ORIGINAL ARTICLE

Low-dose budesonide for maintenance of clinical remission in collagenous colitis: a randomised, placebo-controlled, 12-month trial

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ABSTRACT

Objective This 1-year study aimed to assess low-dose budesonide therapy for maintenance of clinical remission in patients with collagenous colitis.

Design A prospective, randomised, placebo-controlled study beginning with an 8-week open-label induction phase in which patients with histologically confirmed active collagenous colitis received budesonide (Budenofalk, 9 mg/day initially, tapered to 4.5 mg/day), after which 92 patients in clinical remission were randomised to budesonide (mean dose 4.5 mg/day; Budenofalk 3 mg capsules, two or one capsule on alternate days) or placebo in a 12-month double-blind phase with 6 months treatment-free follow-up. Primary endpoint was clinical remission throughout the double-blind phase.

Results Clinical remission during open-label treatment was achieved by 84.5% (93/110 patients). The median time to remission was 10.5 days (95% CI (9.0 to 14.0 days)). The maintenance of clinical remission at 1 year was achieved by 61.4% (27/44 patients) in the budesonide group versus 16.7% (8/48 patients) receiving placebo (treatment difference 44.5% in favour of budesonide; 95% CI (26.9% to 62.7%), p<0.001). Health-related quality of life was maintained during the 12-month double-blind phase in budesonide-treated patients. During treatment-free follow-up, 82.1% (23/28 patients) formerly receiving budesonide relapsed after study drug discontinuation. Low-dose budesonide over 1 year resulted in few suspected adverse drug reactions (7/44 patients), all non-serious.

Conclusions Budesonide at a mean dose of 4.5 mg/day maintained clinical remission for at least 1 year in the majority of patients with collagenous colitis and preserved health-related quality of life without safety concerns. Treatment extension with low-dose budesonide beyond 1 year may be beneficial given the high relapse rate after budesonide discontinuation.

Trial registration numbers http://www.clinicaltrials.gov (NCT01278082) and http://www.clinicaltrialsregister.eu (EudraCT: 2007-001315-31).

Significance of this study

What is already known on this subject?
► Collagenous colitis, a presentation of microscopic colitis, is associated with severely impaired health-related quality of life.
► Oral budesonide at a dose of 9 mg/day for 6–8 weeks induces remission in 77%–100% of patients with collagenous colitis.
► After withdrawal of budesonide, between 61% and 88% of patients experience clinical relapse but long-term data on budesonide maintenance therapy, and on the use of low-dose budesonide, are lacking.

What are the new findings?
► In a prospective, randomised, placebo-controlled trial of low-dose oral budesonide therapy (mean dose 4.5 mg/day) in patients with collagenous colitis, clinical remission was maintained to 1 year in 61.4% (27/44 patients) in the budesonide group versus 16.7% (8/48 patients) receiving placebo (p<0.001).
► Health-related quality of life was maintained to 1 year with low-dose oral budesonide.
► Low-dose budesonide over 1 year resulted in few suspected adverse drug reactions (7/44 patients), all of which were non-serious.

How might it impact on clinical practice in the foreseeable future?
► Maintenance therapy with low-dose budesonide (mean 4.5 mg/day) appears beneficial and safe in patients with collagenous colitis who have achieved clinical remission under standard budesonide therapy and reduces the high relapse rate observed after budesonide discontinuation.

INTRODUCTION

Collagenous colitis, a presentation of microscopic colitis, is a well-recognised cause of chronic non-bloody watery diarrhoea, particularly in elderly women[1] and is associated with severely impaired health-related quality of life.[2]

Oral budesonide, a locally active corticosteroid, has been shown in a number of randomised,

placebo-controlled trials to induce remission in collagenous colitis.[3–8] Budesonide at a dose of 9 mg/day for 6–8 weeks induces clinical response in 77–100% of patients,[3–8] and a recent meta-analysis has confirmed that budesonide therapy is associated with a threefold improvement in both short-term and long-term clinical responses compared with placebo.[9] Budesonide therapy is recommended by the European Microscopic Colitis Group (EMCG) as the treatment of choice for active disease.[1] However, after withdrawal of budesonide 61–88% of patients experience clinical relapse,[5 7 10 11] necessitating long-term intervention in patients with a chronic active course. Small studies (<50 patients) of up to 6 months' duration investigating the efficacy of budesonide at a dose of 6 mg/day in maintaining remission have previously shown a significant benefit versus placebo.[5 7] However, the long-term disease course is not altered by maintenance therapy, as the risk of relapse after 24 weeks' budesonide therapy is similar to that observed after 6 weeks' induction therapy,[5] and more long-term data are therefore required. Moreover, the optimal budesonide dose for maintenance therapy remains undefined and no controlled trial has assessed low-dose budesonide in this setting.

A prospective, randomised, placebo-controlled trial was initiated by the Swedish Organization for the Study of Inflammatory Bowel Disease (SOIBD) to investigate the efficacy and safety of low-dose oral budesonide therapy for the long-term maintenance of clinical remission in patients with collagenous colitis. The study included a 12-month double-blind phase to assess remission rates, with a 6-month treatment-free follow-up period for patients still in remission after 52 weeks to assess the maintenance of remission after cessation of the treatment, and employed a newly established definition for clinical remission in collagenous colitis.[12]

METHODS
Study design and setting
This was a multicentre phase III trial undertaken during April 2008 to March 2013 (with follow-up to September 2013) at 22 hospital clinics or private practices in Sweden, Belgium, Czech Republic, Denmark and Germany. The study was conducted in accordance with the International Conference on Harmonisation

(ICH) Guideline for Good Clinical Practice and was approved by the National Ethics Committee in each participating country. All authors critically reviewed the manuscript and approved it for publication.

The primary objective of the study was to demonstrate the superiority of pH-modified release oral budesonide (Budenofalk 3 mg capsules, Dr Falk Pharma GmbH, Freiburg, Germany) compared with placebo for maintaining patients with collagenous colitis in clinical remission over a 1-year period. The study comprised an initial open-label induction phase with budesonide therapy for 8 weeks to achieve clinical remission of collagenous colitis. Those patients who achieved clinical remission (defined as a mean of <3 stools/day, including a mean of <1 watery stool/day over 1 week) during the last week of the open-label phase were eligible for randomisation into a double-blind, randomised, placebo-controlled, parallel-group, multicentre, 12-month phase for maintenance of clinical remission (figure 1). Patients in clinical remission at the end of the double-blind phase were followed for a maximum of 6 months without study medication.

Relapse was defined as a mean of ≥3 stools/day, including a mean of ≥1 watery stool/day, during the week prior to the study visit.

Stool consistency was described by patients according to the Bristol Stool Chart.

Study population
Adult patients (≥18 years) were eligible if they met the following criteria: (i) histologically established diagnosis of collagenous colitis, defined as thickened subepithelial collagen layer ≥10 μm on well-orientated sections, and increased inflammatory cells indicating chronic inflammation in the lamina propria, (ii) pre-screening history of non-bloody, watery diarrhoea for ≥2 weeks in patients with newly diagnosed collagenous colitis, or a pre-screening history of clinical relapse for ≥1 week in patients with previously established collagenous colitis and (iii) a mean of ≥3 stools/day, including a mean of ≥1 watery stool/day, during the week prior to baseline. Patients were not eligible if they met any of the following main exclusion criteria: (i) diabetes mellitus, infection, glaucoma, tuberculosis, peptic ulcer disease or
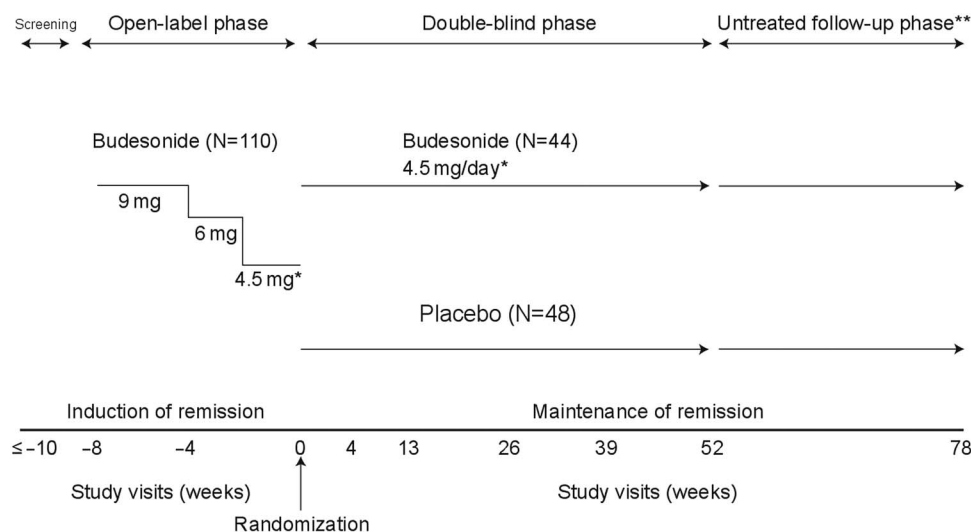
Figure 1 Study design.

hypertension if careful medical monitoring was not ensured, (ii) established cataract, (iii) known hereditary problems of galactose or fructose intolerance, lactase deficiency, increased levels of anti-transglutaminase 2 antibodies and (iv) established osteoporosis with T-score <-2.5. A list of all exclusion criteria is presented in online supplementary table S1.

Screening
A screening visit was performed 2 weeks (minimum 8 days) prior to the baseline visit at week 8. At screening, eligibility criteria were checked and the study diagnosis was confirmed (see 'Study population' section), demographic and medical history data were recorded, ileocolonoscopy was undertaken, local and central laboratory assessments were performed, patient diary cards were issued and screening for drug-induced collagenous colitis was performed.

Randomisation and study treatment
During the open-label induction phase, all patients received once-daily budesonide (Budenofalk 3 mg capsules, Dr Falk Pharma GmbH) at a dose of 9 mg/day for 4 weeks, then 6 mg/day for 2 weeks, followed by alternate daily doses of 6 and 3 mg/day (mean 4.5 mg/day) for the final 2 weeks.

Patients who had achieved clinical remission at the end of the open-label phase were allocated to treatment groups for the double-blind phase based on a computer-generated randomisation list using randomly permuted blocks. During the double-blind phase, the active treatment group continued to receive once-daily budesonide 6 and 3 mg/day on alternate days (mean 4.5 mg/day). The placebo group received two placebo capsules and one placebo capsule on alternate days, administered once daily. After the final visit of the double-blind phase (month 12), there was a 2-week tapering-off period, during which patients in the active treatment group received 3 mg/day budesonide for 1 week followed by 3 mg/day budesonide every second day for 1 week. Patients in the placebo group received one placebo capsule on the corresponding days. Patients who remained in clinical remission at the end of the double-blind phase received no further study drug after the 2-week tapering-off period.

During the entire study period, loperamide or anti-inflammatory drugs, such as oral, rectal or intravenous corticosteroids, and immunosuppressants such as azathioprine, 6-mercaptopurine, methotrexate, cyclosporine or anti-TNF-α were not permitted.

Prophylactic treatment of osteoporosis, with daily administration of calcium and vitamin D3, was strongly recommended and under the responsibility of the investigator.

Study endpoints
The primary endpoint was the proportion of patients remaining in clinical remission during the 12-month double-blind phase, with remission defined as a mean of <3 stools/day, including a mean of <1 watery stool/day over 1 week. The main secondary endpoints during the double-label phase included health-related quality of life using the Short Health Scale (SHS)[13] and the Psychological General Well-Being Index (PGWBI).[14] Further secondary endpoints during the double-blind phase were achievement of histological remission or histological improvement.

Endoscopy and histology
A complete ileocolonoscopy was performed at screening in undiagnosed patients or patients with clinical relapse diagnosed with collagenous colitis >12 months previously, with an optional endoscopic follow-up at the end of the double-blind phase. At ileocolonoscopy, biopsies were obtained from the terminal ileum; caecum; the ascending, transverse, descending and sigmoid colon and the rectum. Biopsy specimens were fixed in 10% formalin and embedded in paraffin. Well-oriented sections in which at least three adjacent crypts were cut in their vertical plane were used to evaluate (i) the thickness of the subepithelial collagen layer, (ii) the inflammation of the lamina propria (semiquantitative score 0–3), (iii) the number of intraepithelial lymphocytes per 100 epithelial cells in the surface epithelium and (iv) the presence of degeneration/detachment of the surface epithelium. All biopsies were analysed centrally in blinded fashion by a single pathologist.

Clinical outcomes
At each visit during the open-label and double-blind phases, the number of watery/soft/formed stools in the preceding week was recorded, based on patient diary cards, which were to be completed on a daily basis. Quality of life was assessed by the SHS[13 15] and PGWBI[14] instruments.

Safety
At each of the eight study visits throughout the whole trial, adverse events (clinical and laboratory) were recorded. Laboratory tests considered safety parameters reflecting a glucocorticoid effect (eg, serum fasting glucose, sodium, potassium). Tolerability was assessed by the patient and the physician at the end of the open-label phase as well as at the end of the double-blind phase (very good, good, satisfactory, poor).

Statistical analyses
The study was performed using a two-stage group sequential adaptive design with possible sample size adjustment after a prespecified interim analysis, conducted by an independent data monitoring committee. The interim analysis indicated that no sample size adjustment was required (see online supplementary appendix 2). Assuming rates of clinical remission of 60% in the budesonide group and 30% in the placebo group at the end of the 12-month double-blind phase, with a sample size of 86 in the intention-to-treat (ITT) analysis (34 patients up to the interim analysis, 52 patient subsequently), the study had 80% power to yield a statistically significant result (one-sided $\alpha=0.025$). In order to include the required number of patients for the double-blind phase, approximately 110 patients were to be treated in the open-label phase.

For hypothesis testing of the primary endpoint, the overall (experimentwise) type I error rate was one-sided $\alpha=0.025$. The rates of remission were compared between treatment groups in a group-sequential adaptive test design using the inverse normal method of combining the p values of normal approximation tests, and additionally by two-sided 95% RCIs. All other statistical tests (Wilcoxon signed-rank test, Fisher's exact test, t test) were performed two-sided with a significance level of $\alpha=0.05$ on an exploratory basis.

In a post hoc multivariate analysis, the predictive values of clinical parameters (ie, age, gender, smoking status, concomitant drugs, family history of IBD, mean number of stools/watery stools per day) at baseline and at randomisation on relapse in the double-blind phase were calculated using a logistic regression model. p Value-based stepwise variable selection was applied to identify the final model. Efficacy was analysed for the ITT population, comprising all randomised patients who received at least one dose of study medication, with a sensitivity analysis for the per-protocol (PP) population. Patients who did not meet eligibility criteria, provided no post-randomisation efficacy criteria, showed lack of compliance (<75% study

medication administration), received study medication for <300 days without early discontinuation or discontinued early due to adverse event without causal relationship with study drug were excluded from PP population. Safety analysis was performed descriptively for the safety population. Statistical testing of the primary endpoint was done via the ADDPLAN system (V.6.0.1, ADDPLAN GmbH, Köln, Germany). All other analyses were conducted using the SAS V.9.2 statistical package for Windows (SAS Institute, Cary, North Carolina, USA).

RESULTS
Study population
In total, 148 patients were screened, of whom 110 met the eligibility criteria and were recruited to the open-label phase. Of these, 92 patients had achieved remission during the open-label phase and were randomised for treatment in the double-blind phase (44 budesonide, 48 placebo), 43 of whom completed the 12-month study visit (32 budesonide, 11 placebo) (figure 2). Eighteen patients were excluded from the PP population, most frequently due to administration of prohibited concomitant medication, such that the PP population comprised 74 patients (33 budesonide, 41 placebo) (figure 2). Thirty-six patients at the end of the double-blind phase (28 budesonide, 8 placebo) entered the follow-up phase.

The baseline demographic and clinical characteristics of the ITT population for the double-blind phase, including previous maintenance treatment, were similar between groups (table 1).

Open-label phase
The proportion of patients in clinical remission at week 4, week 8 and the final visit (last observation carried forward (LOCF)) of the open-label phase was 80.0% (88/110), 77.3% (85/110) and 84.5% (93/110), respectively (ITT population). The median time to remission was 10.5 days (95% CI (9.0 to 14.0 days)). The mean (SD) number of stools per day was 5.4 (2.2) in the week prior to baseline, compared with 1.9 (0.9) at the final visit

(LOCF). The mean (SD) number of watery stools per day decreased from 4.2 (2.5) to 0.2 (0.8) over the same period.

Median IQR scores for the SHS Questionnaire at baseline and the final visit (LOCF) improved for each dimension, with the largest reductions observed for the symptom burden and social function scales (figure 3A, left). The median (IQR) global PGWBI score improved from 63.6 (53.6–74.5) to 80.0 (72.7–87.3) (figure 3A, right).

Double-blind phase
Clinical efficacy
The primary endpoint, proportion of patients remaining in clinical remission during the 12-month double-blind phase, occurred in 61.4% of patients (27/44) in the budesonide group versus 16.7% of patients (8/48) in the placebo group (ITT population). The treatment difference was 44.5% in favour of budesonide (95% CI (26.9% to 62.7%), p<0.001) (figure 4). The between-group difference in the primary endpoint remained significant when the analysis was repeated in the PP population: 63.6% of patients (21/33) in the budesonide group versus 19.5% of patients (8/41) in the placebo arm remained in clinical remission, representing a treatment difference of 44.1% (95% CI (23.7% to 64.5%), p<0.001).

There was a high rate of relapse in the first 100 days of the double-blind phase in the placebo group (figure 5A). For relapsing patients, the median time to relapse was 28 days (IQR (19–70)) in the placebo group (n=25) and median 48 days (IQR (9–91)) for the budesonide group (n=6). The mean (SD) number of stools per day in the budesonide group was 1.7 (0.6) at the start of the double-blind phase compared with 2.1 (1.4) at the final visit (LOCF). For the placebo group, the corresponding numbers were 1.8 (0.9) and 3.8 (2.5). For watery stools, the mean (SD) number was 0.1 (0.2) at baseline and 0.7 (1.6) at last visit (LOCF) in the budesonide group, compared with 0.2 (1.0) and 2.7 (2.9) in the placebo group.

Figure 2 Patient disposition. ITT, intent-to-treat; PP, per-protocol.
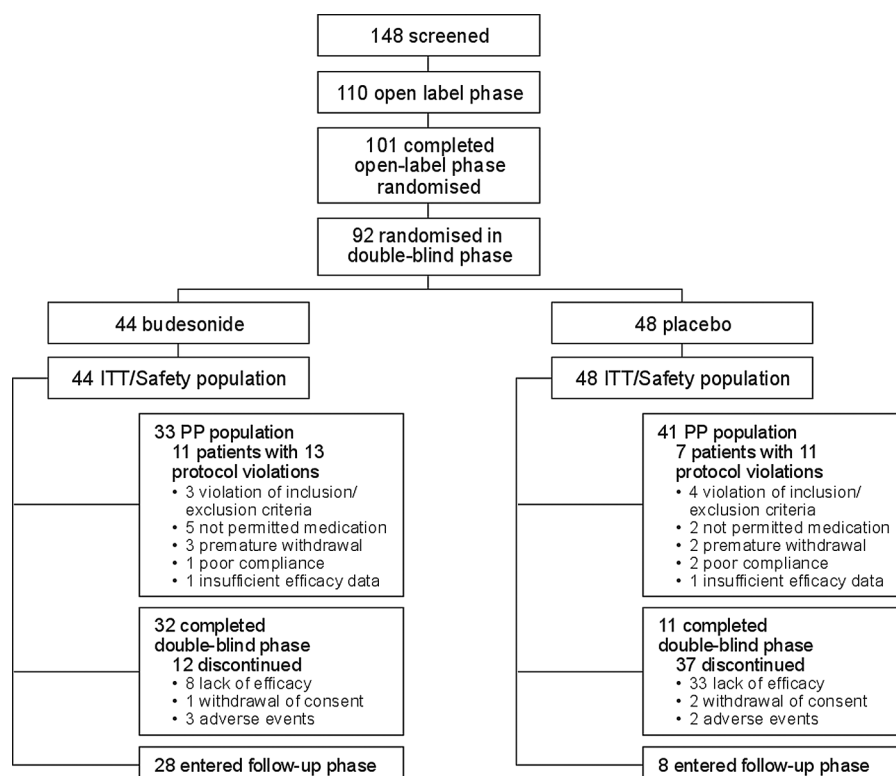
Table 1 Baseline demographic and clinical characteristics at randomisation into the double-blind phase

	Budesonide (n=44)	Placebo (n=48)	p Value*
Gender, n (%)			0.151
Male	4 (9.1)	10 (20.8)	
Female	40 (90.9)	38 (79.2)	
Age (years), mean (SD)	56.7 (9.9)	60.8 (11.7)	0.079
Body mass index (kg/m^2), mean (SD)	26.0 (4.5)	24.6 (3.8)	0.104
Smoking habit, n (%)			0.081
Current	17 (38.6)	21 (43.8)	
Former	18 (40.9)	10 (20.8)	
Never	9 (20.5)	17 (35.4)	
Caffeine intake, n (%)	41 (93.2)	44 (91.7)	1.000
New diagnosis, n (%)	4 (9.1)	2 (4.2)	0.421
Time since diagnosis (years), median (IQR)	1.5 (0.2; 4.8)	0.4 (0.1; 3.7)	0.073
Duration of current symptoms (months), median (IQR)	3.4 (1.6; 10.5)	3.7 (1.5; 8.7)	0.656
<2	14 (31.8)	18 (37.5)	
2 to <6	14 (31.8)	13 (27.1)	
≥6 months	16 (36.4)	17 (35.4)	
Number of previous episodes, mean (SD)	1.9 (2.8)	1.2 (2.0)	0.223
Duration of last acute episode (months), median (IQR)	4.5 (2.0; 7.0)	5.0 (3.0; 11.0)	0.550
Duration of last remission phase (months), median (IQR)	9.0 (4.0; 15.0)	8.0 (2.5; 32.0)	0.962
Treatment of last acute episode, n (%)			
Budesonide	14 (31.8)	15 (31.3)	1.000
Antidiarrhoeals	8 (18.2)	5 (10.4)	0.373
Cholestyramine	9 (20.5)	0 (0.0)	0.001
Antibiotics	2 (4.5)	0 (0.0)	0.226
Bulking agents	0 (0.0)	1 (2.1)	1.000
Previous maintenance therapy, n (%)			
Budesonide	7 (15.9)	7 (14.5)	1.000
Cholestyramine	4 (9.1)	1 (2.1)	0.189
Antidiarrhoeals	2 (4.5)	0 (0.0)	0.226

*Univariate testing performed by Fisher tests, t tests and Wilcoxon tests (depending on the data structure).

Predictors of clinical relapse

A multivariate analysis of the association of clinical variables (i) at baseline (ie, during active disease) and (ii) at randomisation with risk of relapse in the double-blind phase was performed. Factors showing a significant association with relapse were increased age (OR 0.94; 95% CI (0.88 to 0.99); p=0.047), increased mean number of stools per day at randomisation (OR 6.4; 95% CI (1.59 to 25.89); p=0.009) and increased mean number of watery stools per day at baseline (OR 1.4; 95% CI (1.01 to 1.95); p=0.041).

Quality of life

Over the 12-month double-blind phase, there were only minor increases in SHS scores for the budesonide group, but very pronounced increase (ie, loss of quality of life) in the placebo arm, particularly for symptom burden and social function (figure 3B, left). When SHS scores in the budesonide group were analysed in the subpopulations of patients who did or did not remain in remission throughout the double-blind phase, it was apparent that the effect of budesonide was maintained in the patients in remission, but deteriorated markedly in patients who relapsed (figure 3B, right). On the PGWBI global score, there was a more pronounced decrease in quality of life in the placebo group than in the budesonide group during the double-blind phase: median (IQR) was 82.7 (68.2–89.1) at the first visit versus 69.1 (47.3–80.0) at the final visit (LOCF) in the placebo group, compared with 80.9 (74.5–86.4) vs 75.5 (56.8–82.7) in the budesonide group, including patients who did or did not remain in remission. The decrease was greater for placebo-treated patients than budesonide-treated patients for all PGWBI dimensions (see online supplementary table S2).

Follow-up phase

In total, 36 patients were in remission at the final visit of the double-blind phase and were eligible to enter the 6-month treatment-free follow-up phase. Of these, 82.1% (23/28 patients) formerly receiving budesonide and 12.5% (1/8 patients) formerly receiving placebo subsequently relapsed. Patients formerly receiving budesonide showed a progressive rate of relapse after study drug discontinuation (figure 5B). The median time to relapse during follow-up was 40 days (95% CI (27 to 57 days)) in patients treated with budesonide in the double-blind phase.

Safety evaluation

Open-label phase

During the 2 months of open-label treatment, adverse events were reported in 46.4% (51/110) of patients receiving a standard dose of budesonide. The rate of patients showing suspected adverse drug reactions (ie, a causal relationship between study medication and adverse event was at least a reasonable possibility) was 17.3% (19/110 patients). All suspected adverse drug reactions were non-serious.

Double-blind phase

During the 12 months of double-blind treatment, adverse events were reported in 70.5% (31/44) of patients on low-dose budesonide, and 50.0% (24/48) of patients on placebo (table 2A).
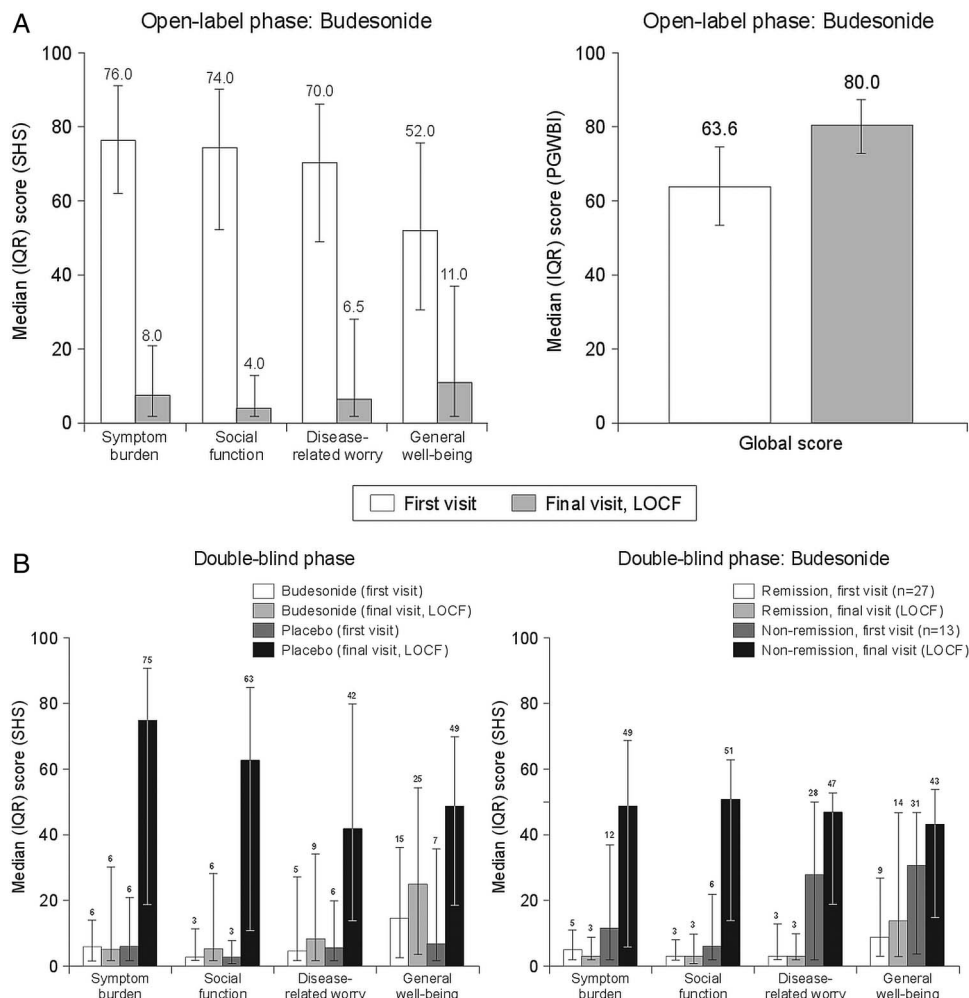
Figure 3 (A) Short Health Scale (SHS) dimension scores (left) and Psychological General Well-Being Index (PGWBI) global scores (right) for the open-label phase of the study during budesonide therapy. (B) SHS dimension scores in the double-blind phase of the study according to treatment group (left) and in the subpopulations of patients randomised to budesonide who did or did not remain in remission throughout the double-blind phase (right). Data are shown as median (IQRs) at the first visit and the last visit (last observation carried forward, LOCF) of each phase. The SHS Questionnaire uses 100 mm Visual Analogue Scales, with higher scores indicating lower quality of life. The PGWBI global score is standardised to a score between 0 and 100, with lower scores indicating lower quality of life.

The proportion of patients in the budesonide group showing suspected adverse drug reactions was 15.9% (7/44 patients), with all suspected adverse drug reactions being non-serious. The
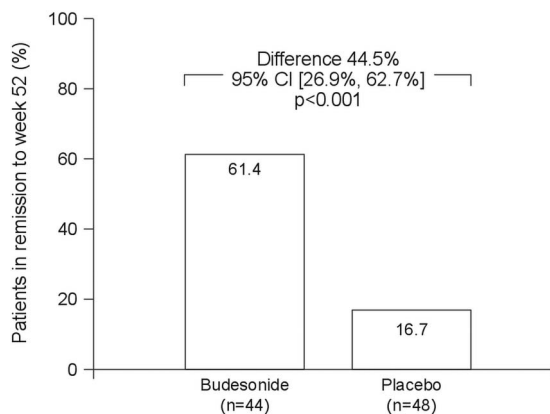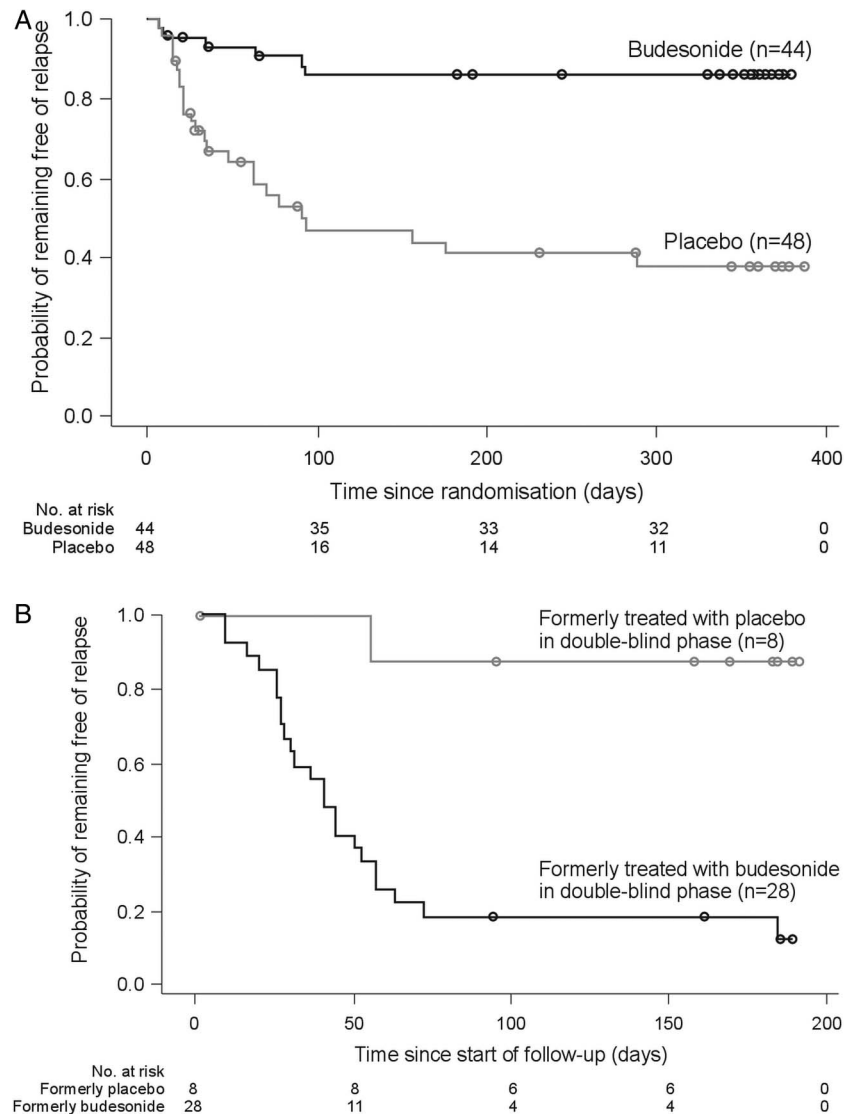

Figure 4 Proportion of patients remaining in clinical remission at the end of the 12-month double-blind phase in the intent-to-treat population. Remission was defined as a mean of <3 stools/day, including a mean of <1 watery stool/day.

majority of suspected adverse drug reactions were skin and subcutaneous disorders (table 2B).

It is noteworthy that double-blind treatment with budesonide was more than twice as long as treatment with placebo (291.2 (141.5) days vs 138.1 (125.1) days; mean (SD)).

Morning serum cortisol, measured precisely between 8:00 and 10:00, was available both at baseline and at final visit in 61.4% (27/44) of budesonide-treated patients and 37.5% (18/48) of placebo-treated patients. A shift from normal morning cortisol levels at baseline to below-normal at the final visit occurred in 3.7% (1/27) of budesonide patients and 5.6% (1/18) of placebo patients. There were no clinically relevant changes in serum fasting glucose, sodium or potassium. A clinically relevant increase in HbA1c was observed in two patients with diabetes in each treatment group (budesonide and placebo). There was no substantial increase in mean (SD) body weight: budesonide group 0.4 (3.4) kg, placebo group 0.1 (2.3) kg. None of the patients on budesonide or placebo gained more than 10% of weight during the entire course of treatment. Mean blood pressure values remained within the normal range: values at the baseline versus final visit were 135/81 mm Hg versus 136/83 mm Hg in the budesonide group, and 131/78 mm Hg vs 130/78 mm Hg in the placebo group.

Figure 5 Time to relapse during (A) double-blind treatment phase and (B) untreated follow-up phase (intent-to-treat population) (Kaplan–Meier estimates). Relapse was defined as a mean of ≥3 stools/day, including a mean of ≥1 watery stool/day. Circles represent censoring of patients who discontinued the study or completed their final study visit without relapse.

A

No. at risk
Budesonide 44   35   33   32   0
Placebo 48   16   14   11   0

B

No. at risk
Formerly placebo 8   8   6   6   0
Formerly budesonide 28   11   4   4   0

Withdrawal of study medication due to an adverse event during the double-blind phase occurred in four patients on low-dose budesonide versus seven patients on placebo. Tolerability of the study medication was mainly assessed by the investigators as very good or good (budesonide: 70.5% very good, 25.0% good; placebo: 62.5% very good, 22.0% good). The corresponding values based on patients' assessments were 75.0% and 20.5% for budesonide, and 62.5% and 25.0% for placebo.

DISCUSSION

This is the first randomised trial to assess low-dose budesonide therapy (mean 4.5 mg/day) for the maintenance of remission in collagenous colitis. The results showed that low-dose budesonide therapy maintained clinical remission for at least a year in 61.4% of patients, which was significantly higher than in placebo-treated patients (16.7%). Furthermore, the open-label phase of the study confirmed the high rate of clinical remission achieved with budesonide 9 mg/day, which has been reported elsewhere.[3–8] Indeed, half of all patients were in remission after only 10 days' treatment. Two previous randomised trials have evaluated the efficacy of oral budesonide in maintaining remission in patients with collagenous colitis.[5 7] Both of these studies used a dose of 6 mg/day and followed patients for 6 months, defining remission as three or fewer stools per day. Bonderup

et al[5] observed a remission rate of 76.5% at month 6 among a cohort of 17 patients treated with budesonide, remarkably similar to the rate of 73.9% reported by Miehlke and colleagues[7] in a group of 23 patients. However, comparisons between these trials and the current study should be regarded cautiously since different definitions of remission and relapse were used. We applied the Hjortswang Criteria[12] for disease activity in microscopic colitis, which takes into account not only the frequency of stools but also the consistency.

When introducing long-term therapy with budesonide, the main goal should be to find the lowest dose that maintains clinical remission while avoiding side effects. Given that the current trial used an average dose of 4.5 mg/day and followed patients for a year instead of 6 months, the remission rate of 61.4% observed here is encouraging. The need for long-term therapy in the majority of patients is reflected by the high rate of relapse (82.1%) observed when low-dose budesonide was discontinued after 1 year. A relapse rate of approximately 80% after cessation of budesonide treatment is a relatively consistent finding in randomised, controlled trials,[5 9] independent of whether high-dose induction or maintenance therapy was given. This indicates that these patients have a chronic active disease and that the long-term course cannot be altered by medical treatment. Interestingly, relapses occurred primarily within 3 months

Table 2 (A) Number (%) of patients with at least one adverse event by system organ class reported in the double-blind maintenance phase and (B) suspected adverse drug reactions (ie, side effects) by system organ class and preferred term reported in the open-label induction and in the double-blind maintenance phase

(A)

System organ class	Number (%) of patients with at least one adverse event in double-blind phase	
	Budesonide (n=44)	Placebo (n=48)
Cardiac disorders	1 (2.3)	0 (0)
Ear and labyrinth disorders	0 (0)	1 (2.1)
Eye disorders	2 (4.5)	0 (0)
Gastrointestinal disorders	4 (9.1)	11 (22.9)
General disorders and administration site conditions	1 (2.3)	2 (4.2)
Hepatobiliary disorders	1 (2.3)	0 (0)
Infections and infestations	12 (27.3)	9 (18.8)
Injury, poisoning and procedural complications	4 (9.1)	1 (2.1)
Investigations	3 (6.8)	0 (0)
Metabolism and nutrition disorders	0 (0)	1 (2.1)
Musculoskeletal and connective tissue disorders	13 (29.5)	4 (8.3)
Arthralgia	2 (4.5)	3 (6.3)
Arthritis	2 (4.5)	0 (0)
Back pain	2 (4.5)	0 (0)
Muscle spasms	2 (4.5)	0 (0)
Other	7 (5.9)	1 (2.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (4.5)	0 (0)
Nervous system disorders	3 (6.8)	0 (0)
Psychiatric disorders	3 (6.8)	2 (4.2)
Reproductive system and breast disorders	1 (2.3)	0 (0)
Respiratory, thoracic and mediastinal disorders	3 (6.8)	2 (4.2)
Skin and subcutaneous tissue disorders	7 (15.9)	4 (8.3)
Hyperhidrosis	2 (4.5)	0 (0)
Eczema	1 (2.3)	1 (2.1)
Other	6 (13.6)	3 (6.3)
Surgical and medical procedures	2 (4.5)	1 (2.1)
Vascular disorders	2 (4.5)	1 (2.1)

(B)

System organ class Preferred term	Number of suspected adverse drug reactions related to budesonide	
	8-week open-label induction phase	52-week double-blind maintenance phase
Cardiac disorders		
Palpitations	1	0
Ear and labyrinth disorders		
Vertigo	1	0
Eye disorders		
Eye swelling	1	0
Glaucoma	0	1
Gastrointestinal disorders		
Abdominal discomfort	1	0
Constipation	3	0
Flatulence	1	0
Nausea	0	1

Table 2 Continued

(B)

System organ class Preferred term	Number of suspected adverse drug reactions related to budesonide	
	8-week open-label induction phase	52-week double-blind maintenance phase
General disorders and administration site conditions		
Sensation of pressure	1	0
Infections and infestations		
Vulvovaginal mycotic infection	0	1
Investigations		
Alanine aminotransferase increased	0	1
Aspartate aminotransferase increased	0	1
Urinalysis abnormal	1	0
Weight increased	0	2
Metabolism and nutrition disorders		
Diabetes mellitus	2	0
Increased appetite	1	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	3	1
Nervous system disorders		
Dizziness	1	0
Headache	1	0
Psychiatric disorders		
Depression	1	0
Mood swings	1	0
Sleep disorder	1	0
Skin and subcutaneous tissue disorders		
Ecchymosis	2	1
Erythema	2	0
Subcutaneous haemorrhage	0	1
Hyperhidrosis	0	1
Increased tendency to bruise	0	1
Night sweats	1	1
Pruritus	2	0
Skin haemorrhage	1	0
Swelling face	1	1
Vascular disorders		
Hypertension	2	1
Total	32	15

irrespective of whether patients received low-dose budesonide, placebo or stopped treatment after 1 year. If patients remained in clinical remission beyond this critical time point, there was a high likelihood that remission would be sustained.

Multivariate analysis indicated that the risk of clinical relapse was higher in patients with more severe symptoms at baseline, that is, a high number of watery stools per day and in younger patients. Furthermore, a higher number of stools per day after induction treatment with budesonide (prior to randomisation) were associated with a greater risk for relapse. This is in line with the observation that budesonide improves the consistency of the stool prior to a decrease in total stool numbers. These results are consistent with a recent multivariate analysis by Miehlke et al[11] based on pooled data from 123 patients in four randomised controlled trials that reported clinical remission after budesonide withdrawal. They found that a baseline stool frequency of more than five per day was associated with almost

a fourfold increase in the risk of relapse after stopping budesonide therapy. Interestingly, we found that the risk of relapse decreased significantly with increasing age (p<0.05) or, in other words, younger patients showed a higher risk of relapse. This is one of the first studies to apply the criteria for clinical remission proposed by Hjortswang and colleagues,[12] that is, a mean of <3 stools/day, including a mean of <1 watery stool/day within the previous 7 days. A careful analysis of quality of life data led to this definition of remission based on both stool frequency and stool consistency[9][12] which are conveniently documented in everyday practice. Stool consistency, rather than frequency of stools, appears to be the main determinant of quality of life impairment in collagenous colitis,[2] and as such is a highly relevant measure of treatment efficacy from the patient's perspective. A patient with fewer than three stools a day may still be a suitable candidate for intervention if the stools are watery, leading to urgency or faecal incontinence and thereby limiting quality of life.

Clinical status was closely mirrored by health-related quality of life measurements. Achievement of clinical remission during the open-label phase was accompanied by a very pronounced improvement in quality of life, particularly in relation to symptom burden and social function. This improvement, importantly, was largely sustained throughout the 1-year maintenance therapy phase.

The safety analysis did not raise any new concerns for this well-known topically acting glucocorticoid. It is noteworthy that during the whole study there were no serious adverse drug reactions due to budesonide. Interestingly, intake of a low dose of budesonide (mean 4.5 mg/day) over 1 year did not result in more frequent suppression of serum morning cortisol than treatment with placebo. It is still prudent to monitor closely any patient on long-term budesonide since synthetic glucocorticoids may have effects on various organ systems and do not only affect skin and subcutaneous tissues.

Some aspects of the study design merit consideration. The trial used a rigorous double-blind methodology and was adequately powered for the primary endpoint. Endoscopy at the final visit of the double-blind phase was optional, but histological samples were available for only 16 budesonide patients and eight placebo patients at this time point. Thus, regretfully, a meaningful assessment of histological remission or improvement was not possible. Lastly, recruitment to the study took place over a period of approximately 4 years, although additional centres in additional countries were initiated.

In conclusion, budesonide at a mean dose of 4.5 mg/day is an effective and safe long-term maintenance therapy in collagenous colitis, which preserves health-related quality of life. This dosage regimen was not associated with a safety concern. Ongoing treatment with low-dose budesonide to maintain clinical remission in collagenous colitis may be beneficial in view of the high relapse rate after budesonide discontinuation.

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Patient consent Obtained.

Ethics approval The National Ethics Committee in each participating country.

Provenance and peer review Not commissioned; externally peer reviewed.

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Appendix 1

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Appendix 2. Interim analysis

The study was conducted using an adaptive two-stage group sequential test design within the Δ-class of critical values according to Wang and Tsiatis (w1). The planned information rates were 0.4 and 1, i.e. the interim analysis was intended to take place after observation of 40% of the originally planned number of patients. These information rates fix the weights for combining the p-values using the weighted inverse normal method (w2). The critical values of the group sequential test design were calculated for the standardized (cumulative) test statistic for the design with boundary shape parameter Δ = 0.0, i.e. O'Brien/Fleming type design.

Stage	Critical value	Sign. level (one-sided)
1	3.110	0.0009
2 (final)	1.967	0.0246

The interim analysis was performed by an Independent Data Monitoring Committee (IDMC) after observation of 34 patients who were evaluable in the intention-to-treat (ITT) analysis. If the study continued without adaptation, the final analysis was to be performed after observation of a further 52 ITT evaluable patients.

From the 34 patients in the interim analysis, 16 patients (47.1%) were in the budesonide group and 18 patients (52.9%) in the placebo group. The proportion of patients in remission over 52 weeks was 56.3% (9/16 patients) in the budesonide group and 11.1% (2/18 patients) in the placebo group. The treatment difference with respect to remission over 52 weeks was 45.1% in favor of budesonide (95% repeated CI: [-5.0%, 78.2%]). The hypothesis test for treatment difference yielded a one-sided observed p-value of 0.0025 (overall one-sided p-value 0.0389) with a corresponding inverse test statistic of 2.808. This was below the pre-defined critical

value of 3.110 for the interim analysis. As a consequence the null hypothesis could not be rejected as the observed inverse test statistic did not exceed the critical level.

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Supplementary Table 1. Exclusion criteria

Other significant abnormalities at ileocolonoscopy that could have caused diarrhoea, with the exception of colonic diverticulosis and polyps <2 cm
An infectious cause of diarrhoea
Untreated active coeliac disease
Clinical suspicion of drug-induced collagenous colitis
Any severe concomitant cardiovascular, renal, endocrine, or psychiatric disorder
Abnormal hepatic function (alanine transaminase [ALT] or aspartate aminotransferase [AST]> 2.5 x upper limit of normal), liver cirrhosis, or portal hypertension
Local intestinal infection
Radiation therapy towards the abdominal or pelvic region
Diabetes mellitus, infection, glaucoma, tuberculosis, peptic ulcer disease, or hypertension if careful medical monitoring is not ensured
Established cataract
Known hereditary problems of galactose or fructose intolerance, glucose-galactose malabsorption, sucrase-isomaltase insufficiency, Lapp lactase deficiency, or congenital lactase deficiency
Established osteoporosis with T-score below -2.5
Pregnancy or lactation
History of cancer in the last five years
History of significant bowel resection
Immunomodulator therapy (azathioprine, 6-mercaptopurine, or methotrexate) in the last three months
Treatment with oral, rectal, or intravenous corticosteroids including budesonide in the last month
Known intolerance/hypersensitivity to study drug or drugs of similar chemical structure or pharmacological profile

| Patients who were unable to adhere to the study visit schedule and other protocol requirements according to the judgment of the investigator |
| Participation in another clinical trial within the last 30 days, except participants in the BUC-60/COC study*, simultaneous participation in another clinical trial, or previous participation in this trial |

*This did not apply to patients who participated in study BUC-60/COC in the event of non-response during double-blind treatment or relapse during the follow-up period, or to patients who completed the study BUC-60/COC according to protocol. The latter, however could enter the current study at the screening visit.

Supplementary Table 2. Psychological General Well Being Index (PGWBI) global score and dimension scores for the double-blind phase of the study. Data are shown as median (IQR) values at the first visit and the last visit (last observation carried forward [LOCF]) of each phase. The PGWBI scores are standardized to a score between 0 and 100, with lower scores indicating lower quality of life.

	Budesonide		Placebo	
	First visit	Final visit	First visit	Final visit
Global score	80.9 (n=35) (74.5, 86.4)	75.5 (n=40) (56.8, 82.7)	82.7 (n=43) (68.2, 89.1)	69.1 (n=43) (47.3, 80.0)
Anxiety	88.0 (n=36) (74.0, 90.0)	78.0 (n=40) (66.0, 88.0)	88.0 (n=43) (72.0, 96.0)	72.0 (n=44) (54.0, 80.0)
Depressed mood	93.3 (n=42) (80.0, 100.0)	100.0 (n=42) (73.3, 100.0)	100.0 (n=44) (80.0, 100.0)	86.7 (n=45) (60.0, 93.3)
Positive well-being	65.0 (n=39) (55.0, 75.0)	60.0 (n=43) (40.0, 75.0)	65.0 (n=46) (55.0, 75.0)	50.0 (n=43) (35.0, 65.0)
Self-control	86.7 (n=39) (73.3, 93.3)	86.7 (n=42) (66.7, 93.3)	90.0 (n=44) (80.0, 100.0)	80.0 (n=43) (60.0, 93.3)
General health	86.7 (n=38) (73.3, 93.3)	73.3 (n=43) (60.0, 93.3)	86.7 (n=47) (80.0, 100.0)	60.0 (n=43) (46.7, 80.0)
Vitality	70.0 (n=39) (55.0, 80.0)	65.0 (n=42) (45.0, 75.0)	72.5 (n=44) (55.0, 82.5)	55.0 (n=44) (35.0, 67.5)