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► **To cite this version:**

Franz Hartmann, Jürgen Stein. Clinical trial: controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide and mesalazine enemas in active left-sided ulcerative colitis. *Alimentary Pharmacology and Therapeutics*, 2010, 32 (3), pp.368. 10.1111/j.1365-2036.2010.04354.x . hal-00599508

HAL Id: hal-00599508

<https://hal.science/hal-00599508>

Submitted on 10 Jun 2011

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Clinical trial: controlled, open, randomized multicenter trial comparing the effects of treatment on quality of life, safety and efficacy of budesonide and mesalazine enemas in active left-sided ulcerative colitis

Journal:	<i>Alimentary Pharmacology & Therapeutics</i>
Manuscript ID:	APT-0715-2009.R1
Manuscript Type:	Clinical Trial
Date Submitted by the Author:	22-Apr-2010
Complete List of Authors:	Hartmann, Franz; Colitis Crohn Clinical Research Center Rhein-Main Stein, Jürgen; St. Elisabeth-Hospital, Gastroenterology and Clinical Nutrition; Colitis Crohn Clinical Research Center Rhein-Main
Keywords:	Inflammatory bowel disease < Disease-based, Ulcerative colitis < Disease-based, Inflammation < Topics, X keyword = no topic

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3 **Clinical trial: controlled, open, randomized multicenter trial**
4 **comparing the effects of treatment on quality of life, safety**
5 **and efficacy of budesonide and mesalazine enemas in active**
6 **left-sided ulcerative colitis**
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Key words: ulcerative colitis, left sided colitis, topical therapy, enema, budesonide,
mesalazine

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3 **BACKGROUND:**
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5 Therapy for active left sided ulcerative colitis (UC) usually involves topical application of
6 mesalazine or budesonide.
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11 **AIM:**
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13 To compare the efficacy and safety of budesonide enema and mesalazine enema in the
14 treatment of active left sided ulcerative colitis
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20 **METHODS:**
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22 237 patients with mild-moderate UC were randomized open 1:1 to receive either budesonide
23 (n=118) or mesalazine enemas (n=119) for 8 weeks. Efficacy variables were clinical activity
24 index (CAI), endoscopic, histological index and IBDQ scores after 4 and 8 weeks.
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31 **RESULTS:**
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33 Clinical remission (intention-to-treat analysis) at week 4 was 63.5 % for budesonide enemas
34 and 77.2% for mesalazine enemas ($p < 0.05$). The respective values for the per protocol
35 population (PP) were 59.9% examined in the budesonide group and 77.5% in the mesalazine
36 group ($p < 0.02$). At the final visit (W8), clinical remission was diagnosed in the ITT analysis for
37 64.4 % of the budesonide group and 77.4 % of the mesalazine group ($p < 0.05$). The
38 respective values for the PP analysis were 59.5% in the budesonide group and 75.3% in the
39 mesalazine group ($p < 0.02$).
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50 **CONCLUSIONS:**
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52 Compared with budesonide, mesalazine enema was associated with a significantly higher
53 remission rate, this was supported by favourable trends in endoscopic, histological remission
54 rates and the IBDQ score.
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INTRODUCTION

Ulcerative colitis (UC) is a chronic relapsing inflammatory bowel disease of unknown etiology and pathogenesis. The inflammation is limited to the mucosa and submucosa. Based on several trials who have demonstrated the efficacy and safety of rectal mesalazine in active distal UC mesalazine liquid enemas are the first-line treatment for active proctosigmoiditis and left-sided colitis since over 25 years (1–7).

Budesonide, a glucocorticoid with a high topical anti-inflammatory efficacy and due an extensive first pass metabolism, a low systemic activity in therapeutic doses has been introduced in topical treatment of UC in early 90th. Several clinical trials have been shown that budesonide enemas, 2 mg/day are equal or even superior to prednisolone and other corticosteroid enema (8-11).

However, large head-to-head clinical trials are not available in the literature in which mesalazine enemas were compared with budesonide enemas in the treatment of mild to moderate left sided colitis. Only two small trials compared treatment on quality of life, safety and efficacy of budesonide and mesalazine enemas in active left-sided ulcerative colitis (12,13). However both trials were unable show a clear advantage of any of the substances. Therefore we performed the first open, multicentre, randomized group-comparative trial to evaluate the efficacy, [safety](#), and IBDQ of budesonide (2 mg/100 ml) with of mesalazine (4 g/60ml) in the treatment of active left sided colitis during a substantially longer treatment period (8 weeks) compared to previous trials.

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PATIENTS AND METHODS

Study design and patients

This was a prospective, open, randomized, reference-controlled parallel group multicenter study, which was performed in 37 German sites. The patients were treated as out-patients with examinations at entry, after 4 and 8 weeks. Men or nonpregnant women between 18 and 70 years of age were eligible, if they had newly diagnosed (at least one acute attack) or relapsing active mild-to-moderate left-sided UC confirmed by endoscopy, histology and a negative stool culture. A clinical disease activity (CAI) according to Rachmilewitz (14) of >4 , and an endoscopic index (EI) of >2 were mandatory. Exclusion criteria were: uncertain diagnosis of UC, symptoms of disease present for <2 weeks, macroscopic lesions proximal to the sinistral flexure, Crohn's disease, prior bowel operation, use of oral/rectal steroids within two weeks prior to baseline, use of immunosuppressants (azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, cyclosporine), within 6 months prior to baseline, nonsteroidal antiinflammatory drug (NSAID) treatment for more than 3 consecutive days, antibiotics during the preceding 2 weeks other than following a defined infection for less than 10 days, and 5-aminosalicylic acid (5-ASA), sulphasalazine, or olsalazine in variable dosages within the preceding two weeks. Patients with known significant hepatic or renal function abnormalities and/or clearance creatinine ≤ 80 mL/min were not included. All patients had to sign an informed consent form prior to entering the study. All patients gave their written informed consent before inclusion. The study was conducted in accordance with good clinical practice and the Declaration of Helsinki, and approved by independent ethics committees for each of the centres.

Medication

At each participating center, patients were randomly assigned in a 1:1 ratio to receive either budesonide (2 mg/100 ml) enema (Entocort; Astra Zeneca, Wedel, Germany) or mesalazine (4g/60 ml) enema (Salofalk; Dr. Falk Pharma GmbH, Freiburg, Germany) based on a central computer generated randomization scheme. The numbers were allocated sequentially in the

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order in which the patients were enrolled. Under no circumstances patients enrolled in the study could be permitted to reenrol for a second time in this study. Because of the different volume of product (60 mL vs. 100 mL) and the different size of the external packs, the investigator could distinguish between the two test treatments, but patients were unaware of the treatment assignment due to the anonymous packaging and labeling of the study medication. Patients' compliance to the test treatments was checked by the investigators at each visit.

Assessment

Patients attended the study centres three times: at visit 1 (baseline, day 1), at visit 2 (W4, day 29 ± 3), and visit 3 (final visit, W8, day 58 ± 6). The baseline visit included case history, physical examination, blood tests, endoscopy (entire colon in case of a new diagnosis, sigmoidoscopy up to the noninflamed colon in cases of established diagnosis), calculation of the CAI, calculation of the EI, assessment of the histological index (HI). The final visit or withdrawal examination included vital signs, blood tests, sigmoidoscopy, calculation of the CAI, calculation of the EI, assessment of the HI, determination of physicians' global assessment, determination of the assessment of tolerability by investigator and patient, and recording of patient's acceptance of the study drugs.

Efficacy and safety variables

The primary efficacy variable was clinical remission at 4 wk and 8 wk defined on the basis of the CAI according to Rachmilewitz (14) that covers clinical symptoms for one week and includes: number of stools/wk, presence of blood in stools, abdominal pain/cramps, temperature (fever), extraintestinal manifestations, laboratory values (ESR, haemoglobin), and investigator's global assessment. Active UC was defined by a CAI ≥ 4 . The Endoscopic findings were graded according to the endoscopic index (EI) of Löfgren (10), that considers granulation, vascular pattern, vulnerability of the mucosa, and mucosal damage (table1).

Primary study end point was clinical remission defined by a CAI < 4 after W4 visit in the per

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3 protocol (PP) population. *Secondary end points* were: clinical remission at W8, endoscopic
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5 remission at W8 defined as an endoscopic score < 2.
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8 In addition, biopsies from the rectum and sigmoid colon were taken at entry and at the end of
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10 the study period and evaluated by a single pathologist (MS). Classification of histological
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12 activity was performed according to Floren er al. (15), whereas mild and moderate activity
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14 were classified separately. The following classes were used: 1, normal mucosa; 2, UC in
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16 remission; 3, UC with mild activity; 4, UC with moderate activity; 5, UC with severe activity;
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18 and 6, no UC.
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20 21 22 **Quality of life (IBDQ)**

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24 To assess the patients' quality of life the Inflammatory Bowel Disease Questionnaire (IBDQ),
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26 was employed. The IBDQ, a standard 32-item questionnaire, evaluates general activities of
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28 daily living, specific intestinal functions such as bowel habit and abdominal pain, as well as
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30 social performance, personal interactions, and emotional status Scores range from 32 to
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32 224, with a higher score indicating better quality of life (16).
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35 36 37 **Safety assessment**

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39 Body weight, blood pressure and signs of Cushing's syndrome were assessed at 0, 4 and 8
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41 weeks, as well as clinically relevant changes in laboratory values (central analysis), and the
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43 overall tolerability, as assessed by the patient and the investigator. All unfavourable,
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45 unexpected symptoms or signs reported by the patients or observed by the investigator
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47 during the study were considered adverse events, regardless of drug.
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50 51 52 **Analysis (Statistical Methods)**

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54 [Considering that the primary efficacy variable was the mean final CAI score, the interval](#)
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56 [width of clinical equivalence was fixed at one point of the mean final CAI score. Type I](#)
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58 [error was set at \$\alpha = 0.05\$ and Type II error was set at \$\beta = 0.2\$ to have a 80% power to reject](#)
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60 [the null hypothesis of nonequivalence in favor of the alternative hypothesis that the](#)

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two treatments were clinically equivalent with regards to the primary efficacy variable. The common standard deviation was estimated to be equal to 2.5 points. On the basis of these assumptions and premature withdrawal (~15%) 115 patients were required in each treatment group.

The intention to treat (ITT) population was defined as all randomized patients who received at least 1 one enema. The patients who completed or terminated the study without protocol violation wre analysed in the per protocol (PP) population. The safety population included all randomized patients. The proportion of patients who were still in remission at the end of the study was calculated for each treatment group. Dichotomic features are checked for statistic significant difference between the groups ($\alpha=0.05$; two-sided) by means of the fisher test. For the others, the generalized (Halton-Freeman) fisher test was used. Systematic differences between the distributions of metric and ordinal variables for both groups were assessed by means of the Mann-Whitney test. Only the p-values concerning the a priori hypotheses about the primary variables were to be classified in regard to significance. All other p-values are to be understood as descriptive measures in an exploratory sense.

RESULTS

Patients demographic data

A total of 237 patients were randomized (118 in the budesonide group and 119 in the mesalazine group), of which 193 could be evaluated for the ITT analysis (budesonide: n = 94, mesalazine enema: n = 99; 44/237 patients (18.6%) were withdrawn from the study, 24/118 (20.3%) in the group 1 (budesonide) and 20/119 (16.8%) in group 2 (mesalazine). The most frequent reason for termination of therapy in both groups was that that the therapy failed: 16/118 patients (13.6%) in the budesonide group and 10/119 patients (8.4%) in the mesalazine group (p=0.219). In total protocol violations at visit 1 were observed in 65/237 patients (27.4%), 29/118 in the budesonide group (24.6%) and 36/119 patients (30.3%) in the mesalazine-group. Figure 1 shows the patients flow and reasons for discontinuation.

mesalazine vs. budesonide in left-sided colitis

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3 The two groups were well balanced for basic demographic data and disease history (Table
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5 1). There was a significant difference ($p < 0.01$) between groups with regard to gender
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7 distribution with more men than women in both groups. Recruitment resulted in more than
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9 95% of proctosigmoiditis or left side colitis. In around 80% of the patients, the current
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11 episode lasted for more than 3 months. There was no inhomogeneity detectable in respect of
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13 the use of oral remission-maintaining therapy (5-ASA, sulfasalazine, olsalazine): 73/118
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15 (61.9%) in the budesonide group vs. 74/119 patients (62.2%) in the mesalazine-group.
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20 Efficacy

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22 The clinical remission was achieved by significantly more patients treated with mesalazine
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24 than with budesonide (Fig. 2). Based on the CAI after 4 weeks in the ITT analysis 63.5 %
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26 (66/104) for the budesonide and 77.2% (78/101) for the mesalazine enema ($p < 0.05$) were in
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28 remission. The respective values for the per protocol population (PP) were 59.9% (44/76)
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30 examined in the budesonide group and 77.5% (55/71) in the mesalazine group ($p < 0.02$).
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32 At the final visit (W8), clinical remission was diagnosed for 64.4 % (65/101) of the
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34 budesonide group and 77.4 % (82/106) of the mesalazine group ($p < 0.05$). The respective
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36 values for the per protocol population were 59.5% (47/79) in the budesonide group and
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38 75.3% (58/77) in the mesalazine group ($p < 0.05$).
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42 Confirming the overall CAI, the diary card data found that mesalazine patients were
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44 statistically significantly less likely to have blood in the stools after four weeks of treatment,
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46 72% versus 48% had no blood ($p < 0.05$). At W 4 the diary data also showed significantly
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48 fewer days with abdominal pain/cramps in mesalazine recipients (15% vs. 28%; $p < 0.05$).
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50 Conversely, patients treated with budesonide had significantly fewer days with abnormal
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52 stool consistency compared with mesalazine: Abnormal stools occurred on three or more
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54 days in week 4 for 35% of patients treated with mesalazine compared with 20% of patients
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56 treated with budesonide ($p < 0.02$).
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Endoscopic findings

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For the initial endoscopy, data were available for 118/118 (100%) patients in the budesonide group and 119/119 (100%) in the Salofalk group. The grades at the final visit (W 8) for (100/118 (84.7%) in the budesonide group and 105/119 (88.2%) in the Salofalk group).

Endoscopic remission was considered to be achieved if the endoscopic index after treatment was 2 or less. Results are summarized in figure 3. As already seen for the clinical remission rate, the endoscopic remission rate was slightly greater, but not significant ($p=0.651$) for patients, who were treated with mesalazine enema, 71.7% (76/106) compared to budesonide enema 68.0 % (76/103).

Biopsy findings

For the initial visit, biopsy findings were available for 116/118 (98.3%) in the budesonide group and 115/119 (96.6%) patients in the mesalazine group (table 3). At the beginning, there was no discernable difference between the two groups. The histological findings at the final visit (W 8) were available for 100/118 (84.7%) patients in the budesonide group and 105/119 (88.2%) patients in the mesalazine group. Compared to visit 1 both treatments resulted in a significant reduction of the scores with a slightly greater, but not significant ($p=0.145$) improvement in the mesalazine group (remission rate 43% in the budesonide group vs 49% in the mesalazine group).

IBDQ

Results of the IBDQ questionnaire are presented in Fig. 5, which showed that a slightly greater improvement was obtained in the mesalazine group compared to the budesonide group both at 4 and 8 weeks; the statistical significance of this small difference was not tested.

Safety

A total of 65 adverse events (AEs) in patients (55%) of the budesonide group and 41 (34%) in patients of the mesalazine group ($p<0.002$). Overall, 36/118 (31%) of patients in the

mesalazine vs. budesonide in left-sided colitis

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3 budesonide group and 31/119 (26%) in the mesalazine group reported 1 or more AEs
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5 (p=0.473). The most frequently reported AEs were gastrointestinal disorders and
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7 infections/infestations. The majority of events were mild or moderate in intensity, and
8
9 considered unrelated to or unlikely related to study medication (table 4).

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11 The maximal intensity of the AEs was classified as severe in 7/65 (10.8%) AEs in the
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13 budesonide and 4/41 (7.8%) AEs in the mesalazine group. A maximal intensity of “moderate
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15 was reported for 32/65 (49.2%) AEs in the budesonide and 11/41 (26.8%) AEs in the
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17 mesalazine group (p < 0.05). Termination of therapy resulted from 2/65 (3.1%) AEs in the
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19 budesonide group and 1/41 AEs (2.4%) in the mesalazine group. The relation of AEs to
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21 medication was classified as “probable” in four AEs in the budesonide group (3.4%) and four
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23 AEs in the mesalazine group (3.4%). No significant changes in leucocyte counts, or in other
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25 laboratory values (except CRP), body weight gain, cushingoid appearance, elevated blood
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27 pressure, heart rate or other symptoms that might suggest systemic glucocorticosteroid
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29 effects were noted within both treatment groups at the end of the treatment period.
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DISCUSSION

This is the first and largest long term randomized controlled trial that directly compares budesonide and mesalazine enemas in patients with active left sided UC over a treatment period of 8 weeks. Our results demonstrate that both formulations are effective in the treatment of left sided UC. The results are in good agreement with earlier studies showing a clinical response rate for between 63% to 82% for mesalazine (17-19) and 55 to 66% and budesonide (4, 20), respectively.

However clinical response rate was significantly higher in patients treated with mesalazine than with budesonide. The efficacy findings were consistent across the ITT (74.5% vs. 63.5%; $p < 0.05$) and the PP populations (77.5 vs. 59.9; $p < 0.02$), indicating the patients withdrawals did not influence the study outcome. The superiority of mesalazine enemas was also supported by the secondary endpoints: As in the case of IBDQ, for all three assessments, there was a difference between both treatment groups in terms of endoscopic (72% vs. 65%; $p = 0.651$), or histological remission (49% vs. 43%; $p < 0.145$) favouring patients treated with mesalazine. This supports earlier findings, indicating that mesalazine enema is more efficacious as budesonide enema in the treatment of distal colitis (12, 13). However, due the relatively small patient groups in both studies, a possible difference between the two treatments may have been concealed, i.e. statistical type II error. It also must be mentioned, that in contrast to the study of Lemann et al., (12), in our study patients treated with mesalazine without success, were not excluded from the our study, since this could favoring the mesalazine treatment.

A second important issue addressed in the study is the extension of the treatment period up to 8 weeks. In clinical practice, treatment time is often prolonged if the patient shows no complete clinical remission after 4 weeks. However, we found only two smaller studies in the literature addressed to the question whether a extension of the treatment up to 8 weeks, could further improve clinical response. In the study of Löfberg et al. (12) budesonide (n= 45) was compared versus prednisolone (n=55) enemas in active distal ulcerative colitis with patients evaluation at 2, 4, and 8 weeks. Clinical remission was seen as early as 4 weeks

mesalazine vs. budesonide in left-sided colitis

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3 and doubled by 8 weeks in both treatment groups. Similar results were reported by Hanauer
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5 et al. (22) in a dose ranging study in 233 patients for budesonide comparing clinical
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7 remission at week 4 and week 6. In contrast to the trials of Löfberg et al. (12) and Hanauer et
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9 al. (23) the present data did not confirm that a prolongation of the treatment from 4 to 8
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11 weeks further improve the clinical remission rate in patients treated with budesonide enema.
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13 This was also supported by the secondary endpoints (IBDQ, endoscopic, and histological
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15 remission).

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18 Our data are confirmed by a recently published study of Biancone et al. (23) comparing
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20 beclomethasone dipropionate versus mesalazine enemas in 99 patients with mild –
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22 moderate distal ulcerative colitis: the efficacy assessed by clinical and endoscopic activity
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24 was not significantly different at week 4, and week 8.
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27 Our study has some limitations, that we want to acknowledge. *First*, as a consequence of the
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29 study design we did not distinguish mild from moderate CU. Thus, as shown in a recent
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31 paper for beclomethasone dipropionate (21), topical budesonide might be more efficacious in
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33 moderate to severe left sided colitis. *Second*, our study does not provide information about
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35 the potential usefulness of budesonide enemas in patients who do not respond to
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37 mesalazine enemas. *Third, since we have no data correlating duration of disease and*
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39 *therapeutic response we can not exclude e.g. that disease with longer duration responds*
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41 *better to budesonide and less likely to mesalazine enemas.*
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44 From the present study, it can be concluded, that mesalazine enema (4 g daily) are superior
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46 to budesonide enema (2 mg daily) in the treatment of mild to moderate left sided ulcerative
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48 colitis and ulcerative proctitis. This was supported by favourable trends in endoscopic,
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50 histological remission rates and the IBDQ score. In both groups a prolongation of the
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52 treatment from 4 to 8 weeks does not improve the clinical response rate.
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References

1. Campieri M, Paoluzzi P, D'Albasio G, et al. Better quality of therapy with 5-ASA colonic foam in active ulcerative colitis. *Dig Dis Sci* 1993;38:1843–1850.
2. Campieri M, Gionchetti P, Belluzzi A, et al. Optimum dosage of 5-aminosalicylic acid as rectal enemas in patients with active ulcerative colitis. *Gut* 1991;32:929–931.
3. Campieri M, Lanfranchi GA, Bazzocchi G, et al. Treatment of ulcerative colitis with high dose 5-aminosalicylic acid enema. *Lancet* 1981;2:270–271.
4. Marshall JK, Irvine EJ. Rectal aminosalicylate therapy for distal ulcerative colitis: A meta-analysis. *Gut* 1997; 40: 775–781
5. Cohen RD, Voseh DM, Thisted RA, et al. A meta-analysis and over view of the literature on treatment options for left sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;95:1263–7126
6. Friedman LS, Richter JM, Kirkham SE, DeMonaco HJ, May RJ. 5-aminosalicylic acid enemas in refractory distal ulcerative colitis: A randomized controlled trial. *Am J Gastroenterol* 1986; 81: 412–418
7. Sutherland LR, Martin F, Greer S. et al. 5-Aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis and proctitis. *Gastroenterology* 1987; 92: 1894–1898
8. Danielsson A, Hellers G, Lyrenäs E, Löfberg R, Nilsson A, Olsson O, Olsson SA, Persson T, Salde L, Naesdal J, et al. A controlled randomized trial of budesonide versus prednisolone retention enemas in active distal ulcerative colitis. *Scand J Gastroenterol* 1987;22:987-992
9. Bianchi Porro G, Prantera C, Camperieri M, et al. Comparative trial of methylprednisolone and budesonide enemas in active distal ulcerative colitis. *Eur J Gastroenterol* 1994;6:125-130
10. Löfberg R, Ostergaard Thomsen O, Langholz E, Schiöler R, Danielsson A, Suhr O, Graffner H, Pålman L, Matzen P, Møller-Petersen JF, et al. Budesonide versus

mesalazine vs. [budesonide in left-sided colitis](#)

1
2
3 prednisolone retention enemas in active distal ulcerative colitis. Aliment Pharmacol
4
5 Ther. 1994;8:623-629.

- 7
8 11. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in
9
10 ulcerative colitis: A meta-analysis. Gut 1997; 40: 775–781.
- 11
12 12. Lémann M, Galian A, Rutgeerts P, Van Heuverzwijn R, Cortot A, Viteau JM, Elewaut
13
14 A, Belaiche J, Froguel E, Modigliani R. Comparison of budesonide and 5-aminosalicy
15
16 acid enemas in active distal ulcerative colitis. Aliment Pharnacol Ther 1995; 9: 557-
17
18 562.
- 19
20 13. Ruffle W, Frühmorgen P, Huber W, Kimmig JM. Budesonide foam as a new
21
22 therapeutic concept in the therapy of distal ulcerative colitis in comparison to
23
24 mesalazine enemas. An open, controlled, randomized and prospective multicenter
25
26 pilot study. Z Gastroenterol 2000; 38: 287–293.
- 27
28 14. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in
29
30 the treatment of active ulcerative colitis: A randomised trial. BMJ 1989; 298: 82–86
- 31
32 15. Floren CH, Benoni C, Willen R. Histologic and colonoscopic assessment of disease
33
34 ex tension in ulcerative colitis. Scand J Gastroenterol 1987; 22: 459–462
- 35
36 16. Irvine EJ, Feagan B, Rochon J, Archambault A, Fedorak RN, Groll A, Kinnear D,
37
38 Saibil F, McDonald JW. Quality of life: a valid and reliable measure of therapeutic
39
40 efficacy in the treatment of inflammatory bowel disease. Gastroenterology 1994;106:
41
42 287-296.
- 43
44 17. Malchow H, Gertz B, and the Clafoam Study Group. A new mesalazine foam enema
45
46 (Claversal foam) compared with a standard liquid enema in patients with active distal
47
48 ulcerative colitis. Aliment Pharmacol Ther 2002;16:415–423
- 49
50 18. Pokrotnieks J, Marlicz K, Paradowski L, Margus B, Zaborowski P, Greinwald R.
51
52 Efficacy and tolerability of mesalazine foam (Salofalk foam) for distal ulcerative colitis:
53
54 A double-blind, randomized, placebo controlled study. Aliment Pharmacol Ther
55
56 2000;14:1191–1198.
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19. Eliakim R, Tulassay Z, Kupcinkas L, et al. Clinical trial: Randomized-controlled clinical study comparing the efficacy and safety of a low-volume vs. a high-volume mesalazine foam in active distal ulcerative colitis. *Aliment Pharmacol Ther* 2007;26:1237–1249.
20. Gross V, Bar-Meir S, Lavy A, Mickisch O, Tulassay Z, Pronai L, Kupcinkas L, Kiudelis G, Pokrotnieks J, Kovács A, Faszczyk M, Razbadauskas A, Margus B, Stolte M, Müller R, Greinwald R; International Budesonide Foam Study Group Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis: *Aliment Pharmacol Ther* 2006; 23: 303–312
21. Gionchetti P, D'Arienzo A, Rizzello F, Manguso F, Maieron R, Lecis PE, Valpiani D, Iaquinto G, Annese V, Balzano A, Varoli G, Campieri M; Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005;39:291-297
22. Hanauer SB, Robinson M, Pruitt R, Lazenby AJ, Persson T, Nilsson LG, Walton-Bowen K, Haskell LP, Levine JG. Budesonide enema for the treatment of active, distal ulcerative colitis and proctitis: a dose-ranging study. U.S. Budesonide enema study group. *Gastroenterology*. 1998;115:525-532
23. Biancone L, Gionchetti P, Blanco Gdel V, Orlando A, Annese V, Papi C, Sostegni R, D'Inca R, Petruzzello C, Casa A, Sica G, Calabrese E, Campieri M, Pallone F. Beclomethasone dipropionate versus mesalazine in distal ulcerative colitis: a multicenter, randomized, double-blind study. *Dig Liver Dis*. 2007;39:329-337

mesalazine vs. [budesonide in left-sided colitis](#)

Figure legends

Figure 1. [Schematic](#) representation of patient flow and reasons for discontinuation.

Figure 2: Course of the CAI (mean \pm SE) in the intention to treat (ITT) analysis set.

Figure 3: Primary endpoint: rates of clinical remission (CAI < 4) at week 4 and 8 in the intention to treat (ITT) and per protocol (PP) analysis set.

Figure 4: Endoscopic remission (EI < 2) after 4 weeks of treatment (ITT population)

Figure 5: IBDQ-score (per-protocol population): absolute values (a) and change (b) at week 4 and [8 compared](#) to baseline.

ACKNOWLEDGEMENTS

This study was sponsored by AstraZeneca GmbH, Germany.

We wish to thank Prof. M. Stolte (Klinikum Bayreuth, Germany) for performing the histological analysis

Members of the BudeMesa study group participating as investigators were:

Dr. Beckh, Ulm; Dr. Bischoff, Hannover; Dr. Boekstegers, Essen; Dr. Brandes, Braunschweig; Dr. Busch Aachen, Dr. Dillmann, Aschaffenburg; Dr. Eisold, Mössingen, Dr. Hartmann, Saalfeld, Dr. Hüppe, Herne; Dr. Kohler, Giessen; Dr. Körber, Berlin; Dr. Krummenerl, Münster; Prof. Dr. Lorenz-Meyer, Friedrichshafen; Prof. Dr. Malchow, Leverkusen; Dr. Mönnikes, Marburg; Prof. Dr. Rabast, Hattingen; Dr. Raedler, Hamburg; Dr. Rehmann, Lippstadt; Dr. Schiller, Göttingen; Prof. Dr. Schmitt, München; Dr. Theuer, Heilbronn; Dr. Wenzel, Wuppertal.

Disclosures:

FH was the Principal Investigator in this multicenter study, and led the development of both the protocol and the manuscript. JS participated in the development of the manuscript, has reviewed the final draft and approve its submission.

Prof. Franz Hartmann has served on advisory boards and received consultancy and lecturing funding from Essex, Falk Foundation, Shire, Abbott GmbH, and UCB.

Jürgen Stein has served on advisory boards and received consultancy and lecturing funding from Essex, Ferring, Falk Foundation, Shire, Abbott GmbH, UCB, and Fresenius Kabi.

Table 1: Endoscopic grading scale (Löfgren et al. 1994)

Score	
0	Non-inflamed mucosa
1	Granular, oedema, lack of vascular pattern
2	Hyperaemia, friability, petechiae (and all off class1)
3	Ulcerations (and all of class1 and 2)

Table 2: Demographic data and disease history

Characteristics	Budesonide group (n= 118)	Salofalk group (n= 119)
Males/Females	69/49	74/45
Age (years), mean (s.d.)	41.8	43.6
Weight (kg), mean (s.d.)	73.8	74.0
Mean height (cm), mean (s.d.)	173.6	171.7
Mean body mass index (kg/m ²), mean (s.d.)	24.4	25.1
Smoking habits, n (%)		
Nonsmoker	86 (72.9%)	94 (79.0%)
Ex-smoker	19 (16.1%)	9 (7.6%)
Smoker	13 (11%)	16 (8.4%)
Course of disease, median (range)		
Duration of UC (months)	64.5 (2.0 – 408.0)	60 (1.0 – 445.0)
<u>Number of previous episodes</u>	<u>4 (1 – 35)</u>	<u>4 (1 – 40)</u>
<u>Duration of current episode (months)</u>	<u>1 (0 – 14.0)</u>	<u>1 (0 – 24.0)</u>
UC extension, N (%)		
Proctitis (5–18 cm)	5 (4.3%)	5 (4.2%)
Proctosigmoiditis (18–60 cm)	67 (57.3%)	70 (58.8%)
Left-sided colitis (>60 cm)	45 (38.5)	44 (37.0)
CAI score at baseline, median (range)	7.0 (4–15)	7.1 (4–15)

Table 3: Histopathological response and remission rates at 8 weeks

Score	Budesonide group (n = 100)	Salofalk group (n = 105)
Normal	4 4.0%	7 6.7%
Remission	43 43.0%	51 48.6%
Slightly active	17 17.0%	25 23.8%
Medium-grade active	26 26.0%	15 14.3%
High-grade active	10 10.0%	6 5.7%
No colitis ulcerosa	-	1 1.0%

mesalazine vs. [budesonide in left-sided colitis](#)**Table 4:** Most common adverse events (AE):

Number of Patients Group N (%)	Budesonide group N=118	Salofalk group N=119	P value
Total number of AE	65 (55%)	41 (34%)	0.002
Patients with 1 ≥ AE	36 (31%)	31 (26%)	0.473
Common cold	7 (5.9)	6 (5)	ns
Nausea and vomiting	8 (6.8)	3 (2.5)	ns
Headache/migraine	6 (5.1)	0	
CRP increased	5 (4.3)	0	
Abdominal pain	2 (1.7)	3 (2.5)	ns
Flatulence	2 (1.7)	2 (1.7)	ns
Viral infection	3 (2.5)	0	
AE related to treatment	4 (6.2)	2 (1.7)	ns
At least one SAE	1 (0.8)	2 (1.7)	ns
Ulcerative colitis worsening	3 (2.5)	0	

N (%) = number of patients with at least one adverse event. Percentage of patients is calculated within each treatment group on the total number of patients included in each group in the safety population.

P value is determined by χ^2 test or Fisher exact test.

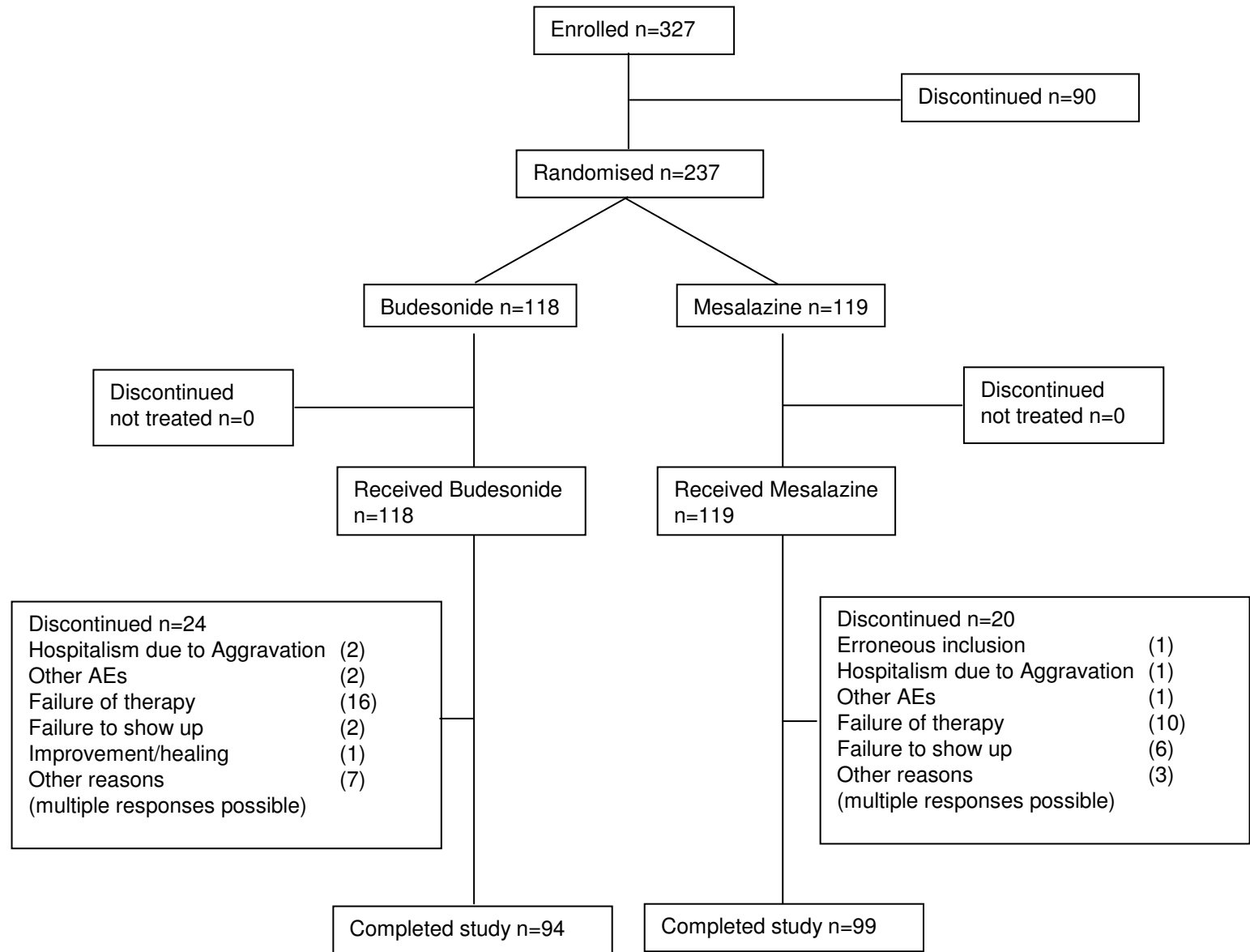


Fig. 1

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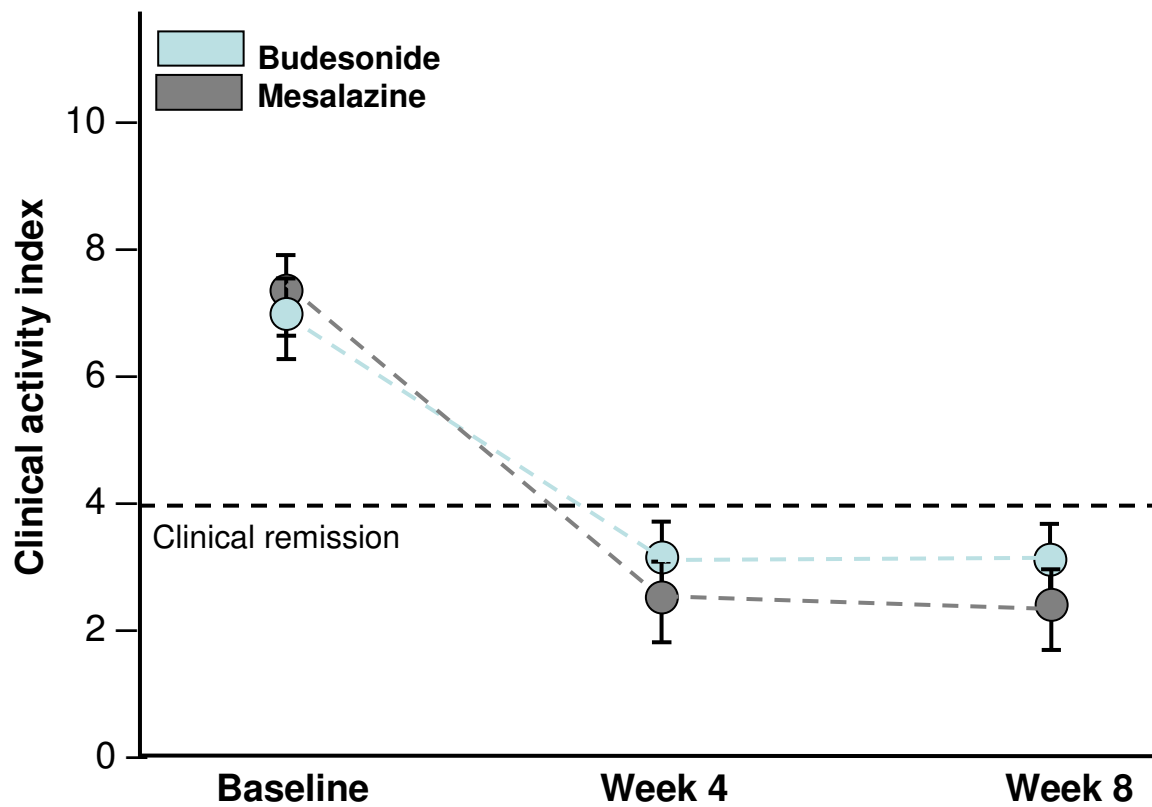


Fig. 2

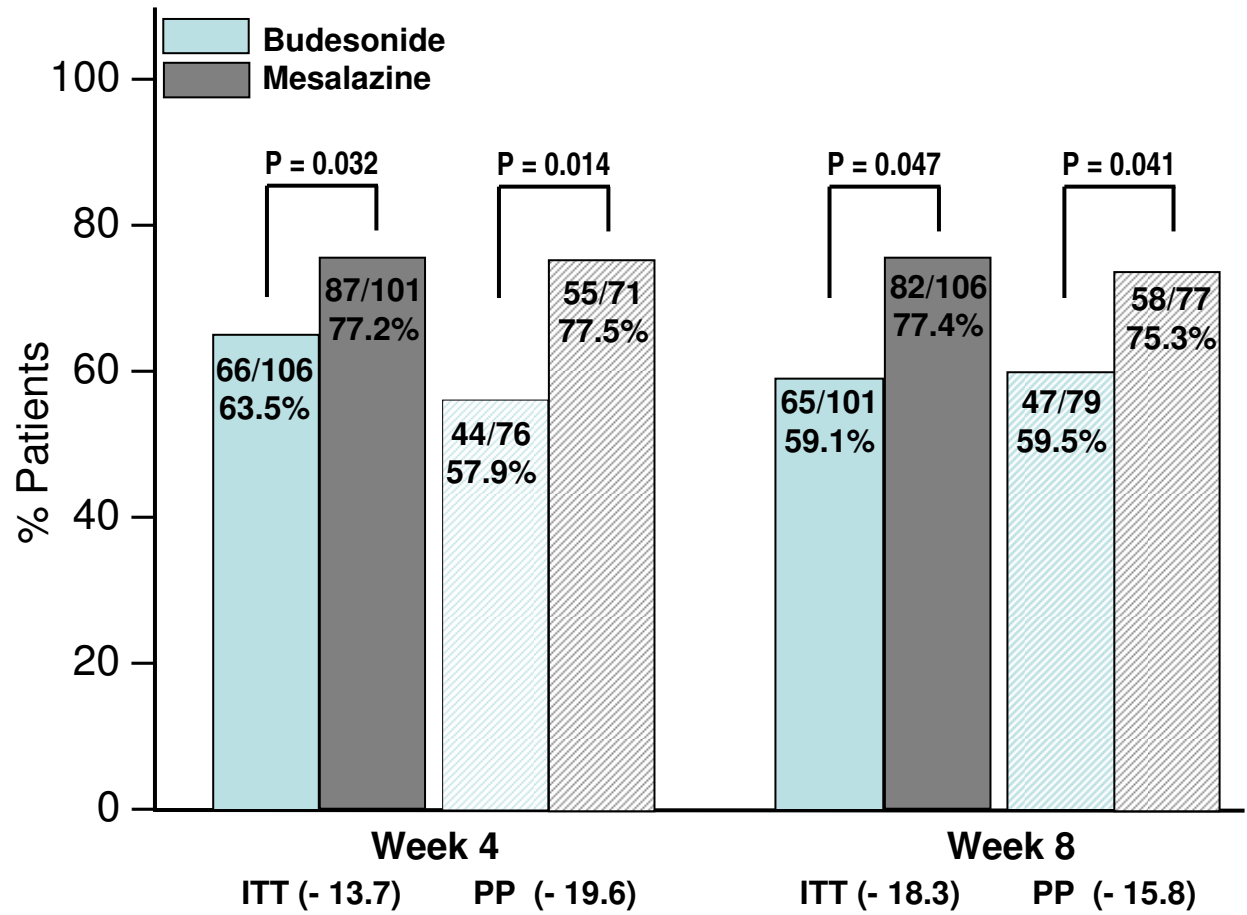


Fig. 3

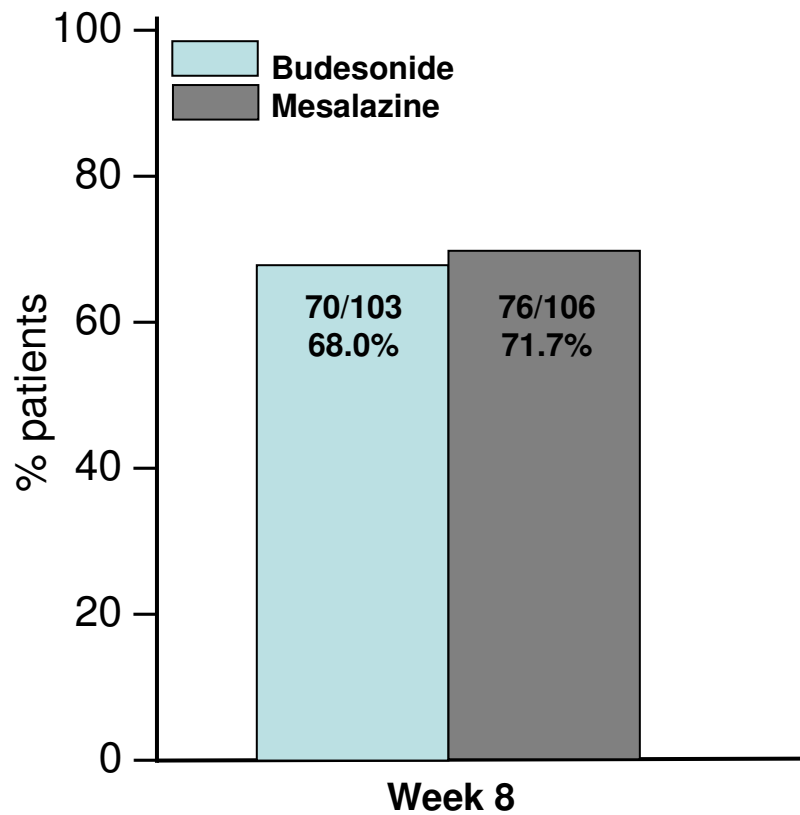


Fig. 4

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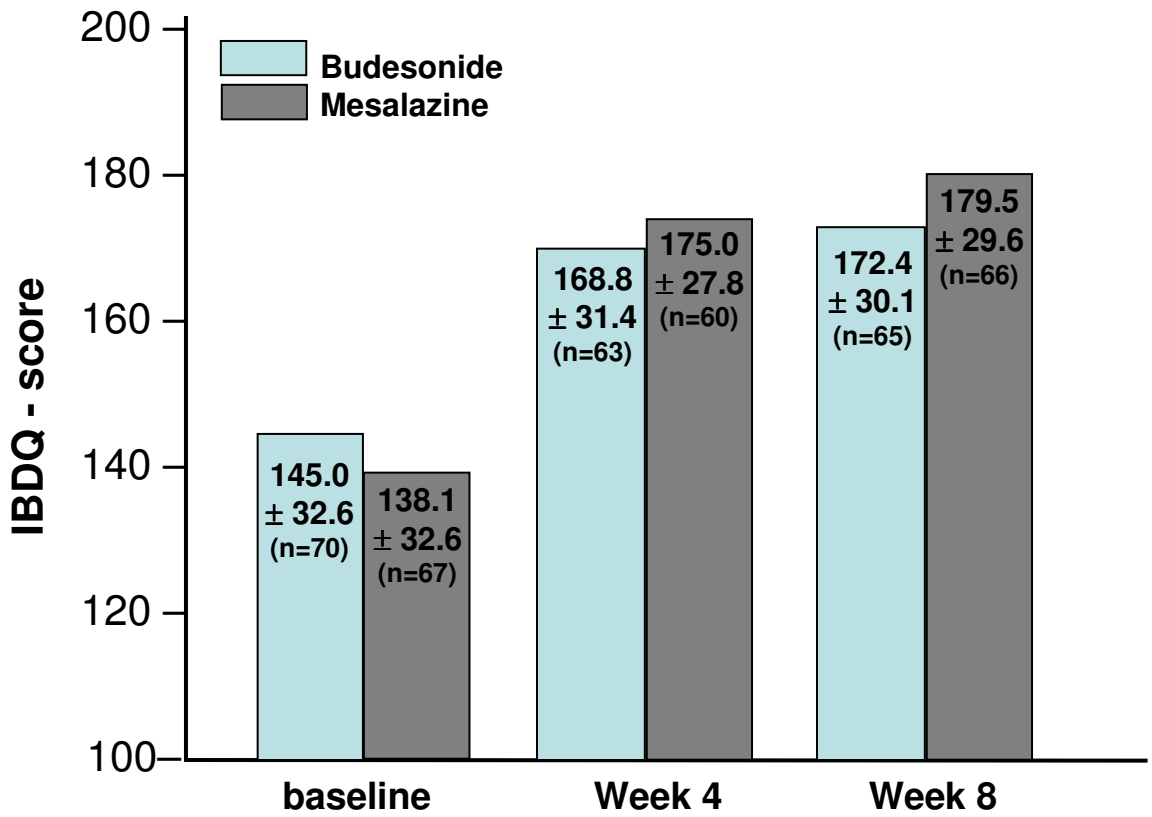


Fig. 5