Journal of Crohn's and Colitis, 2022, **16**, 1714–1724
https://doi.org/10.1093/ecco-jcc/jjac081
Advance access publication 16 June 2022
Original Article

Novel Budesonide Suppository and Standard Budesonide Rectal Foam Induce High Rates of Clinical Remission and Mucosal Healing in Active Ulcerative Proctitis: a Randomised, Controlled, Non-inferiority Trial

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Abstract

Background and Aims: Proctitis is the least extensive type of ulcerative colitis, for which rectal therapy is rarely studied and is underused. This study evaluated the efficacy, safety, and patient's preference of a novel formulation of budesonide suppository 4 mg, compared with a commercially available budesonide rectal foam 2 mg, for the treatment of mild to moderate ulcerative proctitis.

Methods: This was a randomised, double-blind, double-dummy, active-controlled trial. Patients were randomly assigned in a 1:1 ratio to receive either budesonide 4 mg suppository or budesonide 2 mg foam once daily for 8 weeks. The co-primary endpoints were changes from baseline to Week 8 in clinical symptoms, for which clinical remission was defined as having a modified Ulcerative Colitis-Disease Activity Index [UC-DAI]

subscore for stool frequency of 0 or 1 and a subscore for rectal bleeding of 0, and mucosal healing, defined as having a modified UC-DAI subscore for mucosal appearance of 0 or 1. Using a more stringent criterion, we additionally analysed deepened mucosal healing, which was defined as a mucosal appearance subscore of 0. Patient's preference, physician's global assessment, and quality of life were also assessed and analysed.

Results: Overall, 286 and 291 patients were included in the 4 mg suppository and 2 mg foam groups, respectively. Budesonide 4 mg suppository met the prespecified criterion for non-inferiority to the 2 mg foam in both co-primary endpoints of clinical remission and mucosal healing. Secondary endpoints consistently supported the non-inferiority of the suppository. Trends in favour of the suppository were observed in the subgroup of mesalazine non-responders. More patients reported a preference for the suppository over rectal foam.

Conclusions: In patients with ulcerative proctitis, budesonide 4 mg suppository was non-inferior to budesonide 2 mg foam in efficacy, and both were safe and well tolerated.

Key Words: Clinical trials; ulcerative proctitis; budesonide; rectal suppository; rectal foam

1. Introduction

Mucosal inflammation in ulcerative colitis originates in the rectum and may extend proximally throughout the entire colon. At primary diagnosis, 30% to 50% of patients have disease confined to the rectum or the sigmoid colon [distal colitis], 20% to 30% have left-sided colitis, and approximately 20% have pancolitis.[1] In 25% to 50% of patients, the initial distal colitis may progress to more extensive forms of the disease.[2] The predominant symptom of ulcerative colitis is visible blood in the stool. In patients with ulcerative proctitis, urgency and tenesmus are common.[3] As a subtype of ulcerative colitis, the cumbersome symptoms of ulcerative proctitis present a substantial burden for patients.

Treatment of ulcerative colitis should be tailored to disease activity [mild, moderate, severe] and the extent of colonic involvement [proctitis, left-sided colitis, or pancolitis]. Topical treatment is the first-line therapy for proctitis, and suppositories have been reported as the preferred route of application to foam or enema.[4] This preference is supported by a Cochrane systematic review for the treatment of proctitis and left-sided colitis.[5] For rectal treatment of distal ulcerative colitis, aminosalicylates were shown to be superior to rectal corticosteroids for inducing symptomatic remission, with favourable but non-significant trends for endoscopic and histological outcomes.[4,5] However, topical aminosalicylates may only be more effective than conventional corticosteroids.[6] Topical mesalazine and rapidly metabolised steroids, such as budesonide and beclomethasone dipropionate, have similar efficacy.[7-9]

Compared with oral drug formulations, rectal drug formulations offer the advantage of delivering high concentrations of the active ingredient to the inflamed mucosa, thus minimising systemic exposure and maximising efficacy.[10] Rectal formulations include suppositories, foams, and enemas. Scintigraphy studies have demonstrated that suppositories stay in the rectum, foam reaches the proximal sigmoid and descending colon, and enemas spread at least up to the splenic flexure.[11-13] Thus, the choice of drug formulation depends on the extent of mucosal inflammation.

Furthermore, patient's preference of a certain formulation is an important factor in treatment adherence.[14] A comparative trial between budesonide foam and enemas in ulcerative proctosigmoiditis and proctitis found that patients preferred foam,[15] and a study of mesalazine found that patients favoured suppositories to enemas.[16] In a study comparing mesalazine suppositories with hydrocortisone foam in patients with ulcerative proctitis and proctosigmoiditis, patients reported more convenience and better compliance with mesalazine suppositories.[17]

A novel budesonide suppository formulation has recently been developed as an easy-to-use alternative to the corticosteroid-containing rectal foam or enema formulations already available. The non-halogenated glucocorticosteroid budesonide reduces the risk of systemic side effects because of its high first-pass metabolism in the liver and high affinity to the glucocorticosteroid receptor, resulting in a predominantly topical mode of action. A clinical trial was conducted to evaluate the efficacy, safety, tolerability, and patient's preference of this budesonide suppository, developed by Dr. Falk Pharma GmbH, in comparison with a commercially available budesonide rectal foam, for the treatment of mild to moderate ulcerative proctitis.

2. Materials and Methods

2.1. Inclusion and exclusion criteria

Men and women, 18 to 75 years of age with endoscopically established [through documentation of at least one total colonoscopy in the available medical history] or newly diagnosed, mildly to moderately active ulcerative proctitis, confirmed by total colonoscopy or flexible sigmoidoscopy, were enrolled. The extent of inflammation had to be no more than 15 cm from the anal margin, and the severity was defined as having a total score of > 3 and < 11 on the modified Ulcerative Colitis – Disease Activity Index [UC-DAI], along with a rectal bleeding subscore of ≥1 and endoscopic subscore of ≥2. To be eligible for the trial, newly diagnosed patients had to have bloody stools within 28 days prior to baseline visit, and patients with established disease had to have symptoms at least once within 28 days before the baseline visit.

Patients were excluded if they had Crohn's disease; indeterminate, ischaemic, diverticular-associated, or microscopic colitis; proctitis of a different origin [e.g., infection, parasitic infestation, drug-induced]; or local intestinal infection. Regular treatment [longer than 3 days] with significant doses of oral or rectal mesalazine, olsalazine, or sulphasalazine; or oral, rectal, or intravenous corticosteroid within 4 weeks before baseline was prohibited. The use of immunosuppressive drugs or biologics within 3 months before baseline was also prohibited.

All enrolled patients gave informed consent before participation.

2.2. Trial design and treatment

This was a randomised, double-blind, double-dummy, active-controlled clinical trial to compare two rectal formulations of budesonide in patients suffering from ulcerative proctitis.

Patients were randomly assigned in a 1:1 ratio to one of two groups and received either budesonide 4 mg suppository [BUS] or budesonide 2 mg in 1.2 g foam [BUF] for daily rectal application. To maintain the blindness, a double-dummy design was used. Specifically, the BUS group was also given a

placebo foam, and the BUF group was also given a placebo suppository. Patients were instructed to use one formulation in the morning and the other formulation at bedtime. Both treatment groups were stratified according to the sequence of drug application, with Sequence 'S' designated for applying the suppository in the morning [and rectal foam at bedtime] and Sequence 'F' for applying the rectal foam in the morning [and suppository at bedtime].

The entire trial participation included a screening period of up to 10 days, treatment for 8 weeks, and a follow-up visit 28 days after the last dose. Eligible patients were assigned to the next available randomisation number according to the centrally prepared randomisation list and within the set of supplies of a single study centre. During treatment, patients returned to the study sites for efficacy and safety assessments every 2 weeks. Change in mucosal healing was assessed by endoscopy at baseline and Week 8, in which biopsy samples were taken and evaluated for histology by a central pathologist [baseline histology data shown]. Clinical symptoms were recorded daily by patients in a diary, including but not limited to the number of stools, severity of rectal bleeding, numbers of bloody and liquid to solid stools, and abdominal pain and cramp.

2.3. Objectives and endpoints

The primary objective of this trial was to demonstrate non-inferiority of BUS to BUF after 8 weeks of treatment for ulcerative proctitis. We designed our trial as a non-inferiority trial, as we sought to demonstrate that the test product BUS is not worse in efficacy than the comparator BUF. As both preparations were topical applications, bioequivalence cannot be reliably evaluated.[18] Two co-primary endpoints were analysed: the proportions of patients who achieved clinical remission [CR] and mucosal healing [MH] at the end of the 8-week treatment period or the withdrawal visit. Both endpoints were binary [yes/no]. Clinical remission was defined as having a modified UC-DAI subscore for stool frequency of 0 or 1 and a subscore for rectal bleeding of 0. Mucosal healing was defined as having a modified UC-DAI subscore for mucosal appearance of 0 or 1. The modified UC-DAI[19] consists of four subscores: stool frequency, rectal bleeding, mucosal appearance, and physician's rating of disease activity.

Key secondary endpoints were: the proportions of patients who achieved both CR and MH [CR + MH]; patients who achieved a more stringent criterion of deepened clinical remission [dCR, defined as 0 for both the stool frequency and rectal bleeding subscores on UC-DAI]; patients who achieved a more stringent criterion of deepened mucosal healing [dMH, defined as a mucosal appearance subscore of 0]; and time to clinical symptom resolution, defined as the number of days from first dose of study drug to the first of 3 consecutive days in which both the rectal bleeding and stool frequency subscores were 0. In addition, patient's acceptance of the two treatments, based on the ease of administration, interference with daily routine, and preference of formulation, were analysed. Physician's global assessment [PGA], a six-point scale in which 1 represents complete relief of symptoms and 6 represents worsening of symptoms, were collected at the end of the treatment period or early withdrawal visit.

Quality of life was evaluated using the validated Short Health Scale [SHS] questionnaire at each visit from baseline to the follow-up visit. The SHS is a simplified four-item questionnaire, with each question rated on a 100-mm visual analogue scale: [1] symptom burden, [2] social function, [3] disease-related worry, and [4] general well-being.[20,21] Furthermore, the Work Productivity and Activity Impairment [WPAI] questionnaire was used to measure missed work hours and impairment at work and daily activities, due to the specific health problem, during the past 7 days. Both the SHS and WPAI questionnaires were administered at each visit during the study.

A post hoc superiority analysis was performed to compare the efficacy between BUS and BUF within the subgroup of patients who had failed to respond to mesalazine [rectal or oral] treatment before entering the current trial.

Safety was monitored by collecting adverse events regardless of causal relationship with the treatment and adverse drug reactions [ADRs] related to the treatment. In addition, clinical laboratory tests, including haematology, serum chemistry, urinalysis, and faecal calprotectin, were performed. Morning serum cortisol levels in patients' blood samples were measured at each visit.

2.4. Statistical methods

The co-primary endpoints, the remission rates for CR and MH by the end of 8 weeks of treatment or early discontinuation, were analysed using the per-protocol set [PPS] in the primary analysis and the full analysis set [FAS] as supportive. The FAS included all randomised patients who received at least one dose of the study drug, excluding any patients identified as not fulfilling the entry criteria shortly after randomisation ['delayed exclusions']. The PPS included those in the FAS who had no major protocol deviations and had sufficient data for efficacy assessment [e.g., availability of the end-of-study mucosal healing subscore]. The co-primary endpoints were tested at a one-sided type I error rate level of 0.025 [overall] using the Farrington–Manning test of non-inferiority. The treatment effect was estimated as the difference between the remission rates of the two treatments, and the corresponding two-sided 95% repeated confidence intervals were calculated. For the PPS, the Clopper–Pearson exact method was used to calculate the two-sided 95% confidence intervals [CIs]. The non-inferiority margin between the remission rate in both treatment groups was set at 0.10. The decision to set the non-inferiority margin at 10% was based on the results of a meta-analysis that included all placebo-controlled trials of the comparator[22-24] according to relevant guidelines.[18]

For the key secondary endpoints, the same non-inferiority test as was used for the primary endpoint was conducted in a hierarchical fashion [in the order of CR + MH, dMH, dCR] until the first of these comparisons showed a one-sided p-value of >0.025; all subsequent significance tests were considered exploratory. The PPS dataset was used for the key secondary analyses. Time-to-event analysis was performed for the time to clinical symptom resolution using Kaplan–Meier methods [including appropriate censoring of patients not reaching symptom resolution]. Non-inferiority testing was performed with respect to the area under the survival curve, using an approximately normal distributed test.

The sample size was calculated before the study commenced based on the following assumptions: remission rates of 41% for the BUF group[23,24] and 44% for the BUS group; a non-evaluable rate of 20%; a non-inferiority margin of 0.1 [10%] in true remission rates within the PPS; and one-sided alpha level of 0.025. A sample size of 576 patients would achieve an overall statistical power of 80%. The trial was performed

according to an adaptive, two-stage, group sequential design with the possibility for sample size adaptation and early stopping for efficacy at the interim analysis, which allowed the study to proceed to completion as planned.

Safety data were analysed using the safety dataset, which included all randomised patients who received at least one dose of the study drug, and results were summarised descriptively.

The statistical analysis was performed using the software package SAS [SAS Institute Inc., Cary, NC, USA].

2.5. Study conduct

The study was conducted at 41 sites in seven countries, including Germany, Russia, Ukraine, Latvia, Slovakia, Hungary, and Poland, with the approvals of independent ethics committees and in compliance with the Helsinki Declaration and local regulations. Supplementary Table 1 shows the number of the active study centres across the seven countries and the allocation of patients to each country. Informed consents were obtained before any study procedures were performed. The study was registered with the EudraCT number 2016-001921-15. An Independent Data Monitoring Committee reviewed unblinded interim results. The Committee acted according to a written charter and consisted of two gastroenterologists and an independent statistician. None of the committee members was directly involved in the trial conduct. The interim analysis was performed after 368 patients completed the treatment phase. The main purpose of the interim analysis was to confirm the original assumptions regarding the design parameters of the trial. Only one interim analysis was planned and performed. The study was conducted from June 2017 to March 2020.

3. Results

3.1. Patient populations and characteristics

A shown in Figure 1, 577 eligible patients were randomised and received at least one dose of the treatment, including 286 and 291 patients who were assigned to the BUS and BUF groups, respectively. Nineteen [6.6%] and 15 [5.2%] patients in the BUS and BUF groups, respectively, discontinued the trial prematurely. The most common reasons for discontinuation were lack of efficacy, adverse events, and lack of compliance [Table 1].

After excluding six patients who failed the eligibility criteria shortly after the study began, the FAS dataset included 281 patients in the BUS group and 290 in the BUF group. The PPS consisted of 250 and 261 patients in the BUS and BUF groups, respectively.

The demographic and baseline characteristics between the two treatment groups were generally comparable [Table 2]. The mean modified UC-DAI score was 7.0 in both groups.

3.2. Primary efficacy results

In the PPS dataset, 197 [78.8%] patients in the BUS group and 194 [74.3%] patients in the BUF group achieved CR, and 203 [81.2%] and 212 [81.2%] patients, respectively, achieved MH by the end of the 8-week treatment or discontinuation

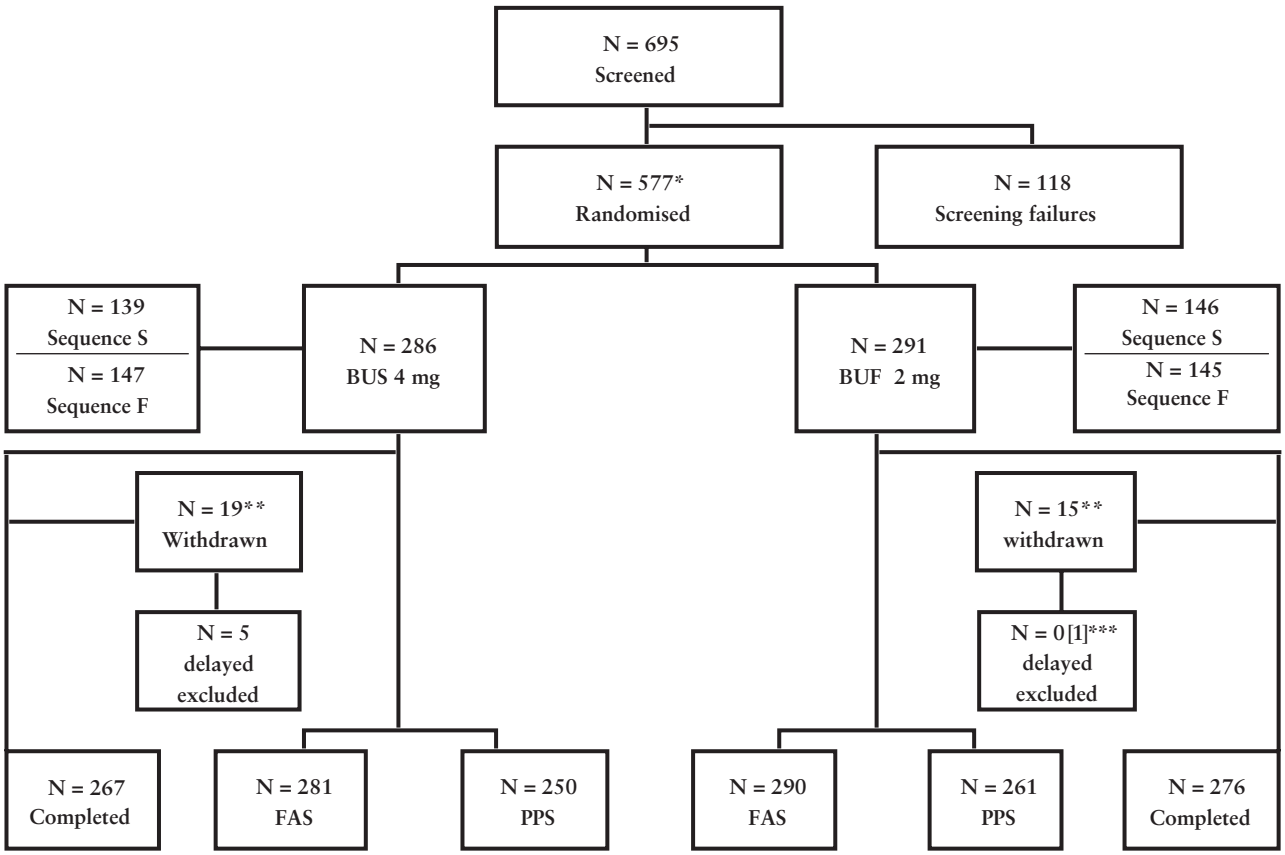

Figure 1. CONSORT disposition diagram. *Safety Set. **For details please see Table 1. ***One patient left the study due to an uncertain pregnancy test but was defined as delayed exclusion, even though 'uncertain pregnancy test' was not specified in the study protocol as one of the criteria for delayed exclusion.

Table 1. Patient's study completion and primary reasons for discontinuation from study—randomised patients

		BUS 4 mg, *N* = 286	BUF 2 mg, *N* = 291	Total *N* = 577
Randomised	*N*	286	291	577
Completed	*n* [%]	267 [93.4]	276 [94.8]	543 [94.1]
Prematurely withdrawn	*n* [%]	19 [6.6]	15 [5.2]	34 [5.9]
Primary reason for withdrawal				
Lack of efficacy	*n* [%]	5 [1.7]	5 [1.7]	10 [1.7]
Intolerable adverse event	*n* [%]	4 [1.4]	5 [1.7]	9 [1.6]
Suspected chickenpox/herpes zoster/measles infection	*n* [%]	1 [0.3]	0 [0]	1 [0.2]
Lack of patient's co-operation	*n* [%]	3 [1.0]	3 [1.0]	6 [1.0]
Delayed exclusion	*n* [%]	5 [1.7]	0 [1] [0.0][a]	5 [0.9]
Other reason	*n* [%]	1 [0.3]	2 [0.7][a]	3 [0.5]

BUS, budesonide suppository; BUF, budesonide foam.
[a]One patient left the study due to 'other reason' uncertain pregnancy test. She was defined as delayed exclusion later at blind data review meeting.

[Figure 2, Table 3]. The 4 mg budesonide suppository met the prespecified criterion for non-inferiority to the 2 mg budesonide rectal foam with a *p*-value of 0.00007 for CR and 0.00224 for MH from the Farrington–Manning test, with a difference margin of 10%. Thus, the non-inferiority was demonstrated for both co-primary endpoints. The FAS analysis yielded results that were consistent with the PPS analysis and supported the non-inferiority of 4 mg budesonide suppository. The sequence of drug application did not have any statistically significant effect on the primary efficacy results [data not shown].

3.3. Secondary efficacy results

Based on the FAS analyses, 186 of 281 [66.2%] patients in the BUS group and 185 of 290 [63.8%] patients in the BUF group achieved the criterion of both CR and MH [Table 4]. Furthermore, 115 [40.9%] patients and 111 [38.3%] patients, respectively, met the criterion for dMH [mucosal appearance subscore 0], and 125 [44.5%] and 118 [40.7%] patients, respectively, met the criterion for dCR [stool frequency and rectal bleeding subscores 0]. Statistical analyses showed that non-inferiority was reached in FAS and PPS [data not shown] for all three key secondary endpoints, confirming that 4 mg budesonide suppository was non-inferior to 2 mg budesonide foam.

The median [95% CI] time to resolution of clinical symptoms, defined as first day of 3 consecutive days with a score of 0 for rectal bleeding and stool frequency, was 39.0 [30.0, 50.0] days in the BUS group and 43.0 [35.0, 55.0] days in the BUF group. Although the BUS group had a numerically shorter time to symptom resolution, statistical comparison confirmed the non-inferiority of 4 mg BUS to 2 mg BUF (p = 0.0007, 95% CI [-6.1%, 1.7%]). The overall change regarding the number of bloody stools at the end of the treatment was comparable between both groups [p = 0.3079]. After only 2 weeks of treatment, however, a statistically significantly greater reduction in the number of bloody stools was observed for BUS group than for the BUF group [p = 0.0354].

As measured by the PGA score at the end of treatment or the early withdrawal visit in the FAS set, 104 [37.0%] patients in the BUS group and 99 [34.1%] patients in the BUF group had a complete relief of symptoms. Therapeutic success, defined as at least marked improvement of symptoms on the PGA scale, was achieved in 72.2% and 64.5% of patients in the BUS and BUF groups, respectively.

In the subgroup analysis, 41 patients in each treatment group who had been non-responders to previous mesalazine treatment were analysed for efficacy outcomes. Of these patients, 29 [70.7%] in the BUS group and 24 [58.5%] in the BUF group achieved CR, and 28 [68.3%] and 21 [51.2%] patients, respectively, achieved MH by the end of treatment or early withdrawal [Supplementary Figure 1].

3.4. Patient preference and quality of life

More patients considered application of rectal therapy in the evening as 'easy' [76.9%] and 'almost not' [80.7%] interfering with the daily routine compared with morning application [68.0% and 62.2%, respectively]. Patients were stratified at randomisation to apply either the suppository in the morning or the foam in the morning. Overall, 46.9% of the patients preferred the suppositories, compared with 22.1% who favoured the foam [Figure 3]. Among patients who were assigned to the sequence of suppository in the morning, 43.2% favoured the suppository in the morning and 22.9% favoured the foam at bedtime. Among those assigned to foam in the morning, 50.5% favoured the suppository at bedtime and 21.3% favoured the foam in the morning. Both comparisons were statistically significant in favour of the suppository [p <0.0001], and the bedtime application of suppository had the highest preference rate.

Using the FAS dataset, the SHS total score decreased significantly by a mean (standard deviation [SD]) value of 119.0 [102.2] in the BUS group and 116.2 [97.0] in the BUF group from baseline to the end of treatment, indicating meaningful improvement in quality of life. In both treatment groups, the change from baseline was significant in each of the four dimensions that form the SHS [Supplementary Figure 2]. The difference between BUS and BUF in SHS score change from baseline was not statistically significant according to Wilcoxon rank sum comparison.

At baseline, 167 patients in the BUS group and 185 patients in the BUF group were employed. With the exception of absenteeism, the WPAI score changes from baseline to the end of treatment showed statistically significant improvements in presenteeism, work productivity loss, and activity impairment in both treatment groups [p <0.0001].

Table 2. Demographics and baseline characteristics [Safety Set].

	Statistics	BUS 4 mg, *N* = 286	BUF 2 mg *N* = 291
Age [years]	Mean [SD]	44.0 [14.0]	43.4 [13.4]
Sex			
Male	*n* [%]	151 [52.8]	135 [46.4]
Female	*n* [%]	135 [47.2]	156 [53.6]
Race			
White	*n* [%]	285 [99.7]	289 [99.3]
Black	*n* [%]	1 [0.3]	1 [0.3]
Other	*n* [%]	0	1 [0.3]
Weight [kg]	Mean [SD]	73.5 [15.2]	71.4 [14.3]
BMI [kg/m²]	Mean [SD]	25.1 [4.7]	24.5 [4.3]
Smoking history			
Current smoker	*n* [%]	11 [3.8]	16 [5.5]
Former smoker	*n* [%]	60 [21.0]	60 [20.6]
Never smoked	*n* [%]	214 [74.8]	215 [73.9]
Unknown	*n* [%]	1 [0.3]	0 [0.0]
Disease status			
New diagnosis	*n* [%]	54 [18.9]	48 [16.5]
Established disease[a]	*n* [%]	232 [81.1]	243 [83.5]
Time since first symptoms [months]	Mean [SD]	47.9 [61.5]	50.3 [67.7]
Disease course			
Continuous [chronically active]	*n* [%]	100 [35.0]	106 [36.4]
Recurrent	*n* [%]	186 [65.0]	185 [63.6]
Modified UC-DAI score	Mean [SD]	7.0 [1.5]	7.0 [1.4]
≤6	*n* [%]	112 [39.2]	113 [38.8]
>6	*n* [%]	173 [60.5]	176 [60.5]
Missing data	*n* [%]	1 [0.3]	2 [0.7]
Endoscopic Index [UCEIS]	Mean [SD]	4.1 [1.3]	4.1 [1.3]
Histological Index [Riley]	Mean [SD]	2.2 [0.9]	2.3 [0.9]
Patients with at least one treatment of former acute episodes	*n* [%]	148 [51.7]	148 [50.9]
Oral mesalazine	*n* [%]	86 [30.1]	90 [30.9]
Rectal mesalazine	*n* [%]	97 [33.9]	92 [31.6]
Oral sulphasalazine	*n* [%]	11 [3.8]	14 [4.8]
Rectal sulphasalazine	*n* [%]	2 [0.7]	4 [1.4]
Oral budesonide	*n* [%]	6 [2.1]	5 [1.7]
Rectal budesonide	*n* [%]	1 [0.3]	4 [1.4]
Other oral steroids	*n* [%]	10 [3.5]	6 [2.1]
Other rectal steroids	*n* [%]	3 [1.0]	5 [1.7]
Immunosuppressants	*n* [%]	3 [1.0]	1 [0.3]
Other	*n* [%]	8 [2.8]	4 [1.4]
Baseline disease characteristics [FAS]		**BUS 4 mg, *N* = 281**	**BUF 2 mg, *N* = 290**
Number of stools per day at baseline	Mean [SD]	3.96 [1.96]	3.88 [1.76]
Number of liquid stools per day at baseline	Mean [SD]	2.12 [1.99]	1.93 [1.73]
Number of soft stools per day at baseline	Mean [SD]	1.87 [1.20]	1.91 [1.30]
Number of solid stools per day at baseline	Mean [SD]	0.43 [0.73]	0.45 [0.97]
Number of bloody stools per day at baseline	Mean [SD]	2.79 [1.74]	2.65 [1.67]

BUS, budesonide suppository; BUF, budesonide foam; BMI, body mass index; SD, standard deviation; UC-DAI, Ulcerative Colitis-Disease Activity Index; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; FAS, full analysis set.
[a]Documentation of at least one total colonoscopy in the disease history available.

No statistically significant differences were seen between the groups [*p*-values for Wilcoxon rank sum test >0.05 for all items] [Supplementary Figure 3].

3.5. Safety

The safety dataset included all 577 patients who were randomised and received at least one dose of the study drugs.

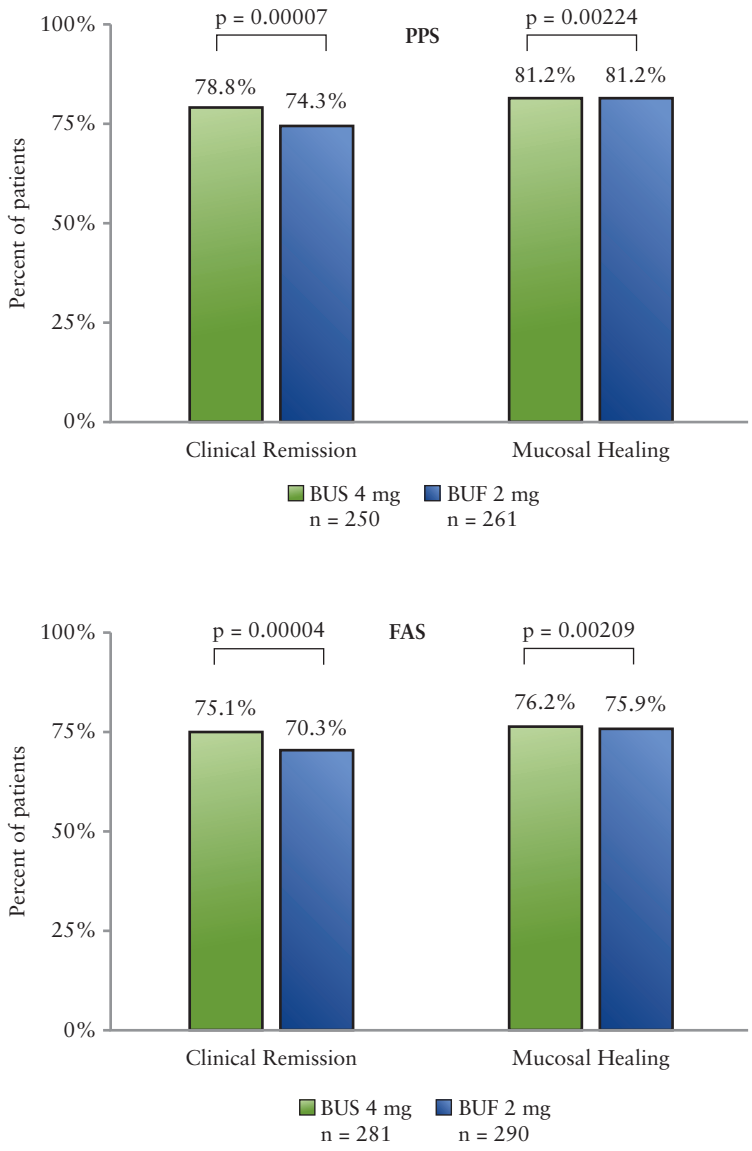

Figure 2. Primary Analysis of remission rates for clinical remission and mucosal healing by the end of treatment or discontinuation [PPS and FAS]. Clinical remission was defined as having a UC-DAI stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. Mucosal healing was defined as having a mucosal appearance subscore of 0 or 1; *p*-value: Farrington–Manning test [one-sided] with non-inferiority margin = 10%. PPS, per-protocol set; FAS, full analysis set; UC-DAI, Ulcerative Colitis-Disease Activity Index.

The incidence of treatment-emergent adverse events [TEAEs], defined as adverse events with onset during the treatment period, was higher in the BUS group [49.3% of patients] than the BUF group [40.9%] [Table 5]. The most common TEAE was cortisol decreased [24.1% and 13.4% of patients, respectively, in the BUS and BUF groups]. Most TEAEs were of mild severity [85.8% of all events]. Serious adverse events occurred in seven patients [Table 5]. None of the SAEs was judged as treatment-related by the investigator. No death was reported. Adverse drug reactions [ADRs], defined as TEAEs related to the study treatment, were reported in 79 [27.6%] patients in the BUS group and 52 [17.9%] patients in the BUF group. The most common ADR was cortisol decreased [22.4% and 11.7% of patients, respectively]. Three cases [1.0%] of adrenal insufficiency in the BUS group, four cases [1.4%] of increased lipase in the BUF group, and three cases [1.0%] of headache in each group were reported. The cases of adrenal insufficiency did not require any steroid replacement, and these patients' serum cortisol levels returned to normal range after the end of the 4-week follow-up phase; none of the events was categorised as Addisonian crisis. All other types of ADRs had an incidence of less than 1%. Three BUS patients and two BUF patients withdrew from the study due to ADRs, including anal pruritis, cortisol decreased, adrenal insufficiency, and two cases of rash.

The mean values of morning cortisol levels changed by up to -0.12 µmol/L in the BUS group and by up to -0.05 µmol/L in the BUF group during the treatment period. Despite the decreases, the mean values per visit stayed within normal ranges. The proportion of patients with a cortisol change from 'normal/above normal' to 'below normal' was 13.2% in the BUS group and 7.3% in the BUF group. The cortisol suppression observed during treatment did not lead to clinically meaningful or continued endogenous cortisol suppression after the end of treatment. During the 4-week follow-up, serum cortisol normalised in both treatment groups, reaching

Table 3. Primary analysis of remission rates for clinical remission and mucosal healing by the end of treatment or discontinuation [PPS and FAS]

	BUS 4 mg	BUF 2 mg	*p*-value	Difference BUS 4 mg—BUF 2 mg	
	n [%]	*n* [%]		Estimate	95% CI
PPS	***N* = 250**	***N* = 261**			
Clinical remission					
Yes	197 [78.8]	194 [74.3]	0.00007	4.5%	-3.0%, 11.9%
No	53 [21.2]	67 [25.7]			
Mucosal healing					
Yes	203 [81.2]	212 [81.2]	0.00224	0.0%	-6.9%, 6.9%
No	47 [18.8]	49 [18.8]			
FAS	***N* = 281**	***N* = 290**			
Clinical remission					
Yes	211 [75.1]	204 [70.3]	0.00004	4.7%	-2.6%, 12.1%
No	70 [24.9]	86 [29.7]			
Mucosal healing					
Yes	214 [76.2]	220 [75.9]	0.00209	0.3%	-6.7%, 7.3%
No	67 [23.8]	70 [24.1]			

Clinical remission was defined as having a UC-DAI stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. Mucosal healing was defined as having a mucosal appearance subscore of 0 or 1. *p*-value: Farrington–Manning test [one-sided] with non-inferiority margin = 10%. 95% CI: 95% confidence interval for the difference of 4 mg BUS—2 mg BUF [asymptotic confidence interval].
BUS, budesonide suppository; BUF, budesonide foam; FAS, full analysis set; PPS, per-protocol set; CI, confidence interval; UC-DAI, Ulcerative Colitis-Disease Activity Index.

Table 4. Key secondary analyses of remission rates by the end of treatment or discontinuation [FAS]

	BUS 4 mg *N* = 281	BUF 2 mg *N* = 290	*p*-value	Difference BUS 4 mg—BUF 2 mg	
	n [%]	*n* [%]		Estimate	95% CI
CR + MH	186 [66.2]	185 [63.8]	0.00093	2.4	-5.4, 10.2
dMH	115 [40.9]	111 [38.3]	0.00095	2.6	-5.3, 10.6
dCR	125 [44.5]	118 [40.7]	0.00040	3.8	-4.3, 11.9
dCR + dMH	74 [26.3]	63 [21.7]	0.00002	4.6	-2.4, 11.7

Clinical remission [CR] was defined as having a modified UC-DAI stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. Mucosal healing [MH] was defined as having a mucosal appearance subscore of 0 or 1. Deepened clinical remission [dCR] was defined as having a stool frequency subscore of 0 and a rectal bleeding subscore of 0. Deepened mucosal healing [dMH] was defined as having a mucosal appearance subscore of 0. 95% confidence interval [CI] was calculated for remission rate by treatment group [Clopper–Pearson] or for the difference of remission rates between groups. *p*-value was calculated from Farrington–Manning test [one-sided] with non-inferiority margin = 10%.
BUS, budesonide suppository; BUF, budesonide foam; FAS, full analysis set; PPI, per-protocol set; CI, confidence interval; UC-DAI, Ulcerative Colitis-Disease Activity Index.

nearly baseline levels [*p*-value for within-group comparison: >0.05] [Supplementary Figure 4].

A slight leukocyte increase, more pronounced in the BUS group [mean change 0.69 × 10^9/L] than the BUF group [mean change 0.16 × 10^9/L], was observed. No other clinically relevant trends were observed in laboratory findings.

4. Discussion

In this study, both budesonide 4 mg rectal suppositories, a novel formulation, and budesonide 2 mg rectal foam demonstrated high therapeutic efficacy in the treatment of active ulcerative proctitis. BUS met the standards of non-inferiority in comparison with BUF in both co-primary endpoints: the induction of clinical remission and mucosal healing, and in both the PPS as well as the FAS population, indicating the robustness of the results.

Notably, results in all key secondary endpoints consistently supported the non-inferiority of BUS, including a more stringent composite endpoint, more stringent endpoints for clinical remission and mucosal healing, and the time to clinical symptom resolution. The time to resolution of clinical symptoms, including cessation of rectal bleeding, was numerically shorter in the BUS group compared with the BUF group. Significant greater reduction in the number of bloody stools in BUS group after only 2 weeks treatment suggested a potentially faster onset of mucosal healing. In addition, physician's global assessment scores indicated that more patients in the BUS group were considered to have achieved therapeutic success.

Of particular interest is the subgroup analysis in patients who were refractory or intolerant to rectal mesalazine treatment in previous flares of the disease. Though rates for clinical remission and mucosal healing were slightly lower in

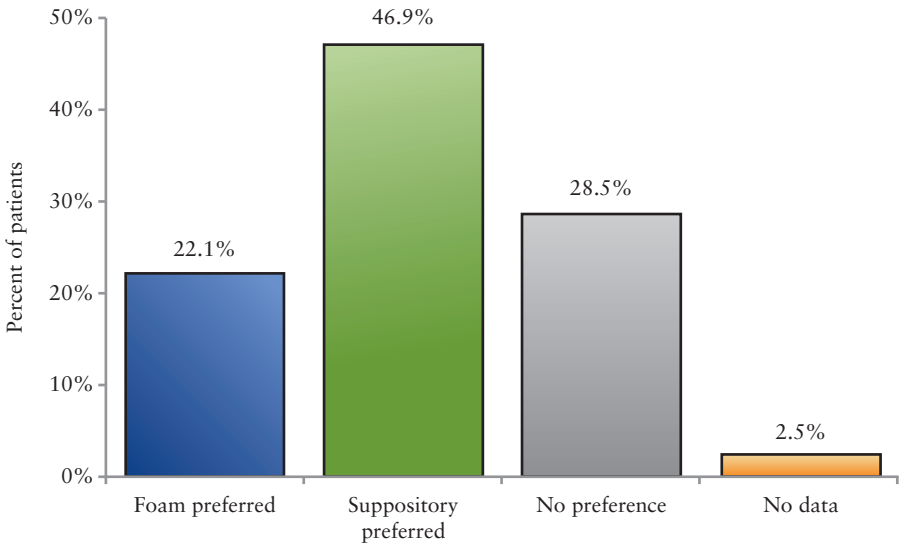

Figure 3. Patients' overall acceptance of budesonide rectal suppository [4 mg] and foam [2 mg], full analysis set [FAS].

Table 5. Overview of treatment-emergent adverse events [Safety Set]

	BUS 4 mg, *N* = 286		BUF 2 mg, *N* = 291		Total *N* = 577	
	n [%]	m	*n* [%]	m	*n* [%]	m
Any TEAE	141 [49.3]	231	119 [40.9]	212	260 [45.1]	443
SAEs	2 [0.7]	4	3 [1.0]	3	5 [0.9]	7
ADRs	79 [27.6]	94	52 [17.9]	63	131 [22.7]	157
Most common TEAEs[a]						
Cortisol decreased	69 [24.1]	71	39 [13.4]	40	108 [18.7]	111
Lipase increased	5 [1.7]	5	8 [2.7]	8	13 [2.3]	13
ALT increased	5 [1.7]	5	9 [3.1]	9	14 [2.4]	14
Nasopharyngitis	6 [2.1]	7	10 [3.4]	11	16 [2.8]	18
Colitis ulcerative	12 [4.2]	12	9 [3.1]	9	21 [3.6]	21
Adrenal insufficiency	3 [1.0]	3	0 [0.0]	0	3 [0.5]	3
Anorectal discomfort	0 [0.0]	0	3 [1.0]	3	3 [0.5]	3
Nausea	0 [0.0]	0	3 [1.0]	3	3 [0.5]	3
Headache	19 [6.6]	29	17 [5.8]	27	36 [6.2]	56
Leukocytosis	4 [1.4]	4	1 [0.3]	1	5 [0.9]	5
Dyspepsia	5 [1.7]	5	0 [0.0]	0	5 [0.9]	5
GGT increased	3 [1.0]	3	3 [1.0]	3	6 [1.0]	6
Abdominal pain	3 [1.0]	5	4 [1.4]	5	7 [1.2]	10
Blood ALP increased	2 [0.7]	2	5 [1.7]	5	7 [1.2]	7
Hypertension	4 [1.4]	4	3 [1.0]	3	7 [1.2]	7
Anaemia	4 [1.4]	4	4 [1.4]	4	8 [1.4]	8
Hyperkalaemia	5 [1.7]	5	3 [1.0]	3	8 [1.4]	8
AST increased	3 [1.0]	3	6 [2.1]	6	9 [1.6]	9

ADR, adverse drug reaction; m, number of events; *N*, number of patients; *n*, number of patients reporting adverse events; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; TEAE, treatment-emergent adverse event; SAE, serious adverse event; ADR, adverse drug reaction.
[a]≥1% of patients.

this subgroup than in the overall population, BUS showed a clear trend for beneficial effects in this distinct group of patients. An earlier study found that BUF 2 mg twice daily led to better outcomes in the subgroup with previous use of mesalazine suppository or enema than BUF 2 mg once daily.[23] The different effects between BUS and BUF may be related to the different doses of budesonide. A dose comparison study showed a daily dose of 2 mg budesonide to be the optimal dosage.[25] Another dose-finding, placebo-controlled trial found budesonide enemas to be effective and safe, with a dose of 2 mg/100 mL budesonide as the lowest effective dose for distal ulcerative colitis and proctitis.[26] A trial with budesonide

foam 2 mg twice daily for 2 weeks, followed by 2 mg once daily for 4 weeks, showed higher efficacy than placebo.[24]

The combination of rectal mesalazine and corticosteroids is recommended for active proctitis.[7,9,27,28] However results from a recent controlled clinical trial, comparing novel budesonide suppositories against a combined budesonide-and-mesalazine suppository therapy, showed no superiority of the combination over monotherapy with mesalazine or budesonide.[29]

Suppositories are a novel formulation of rectal application of budesonide, and few studies on this dose are available. A four-arm trial compared 2 mg budesonide daily, 4 mg budesonide daily, a combination of 2 mg budesonide and 1 g mesalazine, and 1 g mesalazine only. A non-significant trend towards higher efficacy was observed for 4 mg budesonide over 2 mg budesonide. In addition, 2 mg budesonide, but not 4 mg budesonide, was significantly inferior to 1 g mesalazine, making the 4 mg budesonide suppository the only valid alternative to mesalazine. Some clinicians presume that patients find rectal treatment less acceptable than oral treatment. A Swiss cohort study found liquid enema and foam preparations underused.[30] However, patient's acceptance may vary among different types of rectal applications. Previous studies have shown that rectal foam may present less interference with quality of life and better patient preference compared with enema.[15,31] A study comparing mesalamine suppository with hydrocortisone rectal foam reported superior 'practicability', as determined by a visual analogue scale, in favour of the suppository.[17] Since adherence to the therapy is crucial to achieve successful outcomes, patients were carefully questioned in our trial. For the first time, the once-daily application of suppositories at bedtime is shown as being preferred by patients for rectal drug delivery. Overall, the administration of suppositories is highly preferred compared with rectal foam. In addition, patients reported significant improvement from baseline in their quality of life and work productivity on validated questionnaires with both BUS and BUF treatments.

Both formulations of rectal budesonide were safe and well tolerated in this study. The characteristics and frequency of ADRs and laboratory abnormalities were consistent with the known favourable safety profile of topical budesonide.[32] Compared with baseline, morning cortisol levels at the end of treatment were significantly reduced in both treatment groups, but replacement with systemic corticosteroids was not required. In the post-treatment follow-up assessment, plasma cortisol levels returned to normal levels. Similar to a Japanese trial with daily 4 mg rectal BUF, our study showed that BUS 4 mg once daily over 8 weeks was well tolerated, suggesting that this regimen can be used without major safety concerns.[23]

A limitation of the study is the lack of a placebo arm. However, BUF has shown efficacy in placebo-[23] and active treatment-controlled studies and is approved as an established standard of care in the USA, Europe, and Japan. The demonstration of non-inferiority of BUS 4 mg in this study provides clinical evidence to support a new treatment option for ulcerative proctitis for patients who prefer the use of suppositories. In particular, the results of patients' preference for certain modalities of rectal therapy may be influenced by the attitude of the study population and may not be extrapolated to other populations. Centres from European countries participated in this trial; thus mainly White patients entered the trial. There was no intention to include or exclude any particular racial or ethnic groups from the trial. The generalisability of our findings may be limited in those without European ancestry.

Our study has certain strengths. The number of patients included exceeds the sample sizes in most similar trials. The double-dummy design allowed double-blind, direct comparison of both formulations and enabled valid investigation of morning versus evening administration. The extensive patient work-up conducted in the study has provided new insights into the preferences for different formulations of rectal therapy. The trial used an adaptive design with the possibility of a sample size adjustment at the interim analysis. Based on the results of the interim analysis, no adaptation was necessary and the trial proceeded with the original design.

Regarding the therapeutic implications of this study, budesonide suppository can be a valid option to treat active proctitis and an alternative to mesalazine for refractory proctitis. The latest European consensus paper recommends using rectal steroids for patients with active distal colitis.[33] Suppositories are the preferred modality of rectal therapy. Patients expressed a clear preference for a once-daily suppository at bedtime, which causes minor interference with daily life and an improvement of quality of life. Treatment according to patients' preference increases adherence to the therapy and may reduce health care costs.

In conclusion, budesonide 4 mg rectal suppository once daily was non-inferior to budesonide 2 mg rectal foam once daily in clinical efficacy, and was highly effective in inducing mucosal healing in patients with mild-to-moderate active ulcerative proctitis. The novel dosage form is tailored for targeted delivery to the rectum and is easy to administer. In the study, more patients reported preference for the suppository over the rectal foam. Both therapeutic modalities were safe and well tolerated. The safety profile of the novel budesonide suppository is consistent with worldwide experience of budesonide products. Budesonide 4 mg suppository once daily is a useful treatment option in ulcerative proctitis.

The data underlying this article will be shared on reasonable request to the corresponding author.

Funding

The study was sponsored by Dr. Falk Pharma GmbH.

Conflict of Interest

These authors disclose the following: WK, BS, MV have received honoraria from Dr. Falk Pharma GmbH. RG, RM, RMü are employees of Dr. Falk Pharma GmbH. The remaining authors disclose no conflicts.

Acknowledgments

The authors would like to thank: all patients and investigators for their participation and contribution to the study, and Martin Krauss [statistician], Tilo Andus [gastroenterologist], and Axel Dignaß [gastroenterologist] for serving as members of the Independent Data Monitoring Committee. The authors give special thanks to Janine Korn and Alexander Lürbke [both Proinnovera GmbH, Münster, Germany] for assistance in conducting the clinical trial, to Dieter Wohltmann† [X-act Cologne Clinical Research GmbH, Cologne, Germany;

†deceased] for his statistical expertise, and to Jun Yan [of Jun Yan Medical Writings] for providing native-speaker linguistic and grammatical review.

Author Contributions

Concept and study design: WK, SB, RM, RMü, RG; patient recruitment, data collection: KL, VS, LK, MS, GD, SVM, OAS, JP, YM, OD, SA, AD, OL, OA, PA, IPK, EM, OAb, MB, NK, VN, YU; central pathologist: MV; data analysis and interpretation: WK, SB, RM, RMü, RG; drafting the article: WK, RM; critical revision of the article: WK, SB, RM, RMü, RG. All authors had full access to all the data and had final responsibility for the decision to submit for publication.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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