years (19.6% vs. 6.3%, $P = 0.0103$) or >5 years (17.9% vs. 0%, $P < 0.0001$) achieved combined clinical and colonoscopic remission; no treatment effect was apparent in patients with disease duration ≤1 year, (14.3% vs. 16.0% respectively; $P = 0.7887$). With the exception of disease duration >5 years, no significant between-group differences were observed for these subgroups in patients receiving budesonide MMX 6 mg.

The effect of exposure to 5-ASA at screening on efficacy was also examined in the pooled population. A significantly greater percentage of patients receiving budesonide MMX 9 mg achieved combined clinical and endoscopic remission compared with placebo in subgroups of patients with prior 5-ASA use (17.0% vs. 7.4% respectively; $P = 0.0098$; OR, 2.6, 95% CI, 1.2–5.6) and patients without prior 5-ASA use (18.8% vs. 3.3% respectively; $P = 0.0051$; OR, 6.8, 95% CI, 1.5–31.0) at screening.

For secondary endpoints, rates were numerically greater for patients receiving budesonide MMX 9 mg vs. patients receiving placebo for clinical improvement (37.5% vs. 28.6%) and colonoscopic improvement (41.8% vs. 32.4%) (Table 2). Among exploratory endpoints, rates were significantly greater for patients receiving budesonide MMX 9 mg vs. patients receiving placebo for symptom resolution (26.3% vs. 14.3%; $P = 0.0015$) and for mucosal healing (27.6% vs. 17.1%; $P = 0.009$). The percentage of patients with histological healing was numerically greater with the budesonide MMX 9 mg group vs. the placebo group (9.9% vs. 6.7% respectively), but not significantly different. Similar to the results of the

Table 1 | Patient demographics and baseline disease characteristics

Variable	Budesonide MMX 9 mg (n = 232)	Budesonide MMX 6 mg (n = 230)	Placebo (n = 210)
Age, years, mean (s.d.)	42.1 (13.1)	43.7 (13.4)	42.6 (13.4)
Sex, *n* (%)			
Male	141 (60.8)	116 (50.4)	125 (59.5)
Female	91 (39.2)	114 (49.6)	85 (40.5)
Race, *n* (%)			
White	167 (72.0)	169 (73.5)	153 (72.9)
Black	9 (3.9)	11 (4.8)	7 (3.3)
Hispanic/Latino	8 (3.4)	7 (3.0)	9 (4.3)
Asian	45 (19.4)	42 (18.3)	39 (18.6)
Other	3 (1.3)	1 (0.4)	2 (1.0)
Disease duration, years, mean (s.d.)	5.8 (7.1)	6.4 (7.3)	6.1 (7.5)
Disease extent, *n* (%)			
Proctosigmoiditis	81 (34.9)	76 (33.0)	82 (39.0)
Left-sided colitis	64 (27.6)	73 (31.7)	62 (29.5)
Extensive disease/pancolitis	85 (36.6)	78 (33.9)	60 (28.6)
Missing	2 (0.9)	3 (1.3)	6 (2.9)
Endoscopic index score, mean (s.d.)	7.3 (1.8)	7.6 (1.8)	7.3 (2.0)
UCDAI score, mean (s.d.)	6.5 (2.0)	6.6 (1.9)	6.7 (1.9)
Disease severity, *n* (%)			
Mild (UCDAI score = 4–5)	49 (21.1)	57 (24.8)	45 (21.4)
Moderate (UCDAI score = 6–10)	156 (67.2)	155 (67.4)	137 (65.2)
Missing or UCDAI <4 or >10	27 (11.6)	18 (7.8)	28 (13.3)
Prior 5-ASA use,* *n* (%)	147 (63.4)	172 (74.8)	149 (71.0)

5-ASA, 5-aminosalicylic acid; s.d., standard deviation; UCDAI, Ulcerative Colitis Disease Activity Index.

* Includes mesalazine, balsalazide, balsalazide sodium and sulfasalazine.

primary endpoint, no significant differences were observed vs. placebo for any secondary or other exploratory endpoints in patients receiving budesonide MMX 6 mg, except symptom resolution (21.7% vs. 14.3% for budesonide MMX 6 mg vs. placebo; P = 0.029).

Safety

Adverse events were reported by 53.5% of patients in the placebo group compared with 56.5% and 60.6% of patients treated with budesonide MMX 9 mg or 6 mg respectively (Table 3). The most common AEs were exacerbation, relapse or worsening of UC (placebo, 14.0%; budesonide MMX 9 mg, 13.3%; budesonide 6 mg, 16.5% respectively) and headache (10.5%, 11.4% and 14.6% respectively). Rates of serious AEs were low and occurred in similar percentages of patients receiving budesonide MMX 9 mg, budesonide MMX 6 mg or placebo. The incidence of potential glucocorticoid-related AEs was also similar between the budesonide MMX 9 mg, budesonide MMX 6 mg and placebo groups. The most common glucocorticoid-related AEs were mood changes (2.7%, 3.5% and 3.9% for budesonide MMX 9 mg, budesonide MMX 6 mg and placebo respectively), sleep changes (2.7%, 2.4% and 4.3% respectively) and insomnia (2.4%, 2.0% and 3.1% respectively).

DISCUSSION

This pooled analysis of CORE I and II studies was conducted to enable a better understanding of the efficacy and safety profiles of the 9-mg dose of budesonide MMX. The pooled analysis demonstrated that treatment with budesonide MMX 9 mg for 8 weeks was significantly more efficacious than placebo for inducing combined clinical and colonoscopic remission in patients with UC, whether male or female, or whether disease is mild or moderate in severity. In addition to the primary endpoint, other endpoints such as symptom resolution and mucosal healing showed significant improvement with budesonide MMX 9 mg compared with placebo. Furthermore, there was numerically greater benefit with clinical improvement, colonoscopic improvement and histological healing for budesonide MMX 9 mg

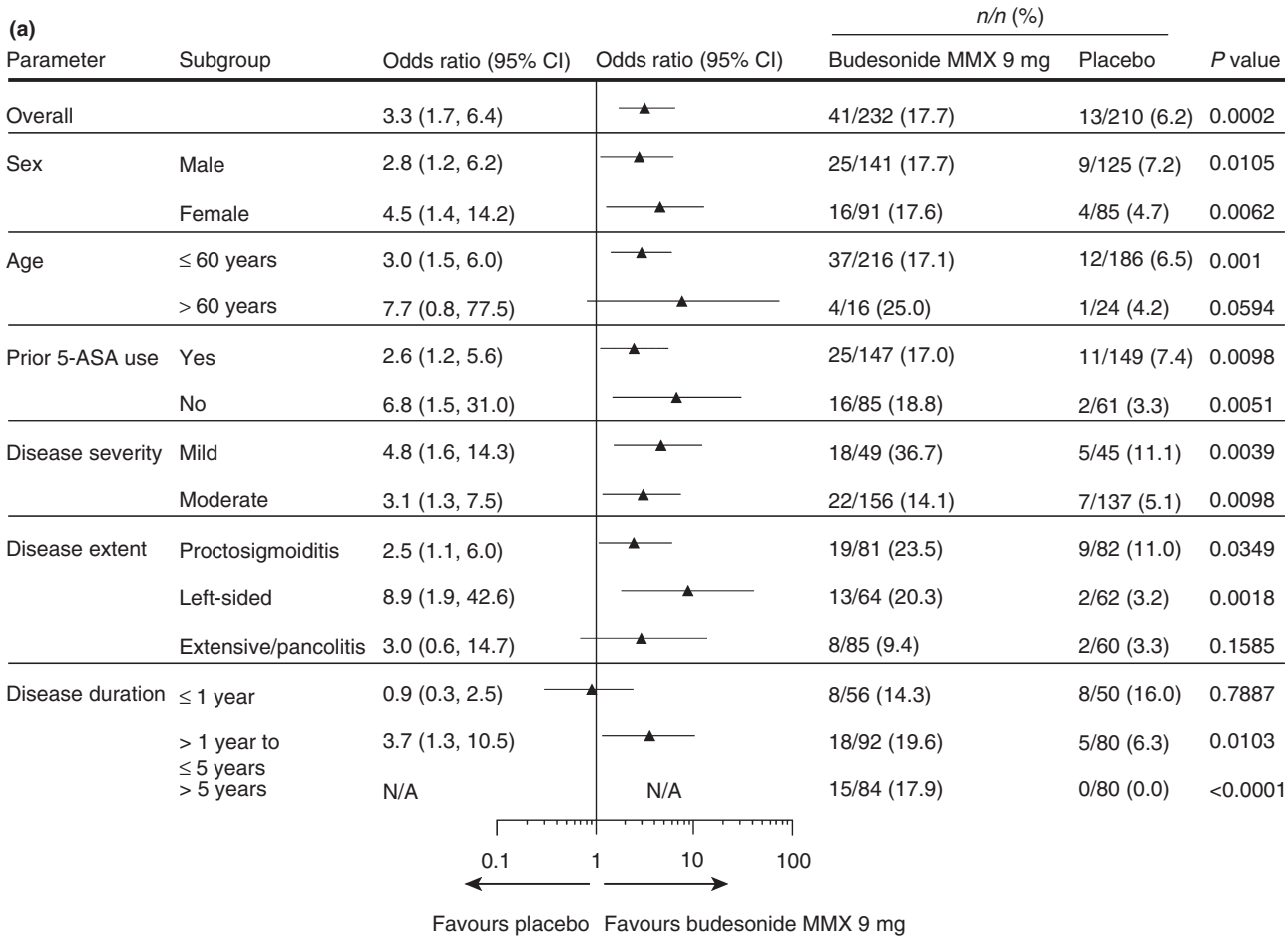

Figure 2 | Odds ratio and percentage of patients meeting primary endpoint, overall and based on sex, age, prior 5-ASA use, disease severity, disease extent and disease duration in (a) budesonide MMX 9 mg and (b) budesonide MMX 6 mg vs. placebo treatment groups after 8 weeks of treatment. CI, confidence interval.

compared with placebo. Data also reaffirmed results of the individual CORE I and II studies that budesonide MMX 9 mg is more efficacious compared with placebo than the lower dose (6 mg) for the induction of UC remission.[10, 11] Only the budesonide MMX 9-mg tablet is currently available.

The primary endpoint data for budesonide MMX 9 mg in this pooled analysis are lower than those observed for other UC therapies at 8 weeks (17.7% vs. 29.2–59.5%) in patients with mild-to-moderate, active UC.[13–15] These reasons are apparent: clinical remission in this study was defined as normal stool frequency with no rectal bleeding, rather than a modest decrease in stool frequency; and endoscopic remission in this study was defined via full colonoscopy (i.e. colonoscopic) results rather than flexible sigmoidoscopy values. Clinical and colonoscopic remission were then combined in the CORE I and II studies into a single endpoint, in contrast with other studies that used an endpoint of clinical remission alone.

In addition, differences in the patient populations may have played a role. Even so, the OR of 3.3 for achieving combined clinical and colonoscopic remission for budesonide MMX 9 mg compares favourably with data from other studies of patients with UC treated with MMX mesalazine administered at 2.4 or 4.8 g/day (OR, 2.4 and 2.5 respectively),[16] or at 4.8 g/day given as a single dose or as two divided doses (OR, 2.8 and 3.5 respectively).[14]

Pooling of data from the two studies permits better evaluation of responsiveness to budesonide MMX in subgroups to examine the potential influence of demographical (sex, age) or baseline disease characteristics (prior 5-ASA use, and extent, severity and duration of UC), which are otherwise difficult to assess in studies with smaller sample sizes. Compared with placebo, combined clinical and colonoscopic remission was significantly

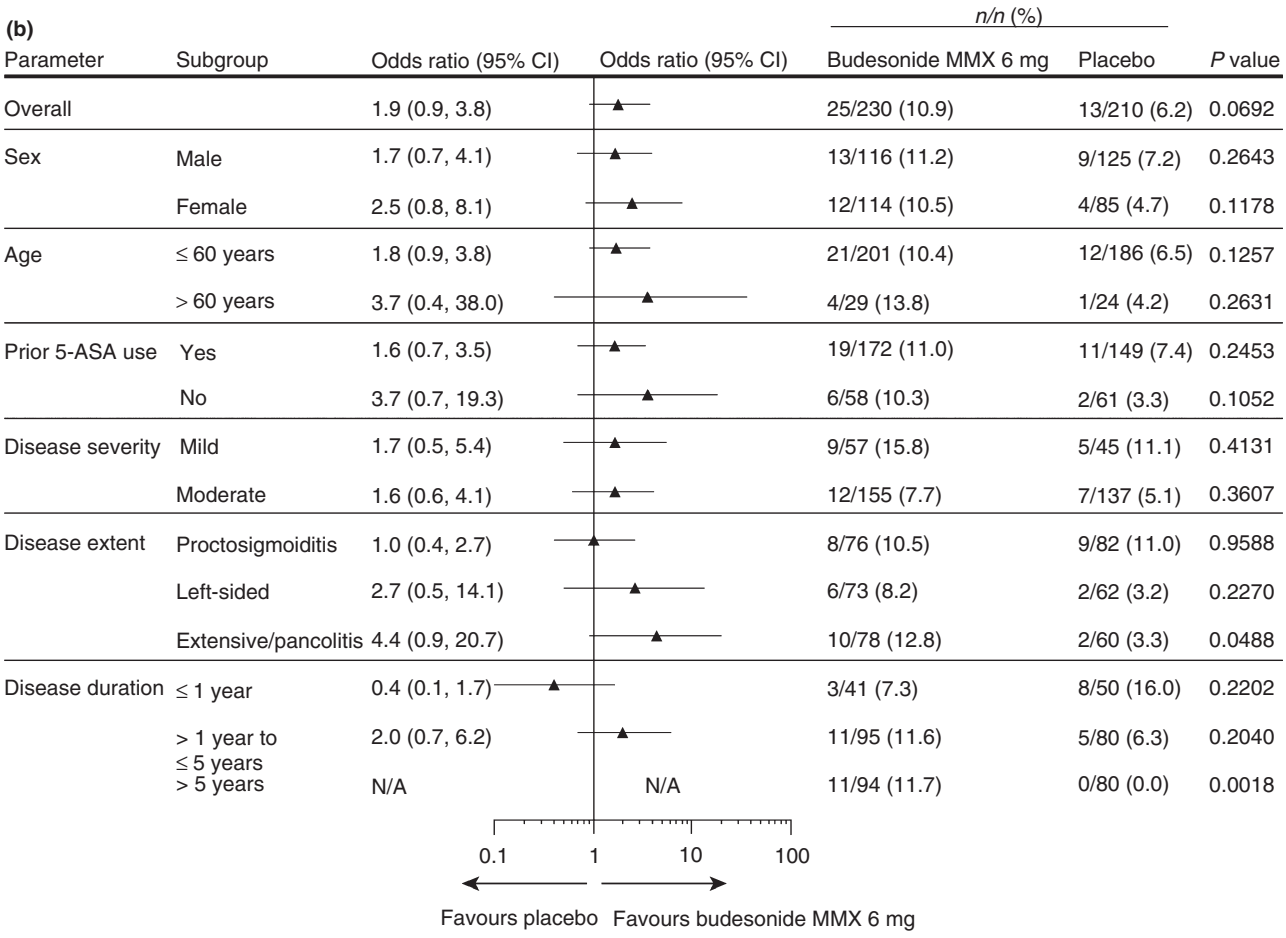

Figure 2 | (Continued)

Table 2 | Secondary and exploratory endpoints

Endpoint	Budesonide MMX 9 mg (n = 232)	Budesonide MMX 6 mg (n = 230)	Placebo (n = 210)
Clinical improvement, n (%)	87 (37.5)	65 (28.3)	60 (28.6)
P value vs. placebo*	0.0572	0.9277	
OR (95% CI)	1.5 (1.0, 2.2)	1.0 (0.6, 1.5)	
Colonoscopic improvement, n (%)	97 (41.8)	71 (30.9)	68 (32.4)
P value vs. placebo*	0.0410	0.7849	
OR (95% CI)	1.5 (1.0, 2.2)	0.9 (0.6, 1.4)	
Symptom resolution, n (%)	61 (26.3)	50 (21.7)	30 (14.3)
P value vs. placebo†	0.0015	0.0294	
OR (95% CI)	2.2 (1.3, 3.5)	1.7 (1.1, 2.9)	
Histological healing, n (%)	23 (9.9)	19 (8.3)	14 (6.7)
P value vs. placebo†	0.2625	0.5401	
OR (95% CI)	1.5 (0.7, 3.0)	1.3 (0.6, 2.6)	
Mucosal healing,* n (%)	64 (27.6)	37 (16.1)	36 (17.1)
P value vs. placebo†	0.0092	0.7847	
OR (95% CI)	1.8 (1.2, 2.9)	0.9 (0.6, 1.5)	

CI, confidence interval; OR, odds ratio.

* Secondary endpoints for each treatment were compared with placebo at the level of $\alpha = 0.025$ level of significance.

† Exploratory endpoints for each treatment were compared at the $\alpha = 0.05$ level of significance.

Table 3 | Summary of adverse events

Adverse event, *n* (%)	Budesonide MMX 9 mg (*n* = 255)	Budesonide MMX 6 mg (*n* = 254)	Placebo (*n* = 258)
Any AE	144 (56.5)	154 (60.6)	138 (53.5)
Drug-related AEs	69 (27.1)	63 (24.8)	65 (25.2)
AEs leading to discontinuation	39 (15.3)	48 (18.9)	43 (16.7)
Serious AEs	7 (2.7)	5 (2.0)	8 (3.1)
Intensity of AEs			
Mild	57 (22.4)	69 (27.2)	49 (19.0)
Moderate	67 (26.3)	67 (26.4)	66 (25.6)
Severe	20 (7.8)	17 (6.7)	21 (8.1)
Most common AEs*			
Abdominal pain	9 (3.5)	7 (2.8)	15 (5.8)
Headache	29 (11.4)	37 (14.6)	27 (10.5)
Nasopharyngitis	4 (1.6)	13 (5.1)	6 (2.3)
Nausea	13 (5.1)	12 (4.7)	11 (4.3)
UC	34 (13.3)	42 (16.5)	36 (14.0)
Glucocorticoid-related AEs			
Any AE	23 (9.0)	13 (5.1)	26 (10.1)
Acne	4 (1.6)	1 (0.4)	5 (1.9)
Fluid retention	2 (0.8)	2 (0.8)	3 (1.2)
Flushing	0 (0.0)	1 (0.4)	2 (0.8)
Insomnia	6 (2.4)	5 (2.0)	8 (3.1)
Mood changes	7 (2.7)	9 (3.5)	10 (3.9)
Moon face	2 (0.8)	0 (0.0)	4 (1.6)
Sleep changes	7 (2.7)	6 (2.4)	11 (4.3)
Striae rubrae	0 (0.0)	0 (0.0)	2 (0.8)

AE, adverse events; mITT, modified intent-to-treat; UC, ulcerative colitis.

* Reported in ≥5% of patients in any group.

improved in response to budesonide MMX 9 mg for many subgroups of interest, including males, females, patients age ≤60 years, patients with and without prior 5-ASA use, patients with mild and moderate disease severity, and patients with left-sided disease and proctosigmoiditis. More variable findings were observed for patients >60 years, patients with extensive colitis/pancolitis, and patients with disease duration ≤1 year. These subgroup analyses support the generalisability of the budesonide MMX 9 mg treatment effect across clinically relevant subgroups.

Endoscopic (with biopsy) demonstration of histological/mucosal healing is associated with a reduction in the number of flare-ups (i.e. long-term remission), the risk for colorectal cancer, and improved patient health-related quality of life.[17, 18] Current treatment guidelines recommend the assessment of histological/mucosal healing as a predictor of long-term outcomes in patients with UC.[4, 5] In this pooled analysis, we demonstrate that patients with UC who received budesonide MMX 9 mg treatment achieved a significantly greater rate of mucosal healing (27.6% vs. 17.1%; $P < 0.01$) and a numerically greater rate of histological healing (9.9% vs. 6.7%) compared with patients who received placebo at 8 weeks. The rates of histological/mucosal healing were lower than those observed with other UC therapies [e.g. MMX mesalazine 4.8 g/day (at 2.4 g twice per day), 42.4%[15]; and oral mesalazine granules 3 g once daily, 58.4%[13]). However, the outcomes reported for budesonide MMX in this pooled analysis are difficult to compare with historical data because of differences in histological indices, evaluation of biopsies taken at full colonoscopy (in CORE I and II studies) compared with those taken following flexible sigmoidoscopy, and other factors in study design, as have been discussed earlier.

The safety profiles for budesonide MMX 6 and 9 mg during the 8-week treatment regimen, including the incidence of AEs, serious AEs and glucocorticoid-related AEs, were not substantially different from the safety profile observed with placebo. Safety profiles reported in this study for both doses of budesonide MMX were similar to results reported in studies of other budesonide formulations in patients with Crohn's disease.[19–21] Because conventional oral corticosteroids are associated with higher systemic exposure and toxicities, budesonide MMX may serve as a well-tolerated alternative to conventional

corticosteroids, especially given that patients with UC rate symptom relief and side effect profile as the most important attributes to consider when selecting a UC therapy.[22] The pooled efficacy and safety data presented here lend further support to the findings of the 2014 publication by Danese *et al.*,[23] which recommended that budesonide MMX be incorporated into treatment algorithms for mild-to-moderate UC, to be administered after failure of 5-ASA therapy, but before initiation of treatment with conventional systemic corticosteroids.

AUTHORSHIP

Guarantor of the article: William Sandborn.

Author contributions: Drs Sandborn, D'Haens and Travis were involved in data collection. Drs Jones and Moro were involved in the conduct of the trials. Dr Bagin performed statistical analyses. Drs Sandborn, Danese, D'Haens, Moro, Ballard, Masure and Travis contributed to the study design of the trials. All authors contributed to the interpretation of data and analyses; and writing, critically reviewing and editing the manuscript. All authors approved the final version of the manuscript.

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