Journal of Crohn's and Colitis (2014) 8, 970–980

Available online at www.sciencedirect.com

ScienceDirect

Once versus three times daily dosing of oral budesonide for active Crohn's disease: A double-blind, double-dummy, randomised trial☆,☆☆

Axel Dignass[a,*], Simeon Stoynov[b], Andrey E. Dorofeyev[c], Galina A. Grigorieva[d,1], Eva Tomsová[e], István Altorjay[f], Daniel Tuculanu[g], Ivan Bunganič[h], Juris Pokrotnieks[i], Limas Kupčinskas[j], Karin Dilger[k], Roland Greinwald[k], Ralph Mueller[k], on behalf of the International Budenofalk® Study Group[2]

[a] *Agaplesion Markus Krankenhaus, 1st Dept. of Medicine, Goethe-University, 60431 Frankfurt am Main, Germany*
[b] *University General Hospital for Active Treatment "Tzaritza Yoanna", Clinic of Gastroenterology, 1527 Sofia, Bulgaria*
[c] *Donetsk City Clinical Hospital No. 3, Gastroenterology Dept., M. Gorkyy Donetsk National Medical University, Donetsk, 83003 Donetsk, Ukraine*
[d] *I.M. Sechenov First Moscow Medical State University, Conservative Coloproctology Dept., 119992 Moscow, Russia*
[e] *District Hospital Mladá Boleslav, 293 01 Mladá Boleslav II, Czech Republic*
[f] *DEOEC, II. sz. Belgyógyászati Klinika, 4012 Debrecen, Hungary*
[g] *Medical Center Tuculanu, 300158 Timisoara, Romania*
[h] *Gastro I. s.r.o., Gastroenterology Dept., 080 01 Prešov, Slovakia*
[i] *Paula Stradina University Hospital, Center of Gastroenterology, 1002 Riga, Latvia*
[j] *Lithuanian University of Health Sciences, Dept. of Gastroenterology, 50009 Kaunas, Lithuania*
[k] *Dr. Falk Pharma GmbH, Clinical Research & Development Dept., 79108 Freiburg, Germany*

Received 2 September 2013; received in revised form 27 January 2014; accepted 27 January 2014

Abbreviations: 6-MP, 6-mercaptopurine; AE, adverse event; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; ECCO, European Crohn's and Colitis Organisation; GIQLI, Gastrointestinal Quality of Life Index; ITT, intention-to-treat; LOCF, last observation carried forward; OD, once daily; PGA, Physician's Global Assessment; PP, per protocol; SES-CD, Simple Endoscopic Score for Crohn's Disease; SHS, Short Health Scale; TID, three times a day.

☆ EudraCT number 2008-006957-42 (https://eudract.emea.europa.eu/).

☆☆ ClinicalTrials.gov identifier NCT01086553 (http://clinicaltrials.gov/).

* Corresponding author at: Agaplesion Markus Krankenhaus, 1st Dept. of Medicine, Goethe-University, Wilhelm-Epstein-Str. 4, 60431 Frankfurt/Main, Germany. Tel.: +49 69 9533 2201; fax: +49 69 9533 2291.

E-mail addresses: axel.dignass@fdk.info (A. Dignass), simeon_stoinov@abv.bg (S. Stoynov), dorofeyev@med.finfort.com (A.E. Dorofeyev), evatomsova@seznam.cz (E. Tomsová), altorjay@med.unideb.hu (I. Altorjay), danieltuculanu@yahoo.com (D. Tuculanu), bunganic.ivan15@zoznam.sk (I. Bunganič), pokrot@latnet.lv (J. Pokrotnieks), likup@takas.lt (L. Kupčinskas), dilger@drfalkpharma.de (K. Dilger), greinwald@drfalkpharma.de (R. Greinwald), mueller@drfalkpharma.de (R. Mueller).

[1] Prof. Galina A. Grigorieva passed away in 2013.

[2] See Appendix A.

http://dx.doi.org/10.1016/j.crohns.2014.01.021

KEYWORDS
Budesonide;
Crohn's disease;
Clinical remission;
Adherence;
Dosing

Abstract

Background: Oral budesonide 9 mg/day represents first-line treatment of mild-to-moderately active ileocolonic Crohn's disease. However, there is no precise recommendation for budesonide dosing due to lack of comparative data. A once-daily (OD) 9 mg dose may improve adherence and thereby efficacy.
Methods: An eight-week, double-blind, double-dummy randomised trial compared budesonide 9 mg OD versus 3 mg three-times daily (TID) in patients with mild-to-moderately active ileocolonic Crohn's disease. Primary endpoint was clinical remission defined as CDAI <150 at week 8 (last observation carried forward).
Results: The final intent-to-treat population comprised 471 patients (238 [9 mg OD], 233 [3 mg TID]). The confirmatory population for the primary endpoint analysis was the interim per protocol population (n = 377; 188 [9 mg OD], 189 [3 mg TID]), in which the primary endpoint was statistically non-inferior with budesonide 9 mg OD versus 3 mg TID. Clinical remission was achieved in 71.3% versus 75.1%, a difference of −3.9% (95% CI [−14.6%; 6.4%]; p = 0.020 for non-inferiority). The mean (SD) time to remission was 21.9 (13.8) days versus 21.4 (14.6) days with budesonide 9 mg OD versus 3 mg TID, respectively. In a subpopulation of 122 patients with baseline SES-CD ulcer score ≥1, complete mucosal healing occurred in 32.8% (21/64) on 9 mg OD and 41.4% (24/58) on 3 mg TID; deep remission (mucosal healing and clinical remission) was observed in 26.6% (17/64) and 32.8% (19/58) of patients, respectively. Treatment-emergent suspected adverse drug reactions were reported in 4.6% of 9 mg OD and 4.7% of 3 mg TID patients.
Conclusions: Budesonide at the recommended dose of 9 mg/day can be administered OD without impaired efficacy and safety compared to 3 mg TID dosing in mild-to-moderately active Crohn's disease.

1. Introduction

Systemic glucocorticosteroids are highly effective for inducing remission in patients with active Crohn's disease, but are associated with a high rate of potentially serious side effects.[1] 'Second generation' topical glucocorticosteroids such as budesonide have been developed which preserve efficacy but have lower systemic toxicity and a more favourable safety profile.[2,3] Randomised clinical studies have shown that budesonide therapy leads to remission in 50–60% of patients with active ileocolonic Crohn's Disease.[4–8] The European Crohn's and Colitis Organisation (ECCO) recommends oral treatment with budesonide at a dose of 9 mg/day as first-line treatment of mild-to-moderately active, ileocolonic Crohn's Disease.[9] However, there is no clear recommendation for a precise regimen of budesonide intake, 9 mg/day once daily (OD) or 3 mg three times a day (TID), due to lack of comparative data. It is estimated that 30–45% of patients with inflammatory bowel disease are non-adherent to oral medication schedules[10] and although the causes of non-adherence to medication in inflammatory bowel disease are complex,[10–12] multiple daily dosing is known to discourage adherence.[13]

In a recent double-blind, double-dummy trial, oral budesonide administered either as 9 mg OD or as 3 mg TID was at least as effective as high-dose oral mesalazine (4.5 g/day) in moderately active Crohn's disease.[8] In an exploratory analysis, the primary endpoint of clinical remission was found to be similar with OD or TID budesonide dosing. The objective of the current eight-week, double-blind, double-dummy randomised trial was to compare the efficacy and tolerability of budesonide 9 mg OD versus 3 mg TID in patients with mild-to-moderately active ileocolonic Crohn's disease in a confirmatory manner. In addition to the primary efficacy endpoint of clinical remission, achievement of mucosal healing in each treatment group was also examined.

2. Methods

2.1. Study design and conduct

This was a double-blind, double-dummy, randomised, multicentre, Phase III study in which patients with mild-to-moderately active ileocolonic Crohn's disease received budesonide at a single daily dose of 9 mg or three daily doses of 3 mg. After screening, an eight-week treatment phase was followed by a two-week follow-up period. The study was planned as a three-stage adaptive design with possible sample size adjustment after pre-specified interim analyses. The first patient visit was in November 2009 with the last visit of the treatment phase in April 2012.

The study was undertaken at 50 gastroenterology centres in Bulgaria, Czech Republic, Germany, Hungary, Latvia, Lithuania, Romania, Russia, Slovakia, and Ukraine. It was conducted in compliance with Good Clinical Practice and the Declaration of Helsinki following approval from the relevant independent ethics committee at each centre. Written informed consent was obtained from all participants.

2.2. Patients

Adult patients (18–75 years) with mild-to-moderately active Crohn's disease (defined as Crohn's Disease Activity Index [CDAI] scores >200 and <400) localised in the terminal ileum, coecum, ascending colon or ileocolitis were eligible, if (i) they had experienced symptoms of Crohn's disease for at least three months, (ii) diagnosis had been confirmed by endoscopy and histology, or by endoscopy and radiology. If endoscopy had been performed ≥12 months previously, then clinical signs and behaviour according to the Montreal classification[14] were to be unchanged compared to former episodes. Key exclusion criteria were known Crohn's lesions in the upper gastrointestinal tract (defined as up to and including the jejunum) or rectum with current symptoms; septic complications; evidence of infectious diarrhoea (i.e. pathogenic bacteria in stool culture); the presence of abscesses, perforation, or active fistulas; ileostomy or colostomy; resection of more than 50 cm of the ileum; bowel surgery within the last three months; indication for immediate surgery; clinical signs of stricturing disease; subileus within the last six months or suspicion of ileus, subileus or corresponding symptoms, abnormal hepatic or renal function; any severe concomitant cardiovascular, renal, endocrine, or psychiatric disorder; a history of metastatic cancer in the last five years; treatment with immunosuppressants or anti-cancer drugs, e.g. thiopurines, methotrexate, tacrolimus, cyclophosphamide or cyclosporine within the last three months (treatment with thiopurines was permitted if used for maintenance of remission only at an unchanged dose within the three months prior to the baseline visit and during the study); treatment with ketoconazole or other CYP3A inhibitors, or with anti-TNF-α therapy, within three months prior to the baseline visit; treatment with conventional or inhaled steroids, or with oral budesonide >6 mg/day, within two weeks prior to the baseline visit; steroid-refractory disease; treatment of Crohn's disease with oral antibiotics or non-steroidal anti-inflammatory drugs within two weeks prior to the baseline visit (≤350 mg/day or short-term acetylsalicylic acid was permitted).

2.3. Randomisation and intervention

Patients who met the enrolment criteria at the baseline visit were included into the double-blind treatment phase and were given a 4-digit randomisation number derived from a computer-generated list that used randomly permuted blocks (RANCODE software, IDV Gauting, Germany). The central randomisation list was held by staff at the contract research organisation who were not involved in the study conduct. Randomisation numbers were assigned consecutively in each centre in the order of patients' inclusion into the double-blind treatment phase, i.e. randomisation was stratified by centre. Patients received the study medication marked with their randomisation number. The first dose of study drug was to be taken on the day after randomisation. Patients were randomised in a 1:1 ratio to receive a 9 mg sachet of budesonide granules (Budenofalk® Uno 9 mg granules, Dr Falk Pharma GmbH, Freiburg, Germany) OD in the morning with one placebo capsule TID, or one sachet of placebo granules OD in the morning and 3 mg capsules of budesonide (Budenofalk® 3 mg capsules, Dr Falk Pharma GmbH, Freiburg, Germany) TID. The appearance and size of the sachets and capsules of budesonide or placebo were identical to preserve the double-dummy nature of the trial.

2.4. Evaluation

Study visits took place at baseline and at weeks 2, 4, 6 and 8, with a follow-up visit two weeks after the end of the study. Study drug intake was determined by counting returned unused medication. Each patient also recorded study drug intake in a daily diary. CDAI score was recorded at each visit during the treatment phase.[15,16] Data for three of these variables were derived from patient diaries from the preceding seven days. If fewer than five days of documentation were available, CDAI was regarded as invalid. Endoscopy and determination of the Simple Endoscopic Score for Crohn's Disease (SES-CD)[17] were optionally assessed at baseline and week 8. The total SES-CD score was calculated as the sum of five bowel segment scores (rectum, left colon, transverse colon, right colon and ileum), ranging from 0 to 56, with higher scores indicating more severe disease. The Short Health Scale (SHS) was administered at each study visit. SHS is a simplified four-item questionnaire based on four questions relating to symptom burden, social function, disease-related worry and general well-being, scored by the patient on visual analogue scales.[18,19] Higher SHS values indicate higher burden. The Gastrointestinal Quality of Life Index (GIQLI) was assessed at baseline, week 4 and week 8. The global GIQLI score ranges from 0 to 144.[20,21] Higher GIQLI values indicate better quality of life. Physician's Global Assessment (PGA)[22] was undertaken at the end of treatment or last study visit. Using the six-point PGA scale, physicians classified the change in the patient's condition as complete relief of symptoms, marked improvement of symptoms, moderate improvement of symptoms, slight improvement of symptoms, no change in symptoms or worsening of symptoms. Central laboratory evaluations were performed at all study visits, including haematology, serum chemistry, kidney and liver function tests, and C-reactive protein (CRP). Morning serum cortisol was measured by the central laboratory on a Roche Modular E170 Analyzer using an electrochemiluminescence immunoassay (Elecsys Cortisol, Roche Diagnostics, Mannheim, Germany) at baseline and at week 8/withdrawal visit. At these visits, blood samples were to be drawn between 8 a.m. and 9 a.m., and at the same time for a particular patient whenever possible. Adverse events (AEs) were monitored at each study visit. Tolerability was classified as 'very good', 'good', 'satisfactory' or 'poor' by investigator and patient independently at week 8 or the last study visit.

2.5. Study endpoints

The primary endpoint was the rate of clinical remission, defined as CDAI <150 at week 8 using the last observation carried forward (LOCF) method. In the event of discontinuation due to lack of efficacy or if no follow-up CDAI was documented after baseline, 'non-remission' was assumed. Secondary efficacy variables included the rate of clinical remission at weeks 2, 4, 6 and 8; the time to clinical remission; the change in CDAI score from baseline to weeks 2, 4, 6 and 8 (LOCF); complete mucosal healing at week 8 (LOCF), defined as an SES-CD score of 0 on the subscore for size of ulcer in all bowel segments ($SES\text{-}CD_{ulcer}$)[23], change in

quality of life as assessed by the change in SHS score and GIQLI score from baseline to week 8 (LOCF); and therapeutic success (defined as complete relief of symptoms or marked improvement of symptoms on the PGA scale from baseline to week 8 [LOCF]) or therapeutic benefit (defined as any improvement on the PGA scale from baseline to week 8 [LOCF]). As a *post-hoc* analysis the rate of deep remission at week 8 (LOCF) was assessed, defined as complete mucosal healing with clinical remission. Safety variables included AEs, vital signs, laboratory parameters (including morning serum cortisol), and assessment of tolerability by the investigator and the patient ('very good', 'good', 'satisfactory' or 'poor'). AEs were reported if they first occurred, or were pre-existing but worsened, after the start of study drug treatment and during the treatment period ('treatment-emergent' AEs).

2.6. Statistical analysis

The study used a group-sequential adaptive design, whereby pre-planned interim analyses were successively undertaken after observation of 201, 301 and 401 intention-to-treat (ITT) patients. Following the third interim analysis, the Independent Data Monitoring Committee recommended that no further patients be recruited since non-inferiority of budesonide 9 mg OD versus 3 mg TID was shown to be confirmed. Patients already recruited at the time of the decision continued in the study, such that the final study population included 471 patients. All patients and staff involved in the conduct and final analysis of the study, including the sponsor, remained blinded to the results of the interim analyses. Access to unblinded data was restricted to the members of the Independent Data Monitoring Committee and to the unblinded statistician of the contract research organisation who was external to the sponsor and was not involved in the study conduct or the final analysis.

Confirmatory analysis of the primary endpoint was based on the interim population, with a sensitivity analysis based on the final study population. The primary analysis for confirmatory testing was based on the per protocol (PP) population, as the more conservative approach, with an exploratory analysis in the ITT population. A non-inferiority test with a one-sided significance level of $\alpha = 0.025$ and a non-inferiority margin of -15% was used, based on the inverse normal method of combining the p-values of the shifted asymptotic χ^2 test for comparing two rates and maximum likelihood estimation for the unknown parameters.[24] The confidence interval (CI) limit of 15% was selected based on an expected remission rate of 55% in both the budesonide 9 mg OD group and the 3 mg TID group, well above the reported placebo remission rate of 25% [25,26] assuring a clinically relevant effect superior to a putative placebo and no clinically relevant inferiority to the control group. A two-sample *t*-test was used to compare CDAI change from baseline to week 8 (LOCF). Changes from baseline in total SES-CD score, and in SHS and GIQLI scores, were compared between treatment groups using the two-sided Wilcoxon test for independent samples. Mucosal healing, deep remission, therapeutic success, and therapeutic benefit were compared between treatment groups using Chi-Square tests. Fisher's exact test was used when the expected cell counts were less than five. Changes from baseline in cortisol or electrolytes were compared between treatment groups using the Wilcoxon two-sample test. Baseline and week 8 (LOCF) values of these parameters were compared within each treatment group using the Wilcoxon Signed Rank test and were based on the subsets of patients with both a baseline and a week 8 (LOCF) value. Tests for secondary endpoints always tested the null hypothesis of equality of treatment groups (or of baseline and week 8 [LOCF] cortisol, sodium and potassium, respectively); small p-values indicate differences.

The ITT population included all randomised patients who received at least one dose of study medication. The PP population included all ITT patients without pre-specified major violations of eligibility criteria or other major protocol deviations. The decision to exclude a patient from the PP population was made during a blinded data review prior to breaking the code. The safety analysis set included all ITT patients who provided at least one follow-up safety evaluation.

3. Results

3.1. Study population and treatment

In total, 473 patients were randomised. Two patients did not receive study medication such that the final ITT study population comprised 471 patients (238 [9 mg OD], 233 [3 mg TID]) (Fig. 1). Of these, 401 formed the interim analysis ITT population (200 [9 mg OD], 201 [3 mg TID]). The study was discontinued prematurely by 23 patients in the ITT population, most frequently due to lack of patient cooperation (Fig. 1). The PP final study population included 439 patients (220 [9 mg OD], 219 [3 mg TID]) and the confirmatory interim PP population included 377 patients (188 [9 mg OD], 189 [3 mg TID]). Premature withdrawal unrelated to study medication was the most frequent reason for exclusion from the PP population (Fig. 1).

The demographic characteristics of the two treatment groups were similar (Table 1). Other than slightly higher mean total CDAI and SES-CD scores in the budesonide 9 mg OD group, no clinically relevant differences between treatment groups were observed. The median time since the first onset of symptoms was 3.0 years in the budesonide 9 mg OD and 4.0 years in the 3 mg TID groups.

The mean (SD) treatment duration in the study was 54.1 days (7.1) in the budesonide 9 mg OD group and 54.4 days (8.0) in the 3 mg TID group. The mean (SD) adherence rate with regard to intake of budesonide was 99.9% (7.6%) in the budesonide 9 mg OD group and 98.9% (8.2%) in the 3 mg TID group. All but ten patients (3 [9 mg OD], 7 [3 mg TID]) were adherent to treatment ($\geq$75%). Concomitant medication in the category 'alimentary tract and metabolism' was used by 87.4% of patients (208/238) in the budesonide 9 mg OD group and 84.5% (197/233) of the 3 mg TID group.

3.2. Clinical remission and symptom severity

The primary endpoint, the rate of clinical remission (CDAI $<$150 at week 8 [LOCF]), was statistically non-inferior in the

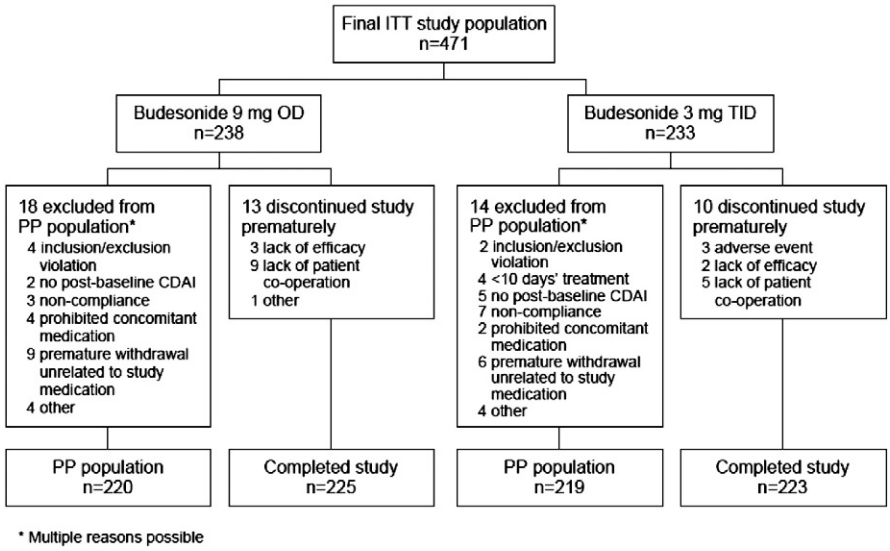

Figure 1 Patient disposition (final study ITT population). ITT, intention-to-treat; PP, per protocol.

budesonide 9 mg OD group versus the 3 mg TID group in the PP population (the primary analysis set) as well as in the ITT interim population (Fig. 2). The proportion of patients with clinical remission was 71.3% versus 75.1%, respectively, a difference of −3.9% (95% CI [−14.6%; 6.4%], p = 0.020 for non-inferiority based on the pre-specified margin of −15%). The ITT analysis led to similar but slightly lower remission rates in both groups (68.5% versus 71.1%), but non-inferiority was again shown (Fig. 2). Results from a sensitivity analysis based on the full study population showed similar results in the PP population but the lower limit of the 95% CI for the difference between groups in the final study ITT population was 15.1% i.e. non-inferiority was borderline (Fig. 2).

The rate of clinical remission was similar in both treatment groups at all time points during the eight-week study (Fig. 3a), as was the mean (SD) time to remission (budesonide 9 mg OD 21.9 [13.8] days, budesonide 3 mg TID 21.4 [14.6] days).

The improvement in the mean CDAI score followed a similar course in both groups (Fig. 3b). At week 8 (LOCF), the mean (SD) change from baseline in CDAI was nearly identical: −153.3 points (83.4) in the budesonide 9 mg OD and −153.2 points (81.6) in the 3 mg TID groups, respectively. The difference [95% CI] between these changes from baseline was −0.1 [−15.2; 14.9] with p = 0.989, highlighting the therapeutic equivalence of the two dosing regimens.

3.3. Mucosal healing

Endoscopy, an optional assessment, was performed both at baseline and week 8 for 72 patients (30.3%) in the 9 mg OD

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

	Budesonide 9 mg OD (n = 238)	Budesonide 3 mg TID (n = 233)
Male gender, n (%)	109 (45.8)	104 (44.6)
Age (years), mean (SD)	38.2 (13.5)	40.6 (13.5)
Smoker, n (%)	34 (14.3)	39 (16.7)
Time since first symptoms (years), median (range)	3.0 (0–43)	4.0 (0–42)
Localisation of disease, n (%)		
Ileum and/or ascending colon only	154 (64.7)	159 (68.2)
Only ileum and/or ascending and distal colon	84 (35.3)	74 (31.8)
Concomitant treatment, n (%)		
Mesalazine	167 (70.2)	148 (63.5)
Azathioprine	27 (11.3)	23 (9.9)
Baseline CRP (mg/L), mean (SD)	10.0 (19.0)	8.6 (15.6)
Baseline SES-CD, mean (SD)	8.5 (5.3) [a]	7.9 (5.2) [b]
Baseline CDAI, mean (SD)	271 (50.1)	264 (42.8)

CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ITT, intention-to-treat; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease.

[a] n = 100.

[b] n = 93.

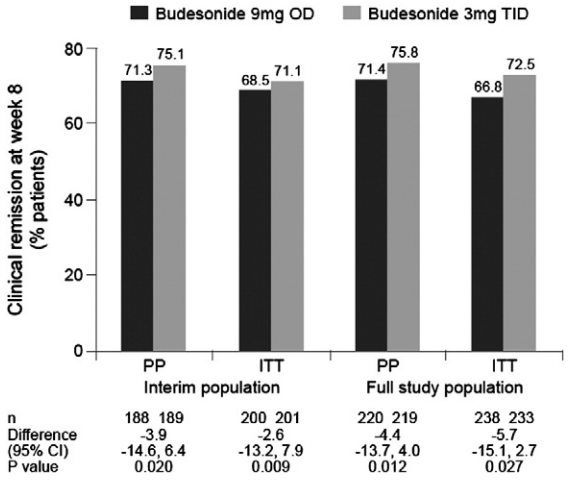

Figure 2 Clinical remission at week 8 (LOCF). Results are shown for the interim population (confirmative analysis) and the full study population (explorative analysis).

group and 63 patients (27.0%) in the 3 mg TID group. The mean (SD) SES-CD total score at baseline was 8.5 (5.3) in the budesonide 9 mg OD group versus 7.9 (5.2) with 3 mg TID,

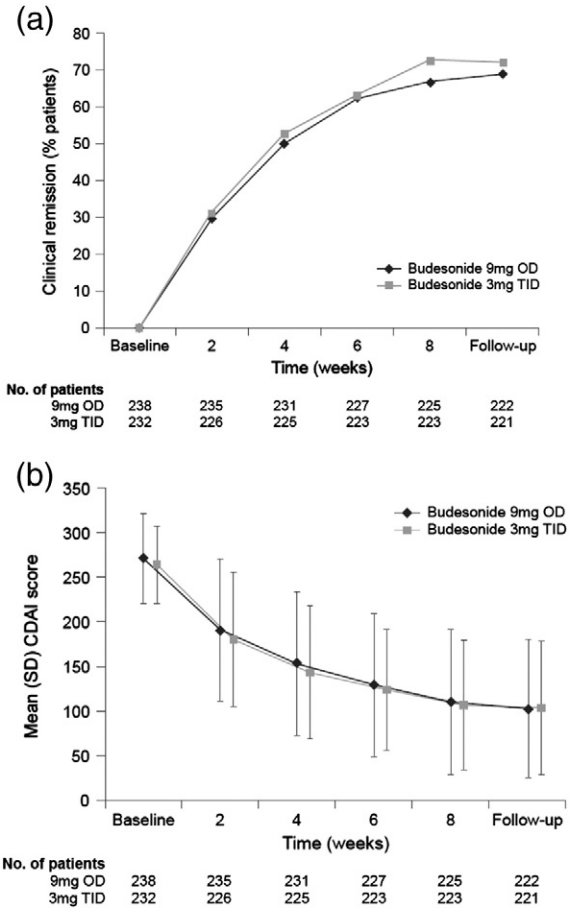

Figure 3 (a) Rate of clinical remission and (b) mean [SD] CDAI score during the study according to treatment group (final study ITT population). CDAI, Crohn's Disease Activity Index.

compared to 4.0 (4.2) versus 3.6 (4.5) at week 8 (LOCF). The mean (SD) change from baseline to week 8 (LOCF) in the total SES-CD score was numerically greater in the 9 mg OD group (−4.3 [4.2]) compared to the 3 mg TID group (−3.4 [3.5]), but did not reach statistical significance (p = 0.372). However, when the change in SES-CD score was compared between treatment groups by bowel segment, the mean (SD) improvement from baseline was significantly greater in the budesonide 9 mg OD group (−1.8 [1.8]; n = 67) versus the 3 mg TID group (−1.1 [1.7], n = 56) for the ileum (difference [95% CI] of −0.7 [−1.3; −0.1], p = 0.017) but not in other segments. When SES-CD subscore data (i.e., size of ulcer, ulcerated surface, affected surface, presence of stenosis) were compared, there was a greater mean (SD) decrease in the size of the affected area with 9 mg OD dosing versus 3 mg TID dosing (−1.5 [1.5], n = 72 versus −0.9 [1.1], n = 63; difference [95% CI] of −0.6 [−1.0; −0.1], p = 0.037) but other subscores showed no significant difference.

Complete mucosal healing, defined as SES-CD_{ulcer} score of 0 in all bowel segments as well as in a *post-hoc* analysis 'deep remission' (defined as mucosal healing and clinical remission at week 8 [LOCF]) was achieved in a substantial proportion of patients in both treatment groups (Table 2). No statistically significant differences between the groups were observed. The mucosal healing rate in the two most frequent areas of mucosal damage, i.e., the right colon and the ileum, was 52.8% (19/36) and 46.9% (23/49), respectively in the 9 mg OD group and 60.5% (26/43) and 39.4% (13/33), respectively in the 3 mg TID group, respectively, indicating a comparable efficacy for both dosing regimens for the induction of mucosal healing in the most frequent location of 'ileal disease'.

3.4. Quality of life

Both treatment arms demonstrated an improvement in quality of life indices from baseline to week 8 (Table 2). The change in SHS dimensions and the GIQLI global score during the eight-week treatment period was comparable between treatment groups (Table 2). No statistically significant differences between the groups were observed.

3.5. Therapeutic effect

Therapeutic success (defined as complete relief of symptoms or marked improvement of symptoms on the PGA scale from baseline to week 8) was achieved in approximately 68% of patients in each treatment group (Table 2). Therapeutic benefit (defined as any improvement on the PGA scale from baseline to week 8) occurred in more than 90% of patients in each group. No statistically significant differences between the groups were observed.

3.6. Safety and tolerability

The frequency of treatment-emergent AEs (i.e. whether or not considered related to the intake of the study drug during the double-blind treatment period), was similar in the budesonide 9 mg OD and the 3 mg TID groups (26.6% and 21.1% of patients, respectively). Headache and gastrointestinal disorders were the most frequently reported AEs

Table 2 Secondary efficacy endpoints at week 8 (LOCF) (final study ITT population).

	Budesonide 9 mg OD		Budesonide 3 mg TID		p value
	n	Value	n	Value	
Patients with baseline and wk 8 (LOCF) endoscopy experiencing:					
Complete mucosal healing at wk 8 (LOCF), n (%) [a]	72 [b]	30 (41.7)	63 [c]	30 (47.6)	0.488 [d]
Deep remission at wk 8 (LOCF), n (%) [e]	72 [b]	26 (36.1)	63 [c]	24 (38.1)	0.812 [d]
Change in SES-CD total score from baseline to wk 8 (LOCF), mean (SD)	72	−4.3 (4.2)	63	−3.4 (3.5)	0.372 [f]
Patients with baseline SES-CD ulcer score of ≥1 experiencing:					
Complete mucosal healing at wk 8 (LOCF), n (%) [a]	64	21 (32.8)	58	24 (41.4)	0.327 [d]
Deep remission at wk 8 (LOCF), n (%) [e]	64 [b]	17 (26.6)	58 [c]	19 (32.8)	0.454 [d]
Change in SES-CD total score from baseline to wk 8 (LOCF), mean (SD)	64 [c]	−4.8 (4.2)	58 [c]	−3.7 (3.5)	0.220 [f]
Change [mm] in SHS 100 mm VAS dimensions from baseline to week 8 (LOCF), mean (SD) [g]	236		230		
Severity of symptoms		−25.3 (25.7)		−24.7 (25.4)	0.555 [f]
Interference with daily life		−25.8 (26.8)		−26.4 (27.2)	0.967 [f]
Worry		−25.4 (26.7)		−27.6 (26.6)	0.472 [f]
Well-being		−23.3 (23.9)		−24.2 (23.8)	0.837 [f]
Change in GIQLI global score [range 0–4] from baseline to week 8 (LOCF), mean (SD) [h]	230	0.61 (0.56)	227	0.58 (0.49)	0.483 [f]
Therapeutic success, n (%) [i]	238 [b]	161 (67.6)	233 [c]	160 (68.7)	0.812 [d]
Therapeutic benefit, n (%) [j]	238 [b]	222 (93.3)	233 [c]	213 (91.4)	0.447 [d]

GIQLI, Gastrointestinal Quality of Life Index; LOCF, last observation carried forward; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; VAS, Visual Analogue Scale.

[a] $SES\text{-}CD_{ulcer}$ score 0 in all bowel segments.
[b] The variable was missing or not evaluable in two of these patients.
[c] The variable was missing or not evaluable in one of these patients.
[d] Chi-Square test (not evaluable or missing counted as 'no').
[e] Complete mucosal healing and clinical remission (CDAI <150) at week 8 (LOCF).
[f] Two-sided Wilcoxon-test for independent samples.
[g] Short Health Score. Higher values indicate greater burden.
[h] Gastrointestinal Quality of Life Index. Higher values indicate better quality of life.
[i] Complete relief of symptoms or marked improvement of symptoms on the PGA scale from baseline to week 8 (LOCF).
[j] Any improvement on the PGA scale from baseline to week 8 (LOCF).

(Table 3). Treatment-emergent suspected adverse drug reactions (i.e., causal relationship between the study drug and the AE is at least a reasonable possibility) were much less common (4.6% [9 mg OD] and 4.7% [3 mg TID]). None of the five serious AEs was classified by the investigators as a suspected adverse drug reaction. In total, eight patients discontinued the study due to AEs: 3 patients (1.3%) in the budesonide 9 mg OD group and five patients (2.2%) in the 3 mg TID group.

Clinical laboratory evaluations did not raise a safety concern. Fig. 4 shows morning serum cortisol levels (between 8 a.m. and 9 a.m.) at baseline and after eight weeks of continuous treatment. The decrease in endogenous cortisol secretion was statistically significant in each treatment group ($p < 0.001$). Interestingly, the decrease in morning serum cortisol levels after eight weeks of treatment was less pronounced following OD dosing (statistically not significant between the groups). A comparison of serum sodium and

Table 3 Number (%) of patients experiencing treatment-emergent adverse events occurring in at least 1% of patients in either treatment group, n (%) (safety population).

	Budesonide 9 mg OD (n = 237)	Budesonide 3 mg TID (n = 232)
Any treatment-emergent adverse event	63 (26.6)	49 (21.1)
Headache	18 (7.6)	12 (5.2)
Abdominal pain	7 (3.0)	2 (0.9)
Upper abdominal pain	4 (1.7)	4 (1.7)
Dyspepsia	3 (1.3)	4 (1.7)
Viral respiratory tract infection	4 (1.7)	2 (0.9)
Crohn's disease [a]	3 (1.3)	2 (0.9)
Nasopharyngitis	1 (0.4)	3 (1.3)
Constipation	3 (1.3)	–
Oropharyngeal pain	3 (1.3)	–

[a] Deterioration during the study.

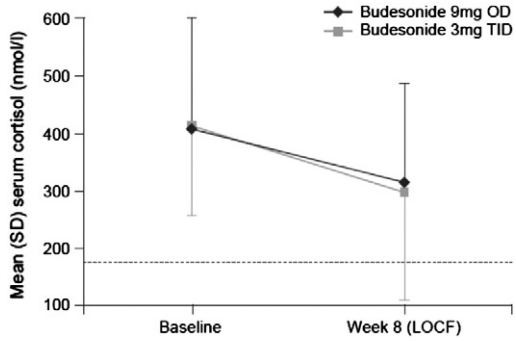

Figure 4 Mean (SD) serum cortisol levels (8 a.m. to 9 a.m.) during the study according to treatment group (safety population). Dashed line presents the lower limit of normal.

serum potassium levels at baseline with those after eight weeks of treatment did not show a clinically relevant effect on electrolyte balance in either treatment group (Fig. 5).

Tolerability was assessed as "very good" or "good" by 94.9% and 94.4% of patients (and by 95.8% and 96.6% of investigators) in the budesonide 9 mg OD group and the 3 mg TID group, respectively.

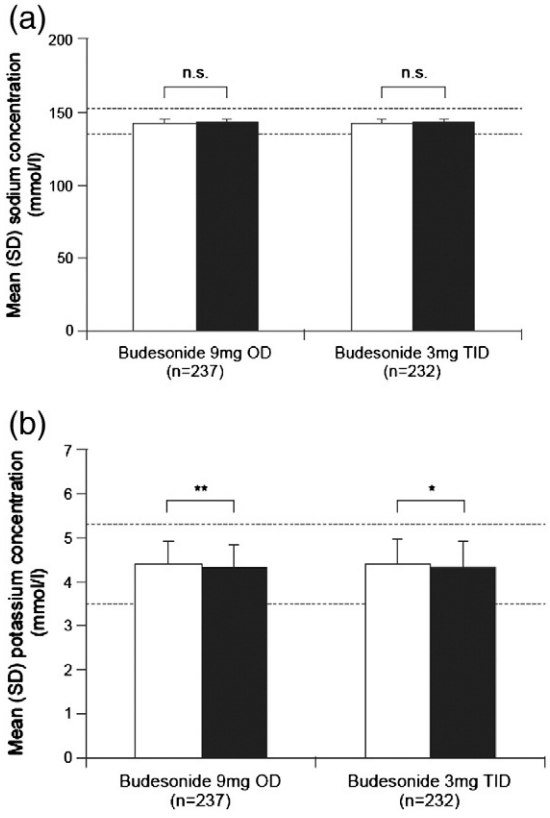

Figure 5 (a) Mean (SD) serum sodium levels and (b) mean (SD) serum potassium levels during the study according to treatment group (safety population). Dashed lines represent the limits of normal. White bars: baseline; black bars: week 8 (LOCF); *p = 0.041, **p = 0.004 (baseline vs. week 8 [LOCF]). Statistical comparison between groups: n.s.

4. Discussion

The results of this double-blind, double-dummy, multicentre trial show that OD administration of budesonide 9 mg offers similar efficacy to 3 mg three-times daily dosing in terms of achieving clinical remission in mild-to-moderately active ileocolonic Crohn's disease. Clinical remission was achieved by approximately 70% of patients in both groups during the eight-week study and, notably, complete mucosal healing occurred in over 30% of patients. There were no clinically relevant differences between the two regimens in the rate at which remission was achieved, in the extent of mucosal healing or in the improvement of patients' quality of life. The safety profiles and tolerability of OD or TID dosing were also similar. These findings suggest that once-daily budesonide should be used in preference to multiple daily dosing in this setting to support adherence to treatment in patients with active Crohn's disease.

The primary efficacy variable was clinical remission based on the CDAI, as recommended in the recent European Medicines Agency guidelines.[27] Baseline CDAI values were similar to those reported in other studies with budesonide in Crohn's disease.[5,7,8,28,29] Non-inferiority of budesonide 9 mg OD compared to budesonide 3 mg TID was confirmed in the PP population (the primary analysis population) as well as in the ITT population of the interim analysis. In the full study population, a sensitivity analysis again showed non-inferiority for the OD regimen in the PP population but did not quite reach significance in the ITT population based on pre-specified statistical criteria. The mean reduction in CDAI during the treatment period was identical with either OD or TID dosing, and was similar to that reported in previous trials of budesonide[8] and mesalazine[30] in mild-to-moderately active Crohn's disease. Other efficacy endpoints were virtually the same in both groups.

When comparing the obtained remission rates with the ones from other studies in Crohn's disease with oral budesonide formulations, one has to keep in mind that the available pharmaceutical formulations, i.e., Entocort® and Budenofalk®, differ in their release-profiles, which might have an influence on the obtained remission rates. The remission rates in the current study were very similar to the ones recently reported with Budenofalk® capsules in a large phase III study by Tromm et al. (67–72%).[8] Earlier studies with Budenofalk® capsules reported slightly lower remission rates in the range of 51–56%.[5–7] Reasons remain speculative, as the baseline characteristics, inclusion criteria, and daily dose of budesonide did not reveal conspicuous differences. For example, the baseline mean CDAI in all trials with Budenofalk® capsules, including the current one, was very comparable (range: 260–271 points), and thus could be excluded as a potential reason for these differences. The lowest remission rate (51%) was observed in the study by Bar-Meir et al.[5] which enrolled however, more smokers (approximately 30%) compared to only 15% in the current study. As smoking is a negative predictor for the outcome in Crohn's disease, this might be one potential explanation for the lower remission rate observed in the Bar-Meir study.

Mucosal healing is associated with a reduced risk of relapse, hospitalisation, fistulas and surgery,[31] and is increasingly recognised as a valuable endpoint for assessing the efficacy of interventions for Crohn's disease.[32] To date, no randomised controlled study of oral budesonide in

mild-to-moderately active Crohn's disease has included endoscopic endpoints. In our population, endoscopic data were available at baseline and at the end of treatment for more than a quarter of patients in each group. Encouragingly, complete mucosal healing was observed in approximately 33% and 41% of patients, respectively, in the budesonide 9 mg OD or 3 mg TID groups. Moreover, approximately 30% of patients achieved both mucosal healing and clinical remission after only eight weeks of treatment. For comparison, the recent EXTEND study reported mucosal healing in 27% of patients and deep remission in 16% of patients after 12 weeks' treatment with adalimumab; however, that population had more severe disease at baseline.[33]

In the ileum and right colon, where the release of oral budesonide starts using the Budenofalk® formulation, the average rate of mucosal healing was approximately 50% in both groups in our population. There was a numerically greater improvement in SES-CD score in the budesonide 9 mg OD group versus TID dosing, which reached significance in the ileum, suggesting that once-daily dosing may be beneficial with regard to mucosal healing in ileocolonic Crohn's disease.

Safety analysis did not reveal any clinically relevant difference between the two different dosage regimens. The presented clinical trial confirmed the well-known safety profile of oral budesonide with a low rate of side effects in active Crohn's disease. The trend to lower morning serum cortisol in the 3 mg TID arm as compared to 9 mg OD dosing was already noted in another clinical trial using budesonide in mildly-to-moderately active Crohn's disease,[8] and might be an argument for preference of OD dosing in patients with pre-existing adrenal suppression.

Adherence to the prescribed regimen was high in both treatment arms, based on returned medication and patient diaries, despite the requirement to take one sachet and three capsules per day. The close monitoring of a controlled trial of this type, and the short eight-week duration of therapy, are likely to have contributed to this level of adherence. It needs to be emphasized that a clinical trial setting is likely to produce much higher adherence rates than a real-life setting, where significantly lower rates have been reported. A systematic review of adherence studies in inflammatory bowel disease concluded that over a third of patients are non-adherent,[10] and that more complex regimens such as TID dosing tend to predict non-adherence[10] as described for other chronic diseases.[34,35]

In conclusion, budesonide at the recommended dose of 9 mg/day can be administered once a day without any loss of efficacy compared to conventional TID dosing in mild-to-moderately active Crohn's disease, with potential benefits for long-term adherence. The high rates of clinical remission and mucosal healing achieved in both treatment arms following an eight-week treatment period support recent recommendations that oral budesonide should be used first-line to induce remission in mild-to-moderately active ileocecal Crohn's disease.[9,36,37]

Role of funding source

The study was funded by Dr Falk Pharma GmbH, Freiburg, Germany. The study sponsor contributed to the design of the study in collaboration with the authors, funded the analysis of the data by an independent biostatistics company, worked in conjunction with the authors to interpret the data, and reviewed the draft manuscript. The sponsor was not involved in data collection. The final decision to publish was made by the first author (AD).

Conflicts of interest

A. Dignass has received travel funding and other support from ECCO, has acted as a consultant to Abbott, MSD, Ferring, UCB, Otsuka and Roche/Genentech, received speaker's honoraria from Falk Foundation, Ferring, MSD, Abbott, Otsuka, Vifor, Immundiagnostik and Shire, received fees for manuscript preparation from Falk Foundation, and fees for the development of educational presentations from Abbott, Pharmacosmos, Falk Foundation and Ferring. KD, RG and RM are employees of Dr Falk Pharma GmbH, Freiburg, Germany. The other authors have no conflicts of interest to declare.

Author contributions

AD, KD, RG and RM developed the study concept and design. AD, SS, AED, GAG, ET, IA, DT, IB, JP and LK collected the data; AD, KD, RG and RM interpreted the data. All authors provided the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

Writing assistance

Writing support was provided by C. Dunstall (freelance), funded by Dr Falk Pharma GmbH.

Acknowledgements

The authors would like to thank all patients and investigators for their participation and contribution to the study.

Appendix A. Study investigators

Bulgaria: S. Stoynov, P. Penchev, H. Kadian (Sofia); I. Kotzev, M. Stamboliyska, A. Atanassova (Varna); A. Petrov, A. Chavushian, R. Balabanska, R. Tsonev (Sofia); G. Vasileva, Y. Novakov (Rousse); D. Kurktschiev, T. Temelkova-Kurktschiev (Sofia).

Czech Republic: M. Lukas, M. Bortlik (Prague); L. Gabalec, V. Šimon (Ústí nad Orlicí); A. Jungwirthová, P. Matějková (Prague); M. Široký, L. Slezák (Hradec Králové); E. Tomsová, J. Marček (Mladá Boleslav); P. Benko, J. Goláňová, V. Komárek (Prague).

Germany: A. Dignass, M. Böhmig, H.A. Schulze (Frankfurt am Main); H.J. Cordes, A. Dienethal, R. Claudé (Frankfurt am Main); T. Klugmann, N. Teich, A. Borkenhagen (Leipzig); M. Schroeder, H Hinrichsen (Kiel).

Hungary: Z. Tulassay, L. Herszényi, M. Juhász, P. Miheller, E. Mihály (Budapest); I. Altorjay, K. Palatka, S. Kacska (Debrecen); P. Demeter, J. Penyige, R. Sike (Budapest); G. Mester, M. Balogh (Pápa); I. Rácz, A. Szabó, T. Karasz, M. Csöndes (Györ).

Latvia: J. Pokrotnieks, A. Pukitis (Riga); J. Derova, A. Derovs (Riga).

Lithuania: L. Kupčinskas, L. Jonaitis, G. Kiudelis (Kaunas); A. Buinevičiūtė, G. Radžiūnas (Vilnius).

Romania: V. Cristea, C.C. Burz, D. Muti (Cluj-Napoca); I. Dina, C. Iacobescu (Bucharest); O. Fratila, T. Ilias (Oradea); L. Gheorghe, G. Smira, R. Vadan (Bucharest); A. Goldis, F. Bob, R. Goldis, S. Kallikkot (Timisoara); D. Tuculanu, M.G. Paunescu, S. Covasintan (Timisoara).

Russia: E.A. Belousova, I.V. Domareva (Moscow); G.A. Grigorieva*, N.Y. Meshalkina, S.V. Golysheva (Moscow); V.B. Grinevich, I.V. Gubonina, A.M. Pershko (St. Petersburg); T.L. Mikhailova**, O.V. Golovenko, L.A. Mayat, P.A. Makarchuk (Moscow); V.I. Simanenkov, N.V. Zakharova, G.N. Belov (St. Petersburg); E.A. Sishkova, T.V. Tinyakova, D.V. Raspereza (St. Petersburg); E.I. Tkachenko, E.B. Avalueva, T.N. Zhigalova, E. Skazyvaeva, E. Mirgorodskaya (St. Petersburg); E.P. Yakovenko, N.A. Agafonova, A.N. Ivanov, A.V. Yakovenko, A.S. Pryanishnikova (Moscow); D.I. Abdulganiyeva, A.H. Odintsova, E.S. Bodryagina, S.G. Glebasheva (Kazan); O.P. Alekseeva, S.V. Krishtopenko (Nizhniy Novgorod); O.Y. Dolgikh, P.P. Andreev, A.V. Lukashova (Samara); V.V. Pavlenko, S.B. Aleksandrovna, G.A. Kataganova, N.V. Korablina (Stavropol); B.D. Starostin, G. Starostina (St. Petersburg); A.V. Tkachev, K.E. Nikitina, L.S. Mkrtchyan (Rostov-on-Don); A.A. Yakovlev, I.G. Stolyarova, A.S. Volkov, V. Krishchenko (Rostov-on-Don); E.Y. Valuiskikh, O.M. Gilinskaya, E. Miroshnichenko (Novosibirsk).

Slovakia: B. Barický (Nitra); I. Bunganič (Prešov); B. Pekárková, B. Pekárek (Trnava).

Ukraine: O.I. Golovchenko, I.A. Nosova, O.N. Zaporozhets (Vinnnitsya); A.E. Dorofeyev, O.A. Rassokhina (Donetsk); Y.S. Lozynskyy, O.V. Leoshyk, I.V. Seplyvyy (Lviv); M.P. Zakharash, Y.M. Zakharash, T.G. Kravchenko (Kyiv).

*Prof. Dr. G.A. Grigorieva (Moscow) recently passed away.

**Prof. Dr. T.L. Mikhailova (Moscow) recently passed away.

References

1. Rutgeerts PJ. Review article: the limitations of corticosteroid therapy in Crohn's disease. *Aliment Pharmacol Ther* 2001;**15**(10):1515–25.
2. De Cassan C, Fiorino G, Danese S. Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? *Dig Dis* 2012;**30**(4):368–75.
3. Ford AC, Bernstein CN, Khan KJ, Abreu MT, Marshall JK, Talley NJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011;**106**(4):590–9.
4. Andus T, Gross V, Caesar I, Schulz HJ, Lochs H, Strohm WD, et al. Replacement of conventional glucocorticoids by oral pH-modified release budesonide in active and inactive Crohn's disease — results of an open, prospective, multicenter trial. *Dig Dis Sci* 2003;**48**(2):373–8.
5. Bar-Meir S, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, et al. Budesonide versus prednisone in the treatment of active Crohn's disease. *Gastroenterology* 1998;**115**(4):835–40.
6. Caesar I, Gross V, Roth M, Andus T, Schmidt C, Raedsch R, et al. Treatment of active and postactive ileal and colonic Crohn's disease with oral pH-modified-release budesonide. *Hepatogastroenterology* 1997;**44**(14):445–51.
7. Gross V, Andus T, Caesar I, Bischoff SC, Lochs H, Tromm A, et al. Oral pH-modified release budesonide versus 6-methylprednisolone in active Crohn's disease. German/Austrian Budesonide Study Group. *Eur J Gastroenterol Hepatol* 1996;**8**(9):905–9.
8. Tromm A, Bunganic I, Tomsova E, Tulassay Z, Lukas M, Kykal J, et al. Budesonide 9 mg is at least as effective as mesalamine 4.5 g in patients with mildly to moderately active Crohn's disease. *Gastroenterology* 2011;**140**(2):425–34.
9. Dignass A, van Assche G, Lindsay JO, Lemann M, Söderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;**4**(1):28–62.
10. Jackson CA, Clatworthy J, Robinson A, Horne R. Factors associated with non-adherence to oral medication for inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 2010;**105**(3):525–39.
11. Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. *Inflamm Bowel Dis* 2009;**15**(6):837–44.
12. Nahon S, Lahmek P, Saas C, Durance C, Olympie A, Lesgourgues B, et al. Socioeconomic and psychological factors associated with nonadherence to treatment in inflammatory bowel disease patients: results of the ISSEO survey. *Inflamm Bowel Dis* 2011;**17**(6):1270–6.
13. Coleman CI, Limone B, Sobieraj DM, Lee S, Roberts MS, Kaur R, et al. Dosing frequency and medication adherence in chronic disease. *J Manag Care Pharm* 2012;**18**(7):527–39.
14. Silverberg MS, Satsangi J, Ahmad T, Arnott ID, Bernstein CN, Brant SR, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;**19**(Suppl A):5–36.
15. Best WR, Becktel JM, Singleton JW, Kern Jr F. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;**70**(3):439–44.
16. Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). *Gastroenterology* 1979;**77**(4, Part 2):843–6.
17. Daperno M, D'Haens G, VanAssche G, Baert F, Bulois P, Maunoury V, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. *Gastrointest Endosc* 2004;**60**(4):505–12.
18. Hjortswang H, Jarnerot G, Curman B, Sandberg-Gertzen H, Tysk C, Blomberg B, et al. The Short Health Scale: a valid measure of subjective health in ulcerative colitis. *Scand J Gastroenterol* 2006;**41**(10):1196–203.
19. Stjernman H, Grännö C, Järnerot G, Ockander L, Tysk C, Blomberg B, et al. Short Health Scale: a valid, reliable, and responsive instrument for subjective health assessment in Crohn's disease. *Inflamm Bowel Dis* 2008;**14**(1):47–52.
20. Eypasch E, Wood-Dauphinee S, Williams JI, Ure B, Neugebauer E, Troidl H. The Gastrointestinal Quality of Life Index. A clinical index for measuring patient status in gastroenterologic surgery. *Chirurg* 1993;**64**(4):264–74.
21. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, et al. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995;**82**(2):216–22.
22. Hanauer SB, Schwartz J, Robinson M, Roufail W, Arora S, Cello J, et al. Mesalamine capsules for treatment of active ulcerative colitis: results of a controlled trial. Pentasa Study Group. *Am J Gastroenterol* 1993;**88**(8):1188–97.
23. Moskovitz D, van Assche G, D'Haens G, Rutgeerts P. Using the simple endoscopic score for Crohn's disease and the Crohn's disease endoscopic index of severity for the measurement of disease activity and remission in Crohn's disease [abstract]. *Gastroenterology* 2005;**128**(4, Suppl 2):A-312.
24. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of

non-zero risk difference or non-unity relative risk. *Stat Med* 1990;**9**(12):1447–54.
25. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008;**3**:CD000296.
26. Su CY, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease (review). *Gastroenterology* 2004;**126**(5):1257–69.
27. EMEA. CPMP/EWP/2284/99 Rev.1 (FINAL): guideline on the development of new medicinal products for the treatment of Crohn's disease. London: EMEA; 2008.
28. Thomsen OO, Cortot A, Jewell D, Wright JP, Winter T, Veloso FT, et al. A comparison of budesonide and mesalamine for active Crohn's disease. *N Engl J Med* 1998;**339**(6):370–4.
29. Tremaine WJ, Hanauer SB, Katz S, Winston BD, Levine JG, Persson T, et al. Budesonide CIR capsules (once or twice daily divided-dose) in active Crohn's disease: a randomized placebo-controlled study in the United States. *Am J Gastroenterol* 2002;**97**(7):1748–54.
30. Gross V, Andus T, Fischbach W, Weber A, Gierend M, Hartmann F, et al. Comparison between high dose 5-aminosalicylic acid and 6-methylprednisolone in active Crohn's ileocolitis. A multicenter randomized double-blind study. German 5-ASA Study Group. *Z Gastroenterol* 1995;**33**(10):581–4.
31. Peyrin-Biroulet L, Ferrante M, Magro F, Campbell S, Franchimont D, Fidder H, et al. Results from the 2nd Scientific Workshop of the ECCO. I: impact of mucosal healing on the course of inflammatory bowel disease. *J Crohns Colitis* 2011;**5**(5):477–83.
32. D'Haens G, Feagan B, Colombel JF, Sandborn WJ, Reinisch W, Rutgeerts P, et al. Challenges to the design, execution, and analysis of randomized controlled trials for inflammatory bowel disease. *Gastroenterology* 2012;**143**(6):1461–9.
33. Rutgeerts P, van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012;**142**(5):1102–11.
34. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;**23**(8):1296–310.
35. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *J Behav Med* 2008;**31**(3):213–24.
36. Hoffmann JC, Preiss JC, Autschbach F, Buhr HJ, Häuser W, Herrlinger K, et al. S3-Leitlinie "Diagnostik und Therapie des Morbus Crohn". Ergebnisse einer Evidenz-basierten Konsensuskonferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten zusammen mit dem Kompetenznetz chronisch entzündliche Darmerkrankungen [Clinical practice guideline on diagnosis and treatment of Crohn's disease. Results of a German Evidence-based Consensus Conference]. *Z Gastroenterol* 2008;**46**(9):1094–146.
37. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;**60**(5):571–607.