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3g mesalazine granules are superior to 9mg budesonide for achieving remission in active ulcerative colitis: A double-blind, double-dummy, randomised trial☆

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Abbreviations AE, Adverse event; CAI, Clinical Activity Index; CI, Confidence interval; EI, Endoscopic Index; HI, Histological Index; ITT, Intention-to-treat; LOCF, last observation carried forward; OD, Once daily; PP, Per protocol; SD, Standard deviation; TID, Three-times daily; UC, Ulcerative colitis.

☆ Trial registration: the study was registered at ClinicalTrials.gov (NCT00747110).

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KEYWORDS
Budesonide;
Mesalazine;
Randomised clinical trial;
Remission;
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Abstract

Background and aims: Budesonide may be an effective therapy for mild-to-moderately active ulcerative colitis (UC). This study aimed to demonstrate non-inferiority for oral 9 mg budesonide once daily (OD) versus 3 g mesalazine granules OD.
Methods: This was an eight-week randomised, double-blind, double-dummy, multicentre study in which patients with mild-to-moderately active UC, defined as Clinical Activity Index (CAI) ≥ 6 and Endoscopic Index (EI) ≥ 4, received budesonide (Budenofalk® 3 mg capsules × 3) or mesalazine (Salofalk® 1000 mg granules × 3). The primary endpoint was clinical remission at week 8 (CAI ≤ 4 with stool frequency and rectal bleeding subscores of "0").
Results: 343 patients were randomised (177 budesonide, 166 mesalazine). Fewer patients achieved the primary endpoint with budesonide versus mesalazine (70/177 [39.5%] versus 91/166 [54.8%]) with a difference in proportions of −15.3% (95% CI [−25.7%, −4.8%]; $p=0.520$ for non-inferiority). The median time to first resolution of symptoms was 14.0 days (budesonide) and 11.0 days (mesalazine) (hazard ratio 1.19; 95% CI [0.94, 1.51]). Mucosal healing was observed in 54/177 (30.5%) budesonide patients versus 65/166 (39.2%) mesalazine patients, a difference of −8.6% (95% CI [−18.7%, 1.4%]; $p=0.093$). The incidences of adverse events (budesonide 26.6%, mesalazine 25.3%) and serious adverse events (budesonide 1.7%, mesalazine 1.2%) were similar.
Conclusions: Once-daily 3 g mesalazine administered as granules is superior to 9 mg budesonide OD administered as capsules for achieving remission in mild-to-moderately active UC. However, it is noteworthy that remission of UC was attained in about 40% of budesonide-treated patients with a rapid onset of resolution.

1. Introduction

For many years, corticosteroids and aminosalicylates have formed the mainstay of treatment for active ulcerative colitis (UC). Whereas corticosteroids are given to patients with high disease activity, aminosalicylates, particularly mesalazine, are first-line treatment in mild-to-moderately active disease.[1] In active distal UC, topical administration of budesonide has proved to be effective. Budesonide enema has proved to be superior to placebo,[2–4] and equivalent to mesalazine enema,[5,6] or corticosteroids enema.[2,7–11] More recently, budesonide rectal foam has proved beneficial in active ulcerative proctitis and proctosigmoiditis.[12–14]

Interestingly, oral budesonide – the drug of choice for treatment of ileo/ileocaecal mild-to-moderately active Crohn's disease[15–17] – is now regarded as the standard of care[18] for both collagenous colitis[19–23] and lymphocytic colitis.[24,25] These conditions are subtypes of microscopic colitis, another inflammatory bowel disease of unknown aetiology affecting the colon.[26] Budesonide therefore seemed to us to be an attractive candidate to compare against standard mesalazine in a large randomised clinical trial of patients with mild-to-moderately active UC.

Budesonide, a potent corticosteroid with a high affinity for the glucocorticoid receptor,[27] has a 90% first-pass metabolism within the liver,[27,28] such that its systemic availability is low. As a result, budesonide is associated with a lower rate of systemic side effects than conventional corticosteroids.[29,30]

To date, only three small studies have assessed the use of oral budesonide in active UC.[31–33] In a double-blind study, 34 patients with mild-to-moderately active UC were randomised to an oral acid-resistant formulation of budesonide or prednisone.[33] Endoscopic improvement was similar in both treatment arms but cortisol levels were not suppressed in the budesonide cohort. A small randomised, double-blind pilot trial using budesonide-MMX® 9 mg tablets found no significant benefit for 9 mg oral budesonide compared to placebo.[31] Remission or 50% clinical improvement was seen in 8 of 17 patients (47.1%) of the budesonide group and in 5 of 15 patients (33.3%) of the placebo group. A small pilot trial suggested 9 mg oral budesonide given as a pH-modified release formulation (Budenofalk®) to be effective in distal UC, with a 71% response rate after 8 weeks.[32] Mucosal biopsy specimens from the distal colon revealed significant budesonide concentrations.[32] Moreover, a small pilot study suggested that oral 9 mg budesonide as a pH-modified release formulation was well tolerated and effective for maintenance treatment in patients with steroid-dependent UC.[34]

Here we describe the results of the first full-scale comparative trial to evaluate the relative efficacy and safety of oral budesonide versus mesalazine, the current standard of care for the management of mild-to-moderately active UC.[35,36] The current study employed mesalazine granules (Salofalk® manufactured by Dr. Falk Pharma GmbH, Freiburg, Germany) which differ from other mesalazine formulations by combining both delayed- and extended-release mechanisms. First, mesalazine release is delayed until pH ≥ 6.0 due to an enteric, acid-resistant film coating, such that absorption in the upper gastrointestinal tract is prevented. Second, due to inner polymer matrix the release of the active ingredient is prolonged throughout the entire colon.[37] The objective of the current study was to demonstrate that budesonide 9 mg once daily is non-inferior to mesalazine 3 g once daily for inducing clinical remission in patients with mild-to-moderately active UC.

2. Methods

2.1. Study design and conduct

This was an eight-week randomised, multicentre, parallel-group phase III study undertaken at 48 gastroenterology centres in Europe that used a double-blind, double-dummy design to compare once-daily oral treatment with budesonide 9 mg or mesalazine 3 g in patients with mild-to-moderately active UC (Fig. 1). The study was performed according to an adaptive three-stage group sequential design with possible sample size adjustments after the planned interim analyses. It was undertaken in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice following approval from the Independent Ethics Committee at each participating centre. Written informed consent was obtained from each participant.

2.2. Patient population

Adult patients (18–75 years) with active UC were eligible to take part in the study if they met the following criteria: (1) presence of established disease, defined by blood or mucus in stools, or newly diagnosed disease, defined as blood in stool within 14 days prior to the baseline visit (2) Clinical Activity Index (CAI) [38] ≥ 6 and Endoscopic Index (EI) [38] ≥ 4. Patients with proctitis limited to 15 cm above the anus were excluded. Other key exclusion criteria were a diagnosis of Crohn's disease, indeterminate colitis, ischaemic colitis, radiation colitis, or microscopic colitis (i.e., collagenous colitis or lymphocytic colitis); toxic megacolon; baseline stool positive for microbial pathogens causing bowel disease; diarrhoea due to other symptomatic gastrointestinal diseases; active peptic ulcer disease; haemorrhagic diathesis; active colorectal cancer or a history of colorectal cancer; treatment with immunosuppressants within the previous 3 months and/or corticosteroid therapy (oral, intravenous or topical rectal) within the previous 4 weeks; or current relapse under maintenance treatment with mesalazine >2.4 g/day.

2.3. Treatment and concomitant medication

Randomisation was performed on day 0 via a computer-generated randomisation list that used randomly permuted blocks, which was held by staff at ClinResearch GmbH who were not involved in the study conduct. Study drugs were budesonide (Budenofalk® 3 mg capsules, Dr Falk Pharma GmbH, Freiburg, Germany) and mesalazine (Salofalk® 1000 mg granules, Dr Falk Pharma GmbH, Freiburg, Germany). Patients were randomised in a 1:1 ratio to budesonide (3×3 mg capsules) with mesalazine placebo, or mesalazine (3×1 g sachets) with budesonide placebo and therapies were despatched according to individual patient randomisation numbers. The placebo budesonide capsules and placebo mesalazine sachets could not be distinguished by the investigators or patients from the active therapies. Treatment was initiated on day 1, with all therapies to be taken in the morning.

Treatment compliance was calculated as the ratio between the administered medication (as determined by returned medication) and the expected intake. Patients with a ratio of $\geq 75\%$ were considered to be sufficiently compliant.

Prohibited concomitant medications included immunosuppressants (e.g., azathioprine, 6-mercaptopurine, methotrexate, cyclosporine); non-steroidal anti-inflammatory drugs for >6 weeks other than acetylsalicylic acid ≤ 350 mg/day or paracetamol for analgesic use; oral, rectal, or intravenous corticosteroids; CYP3A inhibitors for >7 days; oral antibiotics other than for ≤ 7 days for conditions unrelated to UC; and mesalazine-containing or -releasing drugs.

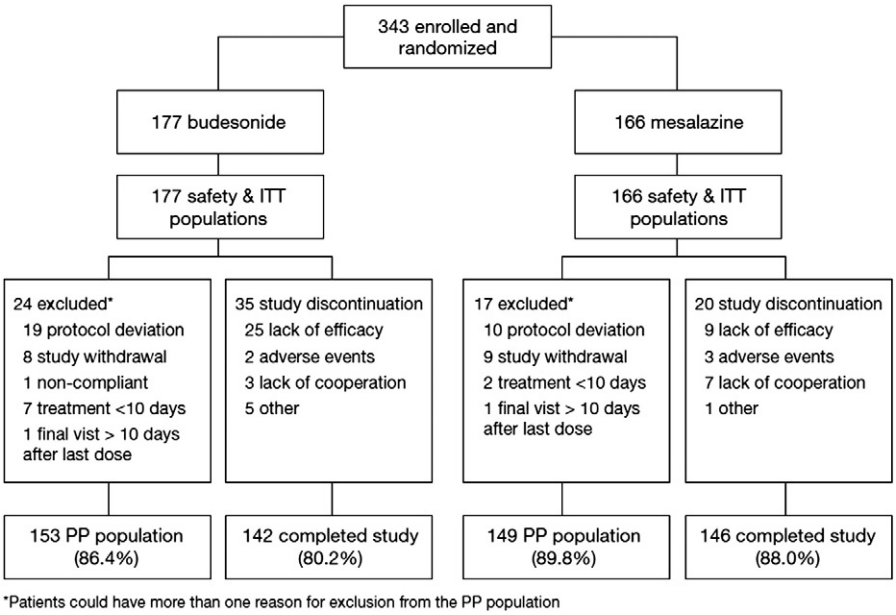

Figure 1 Patient disposition.

2.4. Study visits and evaluation

Study visits took place at baseline and at weeks 2, 4, 6, and 8. Endoscopy was performed and biopsies taken at the baseline visit and at the week 8 visit. Laboratory values as well as CAI score[38] were recorded at each visit. Endoscopic Index (EI)[38] and Histological Index (HI)[39] were recorded at baseline and week 8. At the week 8 visit, Physician's Global Assessment was performed[40] and results categorised as 'therapeutic success' (either complete relief of symptoms or marked improvement of symptoms) or therapeutic benefit (complete relief of symptoms, marked improvement of symptoms, moderate improvement or slight improvement). Global assessment of tolerability was also evaluated at week 8, with patients and physicians grading tolerability as 'very good', 'good', 'satisfactory', 'poor', or 'no remark'. Adverse events and treatment compliance were monitored at all post-baseline visits. Morning serum cortisol was determined using an automated electrochemiluminescence immunoassay (Elecsys Cortisol, Roche Diagnostics, Mannheim, Germany; analytical sensitivity of the test was 0.018 μg/dL).

In the event of premature withdrawal from the study, a full final visit was to be completed when possible.

2.5. Study endpoints

The primary endpoint was clinical remission at week 8, defined as CAI ≤ 4 with stool frequency and rectal bleeding subscores of "0" (i.e., <18 stools/week, 0–1 bloody stool/week) at the final or withdrawal visit. This stringent definition is in line with the recent EMEA guideline on the development of new medicinal products for the treatment of ulcerative colitis.[41] Pre-defined, exploratory subgroup analyses of the primary endpoint to evaluate the consistency of treatment effects across various patient populations included: Disease localization and disease severity.

Secondary endpoints were CAI scores during the study, the time to first symptom resolution (defined as ≤ 3 stools/day, all blood-free), the proportion of patients achieving therapeutic success or benefit on the Physician's Global Assessment, endoscopic remission (defined as an EI ≤ 3), mucosal healing (defined as EI ≤ 1), and histological remission (defined as a HI of ≤ 1), as well as changes from baseline in the activity indices and clinical symptoms.

2.6. Statistical analysis

The population for safety analysis comprised all randomised patients who had taken at least one dose of study medication. Efficacy analyses were performed both on the intention-to-treat (ITT) population, which was identical to the safety population, and on the per-protocol (PP) population, which comprised only those patients without major protocol violations.

The estimated sample size was 180 patients in each treatment group. Based on the assumption that the remission rate would be 50% in both treatment arms, with a non-inferiority margin of 15%, the proposed population in each group would have 80.5% power to yield a statistically significant result. Two interim analyses were planned. The first interim analysis was performed on 208 patients using the inverse normal method of combining the p-values of the one-sided shifted asymptotic χ^2-test for comparing two rates for confirmatory testing of the null hypothesis. Missing CAI scores were determined using the last observation carried forward (LOCF) method, including the baseline visit. This interim analysis showed that the primary objective of the study i.e., non-inferiority of budesonide versus mesalazine, could not be reached and recruitment was therefore terminated on the recommendation of the Independent Data Monitoring Committee. Since a further 135 patients had been recruited in the meantime and the study continued in these patients, the total population for analysis was 343.

The primary endpoint analysis was repeated for pre-defined subgroups i.e., according to disease localisation (distal disease, i.e., proctosigmoiditis/left-sided colitis; extensive disease, i.e. subtotal-/pancolitis), disease severity (mild [CAI ≤ 8] or moderate [CAI >8]) and CRP level (≤ 5 mg/dl, >5 to ≤ 10 mg/dl or >10 mg/dl) at baseline.

Only the primary efficacy endpoint was subject to statistical confirmatory analysis. All other efficacy and safety analyses were only exploratory, and therefore no alpha adjustments were performed.

Data are presented descriptively using standard summary statistics and two-sided 95% confidence intervals (CIs). Between-group comparisons of continuous parameters used the two-sided, two-sample *t*-test. Comparisons of categorical parameters used the shifted asymptotic χ^2-test. Kaplan-Meier analyses were used to estimate the time to first resolution of clinical symptoms.

3. Results

3.1. Patient population and study medication

In total, 343 patients were enrolled at 48 gastroenterology centres in 9 countries during the period November 2007 to August 2008. All patients were randomised and received at least one dose of study medication (ITT and safety populations). In total, 288 patients completed the study (Fig. 1). The most frequent cause of premature study discontinuation was lack of efficacy ($n=34$). Forty-one patients were excluded from the PP population, which comprised 302 patients. One or more major protocol deviation was the most common reason for exclusion from the PP population (19 budesonide patients, 10 mesalazine patients), largely accounted for by consumption of a prohibited medication (14 budesonide patients, 7 mesalazine patients).

The treatment groups did not show any relevant differences in terms of demographics and baseline characteristics (Table 1). A similar proportion of patients in each arm were receiving treatment for the current acute episode of UC at baseline (65/177 budesonide arm [36.7%], 58/166 mesalazine arm [34.9%]), of which the most frequent was oral mesalazine (45/177 budesonide arm [25.4%], 43/166 mesalazine arm [25.9%]).

The mean (SD) treatment duration in the study was 49.6 ± 14.9 days for budesonide and 51.9 ± 12.5 days for mesalazine. All patients in the mesalazine group and 174/177 budesonide patients (98.3%) were treatment compliant ($\geq 75\%$ drug intake).

3.2. Efficacy

All 343 ITT patients were included in the primary endpoint analysis as planned. The proportion of patients achieving the

Table 1 Patient demographics and baseline characteristics (ITT population).

	Budesonide ($n=177$)	Mesalazine ($n=166$)
Male gender, *n* (%)	91 (51.4%)	83 (50.0%)
Age (years), mean ± SD	43.5 ± 13.8	43.5 ± 14.1
Body mass index (kg/m^2), mean ± SD	25.3 ± 4.4	24.9 ± 4.0
Caucasian, *n* (%)	177 (100.0%)	166 (100.0%)
Smoking status, *n* (%)		
Non-smoker	120 (67.8%)	116 (69.9%)
Former smoker	37 (20.9%)	31 (18.7%)
Current smoker	20 (11.3%)	19 (11.4%)
Localisation of disease at baseline, *n* (%)		
Distal disease		
Proctosigmoiditis	98 (55.4%)	92 (55.4%)
Left-sided colitis	42 (23.7%)	42 (25.3%)
Extensive disease		
Subtotal/pancolitis	37 (20.9%)	32 (19.3%)
Length of inflammation (cm), mean ± SD	46.1 ± 24.1 [$n=158$]	46.3 ± 25.0 [$n=147$]
Diagnosis, *n* (%)		
New diagnosis	28 (15.8%)	23 (13.9%)
Established disease	149 (84.2%)	143 (86.1%)
Course of the established disease, *n* (%)	[$n=149$]	[$n=143$]
Chronically active disease	14 (7.9%)	13 (7.8%)
Relapsing disease	135 (76.3%)	130 (78.3%)
Duration of present acute episode (days), median (1st, 3rd Q)	28 (14, 61) [$n=148$]	28 (15, 51) [$n=142$]
Time since diagnosis (years), median (1st, 3rd Q)	3.9 (1.1, 7.7) [$n=172$]	3.3 (1.1, 7.8) [$n=162$]
Number of stools per week, mean ± SD	34.0 ± 18.2	31.5 ± 13.7
Number of bloody stools per week, mean ± SD	23.8 ± 14.6	22.3 ± 13.7
Disease activity, mean ± SD		
Clinical Activity Index (CAI)	8.3 ± 1.7	8.1 ± 1.5
Endoscopic Index (EI)	7.4 ± 1.8	7.4 ± 1.7
Disease severity, *n* (%)		
Mild (CAI ≤ 8)	107 (60.5%)	115 (69.3%)
Moderate (CAI > 8)	70 (39.5%)	51 (30.7%)
C-reactive protein (CRP) levels, *n* (%)		
≤ 5mg/dl	119 (67.2%)	115 (69.3%)
> 5 ≤ 10 mg/dl	31 (17.5%)	18 (10.8%)
> 10 mg/dl	27 (15.3%)	33 (19.9%)
Pre-study maintenance medication [a], n (%)	66 (48.9%) [$n=135$]	71 (54.6%) [$n=130$]
Oral 5-ASA	57 (42.2%)	55 (42.3%)
Oral sulfasalazine	8 (5.9%)	10 (7.7%)
Rectal 5-ASA	6 (4.4%)	6 (4.6%)
Oral systemic corticosteroids	2 (1.5%)	3 (2.3%)
Rectal budesonide	1 (<1%)	–
Immunosuppressants	1 (<1%)	3 (2.3%)

[a] Doses of the pre-study medication did not violate the exclusion criterion.

primary endpoint of clinical remission at week 8, i.e. CAI ≤ 4 with stool frequency and rectal bleeding subscores of "0", was lower in the budesonide group versus the mesalazine group (70/177 [39.5%] versus 91/166 [54.8%]). The between-group difference exceeded the pre-specified non-inferiority margin of 15%. The difference in proportions was −15.3% (95% CI [−25.7%, −4.8%], $p=0.520$ for non-inferiority testing), such that the primary objective of demonstrating non-inferiority of the budesonide regimen to the mesalazine regimen was not met. Similar results were observed in the PP population (Table 2).

All pre-defined exploratory subgroup analyses of the primary endpoint confirmed numerically higher remission rates under mesalazine compared to budesonide treatment (Table 3). For patients with mild disease or distal disease localisation or CRP levels >10 mg/dl at baseline, the observed differences were statistically significant.

Mean CAI score decreased from baseline in both treatment arms, but the score was higher in the budesonide-treated patients throughout the study (Fig. 2) and the mean reduction in CAI from baseline to the final visit was significantly smaller in the budesonide arm (Table 4). A clinically relevant reduction in the number of stools and bloody stools was observed in both treatment groups, with no significant difference between arms (Table 3). The median time to first resolution of symptoms (i.e., ≤3 stools/day, all blood-free) was similar in the budesonide group (14.0 days) and the mesalazine group (11.0 days) (hazard ratio [HR] 1.19; 95% CI [0.94, 1.51]).

EI scores showed a decrease in both treatment groups from baseline to the final visit. This decrease was statistically significant greater in the mesalazine cohort (Table 4). Endoscopic remission (i.e., EI ≤ 3) and histological remission (i.e., HI ≤ 1) were both observed in a significantly lower proportion of budesonide patients compared to mesalazine patients (Table 4).

Results of the Physician's Global Assessment were in line with the other efficacy endpoints and showed that significantly more mesalazine patients achieved therapeutic success and therapeutic benefit (Table 4).

3.3. Adverse events

In total, 67 adverse events were reported in 47 patients (26.6%) in the budesonide group, and 54 adverse events occurred in 42 mesalazine-treated patients (25.3%). The most frequently reported adverse advents were deterioration of UC and headache (Table 5). Deterioration of UC was more often reported as an adverse event in the budesonide group (10.2% versus 3.0% in the mesalazine group). Three serious adverse events were reported in the budesonide group (all deterioration of UC) and two in the mesalazine group (both appendicitis); none of them was related to the study drug. Adverse events with at least a possible relation to study drug (adverse drug reaction) occurred in two (1.1%) budesonide patients (flatulence in turn with constipation, insomnia) and seven (4.2%) mesalazine patients (nausea [2], dyspepsia, gastric disorders, increased lipase [2], and deteriorating cholestasis). Adverse events led to discontinuation of study drug in 16 patients (9.0%) in the budesonide group (deteriorating UC [14], constipation and vomiting) and

Table 2 Clinical remission at week 8 (LOCF) [ITT and PP populations].

	Clinical remission		Difference [95% CI]	*P* value [a]
	Budesonide	Mesalazine		
ITT population	70/177 (39.5%)	91/166 (54.8%)	−15.3% [−25.7%,−4.8%]	0.520
PP population	67/153 (43.8%)	89/149 (59.7%)	−15.9% [−27.1%,−4.8%]	0.566

[a] Shifted asymptotic χ^2-test for non-inferiority testing of budesonide vs. mesalazine (pre-specified non-inferiority margin −15%).

Table 3 Pre-defined exploratory subgroup analyses of clinical remission at week 8 (LOCF) [ITT population].

Baseline	Clinical remission		Difference [95% CI]	*P* value [a]
	Budesonide	Mesalazine		
Disease localisation				
Distal [b]	56/140 (40.0%)	72/134 (53.7%)	−13.7% [−25.4%,−2.0%]	0.023
Extensive [c]	14/37 (37.8%)	19/32 (59.4%)	−21.5% [−44.6%, 1.6%]	0.074
Disease severity				
Mild (CAI ≤ 8)	46/107 (43.0%)	65/115 (56.5%)	−13.5% [−26.6%, −0.5%]	0.044
Moderate (CAI > 8)	24/70 (34.3%)	26/51 (51.0%)	−16.7% [−34.4%, 1.0%]	0.066
CRP [mg/dl]				
≤ 5	55/119 (46.2%)	67/115 (58.3%)	−12.0% [−24.7%, 0.7%]	0.065
> 5 ≤ 10	8/31 (25.8%)	6/18 (33.3%)	−7.5% [−34.2%, 19.1%]	0.574
> 10	7/27 (25.9%)	18/33 (54.5%)	−28.6% [−52.3%, −4.9%]	0.025

[a] χ^2-test (2-sided).
[b] Distal disease: proctosigmoiditis/left-sided colitis.
[c] Extensive disease: subtotal-/pancolitis.

eight patients (4.8%) in the mesalazine group (deteriorating UC [5], chronic pancreatitis, acne and nausea). The steroid-specific reactions acne, buffalo hump, moonface and hirsutism were not observed in any of the patients receiving budesonide.

Measurement of morning serum cortisol levels was introduced by an amendment after the start of enrolment. Therefore, data of the change in serum cortisol levels from baseline to Visit 5 (LOCF) were only available for 91 budesonide treated patients and 83 mesalazine treated patients. Mean (SD) serum cortisol levels at baseline and Visit 5 (LOCF) were 15.5 (7.0) μg/dl and 11.0 (7.8) μg/dl in the budesonide group, and 14.8 (6.2) μg/dl and 14.2 (4.6) μg/dl in the mesalazine group, respectively. In total, 19 of 91 patients (21%) in the budesonide and one of 83 patients (1%) in the mesalazine group, experienced a drop from normal serum cortisol at baseline to a value below normal at final visit (lower limit of normal defined as 6.2 μg/dl).

Results from the Global Assessment of Tolerability at week 8 showed a similar proportion of patients in the budesonide and mesalazine groups grading tolerability as 'very good' (40.7% and 49.4%, respectively) or 'good' (48.6% and 44.6%, respectively). Similar results were reported by the treating physicians.

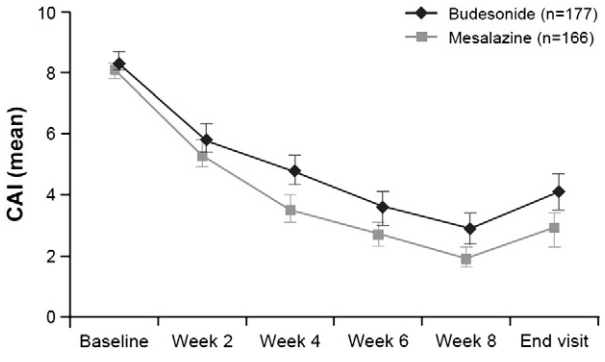

Figure 2 Mean (95% CI) Clinical Activity Index (CAI) during the study. Final visit represents week 8 visit or last visit in study (LOCF).

4. Discussion

Results from this double-blind, double-dummy trial demonstrate that mesalazine granules 3 g OD are superior to oral pH-modified release budesonide capsules 9 mg OD for achieving clinical remission in mild-to-moderately active UC. Thus, the objective of demonstrating non-inferiority for budesonide 9 mg OD versus mesalazine 3 g OD was not achieved.

The study design was rigorous and complied with recently published EMEA guidelines for clinical trials in UC.[41] A robust double-dummy design was used, and the treatment period of 8 weeks was considered adequate to allow an improvement in clinical symptoms for either therapy. Clinical remission was defined strictly, incorporating criteria for stool frequency and rectal bleeding, as per the EMEA guideline. The comparator, mesalazine (Salofalk® granules) at a dose of 3 g/day was appropriate.

While both treatments were effective, most efficacy parameters showed better outcomes in the mesalazine

Table 4 Secondary efficacy endpoints (ITT population).

	Budesonide ($n=177$)	Mesalazine ($n=166$)	Difference [95% CI]	P value
Mean ± SD change from baseline to final visit				
Change in Clinical Activity Index (CAI)	−4.2 ± 4.0	−5.2 ± 3.5	1.0 [0.2, 1.8]	0.015 [a]
Change in number of stools/week	−12.5 ± 23.0 [$n=175$]	−13.8 ± 14.7	1.3 [−2.8, 5.5]	0.522 [a]
Change in number of bloody stools/week	−13.5 ± 20.6 [$n=175$]	−16.1 ± 15.1	2.6 [−1.3, 6.5]	0.184 [a]
Change in Endoscopic Index (EI)	−3.8 ± 3.1 [$n=149$]	−4.6 ± 2.5 [$n=148$]	0.8 [0.1, 1.4]	0.017 [a]
Number (%) of patients with endoscopic outcome at final visit				
Endoscopic remission (EI ≤ 3)	88/177 (49.7%)	105/166 (63.3%)	−13.5% [−23.9%, −3.1%]	0.012 [b]
Distal disease [c]	67/140 (47.9%)	82/134 (61.2%)	−13.3% [−25.0%, −1.7%]	0.027 [b]
Extensive disease [d]	21/37 (56.8%)	23/32 (71.9%)	−15.1% [−37.4%, 7.2%]	0.193 [b]
Endoscopic improvement (drop in EI ≥ 1)	122/177 (68.9%)	136/166 (81.9%)	−13.0% [−22.0%, −4.0%]	0.005 [b]
Mucosal healing (EI ≤ 1)	54/177 (30.5%)	65/166 (39.2%)	−8.6% [−18.7%, 1.4%]	0.093 [b]
Number (%) of patients with histological outcome at final visit				
Histological remission (HI ≤ 1)	84/177 (47.5%)	97/166 (58.4%)	−11.0% [−21.5%, −0.5%]	0.042 [b]
Histological improvement (drop in HI ≥ 1)	101/177 (57.1%)	120/166 (72.3%)	−15.2% [−25.2%, −5.3%]	0.003 [b]
Number (%) of patients with Physician's Global Assessment				
Therapeutic success	91/177 (51.4%)	114/166 (68.7%)	−17.3% [−27.5%, −7.1%]	0.001 [b]
Therapeutic benefit	136/177 (76.8%)	142/166 (85.5%)	−8.7% [−16.9%, −0.5%]	0.040 [b]

[a] Two-sample t-test.
[b] χ^2-test (2-sided).
[c] Distal disease: proctosigmoiditis/left-sided colitis.
[d] Extensive disease: subtotal-/pancolitis.

cohort compared to budesonide-treated patients, including both clinical and endoscopic endpoints. This raises the question whether the different compounds (mesalazine vs. budesonide) or the different galenics (granules vs. capsules) are responsible for this difference. The mesalazine granules used in this study are characterised by a dual-release mechanism, including both an enteric-coating and a prolonged release of mesalazine from a core matrix. In contrast, the budesonide granules, which are contained in a hard-gelatine capsule, are equipped only with an enteric coating but not with a matrix polymer.

Table 5 Adverse events occurring in ≥2 patients.

Preferred term	Budesonide ($n=177$)	Mesalazine ($n=166$)
Ulcerative colitis deterioration	18 (10.2%)	5 (3.0%)
Headache	10 (5.6%)	9 (5.4%)
Nasopharyngitis	3 (1.7%)	2 (1.2%)
Increased lipase	–	4 (2.4%)
Respiratory tract infection	1 (0.6%)	3 (1.8%)
Nausea	1 (0.6%)	2 (1.2%)
Viral respiratory tract infection	2 (1.1%)	1 (0.6%)
Appendicitis	–	2 (1.2%)
Dyspepsia	1 (0.6%)	1 (0.6%)
Flatulence	1 (0.6%)	1 (0.6%)
Cholestatic hepatitis	2 (1.1%)	–
Influenza	1 (0.6%)	1 (0.6%)
Pharyngolaryngeal pain	2 (1.1%)	–
Fever	1 (0.6%)	1 (0.6%)
Respiratory disorder	1 (0.6%)	1 (0.6%)
Urinary tract infection	–	2 (1.2%)
Vomiting	1 (0.6%)	1 (0.6%)

Mesalazine granules have previously been shown to be effective in mild-to-moderately active UC[42–44], and a dose-finding study has shown the selected dose of 3 g to be optimum.[43] Moreover, a double-blind, double-dummy trial has recently confirmed OD administration of 3 g mesalazine to be as effective as 1 g TID.[42] Thus the chosen dose and treatment schedule of the reference product was optimal according to the above mentioned trial data.

The oral pH-modified release budesonide capsules used in this study (Budenofalk® 3 mg capsules) release budesonide at pH >6.4.[45] Two randomised, double-blind studies have shown efficacy of 9 mg oral pH-modified release budesonide in patients with mild-to-moderately active Crohn's disease involving the ileum and/or colon.[16,29] A dose-finding study in patients with active Crohn's ileocolitis showed remission rates of 36%, 55% and 66% with 3×2 mg, 3×3 mg, or 3×6 mg budesonide ($p=0.017$ for 3×6 mg vs. 3×2 mg), respectively.[46] There is conclusive evidence from trials with rectal budesonide in patients with distal ulcerative colitis that budesonide is therapeutically superior to placebo,[2–4] and equivalent to mesalazine.[5,6] Therefore, the treatment of distal ulcerative colitis with rectal budesonide (enema, foam) is effective and recommended by the ECCO guideline.[36] Moreover, a pilot study had suggested efficacy of oral budesonide 9 mg OD in patients with ulcerative colitis.[32] In this study budesonide could be detected in the mucosa of the distal colon. Therefore, oral pH-modified release budesonide capsules at a dose of 1×9 mg/day had been chosen as test drug.

Results of pre-defined subgroup analyses demonstrated that neither the disease localisation, nor the disease severity, nor the baseline CRP levels had a major impact on

the overall study result. Mesalazine consistently was more effective than budesonide throughout all the explored subgroups. The numerical inferiority of budesonide in the subgroup with extensive disease was surprising and casts some doubt whether an improved galenical formulation would perform better, although also the lack to target the most distal part of the colon might be decisive for the observed limited efficacy. Regardless of the CRP level at baseline, mesalazine-treated patients showed higher remission rates than budesonide-treated patients. This finding in UC is in clear contrast to recent results in Crohn's disease, where budesonide efficacy surpasses mesalazine efficacy in patients with higher CRP levels.[47]

Although oral budesonide was inferior to mesalazine, budesonide induced remission in ~40% of patients with mild-to-moderately active UC, with a rapid resolution of symptoms (14 days) and endoscopic remission in ~50% of patients. Since the study contained no placebo group it cannot be firmly concluded that oral budesonide is effective. However, our data, especially taking into account the stringent endpoint definition, suggest effectiveness, since a recent meta-analysis demonstrated a placebo remission rate of ~13% in UC.[48]

Both treatments exhibited a good safety profile. There were no indications of clinically relevant safety signals following the eight-week treatment period for either agent, and no serious adverse events with a suspected relation to either drug occurred. The higher rate of discontinuation due to adverse events in the budesonide group (9% versus 5% for mesalazine) was accounted for by discontinuations due to deteriorating UC, thus in line with the difference in efficacy outcomes. Reflecting the intake of synthetic topical steroid over 8 weeks, approximately one fifth of the patients in the budesonide group showed decreased morning serum levels of endogenous cortisol. Tolerability was assessed as very good or good in the vast majority of patients by both patients and investigators.

In conclusion, once-daily treatment with 3 g mesalazine granules OD is superior to 9 mg budesonide capsules OD for the management of mild-to-moderately active UC, although a clinical, endoscopic, and histological response was also observed in the budesonide arm. Therefore, the further evaluation of oral budesonide including other galenical formulations seems worthwhile. From a clinical perspective the effects of budesonide in mesalazine non-responders would be of great interest.

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Conflict of interest

VG has acted as a speaker for Dr. Falk Pharma GmbH. KD, RG, and RM are employees of Dr. Falk Pharma GmbH. All other authors have no conflicts of interest to declare.

Statement of authorship

VG, IB, EAB, TLM, LK, GK, ZT, LG, AED and JD carried out the study. VG analysed the data and finalised the draft manuscript. KD, RG and RM contributed to the study design and data analysis. All authors read and approved the final manuscript.

Writing assistance

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Appendix A

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