Alimentary Pharmacology & Therapeutics

Clinical trial: randomized-controlled clinical study comparing the efficacy and safety of a low-volume vs. a high-volume mesalazine foam in active distal ulcerative colitis

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SUMMARY

Background
Rectally administered mesalazine (mesalamine; 5-aminosalicylic acid) is the first-line therapy for treatment of distal ulcerative colitis. Recently, a high-volume 5-aminosalicylic acid foam has been shown to be as effective and safe as standard 5-aminosalicylic acid enema.

Aim
To study the efficacy and safety of a low-volume vs. a high-volume 5-aminosalicylic acid foam.

Methods
In this investigator-blinded study, patients with active distal ulcerative colitis [Clinical Activity Index (CAI) > 4, Endoscopic Index ≥ 4] were randomized to receive 2×1 g/30 mL low-volume (n = 163) or 2×1 g/60 mL high-volume 5-aminosalicylic acid foam (n = 167) for 42 days. Primary end point was clinical remission (CAI ≤ 4) at the final/withdrawal visit (per-protocol).

Results
330 patients were evaluable for efficacy and safety by intention-to-treat, 290 for per-protocol analysis. Clinical remission rates at week 6 (per-protocol) were 77% on low-volume foam vs. 77% on high-volume foam (P = 0.00002 for non-inferiority). The low-volume foam was associated with a lower frequency of severe discomfort, pain and retention problems.

Conclusions
Low-volume 5-aminosalicylic acid foam is as effective and safe as a high-volume 5-aminosalicylic acid foam in the treatment of active distal ulcerative colitis, but offers compliance advantages compared to the high-volume preparation.

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INTRODUCTION

Ulcerative colitis (UC), a chronic inflammatory disease of the colon, usually begins in the rectum and spreads proximally via a continuous fashion. It is characterized by bloody diarrhoea, tenesm and abdominal cramps, causing varying degrees of physical as well as social disruption.

Salicylate type drugs are the treatment of choice in mild-to-moderate UC.[1–7] Rectal administration of such drugs is the treatment of choice in proctitis, proctosigmoiditis and left-sided colitis.[8–10] The rectal route is of particular benefit since local concentrations of the active drug are high, while systemic absorption is low. Thus, both efficacy and tolerability are optimized. Both, suppositories and enemas are widely used for the treatment of distal UC. While suppositories are effective only for proctitis, enemas will cover the entire left colon. However, due to their sometimes large volume, patients' acceptance may be a problem because of difficulties in self-administration, retention and prolonged bed rest.

Recently, a high-volume (1 g/60 mL) mesalazine (mesalamine; 5-aminosalicylic acid, 5-ASA) foam has been shown to be therapeutically equivalent to a standard 5-ASA enema.[11] Nevertheless, the totally applied volume of 120 mL is still high and might cause retention problems because of the release of foam under high pressure and its quick expansion, leading to a diminished acceptance and compliance of the patient.

In an effort to optimize further drug delivery and patients' compliance and acceptance, a new low-volume (1 g/30 mL) 5-ASA foam formulation has been developed, which releases the foam under a lower pressure and thus might diminish severe retention problems and thereby improves patients' acceptance and compliance. This low-volume 5-ASA foam was already found to be well tolerated and superior to placebo in the treatment of distal UC.[12] This study presents the head-to-head comparison of the efficacy and safety of this low-volume vs. the high-volume 5-ASA foam given for 6 weeks in patients with mild-to-moderately active distal UC.

MATERIALS AND METHODS

Study design

This was a single-blind (investigator-blinded), randomized, multicentre, parallel-group clinical trial comparing the efficacy and safety of a low-volume vs. a high-volume 5-ASA foam in mild-to-moderately active distal UC patients. The study was planned to be performed according to a sequential adaptive design. The first interim analysis was planned to be performed after 200 intention-to-treat (ITT) evaluable patients had finished the trial. The planned total sample size was 296 patients. The study was conducted in 40 centres in six countries: Israel (13 centres), Germany (nine), Hungary (seven), Lithuania (six), Latvia (three) and Estonia (two). Patients were assigned to the treatment groups based on a computer-generated randomization scheme. Because of the differences in the appearance of both foam cans, the distribution of study medication and handling of returned study medication was performed by a third person at each centre, who was not involved in any assessment, thus all investigators as well as the central pathologist were blinded to the formulation given. Treatment lasted 6 weeks, with control visits at 2 and 4 weeks. Patients were enrolled from March 2004 to March 2005. A sponsor-independent data monitoring committee reviewed unblinded data of the interim analyses. The study was conducted in accordance with GCP and the Declaration of Helsinki, and was approved by independent ethics committees for each of the centre.

Patients

Men and women aged 18–75 years with established or newly diagnosed active distal UC (maximum 40 cm from anus) confirmed by endoscopy, histology and negative stool cultures, and a Clinical Activity Index (CAI) > 4 and Endoscopic Index (EI) ≥ 4 (both according to Rachmilewitz) were allowed to be included.[13] Major exclusion criteria were: Crohn's disease, renal or liver insufficiency, steroids within 1 month and immunosuppressants within 3 months prior to baseline, relapse under daily maintenance of >1 g rectal or >2 g oral 5-ASA, or corresponding doses of rectal or oral sulfasalazine, concomitant use of NSAIDs for >2 weeks, antibiotics, psyllium containing drugs or loperamide. All oral or rectal treatments for UC were stopped at baseline. All patients had to give their written informed consent prior to their participation in this study.

Study medications

The test product was the low-volume (1 g/30 mL) 5-ASA foam (Salofalk 1 g foam), manufactured by

Dr Falk Pharma GmbH (Freiburg, Germany). The reference product was a high-volume (1 g/60 mL) 5-ASA foam (Claversal Rektalschaum), manufactured by Merckle Recordati GmbH (Ulm, Germany). Two puffs of the respective foam were to be administered once daily in the evening, if possible after defecation, resulting in a total foam volume of 60 (Salofalk 1 g foam) and 120 mL (Claversal Rektalschaum), respectively.

Procedures

At baseline, patients were physically examined and their demographics and medical history were recorded. Vital signs and laboratory tests, including haematology, biochemistry and urinalysis, were assessed at each visit. Clinical disease activity was primarily assessed at each visit using the CAI according to Rachmilewitz.[13] Disease was classified as mild if baseline CAI was ≤8 and as moderate if CAI >8. As a secondary efficacy score the Disease Activity Index (DAI) according to Sutherland was assessed at baseline and final visit.[14] The disease activity was also assessed endoscopically, by the same investigator at baseline and final visit, using the EI.[13] Biopsy specimens were taken at baseline and end of treatment, from the most inflamed area from the rectum and sigmoid, respectively, and were separately examined by a central pathologist, who was blinded to treatment, to determine the Histological Index (HI) according to Riley.[15] The total HI was based on the most severely inflamed segment. In addition, the physicians' global assessment (PGA) of efficacy was assessed at week 6.[16] Concomitant medications and adverse events (AEs) were recorded at each visit. Both patients and investigators gave their global assessment of tolerability of study medication ('very good', 'good', 'satisfactory' or 'poor') at the final visit.[11, 12]

Patient diaries

The number of bowel movements, presence of rectal bleeding, abdominal pain and cramps, and general well-being were daily recorded in a diary. In addition, the patient was asked to assess the handling and application of the study medication with respect to following items: 'Discomfort during administration', 'problems in retaining the study drug', 'rectal/abdominal pain during administration', 'abdominal bloating during/after administration' and to rate each item on a 5-point scale ('no problems', 'little problems', 'moderate problems', 'considerable problems' and 'severe problems'). Treatment compliance was assessed on the regular use of the study medication as recorded by the patient on a daily basis in the diary and by weighing the returned foam cans.

Primary objective and efficacy variable

The primary objective was to test the non-inferiority of the low-volume vs. the high-volume 5-ASA foam, with respect to clinical remission (defined by CAI ≤ 4) at the final visit [with last observation carried forward (LOCF) and a non-inferiority margin of 20% (one-sided $\alpha = 0.025$)]. Exploratory subgroup analyses were fixed in the protocol and included analyses by gender, duration of the disease (≤5 years vs. >5 years), baseline severity (CAI ≤ 8 vs. CAI > 8), and extent of disease (proctitis vs. proctosigmoiditis).

Secondary efficacy variables

Secondary efficacy end points included the CAI in the course of the study; clinical improvement at final visit (LOCF) based on the CAI (i.e. ≥1 point decrease from baseline); clinical remission based on the DAI [i.e. <4 at final visit (LOCF)]; mean change from baseline to final visit (LOCF) in the CAI, DAI and EI scores as well as in the number of stools and bloody stools per week; time to first resolution of symptoms defined as no more than three stools per day – all without blood; therapeutic success (i.e. PGA: 'complete relief' or 'marked improvement') and therapeutic benefit (i.e. PGA of at least 'slight improvement') at the final visit; endoscopical remission defined as an EI of <4 at the final visit (LOCF); mucosal healing defined as a $DAI_{mucosal}$ subscore of ≤1 at final visit (LOCF) and histological remission defined as a HI of 1 at the final visit (LOCF).

Safety variables

For the safety population, the frequency of AEs and clinically relevant changes in laboratory parameters and vital signs were assessed.

Statistical analysis

For proving therapeutic equivalence (non-inferiority) of low-volume vs. high-volume 5-ASA foam, a one-sided test hypothesis was used. The non-inferiority

margin was predefined as −20% for the difference of remission rates between treatments. Assuming a remission rate of 60% under treatment with low-volume foam vs. 64% under high-volume 5-ASA foam, a sample size of 148 patients in each treatment arm was calculated to achieve a 80% power to yield a statistical significant result. As the study was conducted using a 4-stage group sequential test design,[17, 18] the boundary *P*-value at the first interim analysis was given as $P_1 = 0.00570$, thus the overall type I error rate of $\alpha = 0.025$ (one-sided) was maintained.[19, 20] For confirmative proof of non-inferiority, the rate of clinical remission was tested using a χ^2 test with maximum likelihood estimation according to Farrington and Manning,[21] and differences between the remission rates and corresponding 97.5% one-sided repeated confidence intervals (CIs) were provided.[22] The confirmatory test was based on the per-protocol (PP) analysis set. For sensitivity analysis the ITT analysis was performed. All other group comparisons were of exploratory nature. For evaluation of secondary efficacy end points, 95% CIs were calculated for the differences between the two treatment groups (low- vs. high-volume foam). The median time to first symptomatic remission, in days, and the corresponding 95% CI was calculated for each treatment group using Kaplan–Meier estimation. Treatment groups were compared by calculating the hazard ratio and the corresponding 95% CI assuming proportional hazards.

RESULTS

Patients

A total of 330 patients were enrolled and randomized (low-volume foam: 163; high-volume foam: 167). There were no statistically significant differences between the treatment groups regarding the demographic variables, baseline disease characteristics or prestudy medication (Table 1).

Treatment compliance and protocol violations

All patients were treated and thus were evaluated in the safety and ITT population. The mean (s.d.) compliance to study drug administration per patient amounted to 97% (6%) in the low-volume and 95% (9%) in the high-volume foam group, respectively (ITT population). A total of 40 patients (low-volume foam: 17; high-volume foam: 23) were excluded from the PP population due to major protocol deviations (low-volume foam: 13; high-volume foam: 15), non-compliance (low-volume foam: 3; high-volume foam: 8) or premature study termination for reasons other than lack of efficacy or drug-related AEs (low-volume foam: 5; high-volume foam: 10). Thus, the PP population consisted of 290 patients.

The criteria used for exclusion from the PP data set were stated in the statistical analysis plan before breaking the blind. Major protocol deviations were almost equally distributed among the treatment groups. The most frequent major protocol violation was non-confirmation of UC (low-volume foam: 7; high-volume foam: 8) by the blinded, central pathologist. In 10 of these 15 patients, the disease was either newly diagnosed at baseline (by the central pathologist) or diagnosed within the very last few weeks or months prior to baseline by a local pathologist. Considerably more patients in the group receiving high-volume foam were excluded from PP analysis because of non-compliance or premature study termination caused by reasons other than lack of efficacy or drug-related AEs. The disposition of the patients enrolled in the study is provided in Figure 1.

Primary efficacy evaluation

Clinical remission at study end (LOCF) – based on CAI

Already at the first interim analysis, performed after approximately the first 200 ITT-evaluable patients, the test on non-inferiority of the two remissions rates [low-volume foam: 73%; high-volume foam: 74%; with difference of proportions (95% CI): −0.7% (−17.2% to 16.1%)] yielded a one-sided observed *P*-value of 0.00153 for the PP analysis set. Therefore, the recruitment of the study was stopped as non-inferiority was confirmatively proven. The final analysis of all 330 randomized patients confirmed the results of the interim analysis with an even more stringent 95% CI for the difference between the remission rates (low-volume foam: 77%; high-volume foam: 77%, see Figure 2). The clinical remission rates at the final/withdrawal visit did not show any difference between treatment groups in the PP population, but were slightly higher in the low-volume foam- than in high-volume foam-treated patients in the ITT population.

Table 1. Demographics and patients' baseline characteristics (intention-to-treat)

	Low-volume foam (n = 163)	High-volume foam (n = 167)
Sex, n (%)		
Male	80 (49)	69 (41)
Female	83 (51)	98 (59)
Ethnic origin [Caucasian, n (%)]	163 (100)	167 (100)
Age [years; mean (s.d.)]	43.9 (15.4)	42.0 (13.9)
Weight [kg; mean (s.d.)]	74.0 (15.0)	71.4 (14.1)
Smoking habits, n (%)		
Non-smoker	118 (72)	120 (72)
Ex-smoker	33 (20)	27 (16)
Smoker	12 (7)	20 (12)
Duration of the disease [years; median (range)]	4.2 (0.1–32.9)	3.5 (0.1–45.5)
Type of disease, n (%)		
New diagnosis	39 (24)	52 (31)
Established disease	124 (76)	115 (69)
Extraintestinal manifestations in the past (established disease)	22 (18%) [n = 124]	14 (12%) [n = 115]
Course of the established disease, n (%)		
Chronically active disease	6 (5) [n = 124]	9 (8) [n = 115]
Relapsing disease	118 (95) [n = 124]	106 (92) [n = 115]
Localization of the disease, n (%)		
Proctitis	91 (56)	85 (51)
Proctosigmoiditis	72 (44)	82 (49)
Number of previous episodes [relapsing disease; mean (s.d.)]	5.0 (6.4) [n = 117]	4.4 (4.6) [n = 105]
Duration of last remission phase [relapsing disease; years; median (range)]	0.7 (0.0–14.3) [n = 118]	0.9 (0.0–8.9) [n = 106]
Duration of present acute episode [relapsing disease; days; median (range)]	35.0 (3.0–687.0) [n = 118]	36.5 (5.0–352.0) [n = 106]
Prestudy maintenance medication*, n (%)	51 (43) [n = 118]	50 (47) [n = 106]
Oral 5-ASA, n (%)	34 (29)	37 (35)
Rectal 5-ASA, n (%)	14 (12)	8 (8)
Oral sulfasalazine, n (%)	7 (6)	10 (9)
Oral corticosteroids, n (%)	1 (0.8)	1 (0.9)
Length of inflammation [cm; mean (s.d.)]	22.6 (9.8)	22.9 (10.2)
CAI, mean (s.d.)	7.3 (1.7)	7.6 (1.9)
Severity of the disease, n (%)		
Mild (CAI ≤ 8)	128 (76)	126 (76)
Moderate (CAI > 8)	35 (25)	40 (24)
DAI, mean (s.d.)	7.1 (1.9)	7.3 (1.9)
EI, mean (s.d.)	7.5 (1.7)	7.5 (1.8)

CAI, Clinical Activity Index; DAI, Disease Activity Index; EI, Endoscopic Index; 5-ASA, 5-aminosalicylic acid.
* Doses of the prestudy medication did not violate the exclusion criterion.

Influence of covariates on clinical remission

The predefined exploratory subgroup analyses of the primary end point are presented for the ITT population in Table 2. Gender evaluation of the clinical remission rates showed no statistically significant differences between male and female patients, indicating that rectal 5-ASA seems to be equally effective in male and female patients. However, it should be noted that in contrast to the low-volume foam group in which males and females showed very similar remission rates (74% vs. 77%), less male patients in the high-volume foam group experienced clinical remission compared with females in this group (65% vs. 78%). Patients

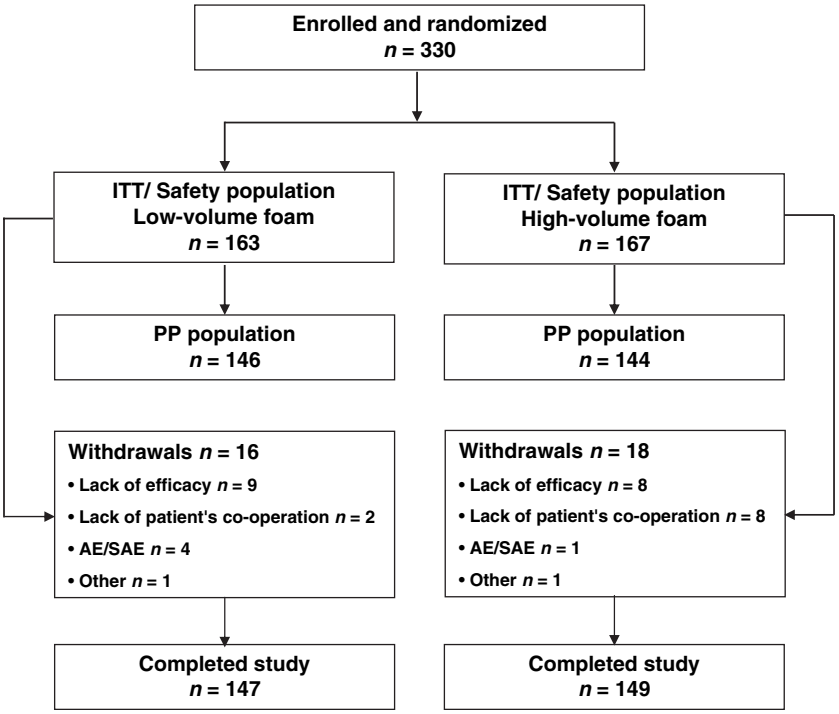
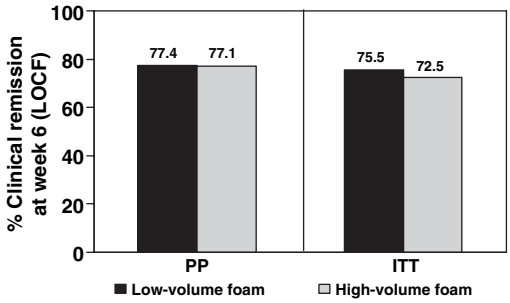


Figure 1. Patient disposition. AE, adverse event; ITT, intention-to-treat; PP, per-protocol; SAE, serious adverse event.

with a longer disease duration (>5 years) showed a slightly lower response to treatment (74% vs. 82% in the low-volume and 70% vs. 83% in the high-volume group, respectively) compared to those with a shorter disease duration; an observation which was also found in other trials of distal UC.[23] With respect to baseline severity, there was no difference in the remission rates between mild and moderately active patients in the low-volume foam group (76% vs. 74%). However, there was a clear difference seen in the high-volume foam group, i.e. patients with mild disease at baseline showed remission rates (78%) which were comparable to those in the low-volume foam group, whereas moderately active patients showed substantially lower remission rates (58%) ($P = 0.012$; χ^2 test, two-sided). The PP population showed nearly identical results.



Set	PP *n* = 290	ITT *n* = 330
P-value (one-sided)	0.00002	< 0.00001
Difference of proportions (Low-high-volume) (95% CI)	0.3% (–9.4%,10.0%)	3.0% (–6.5%, 12.4%)

Figure 2. Clinical remission rates (CAI ≤ 4) at week 6 (LOCF) at the final analysis of all randomized patients. ITT, intention-to-treat; LOCF, last observation carried forward; PP, per-protocol; CAI, Clinical Activity Index.

Secondary efficacy evaluation

The results of the ITT population presented below were nearly identical to the ones observed in the PP population.

CAI

In addition to the three quarters of patients showing clinical remission at week 6 (LOCF), 15% of the patients in both treatment groups showed a clinical improvement. With regard to clinically relevant subscores of the CAI at week 6 (LOCF), 64% and 57% of the patients in the low-volume and high-volume foam group, respectively, showed normalization in the number of stools, and 68% vs. 64% a complete disappearance of blood in their stools. Improvement in the number of stools was observed in further 12% and

Table 2. Clinical remission rates (CAI) by baseline covariates (intention-to-treat)

	Number (%) of patients in clinical remission (CAI ≤ 4) at final visit (LOCF)		
	Low-volume foam (n = 163)	High-volume foam (n = 167)	Adjusted odds ratio* (95% CI)
All	123 (76)	121 (73)	1.17 (0.71–1.91)
Gender			
Male	59/80 (74)	45/69 (65)	1.21 (0.74–1.98)
Female	64/83 (77)	76/98 (78)	
Duration (years)			
≤5	27/33 (82)	30/36 (83)	1.18 (0.72–1.94)
>5	96/130 (74)	91/131 (70)	
Severity (CAI at baseline)			
≤8 points (mild disease)	97/128 (76)	98/126 (78)	1.13 (0.69–1.85)
>8 points (moderate disease)	26/35 (74)	23/40 (58)	
Disease location			
Proctitis	71/91 (78)	64/85 (75)	1.15 (0.70–1.89)
Proctosigmoiditis	52/72 (72)	57/82 (70)	

CAI, Clinical Activity Index; CI, confidence interval; LOCF, last observation carried forward.
* Odds ratio for treatment groups low-volume vs. high-volume foam, adjusted for covariate. An odds ratio >1 indicates a benefit of the low-volume foam.

14% of the patients in the low-volume and high-volume foam group, and an improvement in the number of bloody stools in further 7% and 11%, respectively. A total of 45% of the patients in both treatment groups showed a normalization, and additionally 15% showed an improvement in their general well-being. In line with the above assessments, about 55% and 18% of patients each in both treatment groups had no abdominal pain or at least an improvement at study end, respectively.

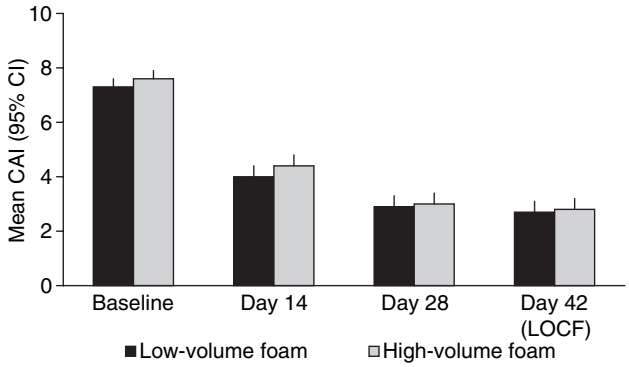


Figure 3. Course of the mean Clinical Activity Index during the study (ITT). ITT, intention-to-treat; LOCF, last observation carried forward.

The course of the CAI during the study (Figure 3), as well as the mean change from baseline in the CAI was nearly identical between both treatment groups (Table 4), indicating also the therapeutic equivalence of both drugs.

Time to first resolution of symptoms

The median time to first resolution of symptoms and the hazard ratios and their 95% CIs were nearly identical between both groups (Table 3).

Table 3. Time to first resolution of symptoms (time to event analysis)

	Median time to first resolution of symptoms (days)*			
	Low-volume foam	High-volume foam	Hazard ratio	95% confidence interval
PP	6.0	6.0	1.090	0.851–1.397
ITT	6.0	7.0	0.987	0.780–1.248

ITT, intention-to-treat, PP, per-protocol.
* Defined as no more than three stools per day – all without blood.

Table 4. Change from baseline to final visit (LOCF) in secondary efficacy end points (intention-to-treat population)

	Mean (s.d.) change [baseline to final visit (LOCF)]			
	Low-volume foam	High-volume foam	Difference between changes* (95% CI)	*t*-Test* (*P*-value)
CAI	−4.7 (3.1)	−4.8 (3.0)	0.2 (−0.5 to 0.8)	0.6089
DAI	−4.4 (2.6)	−4.4 (2.3)	0.1 (−0.5 to 0.6)	0.8481
EI	−4.1 (3.0)	−4.5 (2.8)	0.4 (−0.3 to 1.0)	0.2450
Number of stools/week	−14.0 (14.7)	−13.1 (16.3)	−0.8 (−4.2 to 2.5)	0.6264
Number of bloody stools/week	−17.1 (14.6)	−17.4 (16.9)	0.3 (−3.2 to 3.7)	0.8816

CAI, Clinical Activity Index; CI, confidence interval; DAI, Disease Activity Index; EI, Endoscopic Index; LOCF, last observation carried forward.
* Low-volume foam − high-volume foam.

Clinical remission at study end (LOCF) – based on DAI (secondary efficacy end point)

As a secondary efficacy end point, clinical remission was assessed by using the DAI score. Although the mean remission rates were slightly higher [105 of 157 patients (67%)] in the low-volume foam group compared with those in the high-volume foam group [99 of 162 patients (61%); see Figure 4], the mean change from baseline in the DAI did not differ between the treatment groups (Table 4), thus confirming the therapeutic equivalence of both drugs.

Endoscopic Index and Mucosal Healing (DAI)

A total of 59% and 62% of the patients in the low-volume and high-volume foam group, respectively, were in endoscopical remission at the final visit (LOCF; see Figure 4). An improvement in the EI was observed in further 18% and 17% of the patients in the low-volume and high-volume foam group, respectively. Also, the mean change from baseline in the EI was not significantly different between both treatment groups (Table 4).

Mucosal healing in the low-volume foam and high-volume foam group was observed in 116 of 163 patients (71%; 95% CI: 64.2–78.1%) and 118 of 167 patients (71%; 95% CI: 63.8–77.6%) in the ITT population, respectively (Figure 4), thus was nearly identical between both treatment groups.

Histological Index

Five patients in the low-volume foam group and four patients in the high-volume foam group, all with histological signs of acute UC at baseline recovered completely at the final visit (i.e. HI = 0). About half

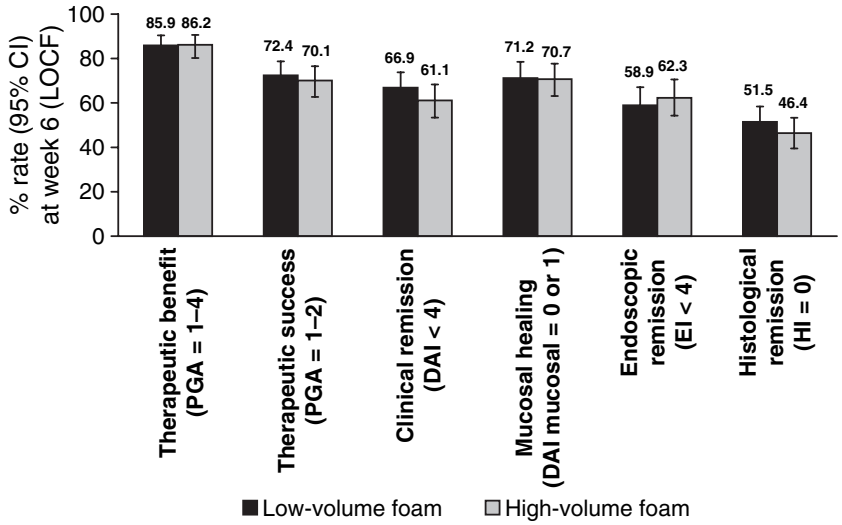


Figure 4. Secondary efficacy end points at week 6 [LOCF; (ITT)]. DAI, Disease Activity Index; EI, Endoscopic Index; HI, Histological Index; ITT, intention-to-treat; LOCF, last observation carried forward; PGA, Physician's Global Assessment.

the patients in both treatment groups showed a histological remission (HI = 1) at the final visit [low-volume foam (N = 136): 52%; high-volume foam (N = 140): 46%; see Figure 4]. Improvement in the HI was observed in approximately another quarter of the patients in both treatment groups [low-volume foam (N = 136): 24%; high-volume foam (N = 140): 26%]. Only one patient in the high-volume foam group had a deterioration in his HI compared to baseline.

Physician's Global Assessment

A total of 30% and 31% of the patients in the low- and high-volume foam group, respectively, reported complete relief of symptoms at the final visit; a marked improvement in symptoms was indicated by further 42% and 40% of the patients in both treatment groups. The proportion of patients with a moderate and slight improvement in symptoms were 7% each in the low-volume foam group, and 10% and 6% in the high-volume foam group, respectively. In the low- and high-volume foam group, 72% and 70% of the patients achieved therapeutic success and 86% and 86%, respectively, had a therapeutic benefit (see Figure 4).

Change from baseline in secondary efficacy end points

In general, no statistically significant or clinically meaningful differences in the mean change from baseline between both treatment groups were observed with regard to any of the secondary efficacy scores presented in Table 4.

Handling and application of the study drug

The vast majority of the patients in both treatment groups rated the handling and application of the foam as 'easy' or 'not too difficult'. Only 4% of all patients in the low-volume and 11% in the high-volume foam group assessed the handling as 'difficult' (ITT). In line with this finding, statistically more patients in the high-volume foam group reported considerable or severe problems regarding abdominal pain, retention and discomfort during administration when administrating the foam (see Table 5).

Adverse events

In total, 100 AEs were reported by 63 patients (39%) in the low-volume foam group, and 96 AEs by 62 patients (37%) in the high-volume foam group. The number of patients experiencing AEs, which were considered to be potentially drug-related (ADRs), were 13 (8%) in the low-volume foam and eight (5%) in the high-volume foam group.

Most frequently reported system organ classes were: gastrointestinal disorders, nervous system disorders, general disorders and administration site conditions, as well as infections and infestations (see Table 6).

Table 5. Problems during administration of the foam (intention-to-treat population)

	Number (%) of patients reporting considerable severe or severe problems during administration (LOCF)		
	Low-volume foam (n = 163)	High-volume foam (n = 167)	t-Test* (P-value)
Problems in retaining	17 (10)	31 (19)	0.0361
Considerable severe	12 (7)	21 (13)	
Severe	5 (3)	10 (6)	
Discomfort during administration	4 (3)	15 (9)	0.0109
Considerable severe	4 (3)	9 (5)	
Severe	–	6 (4)	
Pain during administration	3 (2)	11 (7)	0.0325
Considerable severe	2 (1)	8 (5)	
Severe	1 (0.6)	3 (2)	

LOCF, last observation carried forward.
* Low-volume foam − high-volume foam.

Table 6. Patients with at least one AE (safety population)

System organ class (MedDRA)	Number (%) of patients with at least one AE	
	Low-volume foam (n = 163)	High-volume foam (n = 167)
Gastrointestinal disorders	25 (15)	22 (13)
Nervous system disorders	15 (9)	18 (11)
Infections and infestations	18 (11)	10 (6)
General disorders and administration site conditions	7 (4)	8 (5)
Investigations	7 (4)	5 (3)
Musculoskeletal and connective tissue disorders	4 (3)	5 (3)
Skin and subcutaneous tissue disorders	4 (3)	2 (1)
Respiratory, thoracic and mediastinal disorders	2 (1)	4 (2)
Reproductive system and breast disorders	1 (0.6)	4 (2)
Hepatobiliary disorders	1 (0.6)	2 (1)
Psychiatric disorders	1 (0.6)	2 (1)
Injury, poisoning and procedural complications	0 (0)	2 (1)
Renal and urinary disorders	1 (0.6)	0 (0)
Cardiac disorders	0 (0)	1 (0.6)
Surgical and medical procedures	0 (0)	1 (0.6)
Vascular disorders	0 (0)	1 (0.6)

The vast majority of patients experienced AEs of mild (low-volume foam: 31%; high-volume foam: 29%) or moderate intensity (low-volume foam: 10%; high-volume foam: 11%). Adverse events of severe intensity occurred only in four patients of the low-volume foam group and in two patients of the high-volume foam group (most often 'colitis aggravated'). In total, four AEs, which were, due to the subsequent hospitalization, rated as serious (SAEs), occurred in four patients [low-volume foam: one patient (colitis aggravated); high-volume foam: two patients (colitis aggravated), one patient (total thyroidectomy)]. None of these SAEs was related to the study drug. No death occurred during this study. Eight AEs led to withdrawal of the study drug in seven patients treated with low-volume foam and five AEs led to withdrawal of the study drug in five patients treated with high-volume foam. 'Colitis aggravation' was the most frequent MedDRA term for withdrawal in both groups. All these patients recovered completely or were recovering during the follow-up period under treatment with systemic corticosteroids.

DISCUSSION

This is the first randomized, single-blinded clinical trial comparing head-to-head the efficacy and tolerability of a new low-volume (1 g/30 mL) vs. a high-volume (1 g/60 mL) 5-ASA foam. It was conducted to demonstrate the non-inferiority of the low-volume foam (Salofalk 1 g foam) to the high-volume foam (Claversal foam) with respect to induction of clinical remission in patients with active ulcerative proctitis or proctosigmoiditis.

At the final analysis of all 330 included patients, the clinical remission rates based on the CAI in the PP and ITT population were 77% in both treatment groups in the PP population, and 76% (low-volume) and 73% (high-volume) in the ITT population, respectively. The achieved lower boundaries of the 95% CI of the difference between proportions of the low- vs. the high-volume foam in the PP and ITT population were −9% and −7%, respectively, and thus indicating very robust data. Moreover, the rates for remission and improvement in the secondary end points (DAI, EI, HI and PGA) did not show any significant differences between the treatment groups. Similar to the primary end point, the remission rates in the low-volume foam group were, both in the ITT and in the PP population, nearly in all secondary end points numerically even slightly higher than the ones in the high-volume foam group, giving further proof that the low-volume foam is non-inferior to the high-volume foam. The achieved clinical remission rate for the low-volume foam in this trial (ITT: 76%) was even slightly better than the ones reported in previous trials with this foam: SAF-4 (ITT: 65%),[12] SAF-3 (ITT: 62%; remission defined as CAI <4).[24]

The trial results provide further insight into the question of rectal 5-ASA daily dose: given the high and rapid response observed in this trial, a daily dose of 2 g rectal 5-ASA is appropriate for the treatment of mild-to-moderate active proctosigmoiditis. Rectal 5-ASA induces mucosal healing in a substantial proportion of patients (approximately 70%) with mild-to-moderate active proctosigmoiditis. As mucosal healing is a predictor for risk reduction of colorectal cancer in UC,[25] this might partially explain the beneficial role of 5-ASA as a chemopreventative in UC.[26]

Endoscopic remission rates were remarkably similar between the current trial (ITT: 59%), and previous trials with the low-volume foam – SAF-4 (ITT: 57%)[12] and SAF-3 (57%; EI <6; assessed after 3 weeks).[24] These excellent efficacy data confirm the role of rectal 5-ASA therapy as a first choice strategy for the induction of remission in active distal UC, which is recommended by several guidelines.[1, 4, 5]

As the data confirm in a strong sense that both galenic 5-ASA foam preparations are equally effective in inducing remission in patients with mild-to-moderately active distal UC, the speculations about a potential superiority of the high-volume foam as discussed by Malchow *et al.* were obviously false.[11] However, as the entry criteria and the primary end point used in the current trial and the one published by Malchow *et al.*, are slightly different, we exploratively analysed our current data according to the definition used by Malchow *et al.*, to prove the robustness of our data. In the study of Malchow *et al.*, patients with established, recurrent disease were recruited, who had baseline sum score of the first four subscores of the CAI (CAI_{1-4}) ≥ 4; the primary end point (PP population) was defined as a $CAI_{1-4} \leq 2$ after 4 weeks of treatment (LOCF).[11] Using these definitions, 57 of 109 patients (52%) in the low-volume and 49 of 98 patients (50%) in the high-volume foam group came into clinical remission. Even if the remission rates with this definition were slightly lower compared with the ones reported by Malchow *et al.*, there was no statistical difference between both remission rates in this study.

Subgroup analysis showed that disease severity had no influence on the remission rates of the low-volume foam. The low-volume foam was equally effective both in mild (76%) and in moderate (74%) disease. In contrast, the high-volume foam had significantly less favourable results in moderate (58%) compared with mild disease (78%; $P = 0.012$; χ^2 test, two-sided).

Furthermore, disease extent had no impact on the treatment response. The low-volume foam and the high-volume foam worked reliably both in proctitis and proctosigmoiditis.

Both foam preparations induced a rapid resolution of clinical symptoms, which seems to be superior to oral 5-ASA preparations.[27, 28] This finding confirms that a rectal 5-ASA preparation, or even a combination of oral/rectal 5-ASA,[29] is the treatment of choice, when the extent of the UC is limited to the distal part of the colon. Moreover, as the 5-ASA plasma levels after rectal administration are lower than after oral intake,[30] a rectal administration provides an even better benefit/risk ratio for the treatment of distal UC.

Rectal 5-ASA administered either as a low-volume or a high-volume foam was found to be safe in this short-term trial, which is fully compatible with the published experience,[11, 12, 14, 31] as are the type and frequency of AEs.

The main reason for the development of a rectal 5-ASA foam is that foam preparations in general are easier to retain and are interfering less with daily routine than liquid enemas and hence are the preferred rectal formulation.[12, 23, 32] This finding was impressively confirmed in this trial. Considerable up to severe problems during the administration of a rectal product might have an impact on the long-term compliance to the treatment of such a patient. Interestingly, statistically significant less patients in the low-volume foam group reported considerable or severe pain or discomfort during the administration, or had considerable or severe problems in retaining the drug. These might be attributable to differences in the device (i.e. less rigid, lubricated applicator) and the lower volume per puff of the low-volume foam. Such advantages in application and convenience can contribute to further improvement in patients' adherence to previously fairly unpopular rectal treatment regimens in distal UC.

We conclude that the novel low-volume 5-ASA foam is a strongly effective and well-tolerated preparation, which has some advantages in patients' convenience compared to the comparator. This new preparation could extend patients' adherence to topical treatment.

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APPENDICES

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