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CERTIFICADO DE ESTUDIO POST – COMERCIALIZACIÓN SALOFALK SUPOSITORIOS 500 mg

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Saluda cordialmente,

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Clinical Trial: A Novel High-dose 1 g Mesalamine Suppository (Salofalk) Once Daily Is as Efficacious as a 500-mg Suppository Thrice Daily in Active Ulcerative Proctitis

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Background: Mesalamine suppositories are first-line therapy in active ulcerative proctitis; the standard regime still recommends multiple doses per day. The primary objective of this study was to show the noninferiority of once-daily administration of a novel 1 g mesalamine suppository versus thrice-daily administration of the 0.5 g mesalamine suppository.

Methods: This was a single-blind (investigator-blinded), randomized, multicenter, comparative, Phase III clinical trial. Patients with mild to moderately active ulcerative proctitis inserted either one mesalamine 1 g suppository at bedtime or one mesalamine 0.5 g suppository thrice daily over a 6-week period. The primary endpoint was rate of remission (Disease Activity Index below 4).

Results: In all, 354 patients were evaluable for safety and per-protocol analysis. The new regimen demonstrated noninferiority: The percentage of patients with remission was 87.9% for the once-daily 1 g mesalamine suppository and 90.7% for the thrice-daily 0.5 g mesalamine suppository. Each regimen resulted in prompt cessation of clinical symptoms (e.g., median time to $\leq$3 stools per day (all without blood): 5 days in the 1 g mesalamine once-daily and 7 days in the 0.5 g mesalamine thrice-daily group). Patients preferred applying suppositories once a day.

Conclusions: In active ulcerative proctitis the once-daily administration of a 1 g mesalamine suppository is as effective and safe, yet considerably more convenient, than the standard thrice-daily administration of a 0.5 g mesalamine suppository.

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Key Words: mesalamine, N-acetyltransferase, once-daily, proctitis, suppository, distal ulcerative colitis

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) of the colon. It is characterized by bloody diarrhea, tenesmus, and abdominal cramps. Some patients suffer from bowel symptoms accompanied by extraintestinal and systemic manifestations such as arthropathy, pyoderma gangrenosum, erythema nodosum, keratitis, uveitis, fever, and anemia. Inflammation of the colon can be detected in the rectum alone or extending continuously upwards into the sigmoid colon, part of or the entire colon, and as so-called backwash ileitis even into the terminal ileum.

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Local and systemic administration of aminosalicylates such as mesalamine are the treatment of choice in mild to moderate UC.[1–6] Mesalamine's mechanism of action is not yet fully understood; the latest findings implicate peroxisome proliferator-activated receptor gamma and intestinal bacteria as pharmacological targets.[7,8] Rectal administration of mesalamine is the first-line treatment of choice in mild-moderate proctitis, proctosigmoiditis, and left-sided colitis.[9–11] Local treatment is particularly beneficial, since local concentrations of the active drug are high, while systemic absorption is low. Although there is an increasing appreciation of transport processes as determinants of drug disposition, the role of intestinal drug transporters for absorption of mesalamine, e.g., P-glycoprotein, a product of the multidrug resistance 1 (*MDR1*) gene, is not yet elucidated.[12] The cytosolic N-acetyltransferases (NAT1 and NAT2) expressed in the liver but locally in the intestinal mucosa as well are responsible for the biotransformation of mesalamine to the pharmacologically inactive metabolite N-acetylmesalamine.[13] Thus, both efficacy and tolerability are optimized by local administration of mesalamine.

Suppositories, enemas, and foam preparations are widely used for the treatment of distal UC. While suppositories are effective only for proctitis, enemas and foam preparations cover the entire left colon. The major problem with local treatment is compliance/adherence.[14] Most patients find it easier to take a tablet than insert a suppository or clysma.[15,16] To optimize adherence, one administration per day would be an advantage compared to two or three applications every day. An early study by Gionchetti et al. revealed the superiority of 1 g mesalamine versus 2 $\times$ 0.5 g per day.[17] Therefore, a new mesalamine suppository containing 1 g of mesalamine was developed.

We chose the dose of 1 g because an earlier study had shown a dose of 1 g/d to be just as effective as 1.5 g/d.[18] We compared this new mesalamine suppository given once daily in the evening with the standard regimen of 3 $\times$ 0.5 g per day for efficacy, side effects, and patient satisfaction.

MATERIALS AND METHODS

Study Design

This was a single-blind (investigator-blinded), randomized, multicenter, comparative, Phase III clinical trial in patients suffering from mild to moderately active ulcerative proctitis. The study was planned according to a three-stage group sequential adaptive design with optional sample-size adjustments to be done at two interim analyses. The first interim analysis was to take place after 2 $\times$ 85 per-protocol (PP) evaluable patients had finished the trial. The projected total sample size was 380 patients. The study was conducted in 35 centers in four countries: Israel (10 centers), Germany (5), Russia (13), and Ukraine (7), with two arms (parallel group design) comparing two different rectal mesalamine suppository formulations. In order to ensure blindness of the investigator, the distribution and return of study medication as well as all checks of patient diaries were performed by a third person not involved in any assessment at the center. Treatment lasted for 6 weeks (42 days), with control visits scheduled at 2 and 4 weeks after the start of treatment. An independent data monitoring committee reviewed unblinded data at the interim analyses and provided its recommendations to modify, put on hold, or stop the trial for a center or entirely to the sponsor and coordinating investigator (T.A.), who then took appropriate action. The study was conducted in accordance with good clinical practice, the Declaration of Helsinki, and all applicable national laws, and was approved by independent ethics committees at each of the centers prior to starting the study. The EudraCT number is 2004-005018-35.

Patients

Men and women aged 18–75 years with established or newly-diagnosed active ulcerative proctitis (maximal 15 cm of rectum) confirmed by endoscopy, histology, negative stool cultures, and 3 $<$ Disease Activity Index (DAI) $<$ 11 were included.

Excluded were patients with Crohn's disease, with proctitis of a different origin, prior bowel resection leading to diarrhea, and/or pouch formation, toxic megacolon, hemorrhagic diathesis, present or past colorectal cancer, or serious other secondary disease(s). The use of steroids or cycloferon within 1 month, immunosuppressants or anti-TNF-α within 3 months prior to inclusion was also prohibited. Patients who had relapsed during daily maintenance of $>$0.5 g rectal or $>$2 g oral mesalamine, or corresponding doses of rectal or oral sulfasalazine, as well as those with transaminases or alkaline phosphatase levels $\geq$2 $\times$ upper limit of normal or serum creatinine $>$1.5 mg/dL were excluded as well.

The use of nonsteroidal antiinflammatory drugs (NSAIDs) for $>$6 weeks, as well as antibiotics (metronidazole, ciprofloxacin), drugs containing psyllium, *E. coli* Nissle 1917, or loperamide was forbidden during the trial. All oral or rectal treatments for UC had to have ceased prior to study inclusion. Female patients had to have a negative pregnancy test at baseline. All patients gave written informed consent prior to participating in this study.

Study Medications

The test product was the novel 1 g mesalamine suppository (Salofalk 1 g suppository); the reference product was the 0.5 g mesalamine suppository (Salofalk 500 mg suppository). The novel 1 g mesalamine suppository is

characterized by a slow rate of systemic absorption (time to peak concentration about 7 hours) and a long mean terminal elimination half-life of 8 hours. Both drugs were manufactured by Dr. Falk Pharma (Freiburg, Germany). One 1 g mesalamine suppository was administered once daily (OD) at bedtime, the 0.5 g mesalamine suppositories three times daily (TID; morning, noon, and bedtime).

Procedures

At baseline all patients underwent a physical examination and their demographics and medical history were recorded. Vital signs and routine laboratory values were assessed at each visit. The DAI according to Sutherland et al.[19] was assessed at baseline and the final visit. Furthermore, efficacy was assessed with the following scores/scales: the Endoscopic Index (EI)[20] assessed by the same investigator at baseline and the final visit, the Histological Index (HI) according to Riley et al.[21] assessed from biopsies taken at baseline and the end of treatment, and Physicians' Global Assessment (PGA) of efficacy[22] assessed at week 6. The patients' acceptance of and preference for a study drug was evaluated at the final examination or upon the patient's withdrawal. Concomitant medications and adverse events (AEs) were documented at every visit. The patients had to return unused study medication at every visit.

Patient Diaries

The patients recorded the number of stools, presence and degree of rectal bleeding, abdominal pain and cramps, suffering from tenesmus, mucus in or on the stools, general well-being, and regular use of study medications on a daily basis in a diary.

Primary Objective and Efficacy Variable

The primary objective of this study was to show the noninferiority of once-daily administration of the novel 1 g mesalamine suppository versus thrice-daily administration of the 0.5 g mesalamine suppository, examining the proportion of patients (PP analysis set) with clinical remission defined as DAI <4 at the final visit (with last observation carried forward, LOCF), considering a noninferiority margin of 15% (one-sided $\alpha = 0.025$). Exploratory subgroup analyses of the primary endpoint were already fixed in the protocol and included analyses by gender, disease duration (≤ 5 years versus > 5 years), baseline severity (DAI ≤ 6 versus DAI >6), and smoking history.

Secondary Efficacy Variables

Secondary efficacy endpoints (intention-to-treat, ITT, analysis set) included clinical improvement (≥ 1 point decrease in DAI from baseline to final visit (LOCF)); mucosal healing ($DAI_{mucosal}$ subscore according to the FDA recommendations ≤ 1 at final visit (LOCF)); endoscopic remission (EI <4 at final visit (LOCF)); histological remission (remission according to the assessment of the pathologist at final visit (LOCF)); time to first resolution of symptoms (≤ 3 stools per day (all without blood)); therapeutic success (PGA assessed as "complete relief" or "marked improvement") and therapeutic benefit (PGA at least assessed as "slight improvement") at final visit; and acceptance and preference for the study drug.

Treatment Compliance

Treatment compliance was calculated as the proportion of suppositories taken (difference between the number of suppositories issued and returned) compared to the prescribed number of suppositories.

Safety Variables

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

Pharmacogenetics

The patients were genotyped for polymorphisms of *MDR1* (2677G>T/A and 3435C>T), as well as of the cytosolic N-acetyltransferases *NAT1* (190C>T, 559C>T, 560G>A, 640T>G, 752T>G, 1088T>A, and 1095C>A) and *NAT2* (191G>A, 282C>T, 341C>T, 481C>T, 590G>A, 803A>G, and 857G>A).

Single nucleotide polymorphisms were determined by polymerase chain reaction (PCR) / restriction fragment length polymorphism (RFLP) and sequencing, and addressed haplotype combinations as published previously.[23,24] Patients were stratified for statistical analysis according to the literature[25–27] to distinguish between putatively rapid or slow NAT1 or NAT2 acetylator phenotypes and high or low active *MDR1* haplotype combinations, respectively.

Statistical Analysis

Efficacy analyses were performed according to the ITT principle as well as on patients without major protocol deviations (PP population). The safety analysis set included all patients treated who had at least one follow-up value for safety variables to be analyzed.

The primary objective of the study was to demonstrate the noninferiority of 1 g mesalamine OD compared to 0.5 g mesalamine TID with respect to the rate of patients with clinical remission at the final visit (considering a noninferiority margin of 15%).

The study was conducted using a three-stage adaptive group sequential test design of O'Brien and Fleming.[28] For (one-sided) $\alpha = 0.025$ and information rates of 0.50, 0.75, and 1, the resulting boundary P-values were given by $P1$

TABLE 1. Demographics and Patients' Baseline Characteristics (ITT Population)

		1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
Sex			
Male	*n* (%)	85 (42.5%)	93 (45.8%)
Female	*n* (%)	115 (57.5%)	110 (54.2%)
Ethnic origin	Caucasian: *n* (%)	200 (100.0%)	203 (100.0%)
Age [years]	Mean (SD)	41.4 (13.2)	42.7 (13.9)
Weight [kg]	Mean (SD)	70.3 (15.1)	70.0 (13.9)
Smoking habits			
Nonsmoker	*n* (%)	155 (77.5%)	161 (79.3%)
Exsmoker	*n* (%)	25 (12.5%)	27 (13.3%)
Smoker	*n* (%)	20 (10.0%)	15 (7.4%)
Duration of the disease [years]	Median (range)	2.2 (0.0 – 36.7)	3.8 (0.0 – 31.9)
Patients with extraintestinal disease symptoms	*n* (%)	32 (16.0%)	29 (14.3%)
Course of the disease			
New diagnosis*	*n* (%)	42 (21.0%)	34 (16.7%)
Continuous	*n* (%)	16 (8.0%)	8 (3.9%)
Recurrent	*n* (%)	142 (71.0%)	161 (79.3%)
Number of previous acute episodes			
Based on all patients	Mean (SD)	3.4 (5.7) [$n = 198$]	4.8 (7.0) [$n = 201$]
Based on patients with a recurrent course of the disease only	Mean (SD)	4.8 (6.2) [$n = 140$]	6.0 (7.4) [$n = 159$]
Duration of last remission phase [months]	Median (range)	6.0 (0.00 – 112.0) [$n = 142$]	7.0 (0.00 – 226.0) [$n = 161$]
Duration of current acute episode [months]	Median (range)	1.0 (0.0 – 158.0)	1.0 (0.0 – 110.0)
Patients with previous bowel operations	*n* (%)	11 (5.5%)	7 (3.4%)
Disease Activity Index (DAI)	Mean (SD)	6.2 (1.6) [$n = 200$]	6.2 (1.5) [$n = 201$]
Number of stools [per week]	Mean (SD)	23.1 (15.8) [$n = 200$]	22.7 (13.3) [$n = 201$]
Number of bloody stools [per week]	Mean (SD)	15.9 (15.1) [$n = 200$]	14.9 (11.1) [$n = 201$]
Endoscopic Index (EI)	Mean (SD)	6.8 (2.0)	6.6 (2.0)

*New diagnosis is defined as "duration of disease <6 months" and "course of the ulcerative proctitis" = continuous.

$= 0.00210$, $P2 = 0.00971$, and $P3 = 0.02148$, with critical values 2.863, 2.337, and 2.024, respectively.

The sample size calculation yielded a total of $2 \times 172 = 344$ patients.[29] To prevent a loss of power due to exclusion of protocol deviators from the PP analysis set (≈10%) a total of 380 patients were planned to be enrolled.

For confirmatory testing of H_0 at the interim and final analyses, we used the inverse-normal method of combining the *P*-values of the one-sided shifted asymptotic χ^2-test for comparing two rates and maximum likelihood estimation for the unknown parameters according to Farrington and Manning.[30] All other group comparisons were of an exploratory nature.

Where appropriate, missing values at the final or withdrawal visit were imputed by the last measurement obtained during treatment (LOCF).

Differences in change in DAI, EI, and HI between putatively rapid or slow NAT1 or NAT2 acetylator phenotypes or high or low active *MDR1* haplotype combinations were tested within and between study arms using the Mann–Whitney test.

RESULTS

Patients

A total of 408 patients were allocated to randomized treatment (201 to 1 g mesalamine OD and 207 to 0.5 g mesalamine TID). In all, 403 patients were treated and had at least one follow-up value for safety analysis. Thus, 403 patients were evaluated in the safety and ITT population (200 in the 1 g mesalamine OD and 203 in the 0.5 g mesalamine TID group).

There were no relevant differences between treatment groups regarding demographic variables (Table 1). We observed no relevant difference in anamnestic characteristics at baseline, the exceptions being: longer disease duration, a higher number of previous acute episodes, and a slightly higher proportion of patients with a recurrent acute

ulcerative proctitis in the 0.5 g mesalamine TID group, as well as a slightly higher proportion of patients with a new diagnosis of acute ulcerative proctitis and continuous disease in the 1 g mesalamine OD group (Table 1). The anamnestic characteristics in the PP analysis set were almost identical to those in the ITT analysis set.

Protocol Violations

A total of 54 patients (1 g mesalamine OD: 19; 0.5 g mesalamine TID: 35) were excluded from the PP analysis set due to major protocol deviations, noncompliance or premature study termination caused by reasons unrelated to the study medication. The PP population thus consisted of 354 patients. The criteria used for exclusion from the PP dataset were stated in the Statistical Analysis Plan before breaking the blind. Especially the number of patients showing a major protocol deviation was clearly higher in the 0.5 g mesalamine TID (23 patients) than in the 1 g mesalamine OD group (14 patients).

Primary Efficacy Evaluation

Clinical Remission at Study End (LOCF) - Based on DAI

At the first interim analysis, performed after 145 PP-evaluable patients had completed the study, the shifted asymptotic χ^2-test for comparing two remission rates (1 g mesalamine OD: 82.2%; 0.5 g mesalamine TID: 88.9%) yielded a one-sided observed *P*-value of 0.0819 for the PP analysis set (noninferiority margin: 15%). This *P*-value exceeded the boundary *P*-value of 0.0021. The null hypothesis could thus not be rejected, the study was continued, and the number of patients to be evaluable for PP analysis at the second stage was increased to 120.

At the second interim analysis, performed after another 125 PP-evaluable patients had completed the study, the shifted asymptotic χ^2-test for comparing two remission rates (stage 1: 1 g mesalamine OD: 83.8%; 0.5 g mesalamine TID: 88.7% and stage 2: 1 g mesalamine OD: 89.4%; 0.5 g mesalamine TID: 91.5%) yielded an inverse normal of 2.692 for the PP analysis set (noninferiority margin: 15%). The inverse normal exceeded the critical value of 2.337. The null hypothesis was rejected, noninferiority of 1 g mesalamine OD versus 0.5 g mesalamine TID considering a noninferiority margin of 15% was proven in the confirmatory sense and recruitment was stopped.

Since recruitment continued during the second interim analysis, another 93 patients had been enrolled when the results of the interim analysis became available. We continued to observe these patients, and the final analysis included a total of 354 PP-evaluable patients. At the final analysis the shifted asymptotic χ^2-test comparing two remission rates (overall remission rates: 1 g mesalamine OD: 87.9%; 0.5 g mesalamine TID: 90.7%) yielded a one-sided overall *P*-value of 0.00027 for the PP analysis set (noninferiority margin: 15%). This *P*-value was clearly lower than the global α (0.025). According to the group sequential design, the second interim analysis yielded our confirmatory result. The result of the final analysis was interpreted only in the exploratory sense, yet it demonstrated the robustness of the result.

TABLE 2. Clinical Remission Rates (DAI) by Baseline Covariates (ITT Population)

	Number (%) of Patients in Clinical Remission (DAI <4) at the Final/Withdrawal Visit	
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
All	168 (84.0%)	172 (84.7%)
Smoking status		
Nonsmoker	130/155 (83.9%)	140/161 (87.0%)
Exsmoker	21/25 (84.0%)	21/27 (77.8%)
Smoker	17/20 (85.0%)	11/15 (73.3%)
Duration		
$\leq$ 5 years	112/134 (83.6%)	108/123 (87.8%)
$>$ 5 years	56/66 (84.8%)	64/80 (80.0%)
Gender		
Male	68/85 (80.0%)	73/93 (78.5%)
Female	100/115 (87.0%)	99/110 (90.0%)
Severity (DAI at baseline)		
$\leq$ 6 points (mild)	106/118 (89.8%)	99/114 (86.8%)
$>$ 6 points (moderate, severe)	62/82 (75.6%)	72/87 (82.8%)
Extraintestinal symptoms		
Absence	145/168 (86.3%)	152/174 (87.4%)
Presence	23/32 (71.9%)	20/29 (59.0%)

DAI, Disease Activity Index.

Influence of Covariates on Clinical Remission

The predefined exploratory subgroup analyses of the primary endpoint are illustrated for the ITT population in Table 2. Overall, clinical remission rates were higher in females than in males, in patients with mild active ulcerative proctitis (represented by a DAI $\leq$6 points at baseline) than in patients with moderate or severe active ulcerative proctitis (DAI $>$6 points at baseline), and in patients without than in patients with extraintestinal disease symptoms.

Secondary Efficacy Evaluation

DAI, EI, HI, PGA, and Time to First Resolution of Symptoms (ITT Population)

Remission and improvement rates based on DAI, EI, HI, and mucosal healing rates based on the $DAI_{mucosal}$ subscore

TABLE 3. Secondary Efficacy Endpoints (ITT Population)

			1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
DAI*	Clinical improvement[a]	n (%)	186 (93.5%) $n = 199$	184 (92.0%) $n = 200$
	Mucosal healing[b]	n (%)	172 (86.0%) $n = 200$	175 (86.2%) $n = 203$
EI*	Endoscopic remission[c]	n (%)	153 (80.1%) $n = 191$	164 (85.4%) $n = 192$
HI	Histological remission[d]	n (%)	83 (55.3%) $n = 150$	91 (67.9%) $n = 134$
PGA*	Therapeutic success	n (%)	168 (84.0%) $n = 200$	173 (85.2%) $n = 203$
	Therapeutic benefit	n (%)	192 (96.0%) $n = 200$	196 (96.6%) $n = 203$
Time to first resolution of symptoms*,[e]		days; median [95%-CI]	5.0 [4.0, 6.0] $n = 200$	7.0 [5.0, 8.0] $n = 203$

*No significant difference between treatments.
[a]Decrease in DAI by $\geq$1 point from baseline; DAI >3 at baseline.
[b]$DAI_{mucosal}$ subscore according to the FDA recommendations $\leq$1, i.e., "intact mucosa with preserved or distorted vessels" or "erythema, decreased vascular pattern, granularity, no mucosal hemorrhage."
[c]EI <4.
[d]Remission according to the assessment of the pathologist.
[e]Defined as no more than three stools per day, all without blood.
DAI, Disease Activity Index; EI, Endoscopic Index; HI, Histological Index; PGA, Physician's global assessment; CI, confidence interval.

according to the FDA recommendations, PGA, as well as time to first resolution of symptoms are presented in Table 3.

Except for a higher rate of patients with histological remission in the 0.5 g mesalamine TID than in the 1 g mesalamine OD group, DAI, and EI did not show any relevant differences between treatment groups. Also, the apparent difference in PGA and in median time to first resolution of symptoms were not statistically significant.

Acceptance of and Preference for the Study Drug (ITT Population)

Patients rated the study drug administration better and reported less interference with their daily routine in the 1 g mesalamine OD than the 0.5 g mesalamine TID group (Table 4). The vast majority of patients preferred applying 1 suppository/day in the evening rather than 3 suppositories/day (morning, noon, and bedtime) (Table 4).

TABLE 4. Acceptance of and Preference for the Study Drug (ITT Population)

	Number (%) of Patients with a Certain Assessment of Acceptance and Preference		
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)	χ^2-test* P-value
Administration of the study drug			0.0043
Easy	179 (89.5%)	158 (77.8%)	
Not too difficult	17 (8.5%)	40 (19.7%)	
Difficult	2 (1.0%)	1 (0.5%)	
No remark	2 (1.0%)	4 (2.0%)	
Interference with daily routine			< 0.0001
Considerably	17 (8.5%)	24 (11.8%)	
Not too much	45 (22.5%)	89 (43.8%)	
Almost not	136 (68.0%)	86 (42.4%)	
No remark	2 (1.0%)	4 (2.0%)	
Preference of intake frequency			0.0010
Preference for OD intake	185 (92.5%)	163 (80.3%)	
Preference for TID intake	1 (0.5%)	10 (4.9%)	
No preference	12 (6.0%)	26 (12.8%)	
No remark	2 (1.0%)	4 (2.0%)	

*1 g mesalamine OD – 0.5 g mesalamine TID.

TABLE 5. Effect of *MDR1*, *NAT1*, and *NAT2* Genotypes on DAI, EI, and HI in Each Study Arm

	Mean (SD) Change from Baseline to Final Visit/Final Examination (LOCF) in:		
	DAI	EI	HI
1.0 g mesalamine OD			
MDR1 2677TT/3435TT[a]	−4.7 (2.2) $n = 37$	−4.9 (2.5) $n = 37$	−1.5 (1.2) $n = 36$
MDR1 2677GG/3435CC[b]	−4.9 (1.7) $n = 33$	−5.3 (2.2) $n = 33$	−0.8 (1.2)* $n = 31$
NAT1 slow acetylators	−5.0 (1.8) $n = 105$	−5.4 (2.3) $n = 105$	−1.1 (1.1) $n = 102$
NAT1 rapid acetylators	−4.5 (0.7) $n = 2$	−6.0 (1.4) $n = 2$	−1.0 (1.4) $n = 2$
NAT2 slow acetylators	−4.9 (2.1) $n = 101$	−5.2 (2.6) $n = 101$	−1.0 (1.2) $n = 97$
NAT2 rapid acetylators	−4.9 (1.6) $n = 10$	−4.9 (2.6) $n = 10$	−1.4 (0.8) $n = 10$
0.5 g mesalamine TID			
MDR1 2677TT/3435TT[a]	−5.0 (1.7) $n = 29$	−6.0 (2.1) $n = 29$	−0.9 (1.2) $n = 28$
MDR1 2677GG/3435CC[b]	−4.0 (2.2) $n = 23$	−5.0 (3.4) $n = 23$	−1.0 (1.4) $n = 22$
NAT1 slow acetylators	−4.6 (1.9) $n = 104$	−5.0 (2.4) $n = 104$	−1.0 (1.3) $n = 103$
NAT1 rapid acetylators	−6.0 (0.0) $n = 4$	−7.0 (2.8) $n = 4$	−2.5 (0.6)** $n = 4$
NAT2 slow acetylators	−4.7 (1.9) $n = 92$	−5.0 (2.4) $n = 92$	−1.0 (1.2) $n = 91$
NAT2 rapid acetylators	−4.4 (2.1) $n = 7$	−5.9 (3.7) $n = 7$	−1.4 (2.4) $n = 5$

[a]Putatively low activity.
[b]Putatively high activity.
DAI, disease activity index; EI, endoscopic index; HI, histological index; *MDR1*, multidrug resistance gene 1; NAT1, NAT2; N-acetyltransferases.
*$P < 0.05$ vs. *MDR1* 2677TT/3435TT.
**$P < 0.05$ vs. NAT1 slow acetylators.

Treatment Compliance

In all, 99.5% of the patients in the 1 g mesalamine OD and 98.5% of the patients in the 0.5 g mesalamine TID group were considered compliant since they took at least 80% of the prescribed number of suppositories.

Genotyping

Genotyping was performed in 315 patients of the PP population. The allelic frequency distribution of the single nucleotide polymorphisms investigated in this study population did not differ from our reference population, nor did we observe any significant deviations from the Hardy–Weinberg equilibrium. Mean (SD) changes in DAI, EI, and HI in putatively lowly active (2677TT/3435TT) and highly active (2677GG/3435CC) *MDR1* diplotypes, in NAT1 slow and rapid acetylators, as well as in NAT2 slow and rapid acetylators are compared in Table 5. We found no significant differences except 1) the higher histological response (change in HI) for NAT1 rapid acetylators compared to NAT1 slow acetylators in the 0.5 g mesalamine TID group only, and 2) the lower histological response in patients with putatively high activity of P-glycoprotein compared to those with low activity in the 1 g mesalamine OD group only.

Adverse Events

A total of 48 AEs were reported in 38 patients (19.0%) in the 1 g mesalamine OD group, and 67 AEs occurred in 43 patients (21.2%) in the 0.5 g mesalamine TID group. The number (%) of patients experiencing those AEs considered at least possibly drug-related (ADRs) were 5 (2.5%) in the 1 g mesalamine OD and 7 (3.4%) in the 0.5 g mesalamine TID group.

The most frequently reported AEs by preferred term were headache, nasopharyngitis, and colitis ulcerative. Preferred terms that occurred in at least two patients are presented in Table 6.

All patients experienced AEs of mild (1 g mesalamine OD: 14.5%; 0.5 g mesalamine TID: 16.3%) or moderate (1 g mesalamine OD: 4.5%; 0.5 g mesalamine TID: 6.9%) intensity. No patient experienced a severe AE.

A total of two AEs in two patients were rated as serious (SAE) due to both having required hospitalization. One patient in the 1 g mesalamine OD group experienced a subclavian artery embolism; one in the 0.5 g mesalamine TID experienced anxiety. None of these SAEs was assessed as having been study drug-related. No patient died during the course of this study.

Three patients taking 0.5 g mesalamine TID were withdrawn from the study due to AEs. Two patients were withdrawn due to AEs with possible relationship to the study drug (flatulence, pruritus, defecation urgency, constipation); one patient was withdrawn due to elevated liver values at baseline.

TABLE 6. Patients with at Least One AE by Preferred Term (Safety Population, Only Preferred Terms that Occurred in at Least Two Patients)

Preferred Term (MedDRA)	Number (%) of Patients with at Least One AE	
	1 g Mesalamine OD ($n = 200$)	0.5 g Mesalamine TID ($n = 203$)
Headache	5 (2.5%)	11 (5.4%)
Nasopharyngitis	5 (2.5%)	6 (3.0%)
Colitis ulcerative	3 (1.5%)	5 (2.5%)
Lipase increased	4 (2.0%)	3 (1.5%)
Constipation	3 (1.5%)	1 (0.5%)
ALAT increased	1 (0.5%)	2 (1.0%)
Influenza like illness	1 (0.5%)	2 (1.0%)
Leukopenia	2 (1.0%)	1 (0.5%)
Arthralgia	2 (1.0%)	—
ASAT increased	1 (0.5%)	1 (0.5%)
Platelet count decreased	1 (0.5%)	1 (0.5%)
Pruritus	—	2 (1.0%)

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase.

DISCUSSION

We compared the efficacy and tolerability of a new 1 g suppository versus 3 × 0.5 g mesalamine suppositories in a randomized, single-blinded clinical trial conducted to demonstrate the noninferiority of the 1 g suppository versus 3 × 0.5 g mesalamine suppositories in inducing clinical remission in patients with mild to moderately active ulcerative proctitis.

In the final analysis of all our 403 patients, we observed clinical remission rates based on the DAI in the PP analysis of 87.9% in the 1 g once-daily group and 90.7% in the 0.5 g TID group ($P = 0.00027$ for noninferiority). The clinical remission rates in the ITT analysis were 84.0% versus 84.7% ($P < 0.00008$), respectively. Thus, noninferiority was proven to be statistically highly significant in both analyses.

This conclusion was strongly supported by the analysis of several secondary endpoints (clinical improvement, EI, HI, PGA score). Most revealed no significant differences between the treatment groups. Histological assessment showed higher remission rates in the 0.5 g mesalamine TID (67.9%) than the 1 g mesalamine OD group (55.3%).

This trial's results provide further evidence of the efficacy of the appropriate daily dose of rectal mesalamine given as a suppository. About 90% of all patients went into remission, with resolution of symptoms starting within 5 days. Given the high and rapid responses observed in this trial, we conclude that a daily dose of 1 g rectal 5-aminosalicylate (5-ASA) is appropriate for treating mild-to-moderate active proctitis.

This is supported by the high endoscopic remission rates (80%–85%) we observed. These convincing efficacy data confirm the role of rectal aminosalicylate therapy as a first-choice strategy for inducing remission in active distal UC, and this therapy has been recommended in several guidelines.[1–6]

Rectal mesalamine suppositories even induced mucosal healing in a substantial proportion of patients assessed histologically (histological remission: 55%–68%) with mild-to-moderate active proctitis. This result is confirmed by endoscopy, whereby 86% of the patients presented no mucosal hemorrhage at the final visit. As mucosal healing is a predictor for reducing the risk of colorectal cancer in UC,[31] this might go some way to explain the beneficial role of 5-ASA as a chemopreventive agent in UC.[32]

Both suppository preparations induced a rapid resolution of clinical symptoms apparently superior to oral mesalamine preparations. These results were similar or even better than those of earlier studies with 1 g 5-ASA suppositories.[17,33–36] This finding confirms that a rectal mesalamine suppository is the treatment of choice when the extent of UC is limited to the rectum. Moreover, as mesalamine plasma levels following rectal administration are lower than after oral intake,[37] rectal administration provides an even better benefit-to-risk ratio for the treatment of distal UC.

We found rectal 5-ASA administered as a suppository to be safe in this large, short-term trial, and our findings are fully compatible with published reports,[17,33–36,38,39] as are the type and frequency of AEs.

The main reason for developing this new 1 g suppository was our assumption that once-a-day administration would interfere less with daily routine than applying suppositories three times a day, and that this would improve patient satisfaction and adherence to the therapy.[35,36] This trial effectively confirmed that assumption: 90% of the patients considered it easy to apply one suppository a day, whereas only 78% of the patients regarded TID application to be easy. Therefore, 86% of the patients preferred the 1 g suppository once daily, whereas just 3% preferred the TID administration of 0.5 g suppositories.

Our results are even better in terms of patient acceptance than those of earlier studies demonstrating good tolerance every day in 77% and 54% of patients treated with slow-release 5-ASA suppositories (Pentasa 1 g/day) and 5-ASA suppositories (Rowasa 0.5 g, two times a day), respectively.[35] In addition to the OD administration schedule, the pharmaceutical formulation may account for the differences in patient satisfaction with various 5-ASA suppositories.

This study was not designed to answer the question concerning the effect of this new form of treatment on

long-term adherence, but chances are good that its simplicity will raise compliance and long-term efficacy.

Genetic variants of *MDR1* (gene product P-glycoprotein) may be associated with altered transport activity in the intestinal mucosa, whereas *NAT1* and *NAT2* polymorphisms are associated with the phenotype of a slow and rapid acetylator. Previous studies have provided evidence that both phase-II enzymes are also expressed in the intestinal mucosa.[40] We observed no relevant effect of putatively important *MDR1*, *NAT1*, and *NAT2* gene polymorphisms on clinical and endoscopic response (DAI, EI) to rectal mesalamine in active ulcerative proctitis. Interestingly, in the 0.5 g mesalamine TID group but not in the 1 g mesalamine OD group, the very few NAT1 rapid acetylators reached better histological response (HI) than the NAT1 slow acetylators. Comparison of histological response in NAT1 rapid acetylators between the two different dosing schedules did not show a significant difference. Interpretation of our pharmacogenetic data is limited due to the very small number of NAT1 rapid acetylators ($n = 2$, 1 g mesalamine OD; $n = 4$, 0.5 g mesalamine TID). Moreover, there was a preliminary indication that high activity of the intestinal drug efflux pump, P-glycoprotein, might limit histological response following the 1 g mesalamine suppository OD. However, that histological observation was not reflected in the accompanying EI or DAI results.

In conclusion, our evidence demonstrates that the novel 1 g mesalamine suppository given once a day in the evening is highly effective and well-tolerated. This new preparation may well enhance patients' compliance with topical therapy.

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APPENDIX

Active members of the International Salofalk Suppository OD Study Group were: Germany: Dr. Eisenbach, Leverkusen; Prof. Herold, Mannheim; Dr. Jongen, Kiel; Dr. Kolbert, Hannover; Israel: Dr. Chowers, Tel Hashomer; Dr. Dotan, Tel Aviv; Prof. Eliakim, Haifa; Dr. Faszczyk, Ashkelon; Prof. Konikoff, Kfar Saba; Dr. Lavy, Haifa; Dr. Melzer, Rehovot; Prof. Niv, Petach Tikva; Dr. Safadi, Nazareth; Dr. Wardi, Holon; Russia: Dr. Bakulin, Moscow; Prof. Belousova, Moscow; Prof. Golofeevsky, St. Petersburg; Prof. Grigorieva, Moscow; Prof. Grinevich, St. Petersburg; Dr. Lakhin, Lipetsk; Prof. Nikitin, Moscow; Prof. Pavlenko, Stavropol; Prof. Simanenkov, St. Petersburg; Prof. Tkachenko, St. Petersburg; Dr. Yourkov, Moscow; Ukraine: Prof. Beresnitskiy, Dnipropetrovsk; Dr. Golovchenko, Vinnitsa; Prof. Kharchenko, Kyiv; Prof. Zakharash, Kyiv; Members of the independent data monitoring committee: Prof. W. Lehmacher (statistician), Prof. G. Rogler (gastroenterologist), Prof. A. Tromm (gastroenterologist).

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Abbreviations

Term	Explanation
5-ASA	5-aminosalicylic acid, mesalazine
^{99m}Tc	Meta-stable, gamma-emitting nuclear isomer of technetium
b.i.d.	Twice daily
bw	Body weight
cm	Centimetre
DAI	Disease Activity Index
DGVS	Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (German Society for Digestive and Metabolic Diseases)
F	Female
IBD	Inflammatory bowel disease(s)
M	Male
MA	Marketing authorisation
MAA	Marketing authorisation application
MCi	Millicurie
mg	Milligram
n	Number
PC	Placebo-controlled
Plac	Placebo
ra	Randomized
SD	Standard deviation
Supp	Suppository(ies)
t.i.d.	Three times daily
UC	Ulcerative colitis

2.7.3 Summary of Clinical Efficacy

5-ASA (mesalazine) preparations for treatment of chronic inflammatory bowel diseases (IBD) have first been introduced into the market by Dr. Falk Pharma GmbH in 1984 and have been successfully marketed since then in the form of Salofalk® tablets, granules, suppositories, enemas, and also as Salofalk® foam in some countries, but also under the trade names Claversal®, Mesasal®, Colitofalk®, Rafassal®, and Rowasa®. Salofalk® 500 mg suppositories were first introduced to the market in 1992.

The applicant (Dr. Falk Pharma GmbH) seeks marketing authorisation (MA) for the rectal mesalazine (5-ASA) suppository formulation

- Salofalk® 500 mg suppositories

that is regarded as a completion of the approved oral 5-ASA preparation Salofalk® pellets / granules ('line extension').

The indication claimed as based on the national MA in Germany is as follows:

- 'Acute treatment of ulcerative colitis restricted to the rectum'.

Salofalk® 500 mg suppositories are indicated at the dose of one Salofalk® 500 mg suppository three times daily (equivalent to 1.5 g mesalazine daily).

This MA application (MAA) is therefore primarily grounded on the Clinical Documentation on Salofalk® granules already approved, and on the Clinical Documentation on Salofalk® 250 mg / 500 mg suppositories that has led to national MAs in Germany.

The local availability of 5-ASA, the therapeutic efficacy and tolerability of these specific suppository preparations in the treatment of acute episodes of distal ulcerative colitis (UC) and in the maintenance of remission of this disease (Salofalk® 250 mg only) have been well established and documented in the previous MAA.

This Clinical Documentation on Salofalk® 500 mg suppositories is intended to amend the

- Clinical Documentation on the approved Salofalk® granules (cf. Salofalk® granules - Expert Report on the Clinical Documentation [Kruis 2000]), and the
- Clinical Documentation on Salofalk® 250 mg / 500 mg suppositories that led to a national MA of Salofalk® 500mg suppositories in Germany (Expert Report on the Clinical Documentation [Schölmerich 1997]),

by summarising and evaluating

- Relevant clinical data that has not been implemented in the previous Clinical Documentation on the respective medicinal products (Addendum to the Clinical Documentation) and
- Essential clinical studies on ulcerative proctitis already previously included for providing a more comprehensive picture.

The therapeutic efficacy of Salofalk® suppositories in the treatment of acute inflammations in ulcerative colitis which is restricted to the rectum (also called ulcerative proctitis) is well established and documented in a previous national MAA in Germany (see Expert Report on the Clinical Documentation on Salofalk® enemas: Schölmerich 1997).

5-aminosalicylic acid (5-ASA, synonymous to mesalazine [mesalamine in the US]) is the standard treatment for induction and maintenance of remission in mild to moderate UC. If the inflammation is restricted to the rectum suppositories are the treatment of choice to restrict the exposition of the agent to the inflamed areas and thus minimise loss into the systemic compartment and colonic sections which are not affected by inflammation. 5-ASA suppositories are considered as pharmacotherapeutic mainstay for the treatment of isolated rectal inflammations of UC (Travis et al. 2008, Kornbluth et al. 2010, Cohen et al. 2000, Marshall et al. 2010).

To assess and quantify the intensity and activity of the disease of UC and also to quantify the effect of treatments various indices are used in clinical trials (comprehensively described by D'Haens et al. 2007).

Among the most common indices that were also used in clinical trials with Salofalk® 500 mg suppositories are those established by Sutherland et al. 1987 and by Rachmilewitz 1989.

The disease activity index (DAI) by Sutherland et al. 1987 which includes four variables: Stool frequency, rectal bleeding, mucosal appearance and physicians rating of disease activity. Each variable rates form 0 (none) to 3 (high expression), the total score ranges from 0 to 12 points.

The clinical activity index (CAI) by Rachmilewitz 1989 includes 7 variables: number of stools, blood in stools, investigator's global assessment of symptomatic stae, abdominal pain or cramps, temperature due to colitis, extraintestinal manifestations, and some laboratory findings. The total score ranges from 0 to 29 points and has been validated.

In addition, in study SAS-6/BIO additional indices to specifically assess the disease activity by endoscopic (endoscopic index by Rachmilewitz 1989) or histological (histologic index by Riley 1991) appearance. Quality of life is assed by an abbreviated form (short inflammatory bowel disease Quality of life index, SIBDQ, by Irvine 1996) of the original IDBQ index the same authors (Irvine 1994).

2.7.3.1 Studies relevant for efficacy of Salofalk® 500 mg suppositories

Four relevant clinical studies are presented here: Placebo-controlled studies were published by Williams et al. (1987) and Williams (1990) and a more recent study comparing Salofalk® 500 mg suppositories to a 1 g mesalazine suppository (SAS-6/UCA, published by Andus et al. 2010). The studies evaluated the efficacy and safety of 5-ASA suppositories in a total of 603 patients with ulcerative proctitis.

In the publication by Williams (1990), two separate studies with 5-ASA 500 mg suppositories are presented. Data of one of these studies (Study 1) are presented in detail (Banks Statistical Report 1986).

Study SAS-6/UCA were performed with Salofalk® 500 mg suppositories and a new 1 g mesalazine suppository (Salofalk® 1 g suppositories).

The studies published by Williams et al. 1987 and by Williams 1990 have been performed with the widely marketed rectal 5-ASA preparation Rowasa® containing 500 mg of 5-ASA. Since the equivalence of Salofalk® and Rowasa® has been demonstrated in the bioavailability / pharmacokinetic study SAS-2/BIO (described in detail in Section 2.7.1), it can be reasonably assumed that Salofalk® is equally effective and safe in the treatment of ulcerative proctitis. Thus, these studies are considered to be pivotal for Salofalk® 500 mg suppositories.

Table 2.7.3-1: Overview of efficacy studies with 5-ASA 500 mg suppositories in ulcerative proctitis

Publication	Title	Number of subjects
Williams et al. 1987	Double blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using ^{99m}Tc-labeled 5-ASA suppositories	Ulcerative proctitis: 27 (in addition, for the measurement of the spread: 6 patients with IBD and 6 healthy subjects)
Williams 1990 Study 1 is also presented by Protocol 300 in combination with Banks Statistical Report 1986	Efficacy and tolerance of 5-aminosalicylic acid suppositories in the treatment of ulcerative proctitis: A review of two double-blind, placebo controlled trials	Study 1: 79 Study 2: 94
SAS-6/UCA Publication by Andus et al. 2010	Randomized, single-blind, multi-centre study to compare the efficacy and safety of once daily 1 g mesalazine suppositories versus three times daily 0.5 g mesalazine suppositories in patients with acute ulcerative proctitis	403

2.7.3.1.1 Williams et al. 1987. Double blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using 99mTc-labeled 5-ASA suppositories

This study was conducted to evaluate the efficacy of 500 mg 5-ASA suppositories in patients with active distal proctitis. In addition, in another group of patients and in healthy subjects, the spread of rectal suppositories of ^{99m}Tc (metastable, gamma-emitting nuclear isomer of technetium) -labeled 5-ASA was measured.

Study population and treatments

Twenty-seven subjects with active distal proctitis involving the distal 15 cm or less on sigmoidoscopy were included in this double-blind placebo-controlled study. Subjects

were either unresponsive to treatment with sulfasalazine and / or oral prednisone or betamethasone enemas (which at that time was defined as "standard therapy"), or were newly referred patients.

There were 14 patients (8 men, 6 women, mean age 37.3 ± 14.5 years) in the 5-ASA group, and 13 patients (9 men, 4 women, mean age 42.7 ± 11.2 years) in the placebo group.

At entry into the study, there was no significant difference between the initial mean Disease Activity Index (DAI), of the 5-ASA group (7.1 ± 1.8) and that of the placebo group (7.4 ± 1.8). Likewise, the mean extent of active distal proctitis was not different in the 5-ASA group (women 9.3 cm; men 9.6 cm) or in the placebo group (women 10.5 cm; men 9.3 cm).

The mean duration of symptoms prior to study participation was similar in the 2 treatment groups at 2 to 3 months.

For the treatment in the study subjects received 500 mg 5-ASA suppositories or identical placebo which were taken 3 times daily for 6 weeks.

If the patient was taking oral sulfasalazine and/or oral prednisone (n=15), these were maintained in the same dose throughout the study period.

An additional 6 patients with IBD were offered a ^{99m}Tc-labeled 5-ASA suppository study, dose 1 MCi (millicurie), and the results compared to those in 6 healthy volunteers.

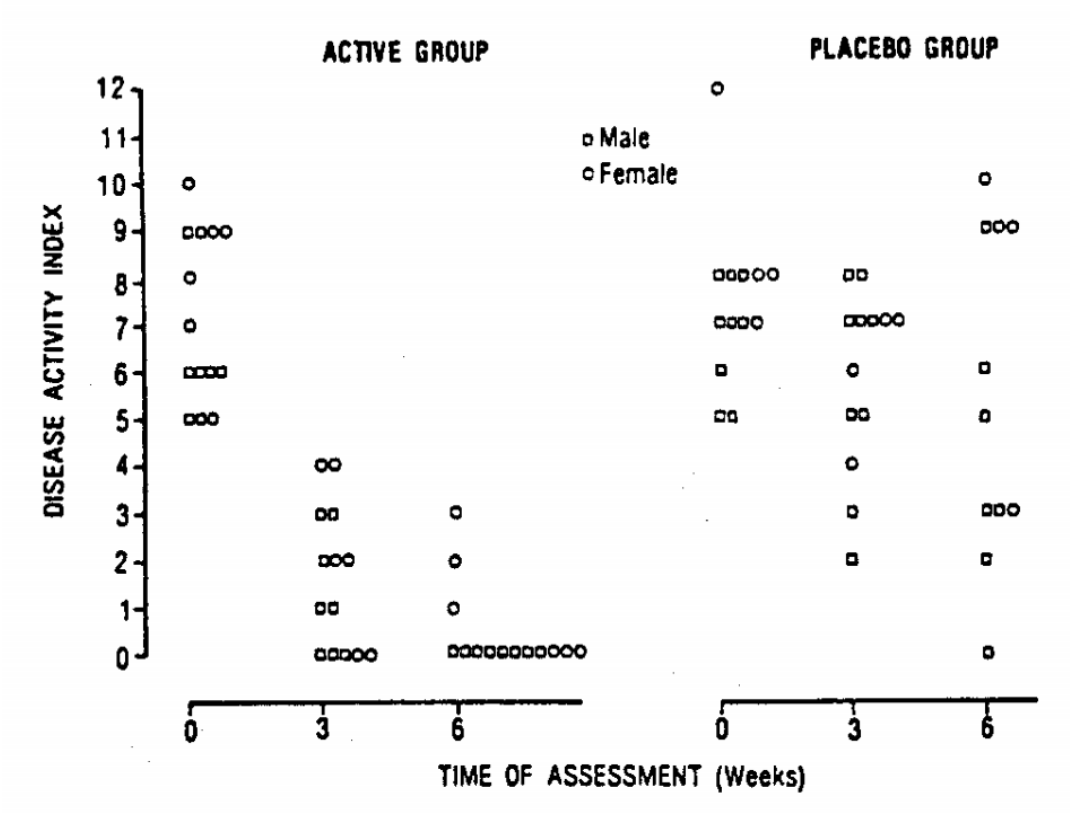
Assessment of efficacy

Patients kept a daily record of symptoms, i.e. number of stools per day, degree of blood present, and noted the length of time the suppository was retained, up to 3 hours or more. Objective assessment of the activity of the disease was assessed by means of the Disease Activity Index (DAI), derived from 4 categories: number of daily evacuations more than usual, evacuations containing blood, sigmoidoscopy appearance, and physician's overall assessment. Each category was graded 0-3. There was thus 0-12 point scored ranging from complete remission to severe disease.

Patients' response to treatment was formally assessed with a repeat evaluation, including sigmoidoscopy, before and at 3 and 6 weeks.

Efficacy results

The DAI of all patients before, during and at the end of the treatment with 5-ASA suppositories or placebo suppositories is graphically shown in Figure 2.7.3-1.



Source: Williams et al. 1987

Figure 2.7.3-1: DAI before, during and at the end of the treatment with 500 mg 5-ASA or placebo suppositories (n=27) (William 1987)

At 3 weeks, the active group had a mean DAI of 1.6 ± 1.5, which was significantly lower than the pre-treatment score ($p<0.001$), whereas the placebo group had a mean DAI of 5.8 ± 1.9, which was not significantly different from the pre-treatment value.

At 6 weeks, the mean DAI in the 5-ASA group was 0.4 ± 0.9 ($p<0.001$). In the placebo group, the mean DAI at 6 weeks was 5.4 ± 3.4, which was not significantly different from the pre-treatment value.

In the 5-ASA group, 11 of 14 patients (78.6%) were in complete remission at 6 weeks. The three failing to obtain a DAI score of 0 at 6 weeks healed with continued treatment with 5-ASA suppositories. In the placebo group, 1 patient went into remission at 6 weeks.

There was no difference in response to treatment when the patients were considered as being on no coincident therapy or maintaining their usual drugs, sulfasalazien or prednisone.

Results regarding the rectal spread of radioactive labelled 500 mg 5-ASA suppositories are presented in section 2.7.1.

In summary, there was a dramatic response to the use of 500 mg 5-ASA suppositories in patients with active distal proctitis, with patients regaining normal daily stools, losing their rectal bleeding, losing any symptoms of tenesmus or urgency, and tolerating and retaining the preparation extremely well. No adverse events were reported.

The study showed that 500 mg 5-ASA suppositories are an effective, safe and well tolerated treatment for patients with distal proctitis.

2.7.3.1.2 Williams 1990. Efficacy and Tolerance of 5-aminosalicylic Acid Suppositories in the Treatment of Ulcerative Proctitis: A Review of Two Double-blind, Placebo-controlled Trials

In this publication two studies are reported. For Study 1, there is a study report available (Protocol 300 by Williams et al. 1987 in combination with Banks Statistical Report 1986) which is the main source of the data reported in this summary. Study 2 is reported on the base of the publication, solely.

Design of Study 1 and Study 2

The efficacy and tolerance of 500 mg 5-ASA suppositories (Rowasa®) in the treatment of ulcerative proctitis were assessed in 2 studies involving a total of 173 patients. Both studies used a 6 week, randomized, double-blind, parallel, placebo controlled, multi-centre design.

Study populations, procedures and treatments

For both studies outpatients with ulcerative proctitis confirmed by sigmoidoscopy involving a maximum of 15 cm measured from the anal margin, and a minimal score of 3 on the 12 point scale of the DAI were recruited. Patients were randomized to receive either placebo or 5-ASA suppositories.

On entry into both studies a complete history, physical examination, flexible sigmoidoscopy were performed and the DAI was calculated. Hematologic complete blood count and biochemical parameters including urinalysis were assessed along with stool cultures to exclude infectious colitis.

Patients were provided with a diary for the daily record of number of stools, rectal bleeding and other symptoms as well as possible side effects.

In Study 1, a total of 79 subjects with a mean age of 38.9 ± 12.6 years were enrolled. The primary diagnosis was proctitis in 73 subjects, and proctosigmoiditis in 6 subjects. The mean upper disease boundary was 10.8 ± 4.9 cm. 39 subjects used 5-ASA 500 mg suppositories, and 40 subjects used placebo, at a dosing regimen of three times a day.

A total of 94 subjects participated in Study 2. They administered one 500 mg 5-ASA suppository (n=50) or placebo (n=44) twice daily (b.i.d.).

In both studies, active and placebo groups were comparable with regard to sex, age and disease boundary. Table 2.7.3-2 shows the patients' characteristics in Study 1 and Study 2.

Table 2.7.3-2: Patients' characteristics in 5-ASA studies in patients with ulcerative proctitis (Williams 1990, Study 1 and Study 2)

	Study 1 (5-ASA 500 mg suppository t.i.d.)		**Study 2 (5-ASA 500 mg suppository b.i.d.)**	
	5-ASA supp. 500 mg	**Placebo**	**5-ASA supp. 500 mg**	**Placebo**
Number of patients	39	40	50	44
Gender (M/F)	16/23	18/22	18/32	18/26
Mean age (years)	35.9 ± 11.9	41.9 ± 12.8	37.0	40.2
Mean upper disease boundary (cm)	10.8 ± 3.8	10.9 ± 5.8	10.5	10.1

Sources: Banks Statistical Report 1986, Appendix B, Table 1; Williams 1990

Concomitant medications

Oral steroids or sulfasalazine were allowed on both studies, provided that they had been used for at least 3 weeks prior to entry and that the dose was held constant during the trial. Concomitant use of other rectal medication was not permitted.

Assessment of Efficacy

In both studies, the efficacy of 5-ASA suppositories was assessed by changes in the overall DAI as well as in the 4 individual disease activity index parameters number of daily evacuations more than normal, rectal bleeding, mucosal appearance in sigmoidoscopy, and physician's rating in disease severity. In addition, the physician provided a final global assessment reflecting the degree of improvement at the end of the treatment period.

At Week 3, repeat sigmoidoscopy was performed and the DAI reassessed.

Upon conclusion of the study at Week 6, a repeat history, physical examination, sigmoidoscopy and haematological and biochemical assessments were carried out. The DAI was again calculated.

An endpoint analysis (last available post-dosing score) was performed to assess the influence of drop-outs.

Statistical analysis

Nonparametric data (physician's global assessment) were analyzed by χ^2 tests. Changes in DAI (ordinal scale) were analyzed by analysis of variance.

Efficacy results of Study 1

The results of Study 1 (Williams 1990) are described in detail in Banks Statistical Report (1986).

There were large differences between the treatment groups with respect to the DAI (sum of parameters 'evacuation frequency', 'rectal bleeding', and 'mucosal appearance') scores at both Week 3 and Week 6 ($p<0.001$). The results from the endpoint analysis were in parallel ($p<0.001$).

Table 2.7.3-3 summarizes the analyses of the DAI at baseline, Week 3, Week 6 and at endpoint.

Table 2.7.3-3: DAI at baseline, Week 3, Week 6, and endpoint (Study 1) (5-ASA 500 mg t.i.d.)

	DAI[1] Mean ± SD		P value
	5-ASA	Placebo	
Baseline	5.28 ± 1.67 (n=39)	5.5 ± 1.36 (n=40)	0.53
Week 3	1.62 ± 1.40 (n=37)	4.23 ± 1.91 (n=40)	<0.001
Week 6	0.95 ±1.73 (n=37)	3.00 ± 2.40 (n=34)	<0.001
Endpoint	0.95 ± 1.73 (n=37)	3.38 ± 2.50 (n=40)	<0.001

1: Sum of factors 'evacuation frequency', 'rectal bleeding', and 'mucosal appearance'
Source: Banks Statistical Report Table 1, Appendix C Tables 1, 2, 3, and 6

A similar picture emerged using relative (percentage) improvement in DAI from baseline (Table 2.7.3-4), i.e. a more pronounced improvement was seen in the 5-ASA group than in the placebo group. At the end of 6 weeks, the DAI was reduced in mean by 82.2% reduction in the 5-ASA treated patients, which is significantly superior ($p<0.001$) than the mean reduction in the placebo group (43.0%).

The results of the endpoint analysis (last available post-dosing score) of DAI parallel those for Week 6, i.e. a significantly greater reduction of the DAI from baseline was seen in the 5-ASA group (82.2%) compared to the placebo group (37.6%, $p<0.001$, see Table 2.7.3-4).

Table 2.7.3-4: Percent change in DAI from baseline to Week 3, Week 6 and endpoint (Study 1) (5-ASA 500 mg t.i.d.)

	Percent change in DAI[1] from baseline mean ± SD		P value
	5-ASA	Placebo	
Week 3	69.8 ± 25.0 (n=37)	19.6 ± 45.1 (n=40)	<0.001
Week 6	82.2 ± 34.2 (n=37)	43.0 ± 45.0 (n=34)	<0.001
Endpoint	82.2 ± 34.2 (n=37)	37.6 ± 44.7 (n=40)	<0.001

1: Sum of factors 'evacuation frequency', 'rectal bleeding', and 'mucosal appearance'
Source: Banks Statistical Report Table 1, Appendix C1, Tables 4, 5, and 7

Each of the individual DAI parameters showed a highly significant difference between the 5-ASA group and the placebo group in the percentage of patients having achieved a DAI score of 0 at the endpoint, i.e. patients assessed as 'normal' (Table 2.7.3-5).

Table 2.7.3-5: Percentage of patients assessed 'normal' in individual DAI parameters at Week 6 (Study 1) (5-ASA 500 mg t.i.d.)

Patients with	5-ASA (%)	Placebo (%)	p
Normal stool frequency	78.4	30.0	p<0.01
No rectal bleeding	89.2	42.5	p<0.001
Normal mucosal appearance	62.2	25.0	p<0.001
Physician's rating of disease severity: normal	62.2	22.5	p<0.001

Source: Banks Statistical Report 1986, Appendix C1, Tables 8, 9, 10, and 11.

The results comparing the two treatment groups with regard to the physicians' overall rating of response to treatment show that the patients in the 5-ASA group were rated significantly more improved that those in the placebo group (p<0.001, see Banks Statistical Study Report 1986, Appendix C3, Table 1). 32 of 38 (84.2%) of the patients in the 5-ASA group were rated 'much improved' compared to 16 of 39 (41.0%) in the placebo group.

After adjusting the analysis for the potential effects of centres and baseline scores, statistically significant ($p<0.05$) treatment group differences were found for all subscales at Week 3 and Week 6, and at endpoint.

Efficacy Results of Study 2

In Study 2, the mean reduction in the overall DAI score was 74.7% in the 5-ASA treated patients and 34.2% in the placebo treated patients ($p<0.001$). As in Study 1, each of the DAI parameters demonstrated in significant difference in the percentage of patients assessed to be 'normal' at the endpoint (Table 2.7.3-6).

Table 2.7.3-6: Percentage of patients assessed 'normal' in individual DAI parameters at 6 weeks (Study 2) (5-ASA 500 mg b.i.d.)

Patients with	5-ASA (%)	Placebo (%)	P value
Normal stool frequency	70.8	35.7	p<0.01
No rectal bleeding	68.8	16.7	p<0.001
Normal mucosal appearance	60.4	9.8	p<0.001
Physician's rating of disease severity: normal	60.4	9.5	p<0.001

Source: Williams 1990

The physician's global assessment showed that 79.2% of 5-ASA treated patients were considered 'much improved' compared to 26.2% of the placebo patients ($p<0.001$).

Comparison of Study 1 and Study 2

The comparison of Study 1 and Study 2 (Table 2.7.3-7) showed that there was no statistically significant difference in efficacy in patients with ulcerative proctitis treated with 500 mg t.i.d. (Study 1) and 500 mg b.i.d. (Study 2).

Table 2.7.3-7: Comparison of efficacy of 5-ASA 500 mg suppositories t.i.d. (Study 1) and b.i.d. (Study 2)

	Study 1			Study 2		
	5-ASA 500 mg supp. t.i.d.	**Placebo**	**P value**	**5-ASA 500 mg supp. b.i.d.**	**Placebo**	**P value**
Total number of patients	39	40		50	44	
Mean reduction in overall DAI (%)	80.4	36.8	<0.05	74.7	34.2	<0.001
Physician's global assessment: 'much improved' (%)	84.2	41	<0.01	79.2	26.2	<0.001
Normal stool frequency	78.4	30	<0.01	70.8	35.7	<0.01
No rectal bleeding	89.2	42.5	<0.001	68.8	16.7	<0.001
Remission: Physician's rating of disease severity as "normal" (%)	62.2	22.5	<0.001	60.4	9.5	<0.001
Endoscopic remission: Normal mucosal appearance (%)	62.2	25.0	<0.001	60.4	9.8	<0.001

Source: Williams 1990

In summary, both studies showed excellent efficacy of 5-ASA 500 mg suppositories in the treatment of ulcerative proctitis. A significant mean reduction in the DAI was achieved with 5-ASA 500 mg suppositories compared to placebo. In addition, each of the individual parameters comprising the DAI demonstrated a significantly greater remission rate, i.e. score of 0, compared to placebo. Finally, the physician's global assessment of patients at the end of the study showed significant improvement. There was no statistical difference in efficacy between patients treated with 500 mg 5-ASA suppositories b.i.d. versus t.i.d.

Efficacy Analyses in Subgroups of Study 1

A subgroup analysis was performed in Study 1 whereby subgroups were stratified to age, gender, previous treatment with steroid enemas, and co-medication. The results are presented below.

Age

The differences between the treatment groups using the DAI total score at endpoint are statistically significant ($p<0.001$) after adjusting the analysis by age (Banks Statistical Report 1986, Appendix C4, Table 1). The estimated difference between the age adjusted treatment group means is 30.7%, whereas it is estimated to be 44.6% between the unadjusted treatment group means.

Gender

Treatment group comparisons using the DAI total scores at endpoint are statistically significant (<0.001) for both male and female patients (Banks Statistical Report 1986, Appendix C4, Table 1).

Steroid enemas for previous episodes

The difference between the treatment groups with regard to the DAI total scores at endpoint for those patients who had taken steroid enemas for previous episodes of ulcerative proctitis was statistically significant ($p<0.001$) and was approximately of the same magnitude as for the entire patient group (Statistical Report Banks 1986, Appendix C4, Table 3). For those patients who had not taken steroid enemas for previous episodes ($n=23$) the treatment group differences were not significant at the 5% level ($p=0.17$). This might be due to the small number of patients without previous steroid enema treatment in the placebo group, resulting in a large standard deviation.

Co-medication

A subgroup analysis was performed in order to evaluate in influence of the co-medication on the efficacy of 5-ASA 500 mg suppositories in patients with ulcerative proctitis.

Table 2.7.3-8 shows the DAI total scores at baseline and at Week 6 in patients receiving only study medication, as well as in patients receiving additional oral prednisone or oral sulfasalazine, or oral prednisone plus sulfasalazine, respectively.

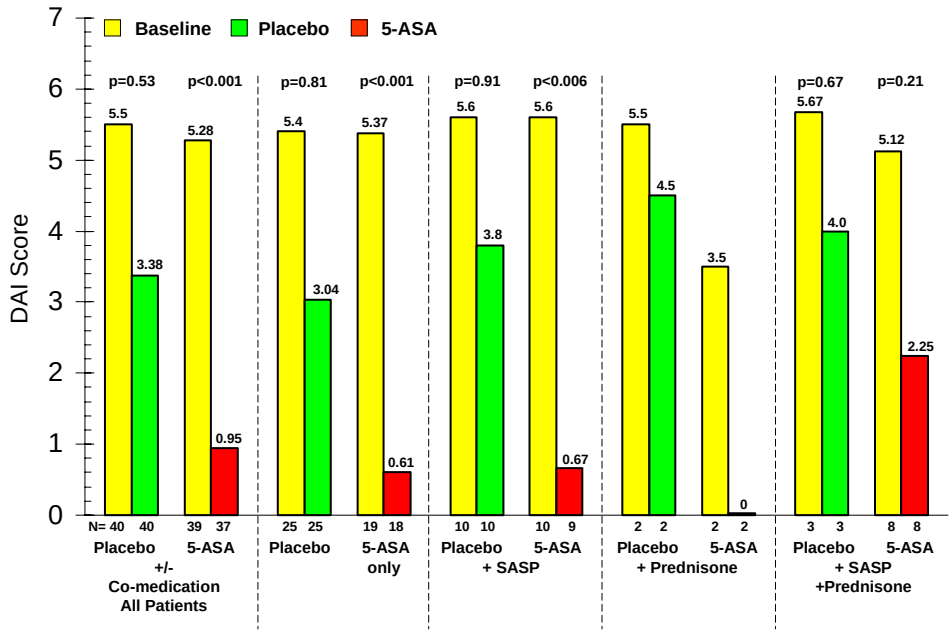
Table 2.7.3-8: DAI total score at baseline and at endpoint of treatment with 5-ASA suppositories 500 mg in subgroups of co-medication (n=79) (Study 1)

Co-medication	DAI-total-score[1]				% change of DAI[1] total score from baseline	
	Baseline (mean ± SD)	N	Endpoint (mean ± SD)	N	(mean ± SD)	N
No co-medication						
5-ASA	5.37 ± 1.89	19	0.61 ± 0.92	18	89.15 ± 16.35	18
Placebo	5.44 ± 1.26	25	3.04 ± 2.41	25	41.57± 48.24	25
P value	0.81		<0.001		<0.001	
Sulfasalazine						
5-ASA	5.60 ± 1.58	10	0.67 ± 1.00	9	87,94 ± 18.39	9
Placebo	5.60 ± 1.58	10	3.80 ± 2.66	10	32.43 ± 38.59	10
P value	0.91		0.006		0.004	
Prednisone						
5-ASA	3.50 ± 0.71	2	0.00 ± 0.00	2	100 ± 0.00	2
Placebo	5.50 ± 0.71	2	4.50 ± 4.95	2	23.33 ± 80.14	2
P value						
Sulfasalazine + Prednisone						
5-ASA	5.12 ± 1.25	8	2.25 ± 4.00		55.51 ± 62.38	8
Placebo	5.67 ± 1.15	3	4.00 ± 2.00		31.43 ± 24.91	3
P value	0.67		0.2		0.18	
Total						
5-ASA	5.28 ± 1.67	39	0.95 ± 1.73	37	82.17 ± 34.15	37
Placebo	5.50 ± 1.36	40	3.38 ± 2.50	40	37.61 ± 44.75	40
P value	0.53		<0.001		<0.001	

1 DAI total score: Sum of factors 'evacuation frequency', 'rectal bleeding' and 'mucosal appearance'
Source: Banks Statistical Report 1986, Appendix C4, Table 4b

The majority of patients (44 of 79) participating in this study was treated with study medication only and did not receive any co-medication. Twenty patients received sulfasalazine, 11 prednisone and sulfasalazine in combination, and 4 patients received prednisone as co-medication.

The decrease of DAI total score from baseline on Week 6 of treatment with 5-ASA suppositories 500 mg or placebo t.i.d. in the subgroups analyzed is graphically presented in Figure 2.7.3-2.



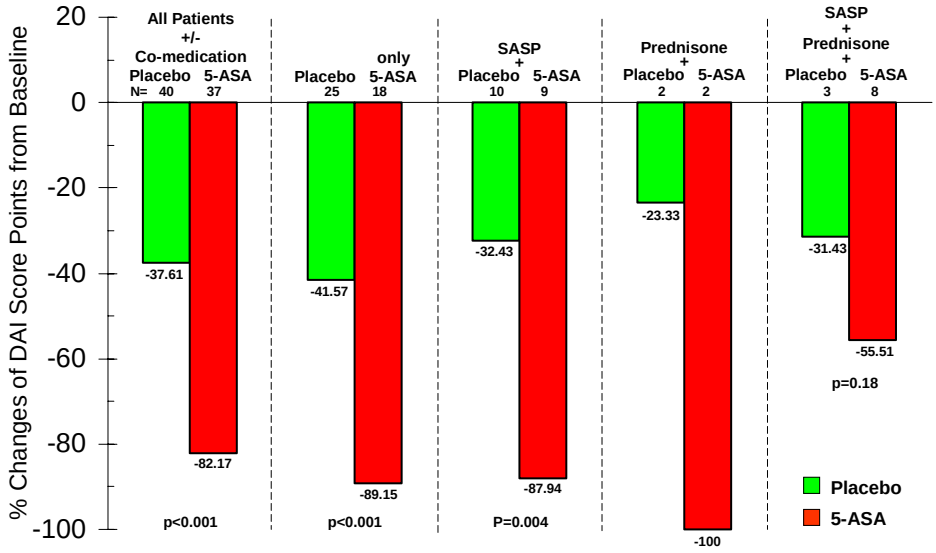
SASP: Sulfasalazine

Source: Banks Statistical Report 1986, Appendix C4, Table 4b

Figure 2.7.3-2: DAI[1] total score at baseline and at endpoint of treatment with 5-ASA suppositories 500 mg in subgroups of co-medication (n=79) (Williams 1990 Study 1)

The percentage change of DAI from baseline to endpoint in the subgroups of co-medication is shown in Figure 2.7.3-3.

[1] DAI total score: Sum of factors ‘evacuation frequency’, ‘rectal bleeding’ and ‘mucosal appearance’



SASP: Sulfasalazine

Source: Statistical Report Banks 1986, Appendix C4, Table 4b

Figure 2.7.3-3: Percentage change of DAI total score[2] from baseline to endpoint in subgroups of co-medication (n=79) (Williams 1990 Study 1)

The results of the subgroup analysis show that 5-ASA 500 mg suppositories alone without any co-medication, as well as 5-ASA 500 mg suppositories in combination with sulfasalazine and/or prednisone is an effective treatment of ulcerative proctitis.

There were statistically significant ($p<0.001$) differences between 5-ASA and placebo group in DAI total scores at endpoint for the entire patients' cohort and for 2 subgroups of concurrent medication users: Patients concurrently taking sulfasalazine, patients not concurrently taking prednisone or sulfasalazine. Patients in the 5-ASA group responded more favourably than placebo group in each of these subgroups.

As the number of patients treated with oral prednisone in combination with 5-ASA or placebo suppositories, respectively, was very small (only 2 patients, respectively) p-values for statistical differences were not calculated.

In patients concurrently treated with orally administered sulfasalazine + prednisone (n=11) the magnitude of differences between 5-ASA and placebo group was much smaller and not statistically significant ($p=0.18$, see Statistical Report Banks 1986, Appendix C4, Table 4b). The smaller decrease of the DAI in these patients may indicate that this subgroup comprised of patients with severe disease who did not achieve

[2] DAI total score: Sum of factors 'evacuation frequency', 'rectal bleeding' and 'mucosal appearance'

satisfactory treatment results with systemically administered corticosteroid + sulfasalazine. However, firm conclusions should be drawn because a small number of patients contributed to the analysis for this subgroup.

Summary of subgroup analysis

Analysis of various subgroups indicates a statistically significant advantage of the treatment with 500 mg 5-ASA suppositories compared to placebo, independent of age, gender and concurrent treatment with oral sulfasalazine. For reasons of low patient numbers no firm statistical statements can be made with regard to patients with previous treatment with steroid enemas and concurrent treatment with oral prednisone. The reason for the absence of a significant difference between treatment with 500 mg 5-ASA suppositories and placebo in patients concurrently treated with oral sulfasalazine plus oral prednisone is not clear but might indicate less efficacy of 500 mg 5-ASA suppositories in patients refractory to combinded oral treatment, indicating very severe disease activity.

2.7.3.1.3 Study SAS-6/UCA: Randomized, single-blind, multi-centre study to compare the efficacy and safety of once daily 1 g mesalazine suppositories versus three times daily 500 mg mesalazine suppositories in patients with acute ulcerative proctitis

This study on clinical efficacy was conducted between 09 June 2005 and 06 June 2007 in 35 centres in four countries (Germany, Israel, Russia, and Ukraine).

Results of this study were published by Andus et al. 2010.

Objectives and design

This was a single-blind (investigator-blind), randomised, multi-centre, comparative, phase III clinical trial, conducted as a parallel-group comparison of two different dosing regimens of mesalazine suppositories:

- Group A: Salofalk® 1.0 g suppositories once daily (OD)
- Group B: Salofalk® 500 mg suppositories three times daily (TID)

The study was conducted in a 3-stage sequential adaptive design whereby sample size adjustments could be made after 2 planned interim analyses.

The **primary objective** was to prove the therapeutic equivalence of Salofalk® 1.0 g mesalazine suppositories OD vs. Salofalk® 500 mg mesalazine suppositories TID in patients with active acute ulcerative proctitis.

Secondary objectives were the following:

- To study safety and tolerability in the form of adverse events and laboratory parameters
- To assess patients' acceptance of the study drug
- To assess patients' preference regarding administration schedule
- To assess patients' quality of life

Efficacy variables

The **primary efficacy variable** was clinical remission, defined as DAI < 4 at the final visit Week 6 or at the withdrawal visit.

A large number of **secondary efficacy variables** was assessed in study SAS-6/UCA and only the most relevant are listed here:

- Absolute and relative number of patients in remission, improved, with no change and/or deteriorated according to DAI1, CAI , EI, HI
- Changes in subscores of the indices
- Time to first symptomatic resolution
- Decrease in ESR
- Absolute and relative number of patients with complete relief and at least marked improvement of symptoms (therapeutic success) indicated by PGA
- Quality of life according to the SIDBQ and it subscores

For a complete list of secondary efficacy variables in study SAS-6/UCA see the Clinical study report (CSR SAS-6/UCA, section 3.6.3).

Interim analysis

The first interim analysis was planned to be performed after 2 × 85 per-protocol (PP) evaluable patients had finished the trial. The second interim analysis was planned to be performed after an additional 2 × 43 PP evaluable patients, and the final analysis after a further 2 × 43 PP evaluable patients had finished the trial. The estimated sample size, without sample size adaptation, was 344 evaluable patients.

Patients, Inclusion Criteria, Demographic and Baseline Characteristics

Adults (men or women aged 18 to 75 years) who had active acute ulcerative proctitis (inflammation/lesions maximal 15 cm of rectum, confirmed by endoscopy and histological examination), either established or newly diagnosed, and who had mild to moderate disease (DAI >3 and < 11) were eligible to participate. Patients with proctitis of a different origin, prior bowel resection, toxic megacolon, presence or history of colorectal cancer, or serious secondary diseases were excluded.

In total 408 patients were randomised; 5 of these patients did not receive study medication. Hence 403 patients comprised the intention-to-treat (ITT) efficacy

population and the safety population. At the final analysis, 354 patients were analyzed for efficacy per protocol.

A total of 403 patients received at least one dose of study medication (178 men, 225 women). All patients were Caucasian. Mean age was 42 years (standard deviation [SD] 13.6 years; range, 18 to 74 years). For baseline demographic data, see Table 2.7.3-9.

Table 2.7.3-9: Baseline demographics Study SAS-6/UCA

Demographic variable		**Salofalk®1 g Suppository OD (n = 200)**	**Salofalk® 500 mg Suppository TID (n = 203)**	**Total (n = 403)**
Sex				
Male	n (%)	85 (42.5%)	93 (45.8%)	178 (44.2%)
Female	n (%)	115 (57.5%)	110 (54.2%)	225 (55.8%)
Ethnic origin				
Caucasian	n (%)	200 (100.0%)	203 (100.0%)	403 (100.0%)
Age [years]	Mean (SD)	41.4 (13.2)	42.7 (13.9)	42.0 (13.6)
	Range	(18.0 – 74.0)	(19.0 – 73.0)	(18.0 – 74.0)
Height [cm]	Mean (SD)	170.2 (8.9)	170.0 (8.8)	170.1 (8.8)
	Range	(151.0 – 195.0)	(150.0 – 194.0)	(150.0 – 195.0)
Weight [kg]	Mean (SD)	70.3 (15.1)	70.0 (13.9)	70.2 (14.5)
	Range	(40.0 – 118.0)	(43.0 – 125.0)	(40.0 – 125.0)
Body Mass Index [kg/m^2]	Mean (SD)	24.1 (4.0)	24.1 (3.8)	24.1 (3.9)
	Range	(16.2 – 36.0)	(15.8 – 38.1)	(15.8 – 38.1)

Source: SAS-6/UCA Study Report, Table 8.

Median duration of ulcerative proctitis was 2.8 years (range, 0 to 36.7 years). The majority of patients (75.2%) had recurrent disease at baseline. The number of previous acute episodes was 4.1 (SD 6.4), and the median duration of the last remission phase was 6 months (0 to 226 months). Only a small proportion (4.5%) had had previous bowel operations. A list of baseline characteristics is shown in Table 2.7.3-10.

Table 2.7.3-10: Baseline characteristics Study SAS-6/UCA

			Salofalk®1 g Suppository OD (n = 200)	**Salofalk®500 mg Suppository TID (n = 203)**	**Total (n = 403)**
Smoking history:	Non-smoker	n (%)	155 (77.5%)	161 (79.3%)	316 (78.4%)
	Ex-smoker	n (%)	25 (12.5%)	27 (13.3%)	52 (12.9%)
	Smoker	n (%)	20 (10.0%)	15 (7.4%)	35 (8.7%)
Duration of disease [years]		Median (range)	2.2 (0.0 – 36.7)	3.8 (0.0 – 31.9)	2.8 (0.0 – 36.7)
Stool frequency in (complete) remission [per day]		Mean (SD)	1.3 (0.6)	1.2 (0.5)	1.2 (0.5)
Patients with extraintestinal disease symptoms		n (%)	32 (16.0%)	29 (14.3%)	61 (15.1%)

		Salofalk®1 g Suppository OD (n = 200)	Salofalk®500 mg Suppository TID (n = 203)	Total (n = 403)
Course of the disease				
New diagnosis [a]	n (%)	42 (21.0%)	34 (16.7%)	76 (18.9%)
Continuous	n (%)	16 (8.0%)	8 (3.9%)	24 (6.0%)
Recurrent	n (%)	142 (71.0%)	161 (79.3%)	303 (75.2%)
Number of previous acute episodes				
Based on all patients	Mean (SD)	3.4 (5.7) [n = 198]	4.8 (7.0) [n = 201]	4.1 (6.4) [n = 399]
Based on patients with recurrent course of disease only	Mean (SD)	4.8 (6.2) [n = 140]	6.0 (7.4) [n = 159]	5.4 (6.9) [n = 299]
Duration of last acute episode [months]	Median (range)	1.0 (0.0 – 142.0) [n = 142]	1.0 (0.0 – 13.0) [n = 161]	1.0 (0.0 – 142.0) [n = 303]
Duration of last remission phase [months]	Median (range)	6.0 (0.00 – 112.0) [n = 142]	7.0 (0.00 – 226.0) [n = 161]	6.0 (0.00 – 226.0) [n = 303]
Duration of current acute episode [months]	Median (range)	1.0 (0.0 – 158.0)	1.0 (0.0 – 110.0)	1.0 (0.0 – 158.0)
Patients with previous bowel operations	n (%)	11 (5.5%)	7 (3.4%)	18 (4.5%)
DAI 1 [b]	Mean (SD)	6.2 (1.6) [n = 200]	6.2 (1.5) [n = 201]	6.2 (1.5) [n = 401]
DAI 2 [c]	Mean (SD)	6.3 (1.5) [n = 200]	6.3 (1.4) [n = 201]	6.3 (1.5) [n = 401]
CAI	Mean (SD)	6.7 (2.2) [n = 198]	6.7 (1.9) [n = 197]	6.7 (2.1) [n = 395]
Number of stools per week	Mean (SD)	23.1 (15.8) [n = 200]	22.7 (13.3) [n = 201]	22.9 (14.6) [n = 401]
Number of bloody stools per week	Mean (SD)	15.9 (15.1) [n = 200]	14.9 (11.1) [n = 201]	15.4 (13.2) [n = 401]
EI	Mean (SD)	6.8 (2.0)	6.6 (2.0)	6.7 (2.0)
HI (remission)	N (%)	38 (20.9) [n = 182]	48 (27.9) [n = 172]	86 (24.3) [n = 354]
SIBDQ total score	Mean (SD)	4.5 (1.1) [n = 196]	4.3 (1.1) [n = 199]	4.4 (1.1) [n = 395]

[a] 'Duration of disease < 6 months' and 'course of the ulcerative proctitis' = 'continuous'. [b] DAI 1 = original DAI as defined according to Sutherland et al. 1987. [c] DAI 2 = original DAI as defined according to the U.S. Food and Drug Administration.
Source: SAS-6/UCA Study Report, Table 9

The two treatment groups showed no relevant differences with regard to demographic and anamnestic characteristics at baseline. The duration of disease, the number of previous acute episodes and the proportion of patients with a recurrent disease was higher in patients taking 500 mg mesalazine TID than in patients taking 1 g mesalazine OD. The prooportion of patients with a new diagnosis and with a continuous disease was higher in the 1 g mesalazine OD than in the 500 mg mesalazin TID group.

Based on baseline characteristics, no difference in the severity of acute ulcerative proctitis can be concluded between patients in either treatment group.

Patient Withdrawals

Of the 408 patients who were randomised to treatment with study medication, 22 terminated the study prematurely. The main reasons for withdrawal are shown in Table 2.7.3-11.

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Table 2.7.3-11: Reasons for premature withdrawal from study SAS-6/UCA

	Salofalk® 1 g Suppository OD (N=201) n (%)	**Salofalk® 500 mg Suppository TID (N=207) n (%)**	**Total (N=408) n (%)**
Patients prematurely withdrawn	**9 (4.5%)**	**13 (6.3%)**	**22 (5.4%)**
Primary reason for withdrawal			
Lack of patient's co-operation	3 (1.5%)	8 (3.9%)	11 (2.7%)
Lack of efficacy	2 (1.0%)	–	2 (0.5%)
Intolerable adverse event	–	3 (1.4%)	3 (0.7%)
Other reason	4 (2.0%)	2 (1.0%)	6 (1.5%)

Note: Percentages based on number of randomised patients
Source: SAS-6/UCA Study Report, Table 4

Overall, lack of patient's co-operation and other reasons were the main reasons for withdrawal. Other reasons for withdrawal were all violations of exclusion criteria, and these patients were withdrawn at the sponsor's decision and excluded from analyses.

The three patients in the Salofalk® 500 mg suppository TID group who discontinued the study prematurely due to AEs are discussed in the Summary of Clinical Safety, Section 2.7.4.2.1.4.

Two patients (both in the Salofalk® 1 g suppository OD group) withdrew for lack of efficacy. One patient withdrew after 33 days of treatment. The other patient was withdrawn after 29 days of treatment because of an exacerbation of the disease which needed treatment with a prohibited concomitant medication for ulcerative colitis.

Efficacy Results

Primary Efficacy Evaluation

The first interim analysis was performed on 145 PP evaluable patients. It did not yield a significant result. Inclusion of patients into the study was continued, and the number of patients to be evaluable for the per-protocol (PP) analysis at the second stage was increased from 2 × 43 patients to 2 × 60 patients.

The second interim analysis was performed on 270 PP evaluable patients. It yielded a significant result. Recruitment of the study was stopped after the results of the second interim analysis were available. However, as recruitment had continued during the time the second interim analysis was being performed, another 93 patients were included in the final analysis.

Clinical remission rates in the PP and ITT analysis sets at both interim analyses and at the final analysis are shown in the table below (Table 2.7.3-12).

Table 2.7.3-12: Clinical remission results (according to DAI 1). Study SAS-6/UCA

		Number (%) of patients with clinical remission at the final/withdrawal examination		Difference between proportions [a] [95% CI]	Shifted asymptotic χ^2 test for comparing two rates [b]
		Salofalk® 1 g Suppository OD	Salofalk® 500 mg Suppository TID		
1st interim analysis	PP	60/73 (82.2%)	64/72 (88.9%)	–6.7% [–18.1%, 4.7%]	0.0819 [c]
	ITT	65/82 (79.3%)	66/82 (80.5%)	–1.2% [–13.5%, 11.1%]	0.0150 [c]
2nd interim analysis	PP	121/140 (86.4%)	117/130 (90.0%)	–3.6% [–11.2%, 4.1%]	2.692 [d]
	ITT	131/157 (83.4%)	129/155 (83.2%)	0.2% [–8.1%, 8.5%]	3.436 [d]
Final analysis	PP	160/182 (87.9%)	156/172 (90.7%)	–2.8% [–9.2%, 3.6%]	3.463 [d]
	ITT	168/200 (84.0%)	172/203 (84.7%)	–0.7% [–7.8%, 6.4%]	3.790 [d]

[a] Difference between proportions [Salofalk® 1 g suppository OD – Salofalk® 0.5 g suppository TID]; asymptotic confidence interval (CI). [b] 'Effect' = difference between proportions [Salofalk® 1 g suppository OD – Salofalk® 0.5 g suppository TID] + 0.15). [c] Observed p-value (one sided). [d] Inverse normal.
Source: SAS-6/UCA Study Report, Table 14, Table 15, and Table 16

At the second interim analysis therapeutic equivalence (non-inferiority margin 15%) of Salofalk® 1.0 g suppositories once daily and Salofalk® 500 mg suppositories three time daily in patients with active ulcerative proctitis was proven.

Secondary Efficacy Evaluations

DAI, CAI and EI and other key features in therapeutic outcome

Table 2.7.3-13 gives a brief overview of three of the main secondary variables, i.e. DAI, CAI and EI from baseline to last observation carried forward (LOCF).

Table 2.7.3-13: Number (%) of patients in PP population with a change in DAI 1, CAI, and EI from baseline to LOCF in study SAS-6/UCA

Change	DAI 1 [a]		CAI		EI [b]	
	Salofalk®1 g Suppository OD n = 182	**Salofalk® 500 mg Suppository TID n = 172**	**Salofalk®1 g Suppository OD n = 182**	**Salofalk® 500 mg Suppository TID n = 172**	**Salofalk®1 g Suppository OD n = 176**	**Salofalk® 500 mg Suppository TID n = 164**
Remission	160 (87.9%)	156 (90.7%)	160 (87.9%)	159 (92.4%)	149 (84.7%)	147 (89.6%)
Improvement	17 (9.3%)	12 (7.0%)	172 (94.5%)	161 (93.6%)	19 (10.8%)	10 (6.1%)
No change	3 (1.6%)	2 (1.2%)	n.a.	n.a.	8 (4.5%)	7 (4.3%)
Deterioration	2 (1.1%)	2 (1.2%)	n.a.	n.a.	---	---

DAI 1: Remission: DAI 1 < 4 at LOCF; improvement/deterioration: decrease/increase by ≥ 1 point from baseline to LOCF and DAI 1 > 3 at LOCF; patients with remission were not included in the number of patients with improvement. **CAI**: Remission: CAI ≤ 4 at LOCF (= clinical remission); improvement: decrease in CAI by ≥ 1 point from baseline to LOCF (= clinical improvement). **EI**: Remission: EI < 4 at final examination; improvement/deterioration: decrease/increase by ≥ 1 point from baseline to final examination and EI ≥ 4; patients with remission were not included in the number of patients with improvement. [a] Patients with (DAI 1) > 3 at baseline. [b] Patients with EI ≥ 4 at baseline.

Source: SAS-6/UCA Study Report, Table 25, Table 33, and Table 44

The numbers and percentages of patients with a change in therapeutic outcome for other key variables from baseline to last observation carried forward (LOCF) are shown in Table 2.7.3-14 below.

Table 2.7.3-14: Number (%) of patients with change from baseline at LOCF in therapeutic outcome (PP analysis) in study SAS-6/UCA

Variable /Score [a]	Suppository Regimen	N	Remission/ Normalisation	Improvement	No Change	Deterioration
Stool frequency	1 g OD	150	94 (62.7%)	27 (18.0%)	27 (18.0%)	2 (1.3%)
	500 mg TID	145	78 (53.8%)	36 (24.8%)	30 (20.7%)	1 (0.7%)
Rectal bleeding	1 g OD	166	145 (87.3%)	9 (5.4%)	9 (5.4%)	3 (1.8%)
	500 mg TID	157	143 (91.1%)	7 (4.5%)	6 (3.8%)	1 (0.6%)
General well-being	1 g OD	156	94 (60.3%)	19 (12.2%)	41 (26.3%)	2 (1.3%)
	500 mg TID	148	98 (66.2%)	12 (8.1%)	36 (24.3%)	2 (1.4%)
Abdom. pain/cramps	1 g OD	123	80 (65.0%)	14 (11.4%)	25 (20.3%)	4 (3.3%)
	500 mg TID	123	95 (77.2%)	9 (7.3%)	15 (12.2%)	4 (3.3%)
Disease activity score	1 g OD	182	121 (66.5%)	40 (22.0%)	20 (11.0%)	1 (0.5%)
	500 mg TID	172	108 (62.8%)	49 (28.5%)	15 (8.7%)	–
Mucosal appearance	1 g OD	182	94 (51.6%)	66 (36.3%)	22 (12.1%)	–
	500 mg TID	172	90 (52.3%)	57 (33.1%)	25 (14.5%)	–

[a] Patients with a score >0 at baseline.
Source: SAS-6/UCA Study Report, Table 28, Table 29, Table 37, Table 38, Table 30, and Table 31

DAI 1, CAI, and EI as well as their sub-scores showed remission/normalisation or improvement in the majority of patients. Most indices and sub-scores did not show any differences between treatment groups. The following differences should be mentioned:

- Normalisation rates of the DAI sub-scores stool frequency (62.7% vs. 53.8%) and disease activity (66.5% vs. 62.8%) were higher in the Salofalk® 1 g suppositories (OD) than in the Salofalk® 500 mg suppositories (TID) group. The normalisation rate of the rectal bleeding sub-score (87.3% vs. 91.1%) turned in favour of the Salofalk® 500 mg suppository (TID) group.
- The proportion of patients with clinical remission according to CAI was slightly higher in the Salofalk® 500 mg suppository (TID) group (92.4%) than in the Salofalk® 1 g suppository (OD) group (87.9%). Normalisation rates of the general well-being (66.2% vs. 60.3%) and abdominal pain or cramps (77.2% vs. 65.0%) sub-scores also turned out in favour of the Salofalk® 500 mg suppository (TID) group.
- The proportion of patients with remission of EI was slightly higher in the Salofalk® 500 mg suppository (TID) group (89.6%) than in the 1 g Salofalk® 1 g suppository (OD) group (84.7%).

In general, differences in remission/normalisation rates in favour of one group were nearly always balanced by differences in improvement rates in favour of the other group.

Histologic Index

Change in therapeutic outcome as assessed by the HI from baseline to final examination is shown below in Table 2.7.3-15.

Table 2.7.3-15: Number (%) of patients with change in therapeutic outcome as assessed by HI from baseline to final visit in study SAS-6/UCA

Therapeutic outcome	PP		ITT	
	Salofalk®1 g Suppository OD n = 182	**Salofalk®500 mg Suppository TID n = 172**	**Salofalk®1 g Suppository OD n = 200**	**Salofalk®500 mg Suppository TID n = 203**
HI = 0 at baseline and final examination	4 (2.2%)	5 (2.9%)	6 (3.0%)	8 (3.9%)
Improvement	114 (62.6%)	104 (60.5%)	121 (60.5%)	114 (56.2%)
No improvement	57 (31.3%)	58 (33.7%)	59 (29.5%)	64 (31.5%)
Not determinable	7 (3.8%)	5 (2.9%)	14 (7.0%)	17 (8.4%)

Source: SAS-6/UCA Study Report, Table 43

The majority of patients showed an improvement of HI from baseline to final examination. There was no relevant difference in the proportions of patients with improvement of HI between the Salofalk® 1 g suppository (OD) group and the Salofalk® 500 mg suppository (TID) group (62.6% vs. 60.5%) .

Time to first resolution of clinical symptoms

The time to first resolution of clinical symptoms (according to Löfberg et al. 1994: ≤ 3 stools/day; all without blood) was slightly longer in patients taking Salofalk® 500 mg suppository (TID) than in patients taking Salofalk®1 g suppository (OD), both in the PP population (Salofalk®1 g suppository (OD): 7.3 [7.4] days, n = 176; Salofalk® 500 mg suppository (TID): 9.1 [8.8] days, n = 166) and in the ITT analysis set (Salofalk®1 g suppository (OD): 7.3 [7.4] days, n = 191; Salofalk® 500 mg suppository (TID): 8.5 [8.6] days, n = 192).

According to the time-to-event analysis, the median time to first resolution of clinical symptoms was longer in patients taking the Salofalk® 500 mg suppository (TID) than in patients taking the Salofalk® 1 g suppository (OD). However, hazard ratios close to 1 and 95% CIs including 1 showed that the difference in median time to first resolution of clinical symptoms was not statistically significant (see Table 2.7.3-16).

Table 2.7.3-16: Time to first resolution of clinical symptoms (time-to-event analysis) in study SA-6/UCA

	Median [95% CI] time to first resolution of clinical symptoms [days]		Hazard ratio	95% CI
	Salofalk®1 g Suppository OD	Salofalk®500 mg Suppository TID		
PP	5.0 [4.0, 7.0] n= 182	7.0 [5.0, 8.0] n= 172	0.850	[0.687, 1.052]
ITT	5.0 [4.0, 6.0] n= 200	7.0 [5.0, 8.0] n= 203	0.888	[0.727, 1.086]

Source: SAS-6/UCA Study Report, Table 45

Erythrocyte sedimentation rate

The median decrease in ESR after the first hour from baseline to LOCF did not show any relevant difference between the the Salofalk® 1 g suppository (OD) group (-2.0 mm) and the Salofalk® 500 mg suppository (TID) group (-3.0 mm).

Physician's Global Assessment

The distribution by number and percentages of patients according to assessment of symptoms by the PGA at the final visit is shown for both population analyses in Table 2.7.3-17 below.

Table 2.7.3-17: PGA of symptoms at the final visit (Study SAS-6/UCA)

	PP		ITT	
Assessment of Symptoms	**Salofalk®1 g Suppository OD n = 182**	**Salofalk®500 mg Suppository TID n = 172**	**Salofalk®1 g Suppository OD n = 200**	**Salofalk®500 mg Suppository TID n = 203**
Complete relief	89 (48.9%)	88 (51.2%)	93 (46.5%)	101 (49.8%)
Marked improvement	73 (40.1%)	65 (37.8%)	75 (37.5%)	72 (35.5%)
Moderate improvement	10 (5.5%)	11 (6.4%)	16 (8.0%)	14 (6.9%)
Slight improvement	5 (2.7%)	7 (4.1%)	8 (4.0%)	9 (4.4%)
No change	3(1.6%)	–	3 (1.5%)	1 (0.5%)
Worsening	1 (0.5%)	1 (0.6%)	2 (1.0%)	1 (0.5%)
No remark	1 (0.5%)	–	3 (1.5%)	5 (2.5%)

Source: SAS-6/UCA Study Report, Table 41

No marked differences in PGA between treatment groups in either population set was observed. If therapeutic success is defined as the number and percentage of patients with 'at least marked improvement of symptoms' (constituting the sum of the first two rows in Table 2.7.3-17 above), then treatment with both Salofalk® suppositories were successful in 89% of all PP patients. If therapeutic benefit is defined as the number and percentage of patients with 'at least slight improvement of symptoms' (constituting the sum of the first four rows in the same table), then treatment with both Salofalk® suppositories provided therapeutic benefit in at least 96% of ITT patients and more than

97% of PP patients with only minimal differences between the treatment groups. These results are further detailed in Table 2.7.3-18 below.

Table 2.7.3-18: Number (%) of patients with therapeutic success and benefit as assessed by PGA at the final visitin study SAS-6/UCA

	PP		ITT	
Assessment	**Salofalk®1 g Suppository OD n = 182**	**Salofalk®500 mg Suppository TID n = 172**	**Salofalk®1 g Suppository OD n = 200**	**Salofalk®500 mg Suppository TID n = 203**
Therapeutic success	162 (89.0%)	153 (89.0%)	168 (84.0%)	173 (85.2%)
Therapeutic benefit	177 (97.3%)	171 (99.4%)	192 (96.0%)	196 (96.6%)

Source: SAS-6/UCA Study Report, Table 42

Change in SIBDQ

Changes from baseline to LOCF and differences in changes between treatment groups were analysed by means of 95% CIs and exploratory t-tests (see Table 2.7.3-19).

Table 2.7.3-19: Change in SIBDQ from baseline to LOCF

	Mean (SD) change in SIBDQ from baseline to LOCF		Difference between changes [a] [95% CI]	t-test p
	Salofalk®1 g suppository OD	**Salofalk®500 mg suppository TID**		
PP	1.3 (1.1) n = 175 [b]	1.5 (1.2) n = 166 [b]	–0.2 [–0.5, 0.0]	0.0718
ITT	1.3 (1.1) n = 189 [c]	1.5 (1.1) n = 192 [c]	–0.2 [–0.4, 0.0]	0.0906

[a] 1 g mesalazine OD – 500 mg mesalazine TID. [b] In 7 patients in the 1.0 g mesalazine OD and 6 patients in the 0.5 g mesalazine TID group no change in SIBDQ from baseline to LOCF could be calculated.
[c] In 11 patients each in the 1.0 g mesalazine OD in the 0.5 g mesalazine TID group no change in SIBDQ from baseline to LOCF could be calculated.
Source: SAS-6/UCA Study Report, Table 46

Based on both the PP and the ITT analysis sets, SIBDQ showed a clear increase from baseline to LOCF in both treatment groups. No relevant difference in the change of SIBDQ between treatment groups could be observed in either analysis set.

Conclusions

- Both, treatment with Salofalk® 1 g suppository (OD) and Salofalk® 500 mg suppository (TID) was highly efficacious, safe and well tolerated in patients with active ulcerative proctitis, and once daily Salofalk®1 g mesalazine suppositories proved to be therapeutically equivalent to three times daily Salofalk®500 mg mesalazine suppositories.
- Treatment with both Salofalk® suppositories induced a prompt cessation of clinical symptoms.

Both the Salofalk® 1 g suppository OD and the Salofalk® 500 mg suppository TID were very well accepted treatment regimens.

Summary Efficacy of 500 mg 5-ASA suppositories

The results of the treatment with 500 mg 5-ASA suppositories (t.i.d. or b.i.d.) in four placebo-controlled clinical trials in patients with distal ulcerative colitis / ulcerative proctitis clearly show that this treatment is highly efficacious, leading to clinical, endoscopic and histological improvement and remission of a large majority of patients.

2.7.3.2 Appendix

Table 2.7.3-20: Description of Clinical Efficacy and Safety Studies

Study ID	No. of Study Centres Location(s)	Study start Enrolment status, date Total enrolment/ enrolment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study objective	No. of subjects by arm entered/ compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Incl. Criteria	Primary Endpoint (s)
Active distal UC (ulcerative proctitis) – Pivotal placebo-controlled clinical trials										
Williams 1987	n.r. Canada	n.r. 39/n.r.	Prospective, ra, PC, double-blind	1a) 5-ASA 500 mg supp (Rowasa®) t.i.d 1b) plac t.i.d 2) ^{99m}Tc-labeled 5-ASA supp once	1) To compare the effect of 5-ASA supp with that of plac in active distal proctitis. 2) To measure spread of rectal supp of ^{99m}Tc-labeled 5-ASA.	1a) 14/14 1b) 13/11 2) 6 pat with IBD; 6 healthy volunteers	1a and 1b) 6 weeks 2) 1 day	1a) 8/6 37.3±14.5y 1b) 9/4 42.7±11.2y	Active distal proctitis involving the distal 15cm or less on sigmoidoscopy, pat with standard therapy or newly referred	DAI at 3 and 6 weeks

Study ID	No. of Study Centres Location(s)	Study start Enrolment status, date Total enrolment/ enrolment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study objective	No. of subjects by arm entered/ compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Incl. Criteria	Primary Endpoint (s)
Williams 1990, Study 1 (Banks Statistical Report 1986)	7 centres in Canada, US	1985 79/n.r	Ra, db, par, PC, mc	500 mg 5-ASA supp (Rowasa®) or plac t.i.d	Efficacy and safety of 500 mg 5-ASA supp in ulcerative proctitis	5-ASA: 39 Plac.: 40	6 weeks	34/45 38.9±12.6	Ulcerative proctitis confirmed by sigmoidoscopy involving a maximum of 15cm from anal margin, minimum DAI score of 3	DAI[1] at 3 and 6 weeks
Williams 1990, Study 2	n.r.	n.r. 94/n.r.	Ra, db, par, PC, mc	500 mg 5-ASA supp (Rowasa®) or plac b.i.d	Efficacy and safety of 500 mg 5-ASA supp in ulcerative proctitis; Comparison of dosing schedules t.i.d. and b.i.d.	5-ASA: 50 Plac.: 44	6 weeks	18/32	Ulcerative proctitis confirmed by sigmoidoscopy involving a maximum of 15cm from anal margin, minimum DAI score of 3	DAI at 6 weeks

Study ID	No. of Study Centres Location(s)	Study start Enrolment status, date Total enrolment/ enrolment goal	Design Control type	Study & Ctrl Drugs Dose, Route & Regimen	Study objective	No. of subjects by arm entered/ compl.	Duration	Gender M/F Median Age (Range)	Diagnosis Incl. Criteria	Primary Endpoint (s)
SAS-6/UCA Completed. Final full study report. (Publicat-ion by Andus 2010)	35 centres Germany 5 Israel 10 Russia 13 Ukraine 7	June 2005 408 ra ITT/safety 403	Single (investigator)-blind, multi-centre, randomised, active-control, comparative, phase III study.	Salofalk® 1 g supp OD; Salofalk® 500 mg supp TID Rectal administration.	To prove therapeutic equivalence of mesalazine 1 g sup OD vs mesalazine 0.5 g sup TID in patients with active ulcerative proctitis.	1 g group: 201/200 500 mg group: 207/203	6 weeks	M: 178; F: 225 mean age: 42 y; age range: 18–74 y.	Mild to moderate (3<DAI<11) active ulcerative proctitis (max. 15 cm of rectum) confirmed by endoscopy and histology	Therapeutic equivalence of 1 g supp OD vs 500 mg supp TID. Clinical remission (DAI<4) at week 6 /withdrawal

1: DAI defined as sum of factors ‘evacuation frequency’, ‘rectal bleeding’, and ‘mucosal appearance’

Table 2.7.3-21: Results of Efficacy Studies

Study	Treatment Arm	No. Enrolled/ Completed	Primary Endpoint	Statistical test/ P value	Secondary Endpoints	Other Comments
Distal UC (ulcerative proctitis) – Pivotal placebo-controlled clinical trial						
Williams 1987	1a) 5-ASA supp 500 mg (Rowasa®) t.i.d 1b) Plac t.i.d 2) ^{99m}Tc-labeled 5-ASA supp once	1a) 14/14 1b) 13/11 2) IBD (n=6); healthy volunteers (n=6)	<u>At 3 weeks</u>: 1a) DAI decreased from initial 7.1±1.8 to 1.6±1.5 1b) DAI decreased from initial 7.4±1.8 to 5.8±1.9 <u>At 6 weeks</u>: 1a) DAI: 0.4±0.9 1b) DAI: 5.4±3.4 2) ^{99m}Tc-labeled 5-ASA supp remained localized to rectum and sigmoid colon in all controls and patients at 1 and 3 hours	Group and paired *t*-testing and analysis of variance using a repeat measures design <u>At 3 weeks</u>: 1a) p<0.001 1b) n.s. <u>At 6 weeks</u>: 1a) p<0.001 1b) n.s.	n.a.	There was no difference in response to treatment when the patients were considered as being on no coincident therapy or maintaining their usual drugs, sulfasalazine or prednisone.
Williams 1990, Study 1 (Banks Statistical Report 1986)	5-ASA supp 500 mg (Rowasa®) t.i.d Plac t.i.d	5-ASA: 39/37 Plac: 40/34	<u>DAI mean score at Week 6</u>: 5-ASA: 0.95 ±1.73 Plac: 3.00 ± 2.40 <u>Percentage change from baseline in DAI at Week 6:</u> 5-ASA: 82.17% Plac: 42.97%	χ^2-test, analysis of variance, Wilcoxon rank test/ p<0.001 p<0.001	n.a.	In patients concurrently treated with orally administered sulfasalazine + prednisone (n=11) the magnitude of differences between 5-ASA and plac group was much less and not statistically significant (p=0.18).

Study	Treatment Arm	No. Enrolled/ Completed	Primary Endpoint	Statistical test/ P value	Secondary Endpoints	Other Comments
Distal UC (ulcerative proctitis) – Pivotal placebo-controlled clinical trial						
Williams 1990, Study 2	5-ASA supp 500 mg (Rowasa®) b.i.d Plac b.i.d	94/77	Mean reduction in the overall DAI score: 5-ASA: 74.7% pl: 34.2% Physician's global assessment 'much improved': 5-ASA: 79.2% pl: 26.2%	χ^2-test, analysis of variance / p<0.001 p<0.001	n.a.	Comparison of Study 1 and Study 2: No statistically significant difference in efficacy between t.i.d. and b.i.d dosing regimen
SAS-6/UCA (Publicat-ion by Andus 2010)	Salofalk® 1 g supp OD; Salofalk® 0.5 g supp TID	ra 201 / ITT 200 ra 207 / ITT 203	No. (%) of pts with clinical remission at 2nd interim analysis: 1g supp OD: PP: 121/140 (86.4%); ITT: 131/157 (83.4%). 500 mg supp TID: PP: 117/130 (90.0%); ITT 129/155 (83.2%)	Shifted asymptotic χ^2-test for comparing two rates* PP: 2.692**; ITT: 3.436** Clinical remission at the final visit did not show any difference between the 500 mg and 1 g groups. Mesalazine 1 g supp OD was not inferior to mesalazine 500 mg supp TID.	DAI1, CAI and EI as well as their sub-scores showed remission /normalisation or improvement in most pts. Most indices /sub-scores did not show any differences between treatment groups	According to SIDBQ ant its sub-scores quality of life improved from baseline to the final visit in both treatment groups

b.i.d.: twice daily; CAI: clinical activity index; Compl: completed; DAI: Disease activity index; db: double-blind; EI: endoscopic index; F: female; ITT: intention to treat; M: male; n.r.: not reported; n.s.: not significant; PC: placebo-controlled, plac: placebo; OD: once daily; PP: per protocol; ra: randomized; supp: suppository/ies; t.i.d.: three times daily; * 'Effect'= difference between proportions [1 g supp OG – 500 mg supp TID] +0.15; ** inverse normal;

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Abbreviations

Term	Explanation
5-ASA	5-aminosalicylic acid, mesalazine, mesalamine
Ac-5-ASA	N-acetyl-5-aminosalicylic acid
ADR	Adverse drug reaction
AE	Adverse event
$Ae_{0\text{-}48h}$	Urinary excretion
alk-SMase	Alkaline sphingomyelinase
ALL	All studies
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the (plasma) concentration-time curve
$AUC_{0\text{-}inf}$	Area under the concentration-time curve extrapolated to infinity
b.i.d.	Twice daily
bw	Body weight
CAI	Clinical Activity Index
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CI	Confidence interval
C_{max}	Maximum (plasma) concentration
CRC	Colorectal cancer
d	Day(s)
DAI	Disease Activity Index
E	Endoscopic
EI	Endoscopic Index
GI	Gastrointestinal
h	Hours(s)
HI	Histlogic Index
HPLC	High-pressure liquid chromatography
IBD	Inflammatory bowel disease(s)
IC	Indeterminate colitis
ICH	International Conference on Harmonisation

Term	Explanation
IL-1	Interleukin-1
ITT	Intention-to-treat
MA	Marketing authorisation
MAA	Marketing authorisation application
n	Number
N-Ac-5-ASA	N-acetyl-5-aminosalicylic acid
NF κB	Nuclear factor κB
o.d.	Once daily
PAF	Platelet-activating factor
PC	Placebo-controlled studies
PIL	Patient Information Leaflet
PP	Per-protocol
PPAR	Peroxisome proliferator-activated receptor
PSUR	Periodic Safety Update Report
QA	Placebo-controlled trials passing quality assessment scoring
QoL	Quality of life
S.D.	Standard deviation
SIBDQ	Short Inflammatory Bowel Disease Questionaire
SmPC	Summary of Product Characteristics
t.i.d.	Three times daily
t_{max}	Time to maximum (plasma) concentration
TNF	Tumour necrosis factor
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis
vs.	Versus
β-NAG	β-N-acetyl-D-glucosaminidase

2.5 Clinical Overview

5-ASA (mesalazine) preparations for treatment of chronic inflammatory bowel diseases (IBD) have first been introduced into the market by Dr. Falk Pharma GmbH in 1984 and have been successfully marketed since then in the form of Salofalk® tablets, granules, suppositories, enemas, and also as Salofalk® foam in some countries, but also under the trade names Claversal®, Mesasal®, Colitofalk®, Rafassal®, and Rowasa®. Salofalk® 500 mg suppositories were first introduced to the market in 1992.

The applicant (Dr. Falk Pharma GmbH) seeks marketing authorisation (MA) for the rectal mesalazine (5-ASA) suppository formulation

- Salofalk® 500 mg suppositories

that is regarded as a completion of the approved oral 5-ASA preparation Salofalk® granules ('line extension').

The indication claimed as based on the national MA in Germany is as follows:

- 'Acute treatment of ulcerative colitis restricted to the rectum'.

Salofalk® 500 mg suppositories are indicated at the dose of one Salofalk® 500 mg suppository three times daily (equivalent to 1.5 g mesalazine daily).

This MA application (MAA) is therefore primarily grounded on the Clinical Documentation on Salofalk® granules already approved, and on the Clinical Documentation on Salofalk® 250 mg / 500 mg suppositories that has led to national MAs in Germany.

The local availability of 5-ASA, the therapeutic efficacy and tolerability of these specific suppository preparations in the treatment of acute episodes of distal ulcerative colitis (UC) and in the maintenance of remission of this disease (Salofalk® 250 mg only) have been well established and documented in the previous MAA.

This Clinical Documentation on Salofalk® 500 mg suppositories is intended to amend the

- Clinical Documentation on the approved Salofalk® granules (cf. Salofalk® granules - Expert Report on the Clinical Documentation [Kruis 2000]), and the
- Clinical Documentation on Salofalk® 250 mg / 500 mg suppositories that led to a national MA of Salofalk® 500mg suppositories in Germany (Expert Report on the Clinical Documentation [Schölmerich 1997]),

by summarising and evaluating

Relevant clinical data that has not been implemented in the previous Clinical Documentation on the respective medicinal products (Addendum to the Clinical Documentation) and

Essential clinical studies on ulcerative proctitis already previously included for providing a more comprehensive picture.

2.5.1 Product Development Rationale

Clinical background Ulcerative Colitis

Ulcerative colitis (UC) is one of several complex disorders which are designated as inflammatory bowel diseases (IBD), the other entities being Crohn's disease (CD), microscopic colitis and 'colitis yet to be classified' or 'indeterminate colitis' when no clear assignement can be made.

UC is characterised by diffuse mucosal inflammation limited to the rectum and the colon. Subgroups of UC patients can be defined by the extent of colorectal inflammation by endoscopic appereance: 1) ulcerative proctitis, refering to inflammation confined to the rectum; 2) left-sided UC, where the involvement is limited to the colorectum distal to the splenic flexure – ulcerative proctitis and left-sided UC together are often denominated as "distal ulceratice colitis" - , and 3) more extensive disease, including also 'pancolitis' (Silverberg et al. 2005, Stange et al. 2008). In addition, even if abandoned in the official classifications, for practical reasons, often the term 'proctosigmoiditis' is used as a subgroup of distal UC to characterise the limitation of the inflammation to the rectum and the sigmoidal part of the colon.

The cardinal symptom of UC is bloody diarrhoea, which is associated with colicky abdominal pain, urgency or tenesmus. Potentially, untreated UC is a severe disease with high mortality and major morbidity. Today, with modern medical and surgical management, the overall mortality risk in patients with UC is not significantly different from that of the background population, although certain subgroups of patients, e.g. during the first years of the disease and in patients with extensive inflammation may carry an increased mortality risk (Jess et al. 2007). Even today, a severe attack of UC is still a potentially life-threatening illness. Primarily due to the colorectal loss of blood anemia is seen frequently in patients with UC (Gomollon & Gisbert 2009) and also other extraintestinal manifestatations e.g. rheumatic and dermatologic disorders are common (Larsen et al. 2010).

In Europe and Noth America the findings for the incidence of UC range from 2.3 to 20.3 per 100.000 inhabitants per year with a reported prevalence rates ranging from of 21.4 to 264 / 100.000. UC is mainly a diseases of younger ages with a peak incidence between the ages of 10 and 40 years, however, people at any age may be affected (Loftus et al. 2004a, Shivananda et al. 1996).

In most cases the course of the diseases in UC is characterised by periods of remissions and relapsing exacerbations but courses with chronic activity are not rare (Henriksen et al. 2006). Diagnosis and monitoring of UC includes several clinical, endoscopic, histological, haematochemical and immunological parameters. According to such comprehensive assessment, UC activity is qualified either as quiescent (remission) or by mild, moderate and severe attacks (Silverberg et al. 2005, Stange et al. 2008). Depending on the extent, the duration of the disease, the level of mucosal inflammation and additional risk factors patients with UC have an increased risk of colorectal carcinoma (Eaden 2004).

Despite huge efforts in the last decades, the aetiology of IBD is far from being comprehensively elucidated. IBD are considered to be an inadequate inflammatory and

immune response to environmental triggers in genetically susceptible individuals. In the last years evidence increased that microbes of the physiological intestinal microbiota may be targets of the inflammatory and immune responses that are typical in IBD. IBD appear to result from a dysregulated response of the mucosa that is facilitated by defects in the protective barrier function of the intestinal epithelium. The nature of the primary pathogenetic events responsible for triggering the inflammatory cascade and initiating tissue damage as well as many details in the interaction of genetic and environmental factors are still not understood. Immunogenetics, hormonal and cell-mediated immunity play an important role in the predisposition, modulation and perpetuation of IBD (Khor et al. 2011, Xavier & Podolsky 2007).

Drug therapy approaches in IBD

To date no curative therapy is available for IBD even if - in constrast to CD - in UC, complete proctocolectomy may be considered as a method of resolution of the disease. Thus, treatment of UC mainly aims at suppressing inflammation and associated symptoms during acute episodes, preventing recurrence of inflammation and increasing the quality of the patient's life (Kornbluth & Sachar 2010).

In the treatment of active UC, aminosalicylates, either in the form of inactive prodrugs (sulfasalazine, balsalazide, olsalazine) or as specific oral slow- / controlled-release mesalazine formulations, and/or as rectal formulations (suppositories, enemas and foams), are the foundational therapy, as they are also in the maintenance of remission. In the case of more severe acute episodes or failure of therapy, glucocorticoids, immunosuppressive agents (azathioprine, cyclosporine), and antibodies against the key proinflammatory cytokine tumor necrosis factor α (TNF- α) are used (Travis et al. 2008, Kornbluth & Sachar 2010, Rogler 2009, Munkholm et al. 2010).

The clinical efficacy of mesalazine is based on its multiple mechanisms of action in inflammatory processes (Desreumaux 2007, Rousseaux et al. 2005, Nikolaus et al. 2000). It is important to mention that mesalazine acts exclusively topical, i.e. on epithelial cells and macrophages in the mucosa (Travis et al 2008, Frieri et al. 2000, DeVos et al. 1992). Uncoated oral mesalazine is rapidly absorbed and metabolised in the upper gastrointestinal tract, and is thus not locally available in the colon. Various oral formulations of mesalazine have been developed to resolve this problem, ensuring a release of the active ingredient also in more distal parts of the bowel, and thus providing oral therapy of ulcerative colitis. If inflammation in the distal sections of the colon is to be treated specifically, pharmaceutical forms designed for rectal administration (enemas, suppositories, or foam) are the treatment of choice to ensure high local availability of the agent, thus providing local and topical action rather while minimising systemic absorption (Marshall & Irvine 2000).

For isolated proctitis suppositories remain the treatment of choice, while proctosigmoiditis and left-sided (distal) ulcerative colitis are best treated with mesalazine as rectally applied liquid or foam enemas eventually combined with oral mesalazine preparations (Travis et al. 2008, Kornbluth & Sachar 2010, Rogler 2009, Munkholm et al. 2010).

Therapeutic rationale for Salofalk 500 mg suppositories

Although even modern oral 5-ASA modified-release preparations proved to be effective in left-sided or distal UC, rectal 5-ASA preparations are deemed the optimally targeted treatment of this disease (Marshall & Irvine 2000; Rogler 2009). UC often begins in the rectum and then extends proximally. But even irrespective of the proximal disease extent, distal parts of the colon are always co-affected in UC. Therefore, a majority of UC patients will benefit from treatment with rectal 5-ASA over the course of their disease.

Salofalk® 500 mg suppositories provide the advantage of effectively delivering 5-ASA directly to the site of maximal inflammation while potentially minimising loss of active substance by systemic absorption. Salofalk® 250 mg suppositories were first introduced to the market in 1984, and Salofalk® 500 mg suppositories in 1992.

In a number of clinical trials therapeutic success had been achieved in the treatment of active ulcerative proctitis following a daily dose of 1.5 g 5-ASA (5-ASA 500 mg suppositories t.i.d.) (summarised in the expert report by Schölmerich 1997).

This Clinical Overview particularly evaluates relevant clinical study data on Salofalk® 500 mg suppositories in addition to those already submitted with the previous MAAs on Salofalk® granules (Kruis 2000) and on Salofalk® suppositories (Schölmerich 1997).

Where appropriate, essential studies on the pharmacology, clinical efficacy and safety that are of major importance for Salofalk® suppositories, although already presented in the previous Clinical Documentation (see Schölmerich 1997) have also been included and summarized here.

2.5.2 Overview of Biopharmaceutics

As in UC inflammation is largely restricted to the muocsa of the colon and/or the rectum, ideally, a therapeutic principle should be targeted directly to these sites. By acting from the luminal side, effective mucosal drug concentrations should be achieved and concentrations of active drug substance in other compartments, including serum and other systemic localisations should be minimized in order not to waiste active substance.

The rectal spread of the active agent is important for the efficacy of the preparation. A number of studies have thus investigated the retrograde distribution of 5-ASA suppositories that have already been included and discussed in the previous national MAA on Salofalk® suppositories (Schölmerich 1997).

2.5.2.1 Study on bioavailability / colonic spread of Salofalk® suppository formulations

Relevant clinical pharmacokinetic studies on the topical and systemic availability of 5-ASA after rectal administration of Salofalk® suppositories have been already included in the original Clinical Documentation on Salofalk® (250 mg / 500 mg) suppositories

leading to national MAs in Germany. Therefore, reference is made to the respective Clinical Documentation (Schölmerich 1997).

Since then, one additional pharmacokinetic trial with Salofalk® 500 mg suppositories, study SAS-5/BIO, has been performed. This new study is presented in short in this Clinical Overview and in details in the acompanying Clinical Summaries (2.7.1 and 2.7.4).

In addition, the pivotal bioequivalence / pharmacokinetic study demonstrating the bioequivalence of Salofalk® 500 mg suppositories and the widely marketed rectal 5-ASA preparation Rowasa® 500 mg suppositories, SAS-2/BIO already presented in the previous clinical documentation, is summarized and discussed in this Clinical Overview. The study is presented in detail in Section 2.7.1 ('Summary of Biopharmaceutic Studies and Associated Analytical Methods').

2.5.2.1.1 SAS-2/BIO

An open, randomised multiple dose (steady-state) crossover study to compare the bioavailability of Salofalk (mesalazine) 500 mg suppositories with Rowasa (mesalazine) 500 mg suppositories in healthy subjects

SAS-2/BIO is an open, randomized, multiple dose (steady-state) crossover study to compare the serum concentrations of mesalazine and its metabolite after rectal administration of Salofalk® (mesalazine) 500 mg suppositories with Rowasa® (mesalazine) 500 mg suppositories.

Twenty-four healthy subjects (9 females, 15 males) aged 21 to 50 years (mean 33) were randomized to receive either Salofalk® 500 mg (test) suppositories or Rowasa® 500 mg suppositories (reference) three times daily on days one to five during the first study period. After a wash-out period of at least 14 days, subjects repeated the study procedure with the alternative study medication.

On Day 6, blood samples were collected prior to first dosing, and at 1.0, 2.0, 3.0, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, and 8.0 hours post-dose. Plasma concentrations for 5-ASA and the main metabolite N-acetyl-5-ASA were measured using a fully validated HPLC procedure.

All urine passed in the 8 hours following the morning dose was collected on Days 5 and 6 for determination of both 5-ASA and N-acetyl-5-ASA.

The pharmacokinetic data for 5-ASA on Day 6 are given in Table 2.5-1.

Table 2.5-1: SAS-2/BIO: Pharmacokinetics of 5-ASA (Day 6)

	Rowasa® 500 mg suppositories (reference) Mean (range) (n=24)	**Salofalk® 500 mg suppositories** (test) Mean (range) (n=24)	**P value**	**90% CI**
C_{max} (ng/mL)	411; 418[b] (96-721)	426; 364[b] (207-1038)	ns	92-131[a]
T_{max} (h)	2.0[b] (1.0-8.0)	1.5[b] (1.0-4.5)	ns	-1.00-0.00
AUC_{0-8} (h•ng/mL)	2077 (282-4213)	1901 (537-5277)	ns	73-123[a]
C_{av} (ng/mL)	260 (35-527)	238 (67-660)	-	-
UE_{0-8} (mg)	4 (0-20)	3 (0-12)	ns	71-143[c]

a: log transformed data; b: median; c: based on median values; ns: not significant
Source: Study Report SAS-2/BIO, Table 1.1

No significant differences were found between Rowasa® 500 mg suppositories and Salofalk® 500 mg suppsositories with regard to the mean values of the pharmacokinetic parameters C_{max}, AUC_{0-8}, t_{max} and urinary excretion (UE_{0-8}). As expected, determined plasma concentrations of 5-ASA showed wide inter- and intra-subject variability.

The 90% CI on the log scale indicates that Salofalk® $\log_e C_{max}$ lay between 92 and 131% of that for Rowasa®, just outside the window of 80-125% required to formally demonstrate bioequivalence. Similarely, for logarithmically transformed AUC_{0-8} data, the CI was 73 to 123% of Rowasa®.

Metabolite levels followed a similar pattern to that of the parent drug showing wide ranges but similar mean data. The pharmacokinetic data for N-acetyl-5-ASA on Day 6 are given in Table 2.5-2.

Table 2.5-2: SAS-2/BIO: Pharmacokinetics of N-acetyl-5-ASA (Day 6)

Heading	**Rowasa® 500 mg suppositories** (reference) Mean (range) (n=24)	**Salofalk® 500 mg suppositories** (test) Mean (range) (n=24)	**P value**	**90% CI**
C_{max} (ng/mL)	743; 717[b] (258-1524)	753; 694[b] (343-1629)	ns	91-123[a]
T_{max} (h)	2.0[b] (1.0-8.0)	2.0[b] (1.0-4.5)	ns	-1.00-0.25
AUC_{0-8} (h•ng/mL)	4345 (878-9172)	4142 (1319-10535)	ns	80-121[a]
C_{av} (ng/mL)	543 (110-1147)	518 (165-1317)	-	-
UE_{0-8} (mg)	84 (23-178)	78 (32-214)	ns	74-116

a: log transformed data; b: median; ns: not significant
Source: Study Report SAS-2/BIO, Table 1.2

CIs for $\log_e C_{max}$ and $\log_e AUC_{0-8}$ for N-acetyl-5-ASA were within the range required to demonstrate bioequivalence (91 to 123% and 80 to 121%, respectively).

A direct comparision of the curves of the sum of the mean serum concentration of the parent drug and the metabolite impressively shows the similarity of both 500 mg 5-ASA suppositories (Figure 2.5-1).

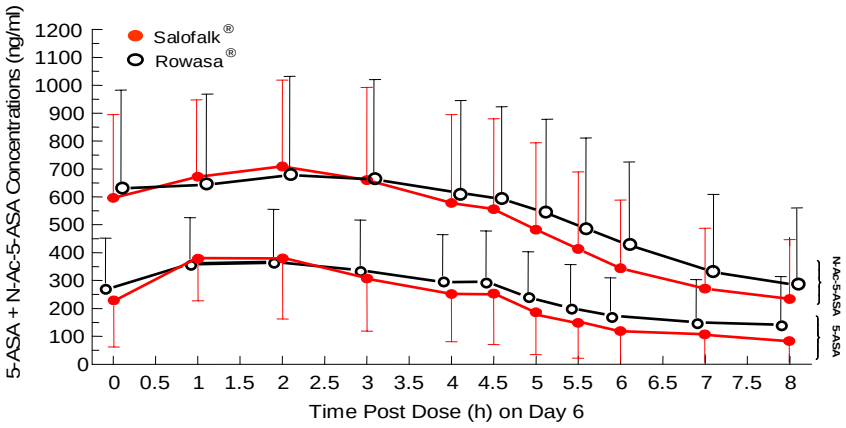


Figure 2.5-1 SAS-2/BIO: Comparision of the mean 5-ASA and N-Ac-5-ASA plasma concentration curves of Rowasa 500mg Suppositories and Salofalk® 500 mg Suppositories after daily rectal administration of 3x1 Suppositorium for 6 Days (x ± SD)

In the light of the very similar serum concentrations curves of 5-ASA and N-Ac-5-ASA from Rowasa ® and Salofalk® 500 mg suppositories it seems obvious that both preparations are to be considered to be equivalent with regard to serum concentrations. So, the fact that the criteria of bioequivalence were only fullfilled with regard to the main metabolite but not with regard to the drug substance might be primarily a mathematical problem due to the high interindividual variability.

Limits calculated for both 5-ASA and N-acetyl-5-ASA in urine were outside the range required to demonstrate bioequivalence (71-143% and 74 to 116%, respectively). These values again reflect the large variability. 5-ASA concentrations were largely below the limits that allowed an accurate quantification and therefore must be viewed with caution.

In summary, although the serum concentrations of 5-ASA formally do not strictly fullfil the criteria of bioequivalence the metabolite levels show bioequivalence and the serum concentration curves demonstrate a high degree of similarity. In addition, no significant difference has been demonstrated between Salofalk® and Rowasa® for parent drug C_{max}, t_{max} and AUC data, and CIs range either side of 100% of Rowasa®.

Based on these considerations the results of Study SAS-2/BIO are considered to show bioequivalence of Rowasa® and Salofalk® 500 mg suppositories.

The slightly wider CIs for 5-ASA are of no clinical significance particularly as CIs span 100% of Rowasa. It is considered that wider confidence limits for serum concentrations are acceptable for this topical acting drug since it has a wide therapeutic index. Therapeutic efficacy is related to topical drug concentrations in the rectal mucosa rather than to systemically available drug (Frieri et al. 2000). Most important, no specific safety questions are raised by rectal administration of Salofalk® 500 mg suppositories as incidence, severity and relationship to treatment of AEs in study SAS-2/BIO confirmed that reference and test product were equally well tolerated.

2.5.2.1.2 Study SAS-5/BIO
Bioequivalence Study on Salofalk® 1 g Suppository and Salofalk® 2 × 500 mg Suppositories and Pentasa® 1 g Suppository in Healthy, Male Subjects

Study SAS-5/BIO was an open-label, randomised, single centre, single dose, three-way crossover, phase I clinical trial in healthy male subjects to determine the pharmacokinetic properties of mesalazine and its main metabolite from plasma and urine after administration of one Salofalk® 1 g suppository and to compare the results to equivalent amounts of mesalazine administered as Salofalk® 500 mg suppositories and the Pentasa® 1 g suppository. For reasons of conciseness, in this Clinical Overview on Salofalk® 500 mg suppositories, primarily the data on the comparison of Salofalk® 1 g and Salofalk® 500 mg suppositories will be reported but data on the comparison of Salofalk® 1 g suppositories and Pentasa® suppositories are not shown here.

Blood sampling for pharmacokinetics was performed prior to dosing and in narrow intervals up to 24 h after dosing. Urine was collected prior to dosing and 0–8 h, 8–24 h, and 24–48 h after dosing.

The primary objective of this study was to show bioequivalence according to the parameters C_{max} and AUC for 5-ASA and Ac-5-ASA of Salofalk® 1 g suppository in comparison to Salofalk® 2 × 500 mg suppositories (and Pentasa® 1 g suppository) after single rectal administration.

AUC was estimated by two variables: AUC of observed data up to 24 hours (AUC_{0-24h}) and the AUC of observed data up to the time of the last quantifiable concentration plus the extrapolation to infinity ($AUC_{0-\infty}$). 90% CIs were calculated for C_{max} and AUC.

As 5-ASA and Ac-5-ASA plasma concentrations following the rectally administered suppositories were expected to show a high degree of variability (Norlander et al. 1989; Vree et al. 2000), a wider acceptance range of 0.70–1.43 was chosen for C_{max} (described in the statistical analysis plan CSR SAS-5/BIO, Appendix 16.1.9). For AUC the standard acceptance range 0.80–1.25 for the CIs was defined.

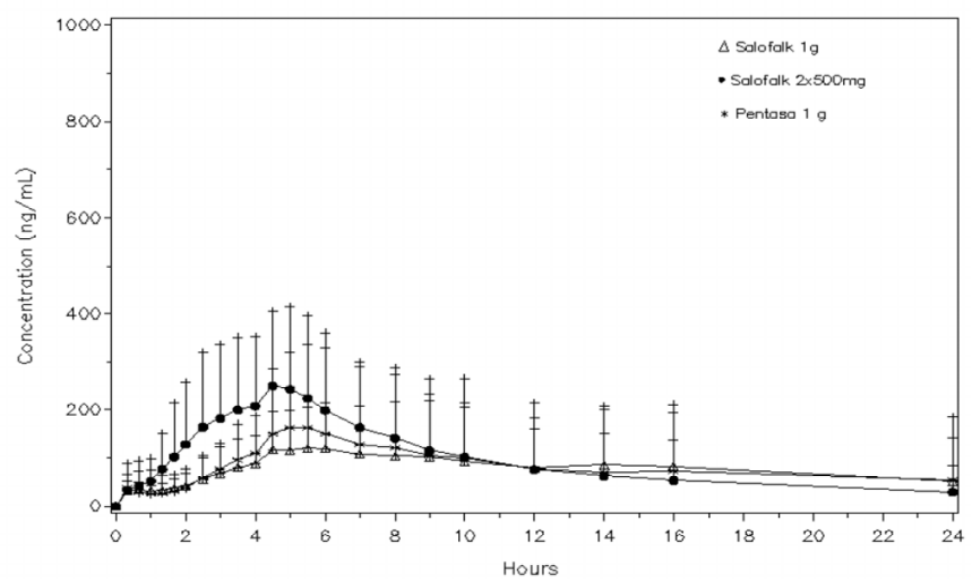
The primary endpoint of the study was the determination of the pharmacokinetic parameters of mesalazine (5-ASA) and its metabolite Ac-5-ASA from plasma and urine

concentrations (C_{max}, AUC_{0-24h}, $AUC_{0-\infty}$, t_{max}, $t_{1/2}$, Ae_{0-48h}, CL_R, and $V_{z/f}$) after single rectal administration.

All 48 subjects included were Caucasian men (mean age 36.5 ± 9.3 years).

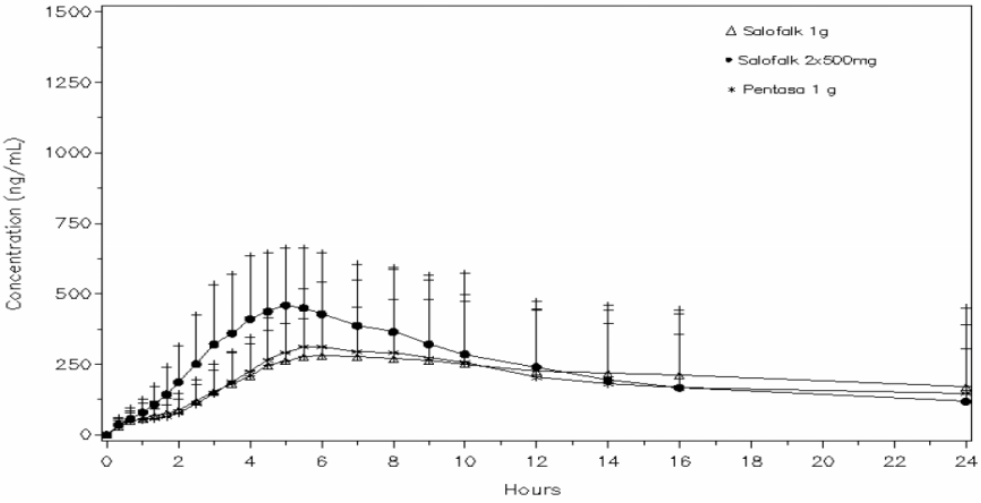
Pharmacokinetics Results and Bioavailability

The time courses of the mean plasma concentrations for 5-ASA and Ac-5-ASA over the 24 hours following administration are shown in Figure 2.5-2 and Figure 2.5-3, respectively. There was no effect of period and sequence, but a high degree of inter-subject variability was observed for plasma concentrations of both 5-ASA and Ac-5-ASA.



Source: SAS-5/BIO Study Report, Section 14.2.6

Figure 2.5-2 SAS-5/BIO: Mean plasma concentrations of 5-ASA following administration of Salofalk® 1 g, Salofalk® 2 × 500 mg, (and Pentasa® 1 g) suppositories.



Source: SAS-5/BIO Study Report, Section 14.2.6

Figure 2.5-3 SAS-5/BIO: Mean plasma concentrations of Ac-5-ASA following administration of Salofalk® 1 g, Salofalk® 2 × 500 mg (and Pentasa® 1 g) suppositories.

The relative bioavailability findings for the pharmacokinetic variables C_{max} and AUC are summarized in Table 2.5-3 for the comparison of Salofalk® 1 g to Salofalk® 2 × 500 mg.

Table 2.5-3: SAS-5/BIO: Summary of C_{max} and AUC for the comparison of Salofalk® 1 g to Salofalk® 2 × 500 mg for 5-ASA and Ac-5-ASA

	Geometric Mean (Minimum, Maximum)		Point Estimate	90% CI
	Salofalk® 1 g	Salofalk® 2 x 0.5 g		
5-ASA				
C_{max} (ng/mL)	155 (19–557)	288 (49–846)	0.5389	0.46–0.64
AUC_{0-24h} (ng*h/mL)	1326 (238–7755)	1789 (276–6991)	0.7410	0.60–0.92
$AUC_{0-\infty}$ (ng*h/mL)	1523 (301–8733)	1727 (164–10795)	0.8624	0.64–1.16
Ac-5-ASA				
C_{max} (ng/mL)	353 (57–1070)	526 (130–1190)	0.6720	0.58–0.78
AUC_{0-24h} (ng*h/mL)	3675 (638–18520)	4535 (665–16010)	0.8104	0.66–1.00
$AUC_{0-\infty}$ (ng*h/mL)	4471 (652–31535)	4536 (610–25084)	0.8133	0.58–1.14

Source: SAS-5/BIO Study Report, Tables 9–12

Based on the results of this study, equivalence of the Salofalk® 1 g suppository to Salofalk® 2 × 500 mg suppositories based on plasma concentrations of mesalazine and its metabolite coulc not be established. Based on C_{max} of 5-ASA or Ac-5-ASA the relative availability of these substances after administration of one Salofalk® 1 g suppository compared to two Salofalk® 500 mg suppositories in plasma was 54% for 5-ASA and 67% for Ac-5-ASA. Based on AUC_{0-24h}, the relative availability of these substances after administration of one Salofalk® 1 g suppository compared to two Salofalk® 500 mg suppositories in plasma was 74% for 5-ASA and 81% for Ac-5-ASA. Based on $AUC_{0-\infty}$ the relative availabilities in plasma were 86% for 5-ASA and 81% for Ac-5-ASA. All parameters had 90% CIs below the relevant acceptance range of 0.7–1.43 and 0.80–1.25, respectively.

Comment on the relevance of the findings in study SAS-5/BIO

According to the EMEA guideline Clinical Requirements for Locally Applied, Locally Acting Products, Containing Known Constituents (CPMP/239/95 1995) bioequivalence via plasma levels is not a suitable way to show therapeutic equivalence for locally applied, locally acting products such as mesalazine suppositories. For the topical-acting drug mesalazine it is the concentration of the drug in the colonic mucosa, not the plasma concentrations, which is relevant for efficacy (Frieri et al. 2000; Naganuma et al. 2001). As also side-effects, mainly hypersensitivity reaction, have been shown to be independent from the dose, plasma levels are also without relevance with respect to safety (Marteau 1996; Moss & Peppercorn 2007).

Study SAS-5/BIO has to be seen given the fact that in the absence of an established and validated method to determine the mucosal concentrations of mesalazine and its metabolite, a standard requisite study was carried out to determine plasma concentrations of mesalazine and its main metabolite and to compare them to the

pharmacokinetics of equivalent amounts of mesalazine delivered by two Salofalk® 500 mg suppositories. Since the action of mesalazine on colonic epithelial cells is exclusively topical, systemic exposure is unnecessary and systemically available drug levels have even to be regarded as lost for therapeutically relevant action.

Equivalence of plasma concentrations was not shown between one Salofalk® 1 g suppository and the two Salofalk® 500 mg suppositories. This result is attributed to the well-known high inter-individual variability in the plasma concentrations, observed for all three 5-ASA suppository treatments (Norlander et al. 1989; Vree et al. 2000).

In summary, plasma concentrations of mesalazine and its metabolite after application of the Salofalk® 1 g suppository were lower than those delivered by two Salofalk® 500 mg suppositories.

However, as mentioned above, the lack of equivalence for plasma concentrations of mesalazine and its metabolite should not be regarded as having an impact on the clinical efficacy of the different Salofalk® suppositoriesy. Direct determination of the clinical efficacy and the safety of Salofalk® 1 g suppositories in comparison to Salofalk® 500 mg suppositories dosed according to the recommendations given in the Summary of Product Characteristics and patient leaflet, i.e. 3 × 500 mg suppositories daily, has been carried out in a large phase III study (SAS-6/UCA), the results of which are presented in the section 2.5.4 and in the Summary of Clinical Efficacy, Section 2.7.3.

2.5.2.2 Colonic spread of 5-ASA 500 mg suppositories

Williams et al. (1987) examined the spread of 500 mg 5-ASA suppositories in 6 patients with inflammatory bowel disease and in six healthy volunteers by labelling the suppository with 1 mCi ^{99m}Technetiumand scintigrafic imaging over 3 hours. The stability of the compound was assessed by in vitro testing over the time and in vivo testing with assessment of counts over the thyroid, parietal cells of the stomach and accumulated counts excreted in urine over a 3 hours period.

The ^{99m}Tc-labeled 5-ASA suppositories remained localized to the rectum and sigmoid colon in all controls and subjects studied over 3 hours of the monitoring period. The preparation was stable; no radioactivity was detected over the thyroid or stomach in any patient or volunteer. Urine counts were barely above background.

These results were interpreted that 500 mg 5-ASA suppositories cover the inflamed area in patients with ulcerative proctitis in which inflammation involved the distal 15 cm or less and are in adequate contact with the inflamed mucosa to promote healing.

2.5.3 Overview of Clinical Pharmacology

2.5.3.1 Pharmacodynamics

Mesalazin exerts its anti-inflammatory action primarily in epithelial cells and macrophages of the mucosa (DeVos et al. 1992). Until recently, multiple anti-inflammatory effects have been noted with 5-ASA, but no single mechanism was considered to be predominant or primary (Kruis 2000, Schölmerich 1997).

There is consensus that 5-ASA has multiple antiinflammatory effects e.g. on epithelial cells (see Table 2.5-4). However, the exact mechanisms of action of aminosalicylates in IBD remain to be determined. Mesalazine influences many proinflammatory cytokines and other signalling substances (Nikolaus et al. 2000) at least partially by inhibiting the nuclear factor κB (NF κB) and tumour necrosis factor activation (TNF) (Kaiser et al. 1999) .

Table 2.5-4: Antiinflammatory effects of 5-ASA in IBD

- Disruption of arachidonic acid metabolism by
  - Inhibition of 5-lipoxygenase pathway
  - Inhibition of cyclo-oxygenase
- Inhibition of cytokine generation
- Diminishing antibody secretion and lymphocyte function
- Scavenging of reactive oxygen metabolites
- Reduction of neutrophil / macrophage chemotaxis
- Enhancing expression of heat shock proteins to protect intestinal epithelium
- Inhibition of platelet activation
- Inhibition of nuclear factor κB

Source: Schroeder 2002

More recently, 5-ASA was shown to interact with peroxisome proliferator-activated receptors (PPARs), which are members of the nuclear receptor superfamily. PPARs are activated by fatty acids and are involved in the transduction of metabolic and nutritional signals into transcriptional responses. Among these transcription factors, PPAR-γ plays an important role in the maintenance of mucosal integrity in the intestine. Based on the common activities of PPAR-γ ligands and 5-ASA, this nuclear receptor appears to mediate 5-ASA therapeutic action. Non-clinical investigations in mice with induced colitis revealed that 5-ASA increases PPAR-γ expression, promotes its cytoplasma-nucleus translocation and induces a modification of its conformation, permitting the recruitment of coactivators and the activation of peroxisome-proliferator response element-driven gene. These results were validated in organ cultures of human colonic biopsies. PPAR-γ is therefore identified as a potential primary target of 5-ASA underlying anti-inflammatory effects in the colon (Rousseaux et al. 2005; Desreumaux 2007).

Prevention of colorectal malignoma

Colonic involvement in IBD is associated with an increased risk of colorectal cancer, and long-term treatment with 5-ASA is described to considerably reduce the risk of colorectal cancer (Eaden et al. 2000).

Sphingomyelin metabolism represents a novel signal transduction pathway that has close implications to tumorigenesis. It generates both antiproliferative and proliferative factors, whose balance is of importance in initiation and progress of tumorigenesis. A reduction of intestinal alkaline sphingomyelinase (alk-SMase) activity was found in human colorectal adenoma, carcinoma, familial adenomatous polyposis and also in human chronic colitis. Purified human alk-SMase inhibited the proliferation of colon cancer cells. 5-ASA administration in rats selectively increased alk-SMase activity in rat colon. The stimulating effect of 5-ASA on the activity of intestinal alk-SMase could be one mechanism behind its chemopreventive effect against colon cancer (Duan 2003).

In-vitro investigations of the growth-inhibitory effects of 5-ASA on human colon cancer cells demonstrated that 5-ASA dose- and time-dependently inhibits the proliferation of these cells. Growth-effective 5-ASA concentrations were comparable with concentrations achievable in vivo under standard 5-ASA treatment. 5-ASA specifically blocks cancer cells in mitosis although microtubule polymerisation or spindle orientation is not affected. Recent data demonstrate that 5-ASA causes cells to reversibly accumulate in S-phase by activating a cell-cycle checkpoint. The activation of replication checkpoint may slow down DNA replication and improve DNA replication fidelity, which increases the maintenance of genomic stability and counteracts carcinogenesis (Luciani et al. 2007). In addition, 5-ASA induces apoptosis possibly through activation of caspase-3, whereas the levels of bcl-2 family proteins is not altered (Reinacher-Schick et al. 2003). Activation of PPAR-γ by mesalazine is thought to have not only antiinflammatory but also antineoplastic effects and thus might be a common mechanism of its different beneficial actions in IBD (Schwab et al. 2008, Desreumaux 2007).

A systematic review with meta-analysis of observational studies evaluating the association between 5-ASA use and colorectal cancer (CRC) or dysplasia among patients with UC support a chemopreventive effect of 5-aminosalicylates on the development of CRC. Nine cohort and case-control studies containing 334 cases of CRS and 140 cases of dysplasia comprising a total of 1,932 UC patients were included. Pooled analysis showed a protective association between use of 5-aminosalicylates and CRC or a combined endpoint of CRC / dysplasia. 5-ASA use was not associated with a lower risk of dysplasia, although only two studies evaluated this outcome, indicating insufficient power for an appropriate demonstration of a preventive effect (Velayos et al. 2005).

2.5.3.2 Pharmacokinetics

With regard to the pharmacokinetic properties (absorption, distribution, metabolism, elimination, placental passage and transfer into breast milk) and assay methods (HPLC, scintigraphic techniques) of 5-ASA, reference is made to the previous MAAs (Kruis 2000, Schölmerich 1997).

Comprehensive summaries and comparisons of pharmacokinetic properties of 5-ASA in general and key pharmacokinetic properties of different rectal 5-ASA preparations are presented in the reviews of Hanauer (2004), and Klotz & Schwab (2005).

Pharmacokinetic data evaluated in studies SAS-2/BIO and SAS-5/BIO comparing the bioavailability of Salofalk® 500 mg suppositories and Rowasa® 500 mg suppositories and Salofalk® 1 g suppositories, respectively are presented in Section 2.5.2.

Pharmacokinetics in children

Investigations of single-dose and steady-state plasma concentration-time profiles of 5-ASA and N-Ac-5-ASA following oral and rectal administration of 5-ASA in children report values comparable to those obtained in adults. Absorption rate and elimination rate in faeces are in the ranges observed in adults (Kruis 2000, Schölmerich 1997).

A recent study conducted with orally administered Salofalk® granules in 13 children with UC - aged between 5 and 16 years - confirmed that the pharmacokinetics of children and adults are similar (Study Report SAG-18/BIO, Wiersma et al. 2004). This study is presented as the results appear to be basically also transferable to rectal 5-ASA administration.

The t_{max} and C_{max} values of 5-ASA were comparable to data obtained in healthy adult volunteers (adjusted for 20 mg 5-ASA/kg bw/day[1]), and so were the adjusted sum values of AUC for 5-ASA + N-Ac-5-ASA (Table 2.5-5). The differences between 5-ASA and N-Ac-5-ASA values are clearly due to the dose-dependent metabolism at the gut mucosa, being much higher at low 5-ASA doses (based on kg bw) than at higher doses.

Table 2.5-5: Comparison of the pharmacokinetic parameters obtained from healthy volunteers and IBD children

Parameter	**SAG-16/BIO Mean ± S.D.**	**SAG-18/BIO Mean ± S.D.**
Study subjects	**Healthy adults**	**Children, IBD**
Age (years)	26.6 ± 3.3	12.9 ± 2.6
Body weight (kg)	74.4 ± 3.9	46.5 ± 9.9
5-ASA-dose	1 x 500 mg/d	1 x 20 mg/kg bw/d
t_{max} – 5-ASA (h)	4.11 ± 0.96	4.95
t_{max} – N-Ac-5-ASA (h)	4.36 ± 1.01	5.70
C_{max} – 5-ASA (µg/ml)	0.429 ± 0.262	---
C_{max} – 5-ASA based on 20 mg/kg bw/d (µg/ml)	1.28 ± 0.78	1.49 ± 0.65
C_{max} – N-Ac-5-ASA (µg/ml)	0.986 ± 0.436	---
C_{max} – N-Ac-5-ASA based on 20 mg/kg bw/d (µg/ml)	2.94 ± 1.30	1.78 ± 0.71
Σ C_{max} – 5-ASA + N-Ac-5-ASA based on 20 mg/kg bw/d	23.42	18.85

[1] Refer to Study Report SAG-16/BIO; included in Clinical Documentation on Salofalk® granules (Kruis 2000).

Parameter	SAG-16/BIO Mean ± S.D.	SAG-18/BIO Mean ± S.D.
(mmol/ml)		
$AUC_{0\text{-}24\ h}$ – 5-ASA (µg x h/ml)	0.968 ± 0.624	---
$AUC_{0\text{-}24\ h}$ – 5-ASA based on 20 mg /kg bw/d (µg x h/ml)	2.88 ± 1.87	8.84 ± 3.72
$AUC_{0\text{-}24\ h}$ – N-Ac-5-ASA (µg x h/ml)	6.408 ± 2.026	---
$AUC_{0\text{-}24\ h}$ – N-Ac-5-ASA based on 20 mg/kg bw/d (µg x h/ml)	19.10 ± 6.04	17.86 ± 6.35
Σ $AUC_{0\text{-}24\ h}$ – 5-ASA + N-Ac-5-ASA based on 20 mg/kg bw/d (mmol x h/ml)	116.63	149.21
Ratio $AUC_{0\text{-}24\ h}$ – N-Ac-5-ASA / 5-ASA	6.6	2.0

Source: Study Report SAG-18/BIO

A subgroup analysis of the age groups 6-11 years and 12-16 years did not reveal any significant difference (Table 2.5-6).

Table 2.5-6: Subgroup analysis of main pharmacokinetic parameters of IBD children treated with Salofalk® granules

Age group	No. of patients	5-ASA Mean ± S.D.		N-Ac-5-ASA Mean ± S.D.	
		C_{max} (ng/ml)	$AUC_{0\text{-}24\ h}$ (ng x h/ml)	C_{max} (ng/ml)	$AUC_{0\text{-}24\ h}$ (ng x h/ml)
6-11 years	4	1,436 ± 540	7,553 ± 4,077	1,622 ± 627	16,224 ± 10,011
12-16 years	9	1,515 ± 683	9,417 ± 3,445	1,853 ± 767	18,592 ± 4,578

Source: Study Report SAG-18/BIO

Pharmacokinetics and mucosal concentrations depending on IBD disease severity

Following administration of 5-ASA enemas, the urinary recovery rate in patients with active UC is significantly lower than in patients in remission (Kruis 2000).

Similarly, Frieri et al. (2000) found after administration of oral 5-ASA that mucosal concentrations of 5-ASA were significantly higher in patients with lower endoscopically perceivable inflammation (endoscopic scores of 0-1) compared to those with more severe endoscopic inflammation (endoscopic scores of 2-3) and in patients with lower histological inflammation compared to those with more severe scores.

2.5.3.3 Drug Interactions

Early assumptions on hypothetical interactions of 5-ASA with other drugs were based on its structural similarity with other salicylate drugs e.g. acetylsalicylic acid and other NSAIDs but many of these interactions appear not to be clinically relevant with 5-ASA.

Today, after clinical and experimental experience with 5-ASA of more than 20 years and given the predominat topical availability and action of 5-ASA, particularly when it is applied rectally there is evidence for relevant interactions of 5-ASA only with few drugs and substances (Irving et al. 2008). This was confirmed during a recent procedure on harmonisation of the core safety profile (CSP) of mesalazine during which all relevant safety issues of mesalazine which are summarised in the Summary of Product Characteristics (SmPC) were reviewed and updated according to the state of the available relevant scientific information in an EU-wide PSUR harmonisation procedure (see Mesalazine Core Safety Profile April 2011 and Final Assessment Report UK/H/PSUR/0052/001).

5-ASA appears to interact with the metabolism of azathioprine and 6-mercaptopurine. Coadministration of 5-aminosalicylic acid and azathioprine may lead to an increased production of thioguanine-phosphate metabolites which are considered to be the active metabolites for its immunosuppressive effect thus enhancing its therapeutic efficacy. However, there is also an association of the intracellular levels of thioguanine-phosphate metabolites with the suppression of white blood cells (leukopenia, myelosuppression), particularily lymphopenia. As both drugs are part of the standard treatment of IBD, this drug interaction is relevant. When coadministered with 5-ASA the dose of azathioprine should be carefully adjusted to avoid myelosuppression. This is also relevant when the dose of mesalazine is reduced or mesalazine is withdrawn as this may reduce the level of active azathioprine metabolites and impair its immunosuppressive activity (Andrews et al. 2009, de Graaf et al. 2010, Hande et al. 2006, Gilissen et al. 2005).

Based on the experience of a single case 5-ASA is supposed to decrease the effect of cocomittantly used warfarin (Marinella 1998).

2.5.4 Overview of Efficacy

Management of UC must be governed by the sites involved and the intensity of the inflammation. Goals of treatment are directed at inducing and maintaining remission of symptoms and mucosal inflammation to provide an improved quality of life (QoL)) and reducing additional risks such as increased risk to develop colorectal carcinoma (Kornbluth & Sachar 2010).

5-ASA is the gold standard for induction and maintenance of remission in mild to moderate UC. Adapted to the extension of the inflammation in the colon 5-ASA preparations for oral and/or rectal application should be used (Travis et al. 2008, Kornbluth & Sachar 2010, Munkholm et al. 2010).

For distal inflammations rectal 5-ASA is the treatment of choice for inducing and also for maintaining remission in active distal UC (Marshall et al. 2010, Bergman & Parkes

2006, Marshall & Irvine 2000, Cohen et al. 2000, Marshall & Irvine 1995) or - in combination with oral 5-ASA preparations – to treat the commonly heavily affected parts of the distal colon with high concentrations of 5-ASA in addition to the treatment with 5-ASA released by orally administered preparations (Marteau et al. 2005, Safdi et al. 1997).

According to national and European (ECCO) guidelines, rectal aminosalicylates are recommended for the treatment of distal mild to moderate active UC, for maintenance of remission as well as for more extensive UC in combination with oral 5ASA (Travis et al. 2008, Mowat et al. 2011, Kornbluth & Sachar 2010, Hoffmann et al. 2004).

If inflammation in UC is restricted to the rectum, suppositories conatining mesalazine are considered as standard treatment to ensure local availability of the agent (Travis et al. 2008, Kornbluth & Sachar 2010).

The criteria used to evaluate the severity of the disease as well as the efficacy of a treatment include symptomatic, mucosal (endoscopic) and histologic parameters, most often summarized and weighted in complex indices (D'Haens et al. 2007).

2.5.4.1 Acute Exacerbation of Ulcerative Proctitis/Active Ulceratice Proctitis

The therapeutic efficacy and tolerability of rectal 5-ASA suppository preparations in the treatment of acute episodes of UC is well established, and clinical trials have been documented and evaluated in the previous MAA that led to approval in Germany (Schölmerich 1997).

This Clinical Overview focusses on the relevant clinical trials and summarizes the outcomes of the most recent systematic integrated study analyses.

The Clinical Documentation confirmes that Salofalk® 500 mg suppositories given t.i.d. represent an effective treatment of active distal UC (ulcerative proctitis), administered either alone or in combination with other therapies. This is further supported by recent systematic reviews, which also clearly demonstrated that 5-ASA suppositories are an effective approach in distal UC (ulcerative proctitis) (Cohen et al. 2000, Gisbert et al. 2002, Marshall & Irvine 2010).

This Clinical Overview comprises two relevant publications (Williams et al. 1987, Williams 1990, already included in the previous clinical documentation) which describe three clincial trials with 5-ASA 500 mg suppositories (Rowasa® 500 mg suppositories). The studies demonstrated the excellent efficacy of Rowasa® 500 mg in patients with active distal proctitis. It appears reasonable to assume that Salofalk® 500 mg suppositories are equally effective in the treatment of ulcerative proctitis as Rowasa® 500 mg suppositories since the equivalence of Rowasa® 500 mg suppositories and Salofalk® 500 mg suppositories has been demonstrated in the bioavailability / pharmacokinetic 'bridging' study SAS-2/BIO (see Section 2.5.2.1.1). The placebo-controlled studies published by Williams et al. (1987) and Williams (1990) are considered to be "pivotal" studies for Salofalk® 500 mg suppositories.

In addition, a recent clinical study comparing the efficacy and saftey of Salofalk® 500 mg suppositories and Salofalk® 1 g suppositories (SAS-6/UCA) is presented here.

2.5.4.1.1 Controlled Clinical Trials

A tabular overview of the studies on the efficacy of 5-ASA in ulcerative proctitis is given in Table 2.5-7. The studies included a total of 200 patients with ulcerative proctitis and are described in detail in Section 2.7.3.

Table 2.5-7: Studies with 5-ASA 500 mg suppositories in ulcerative proctitis

Publication	Title	Objective	Design	Treatment Duration	Number of subjects
Williams et al. 1987	Double blind, placebo-controlled evaluation of 5-ASA suppositories in active distal proctitis and measurement of extent of spread using ^{99m}Tc-labeled 5-ASA suppositories	Efficacy in ulcerative proctitis; Spread of rectal 5-ASA suppositories	Double-blind, randomized, placebo-controlled	t.i.d 6 weeks	Ulcerative proctitis: 27; IBD:6; Heathy volunteers: 6
Williams 1990 Study 1 is also presented by Protocol 300 in combination with Banks Statistical Report 1986	Efficacy and tolerance of 5 aminosalicylic acid suppositories in the treatment of ulcerative proctitis: A review of two double-blind, placebo controlled trials	Efficacy in ulcerative proctitis, comaprison of dose schedules t.i.d. and b.i.d.	Double-blind, randomized, placebo-controlled	Study 1: t.i.d. Study 2: b.i.d. 6 weeks	Study 1: 79 Study 2: 94
SAS-6/UCA Publication by Andus et al. 2010	Randomized, single-blind, multi-centre study to compare the efficacy and safety of once daily 1 g mesalazine suppositories versus three times daily 500 mg mesalazine suppositories in patients with acute ulcerative proctitis	Comparison of efficacy of 1 g 5-ASA suppositories o.d. to 500 mg 5-ASA suppo-sitories t.i.d.	Single-blind (in-vestigator-blind), randomised, multi-centre, comparative, parallel-group	Salofalk® 1 g supp-ositories o.d. Salofalk® 1 g supp-ositories o.d. 6 weeks	403

2.5.4.1.1.1 Williams et al. 1987
Double blind, Placebo-controlled Evaluation of 5-ASA Suppositories in Active Distal Proctitis and Measurement of Extent of Spread using 99mTc-labeled 5-ASA Suppositories

This study was conducted to evaluate the efficacy of 5-ASA suppositories in patients with active distal proctitis. In addition, in another group of patients with IBD and in healthy volunteers the spread of rectal suppositories of ^{99m}Tc-labeled 5-ASA was measured.

27 subjects with active distal proctitis (minimum DAI[2] score of 3) involving the distal 15 cm or less on sigmoidoscopy were included. If the patient was taking oral sulfalazine or oral prednisone (n=15), these were maintained in the same dose throughout the study period. Subjects received 500 mg 5-ASA suppositories or identical placebo which was taken 3 times daily for 6 weeks. There were 14 patients (8 men, 6 women, mean age 37.3 ± 14.5 years) in the 5-ASA group, and 13 patients (9 men, 4 women, mean age 42.7 ± 11.2 years) in the placebo group.

Disease activity was assessed at 3 and 6 weeks by means of the DAI, derived from four categories: Number of daily evacuations more than usual, evacuations containing blood, inflammatory mucosal changes in sigmoidoscopy, and physician's overall assessment of disease.

At 3 weeks, the 5-ASA group had a mean DAI of 1.6 ± 1.5, which was significantly lower than the pre-treatment score of 7.1 ± 1.8 ($p<0.001$), whereas the placebo group had a mean DAI of 5.8 ± 1.9, which was not significantly different from the pretreatment value of 7.4 ± 1.8.

In the 5-ASA group, 11 of 14 (78.6%) patients were in complete remission at 6 weeks. The mean DAI was reduced from initial 7.1 ± 1.8 to 0.4 ± 0.9 ($p<0.001$). The three patients failing to obtain a DAI score of 0 at 6 weeks achieved complete remission with continued treatment with 5-ASA.

In the placebo group, only one patient went into remission. And the mean DAI at 6 weeks was 5.4 ± 3.4 which was not significantly different from the pre-treatment value of 7.4 ± 1.8.

There was no difference in response to treatment with 5-ASA suppositories when patients were considered as being on no coincident therapy or maintaining their usual drugs, sulfasalazine or prednisone. Within this published trial the rectal spread of 99 Tc 5-ASA suppositories was assessed. The results are described in Section 2.5.2.2 and in 2.7.1

In summary, the study showed that treatment with three times daily one 500 mg 5-ASA suppository is very effective in the treatment of patients with distal proctitis irrespective of a concomitant treatment with oral sulfasalazine or prednisolone

[2] DAI is a qualitative rating scale measuring stool frequency, rectal bleeding, mucosal appearance (on endoscopy), and physician's rating of disease severity, which each parameter scored form 0 (normal) to 3 (severe). A total DAI score, ranging from 0-12, is derived by adding the four individual scores.

2.5.4.1.1.2 Williams 1990

Efficacy and Tolerance of 5-aminosalicylic Acid Suppositories in the Treatment of Ulcerative Proctitis: A Review of Two Double-blind, Placebo-controlled Trials

The efficacy and tolerance of 500 mg 5-ASA suppositories (Rowasa®) in the treatment of ulcerative proctitis were assessed in 2 double-blind, placebo-controlled multicenter studies of 6 weeks duration involving a total of 173 patients with active ulcereative proctitis involving a maximum of 15 cm beyond measured from the anal margin.

In Study 1, patients used one 500 mg suppository (n=39) or placebo (n=40) three times daily. For this study a study report (5-ASA (Rowasa) Suppositories in ulcerative colitis (Williams et al. 1987, including a statistical report (Banks, 1986)) is available.

In Study 2, patients used one 5-ASA 500 mg suppository (n=50) or placebo (n=44) twice daily. Efficacy of 5-ASA was assessed by physician's global assessment and DAI based upon patients' symptoms and sigmoidoscopic appearance. Oral steroids or sulphalazine were allowed as co-medication in both studies provided they had been used for at least three weeks prior to entry and that the dose was held constant during the trial.

In Study 1, there was an 80.4% mean reduction in DAI in patients treated with 5-ASA compared to a 36.8% mean reduction in the placebo group ($p<0.05$). Analysis of the physician's global assessment indicated that 84.2% of patients receiving 5-ASA were considered to be 'much improved' compared to 41% of patients in the placebo group ($p<0.01$).

In Study 2, there was a 74.7% mean reduction in DAI compared to 34.2% in the placebo group ($p<0.001$). Analysis of the physician's global assessment indicated that 79.2% of the 5-ASA group was considered to be 'much improved' compared to 26.2% on placebo ($p<0.001$).

There was no significant difference in efficacy seen in patients treated with 500 mg 5-ASA suppositories twice daily or three times daily.

A subgroup analysis of Study 1 by co-medication showed that 5-ASA 500 mg suppositories alone without any co-medication, as well as 5-ASA 500 mg suppositories in combination with sulfasalazine and/or prednisone is an effective treatment of ulcerative proctitis. However, in patients concurrently treated with orally administered sulfasalazine plus prednisone (n=11) the magnitude of differences between the group treated with 5-ASA 500 mg suppositories and placebo group was much less and not statistically significant. The smaller decrease of the DAI in these patients may indicate that this subgroup comprised patients with severe disease who did not achieve satisfactory treatment results inspite of treatment with orally administered systemically acting corticosteroids plus sulfasalazine plus rectal 5-ASA. However, firm conclusions cannot be drawn because a small number of patients contributed to the analysis for this subgroup.

In summary, the studies showed the excellent efficacy of 5-ASA 500 mg suppositories in the treatment of ulcerative proctitis.

2.5.4.1.1.3 Study SAS-6/UCA: Randomized, single-blind, multi-centre study to compare the efficacy and safety of once daily 1 g mesalazine suppositories versus three times daily 500 mg mesalazine suppositories in patients with acute ulcerative proctitis

Results of this study were published by Andus et al. 2010.

The study was conducted in 35 centres in Germany, Israel, Russia, and Ukraine. It was a single-blind (investigator-blind), randomised, multi-centre, comparative, phase III clinical trial, conducted as a parallel-group comparison of two different dosing regimens of mesalazine suppositories:

- Group A: Salofalk® 1.0 g suppositories once daily (OD)
- Group B: Salofalk® 500 mg suppositories three times daily (TID)

The study was conducted in a 3-stage sequential adaptive design with 2 planned interim analyses (the first interim analysis was planned after 2 × 85 per-protocol (PP) evaluable patients had finished the trial; the second interim analysis was planned to be performed after an additional 2 × 43 PP evaluable patients, and the final analysis after a further 2 × 43 PP evaluable patients had finished the trial).

The primary objective was to prove the therapeutic equivalence of Salofalk® 1.0 g mesalazine suppositories OD vs. Salofalk® 500 mg mesalazine suppositories TID in patients with active acute ulcerative proctitis.

Secondary objectives were to study safety and tolerability, to assess patients' acceptance of the study drug, to assess patients' preference regarding administration schedule and to assess patients' quality of life.

The primary efficacy variable was clinical remission, defined as DAI < 4 at the final visit Week 6 or at the withdrawal visit.

A large number of secondary efficacy variables was assessed in study SAS-6/UCA. The the most relevant were:

- Absolute and relative number of patients in remission, improved, with no change and/or deteriorated according to DAI1, CAI , EI, HI
- Changes in subscores of the indices
- Time to first symptomatic resolution
- Decrease in ESR
- Absolute and relative number of patients with complete relief and at least marked improvement of symptoms (therapeutic success) indicated by PGA
- Quality of life according to the SIDBQ and its subscores

For a complete list of secondary efficacy variables in study SAS-6/UCA see the Clinical study report (CSR SAS-6/UCA, section 3.6.3).

Adults (men or women aged 18 to 75 years) with active mild to moderately active (DAI >3 and < 11) ulcerative proctitis (inflammation/lesions maximal 15 cm of rectum, confirmed by endoscopy and histological examination) were eligible to participate.

Of a total of 408 patients who were randomised 5 did not receive study medication, so 403 patients (178 men, 225 women) comprised the intention-to-treat (ITT) efficacy population and the safety population. At the final analysis, 354 patients were analyzed for efficacy per protocol. Mean age was 42 years (standard deviation [SD] 13.6 years; range, 18 to 74 years).

Median duration of ulcerative proctitis was 2.8 years (range, 0 to 36.7 years). The majority of patients (75.2%) had recurrent disease at baseline. The number of previous acute episodes was 4.1 (SD 6.4), and the median duration of the last remission phase was 6 months (0 to 226 months). Only a small proportion (4.5%) had had previous bowel operations.

The two treatment groups showed no relevant differences with regard to demographic and anamnestic characteristics at baseline.

The first interim analysis did not yield a significant result. Inclusion of patients into the study was continued, and the number of patients to be evaluable for the per-protocol (PP) analysis at the second stage was increased from 2 × 43 patients to 2 × 60 patients. The second interim analysis performed on 270 PP evaluable patients yielded a significant result. Recruitment of the study was stopped. However, as recruitment had continued during the time the second interim analysis was being performed, another 93 patients were included in the final analysis.

Clinical remission rates according to the Disease Activity Index 1 (DAI 1) in the PP and ITT analysis sets at both interim analyses and at the final analysis are shown in the table below (Table 2.5-8).

Table 2.5-8: Study SAS-6/UCA: Results on clinical remission (DAI 1).

		Number (%) of patients with clinical remission at the final/withdrawal examination		Difference between proportions [a] [95% CI]	Shifted asymptotic χ^2 test for comparing two rates [b]
		Salofalk® 1 g Suppository OD	Salofalk® 500 mg Suppository TID		
1st interim analysis	PP	60/73 (82.2%)	64/72 (88.9%)	–6.7% [–18.1%, 4.7%]	0.0819 [c]
	ITT	65/82 (79.3%)	66/82 (80.5%)	–1.2% [–13.5%, 11.1%]	0.0150 [c]
2nd interim analysis	PP	121/140 (86.4%)	117/130 (90.0%)	–3.6% [–11.2%, 4.1%]	2.692 [d]
	ITT	131/157 (83.4%)	129/155 (83.2%)	0.2% [–8.1%, 8.5%]	3.436 [d]
Final analysis	PP	160/182 (87.9%)	156/172 (90.7%)	–2.8% [–9.2%, 3.6%]	3.463 [d]
	ITT	168/200 (84.0%)	172/203 (84.7%)	–0.7% [–7.8%, 6.4%]	3.790 [d]

[a] Difference between proportions [Salofalk® 1 g suppository OD – Salofalk® 0.5 g suppository TID]; asymptotic confidence interval (CI). [b] 'Effect' = difference between proportions [Salofalk® 1 g suppository OD – Salofalk® 0.5 g suppository TID] + 0.15). [c] Observed p-value (one sided). [d] Inverse normal.
Source: SAS-6/UCA Study Report, Table 14, Table 15, and Table 16

At the second interim analysis therapeutic equivalence (non-inferiority margin 15%) of Salofalk® 1.0 g suppositories once daily and Salofalk® 500 mg suppositories three time daily in patients with active ulcerative proctitis was proven.

Table 2.5-9 gives a brief overview of three of the main secondary variables, i.e. DAI, Clinical Activity Index (CAI) and Endoscopic Index (EI) from baseline to last observation carried forward (LOCF).

Table 2.5-9: Number (%) of patients in PP population with a change in DAI 1, CAI, and EI from baseline to LOCF in study SAS-6/UCA

Change	DAI 1 [a]		CAI		EI [b]	
	Salofalk®1 g Suppository OD n = 182	Salofalk®0.5 g Suppository TID n = 172	Salofalk®1 g Suppository OD n = 182	Salofalk®0.5 g Suppository TID n = 172	Salofalk®1 g Suppository OD n = 176	Salofalk®0.5 g Suppository TID n = 164
Remission	160 (87.9%)	156 (90.7%)	160 (87.9%)	159 (92.4%)	149 (84.7%)	147 (89.6%)
Improvement	17 (9.3%)	12 (7.0%)	172 (94.5%)	161 (93.6%)	19 (10.8%)	10 (6.1%)
No change	3 (1.6%)	2 (1.2%)	n.a.	n.a.	8 (4.5%)	7 (4.3%)
Deterioration	2 (1.1%)	2 (1.2%)	n.a.	n.a.	---	---

DAI 1: Remission: DAI 1 < 4 at LOCF; improvement/deterioration: decrease/increase by ≥ 1 point from baseline to LOCF and DAI 1 > 3 at LOCF; patients with remission were not included in the number of patients with improvement. **CAI**: Remission: CAI ≤ 4 at LOCF (= clinical remission); improvement: decrease in CAI by ≥ 1 point from baseline to LOCF (= clinical improvement). **EI**: Remission: EI < 4 at final examination; improvement/deterioration: decrease/increase by ≥ 1 point from baseline to final examination and EI ≥ 4; patients with remission were not included in the number of patients with improvement. [a] Patients with (DAI 1) > 3 at baseline. [b] Patients with EI ≥ 4 at baseline.

Source: SAS-6/UCA Study Report, Table 25, Table 33, and Table 44

DAI 1, CAI, and EI as well as their sub-scores showed remission/normalisation or improvement in the majority of patients. Most indices and sub-scores did not show any differences between treatment groups.

Change in the Histological Index (HI) from baseline to final examination is shown below in Table 2.5-10.

Table 2.5-10: SAS-6/UCA: Number (%) of patients with change in the HI

	PP		ITT	
Therapeutic outcome from baseline to last visit	Salofalk®1 g Suppository OD n = 182	Salofalk®500 mg Suppository TID n = 172	Salofalk®1 g Suppository OD n = 200	Salofalk®500 mg Suppository TID n = 203
HI = 0 at baseline and final examination	4 (2.2%)	5 (2.9%)	6 (3.0%)	8 (3.9%)
Improvement	114 (62.6%)	104 (60.5%)	121 (60.5%)	114 (56.2%)
No improvement	57 (31.3%)	58 (33.7%)	59 (29.5%)	64 (31.5%)
Not determinable	7 (3.8%)	5 (2.9%)	14 (7.0%)	17 (8.4%)

Source: SAS-6/UCA Study Report, Table 43

The majority of patients showed an improvement of HI from baseline to final examination with no relevant difference in the proportions of patients with improvement of HI between the Salofalk® 1 g suppository (OD) group and the Salofalk® 500 mg suppository (TID) group (62.6% vs. 60.5%) .

The time to first resolution of clinical symptoms (≤ 3 stools/day; all without blood) was slightly longer in patients taking Salofalk® 500 mg suppository (TID) than in patients taking Salofalk®1 g suppository (OD) in the PP population (Salofalk®1 g suppository (OD): 7.3 [7.4] days, n = 176; Salofalk® 500 mg suppository (TID): 9.1 [8.8] days, n = 166) and likewise in the ITT analysis set.

No marked differences in the Physicians Global Index (PGA) between treatment groups in either population set was observed. If therapeutic success is defined as the number and percentage of patients with 'at least marked improvement of symptoms', then treatment with both Salofalk® suppositories were successful in 89% of all PP patients. If therapeutic benefit is defined as the number and percentage of patients with 'at least slight improvement of symptoms', then treatment with both Salofalk® suppositories provided therapeutic benefit in at least 96% of ITT patients and more than 97% of PP patients with only minimal differences between the treatment groups.

Based on both the PP and the ITT analysis sets, the Short IBD Questionaire as a measure of the Health-related quality of life showed a clear similar increase from baseline to LOCF in both treatment groups.

Conclusions: Treatment with Salofalk® 1 g suppository (OD) as well as with Salofalk® 500 mg suppository (TID) was highly efficacious, safe and well tolerated in patients with active ulcerative proctitis. Once daily Salofalk®1 g mesalazine suppositories proved to be therapeutically equivalent to three times daily Salofalk®500 mg mesalazine suppositories. Treatment with both Salofalk® suppositories induced a prompt cessation of clinical symptoms. Both the Salofalk® 1 g suppository OD and the Salofalk® 500 mg suppository TID were very well accepted treatment regimens.

2.5.4.1.1.4 Systematic Integrated Analyses of Clinical Studies

A total of four relevant systematic clinical study reviews are included in this Addendum to the Clinical Documentation on Salofalk® 500 mg suppositories.

Cohen et al. (2000) conducted a systematic review (and meta-analysis where appropriate) of all published therapeutic trials in left-sided (distal) UC and ulcerative proctitis (1958-1997). Improvement and remission rates were recorded for all studies (ALL), the placebo-controlled trials (PC) and for placebo-controlled trials passing quality assessment scoring (QA). As more proximal left-sided UC is primarily a domain of rectal formulations providing a more proximal distribution, namely liquid or gel enemas, only integrated analysis results for ulcerative proctitis, primarily suitable for suppositories, are taken into account.

In total, 18 studies on active diseases were identified (nine PC, three QA). 5-ASA suppositories achieved clinical improvement and remission in a duration- but not a

dose-response relationship, with higher remission rates than most of the topical corticosteroids (ALL).

In conclusion, this systematic review and metaanalysis clearly showed that 5-ASA suppositories are the agents of choice in the treatment of ulcerative proctitis. The efficacy profile of topical 5-ASA is superior to oral therapies and topical corticosteroids.

Very similar results were obtained in meta-analyses of published clinical trials by Marshall & Irvine (2000), showing that rectally delivered 5-ASA is superior to placebo (Table 2.5-11) and to rectal corticosteroids in inducing remission of distal UC, whereas the combination of rectal 5-ASA with a rectal corticosteroid or oral 5-ASA preparation is superior to rectal 5-ASA alone.

Table 2.5-11: Comparison of rectal 5-ASA vs. placebo for induction of remission of active distal UC. Meta-analysis of 7 placebo-controlled clinical trials

	Mantel-Haenszel pooled Odds ratios (95% CI)
Remission	
• Symptomatic	7.71 (4.84-12.30)
• Endoscopic	6.55 (4.15-10.36)
• Histological	6.91 (3.82-12.50)
Improvement	
• Symptomatic	6.85 (4.80-9.78)
• Endoscopic	10.04 (5.72-17.61)
• Histological	10.31 (5.85-18.18)

Homogeneity among studies for each endpoint confirmed by Breslow-Day test ($p > 0.05$)
Marshall & Irvine (2000)

In conclusion, there is strong evidence from randomized controlled clinical trials to support rectal 5-ASA as first-line treatment in active distal UC. The choice of dosage form (suppository, enema, foam, gel) should reflect both the proximal disease extent and patient preference. There is no evidence in support of a dose-response effect for rectal 5-ASA. Combination therapy with oral 5-ASA or rectal corticosteroids may be useful in refractory patients or in case of more frequent relapse.

A systematic review of clinical trials by Gisbert et al. (2002) also revealed that rectal 5-ASA (as suppository, foam, liquid enema) are at least as effective, and probably more effective, than topical corticosteroids for the treatment of distal UC. Therefore, rectal 5-ASA should be considered the topical therapy of choice for the management of active distal UC. Rectal corticosteroids may be regarded as an alternative treatment for active distal UC once 5-ASA has failed, or in patients allergic to 5-ASA.

In a recent systematic review, Marshall et al. (2010) evaluated the efficacy of rectal preparations with 5-aminosalicylic acid for induction of remission in distal ulcerative colitis. A total of 38 randomised trials comparing rectal 5-ASA to placebo or another

active therapy in patients older than 12 years with distal UC were retrieved and analysed.

The pooled results from these studies confirmed the results in former systematic metaanalyses or reviews in that rectal 5-ASA was superior to placebo for inducing symptomatic, endoscopic and histological improvement and remission with peto-odds ratios (POR) for symptomatic improvement 8.87 (95% CI: 5.3 to 14.83; P<0.00001), endoscopic improvement 11.18 (95% CI: 5.99 to 20.88; P<0.00001), histologic improvement 7.69 (95% CI: 3.26 to 18.12; P<0.00001), symptomatic remission 8.30 (95% CI: 4.28 to 16.12; P<0.00001), endoscopic remission 5.31 (95% CI: 3.15 to 8.92; P<0.00001), and histologic remission 6.28 (95% CI: 2.74 to 14.40; P<0.0001). Rectal 5-ASA was superior to rectal corticosteroids for inducing symptomatic improvement and remission with POR 1.56 (95% CI: 1.15 to 2.11; P=0.04) and 1.65 (95% CI: 1.11 to 2.45; P=0.01), respectively. In contrast to former metaanalyses, rectal 5-ASA was found not to be superior to oral 5-ASA for symptomatic improvement (2.25; 95% CI: 0.53 to 19.54; P=0.27). Neither total daily dose nor 5-ASA formulation affected treatment response. Side effects were found to be generally mild in nature and included abdominal pain or distension, nausea and anal discomfort or irritation.

The authors concluded that rectal 5-ASA should be considered a first-line therapy for patients with mild to moderately active distal UC.

In conclusion,

- **The efficacy of rectal 5-ASA suppository preparations in the treatment of active distal UC (ulcerative proctitis) has been demonstrated by various controlled clinical trials and is well established. In particular, the excellent efficacy of 5-ASA suppositories in the treatment of UC has been demonstrated in 4 double-blind, placebo-controlled clinical trials published by Williams et al. (1987) , Williams (studies 1 and 2; 1990) and Andus et al. 2010. As the equivalence of Rowasa® 500 mg suppositories used in three of these trials and Salofalk® 500 mg suppositories has been shown in the bioequivalence / pharmacokinetic "bridging" study SAS-2/BIO, the studies are considered to be pivotal studies for Salofalk® 500 mg suppositories. The most recent study SAS-6/UCA (published by Andus et al. 2010) directly showed the excellent efficacy of Salofalk® 500 mg suppositories as well as Salofalk® 1 g suppositories.**
- **Controlled clinical trials and extensive systematic analyses of published clinical trials provide further support for the effectiveness (and safety) of rectal 5-ASA suppository preparations in active distal UC. Rectal 5-ASA preparations are consiered to be more effective as rectal corticosteroids.**
- **The dose recommendation for the treatment of patients with active distal UC remains unaffected to be 500 mg 5-ASA t.i.d.**

2.5.5 Overview of Safety

2.5.5.1 General Safety Profile

A considerable number of clinical trials were conducted with 5-ASA preparations that have been already evaluated in the previous MAAs (Kruis 2000, Schölmerich 1997), demonstrating a favourable safety profile.

5-ASA in generall, and particularly rectal preparations of 5-ASA are generally accepted as safe and well tolerated with low adverse event rates and generally low intensity of adverse reaction (Loftus et al. 2004b, Baker & Kane 2004, Schroeder 2002).

With regard to the safety profile of rectal and oral modified-release 5-ASA formulations and contra-indications and precautions, reference is made to the previous MAAs (Kruis 2000, Schölmerich 1997) and the current product information texts[3].

The favourable safety and tolerability profile of rectal 5-ASA preparations in general has been further supported by systematic integrated clinical study analyses (Cohen et al. 2000, Gisbert et al. 2002, Marshall & Irvine 2000, Marshall et al 2010) and is also confirmed by the most recent Periodic Safety Update Reports (PSUR) on oral and rectal Salofalk® preparations (PSURs 2007 and PSUR 2010; see Section 2.5.5.3 ['Post-Marketing Experience']).

Recently, all relevant safety issues of mesalazine as they are summarised in the Summary of Product Characteristics (SmPC) were reviewed, updated according to the latest relevant scientific information and harmonised in a Core Safety Profile (CSP) in an EU-wide PSUR harmonisation procedure. Some substantial changes in the CSP of mesalazine resulted from this process. These include a reduction of the contraindications of use to patients with hypersensitivity to salicylates or any of the excipients and to patients with severe impairment of the hepatic or renal function. In addition, the section on drug interactions was adapted mentioning now only the interactions of 5-aminosalicylates and thiopurines and warfarin (see section 2.5.3.3). Furthermore, the section listing the side effects was revised and some preferred terms were re-grouped to other system organ classes. For a complete reformulation see Mesalazine Core Safety Profile and Final Assessment Report UK/H/PSUR/0052/001.

The safety pofile of Salofalk® 500 mg suppositories in the clinical studies corresponds well with the informations in the current summary of product characteristics and the patient information of this preparation.

For further clarification some safety issues of 5-ASA which appear of special interest shall be discussed here in more detail.

Nephrotoxicity

Deemed as a class effect of (highly systemically available) non-steroidal antiinflammatory drugs and from some preclinical studies with high doses, in the early years of its clinical use 5-amionosalicylates where feared to be associated with nephrotic inflammations. This suspected potential of 5-ASA with respect to damaging

[3] Summary of Product Characteristics (SmPC) / data sheet; Patient Information Leaflet (PIL)

effects on the kidneys has already been comprehensively discussed in the Clinical Documentation on Salofalk® granules (Kruis 2000). Based on the experience of a multitude of clinical trials and on decades of clincial practice with 5-aminosalicylates negative effects of 5-aminosalicylate on the kidney such as interstitial nephritis are now considered as rare cases of idiosyncratic reactions but not as dose-dependent common side effects (Gisbert et al. 2007). In many cases, several lines of evidence point to a disease-related risk of impaired renal function rather than a drug-related risk (Herrlinger et al. 2001, Poulou et al. 2006). This point of view is supported by several recent studies which were specially performed to clarify this issue.

In a recent open, prospective study, patients with CD (n=18) and UC (n=29) were treated with daily doses of at least 3 g 5-ASA (Salofalk® 500 mg tablets) (Study Report SAT-11/IBD, Dehmer et al. 2003). Clinical activity (CDAI, CAI) and renal tubular markers (β-N-acetyl-D-glucosaminidase [β-NAG] and other proteins in urine) were measured for 6 weeks. The mean daily dose was 3.7 g 5-ASA/day. The primary evaluation criterion was the rate of patients with abnormally increased ß-NAG values (β-NAG activity > 4.1 U/g creatinine). The authors examined whether the proportion of patients with elevated β-NAG was more than 15% higher (absolute difference) than that prior to treatment. However, there was no increase of β-NAG under 5-ASA (Salofalk®) therapy, but in contrast, the proportion of patients with elevated ß-NAG decreased from 19.2% prior to treatment to 12.8% after 6 weeks of treatment with high oral doses of 5-ASA in the ITT (n=47) and from 24.3% to 13.5% in the PP analysis (n=37). Mean CDAI decreased from 222 to 146 and mean CAI from 7.3 to 3.1 (ITT analysis). Response to therapy was shown by 61% of patients with CD and 66% of patients with UC. The cumulative dose of 5-ASA did not correlate with β-NAG levels in urine.

Summarising these findings, even under high dosages, which were very effective in clinical treatment no dose dependent nephrotoxic side effects have been reported to date, in clinical trials following short-term and long-term use of the substance. Thus, the majority of renal abnormalities detected in IBD patients reflect renal effects of inflammation due to the underlying disease, or in rare isolated cases nephritis as expression of hypersensitivity but not dose-related nephrotoxicity. Even with long-term treatment at high doses, no nephrotoxic side effects were observed (de Jong et al. 2005). However, as mentioned above nephritis as expression of hypersensitivity may occur in isolated cases.

Although the association between chronic tubulo-interstitial nephritis is described in several case reports, a prospective study comprising 1,529 IBD patients revealed the reassuring conclusion that renal impairment in IBD patients is not frequently observed and is rarely associated with 5-ASA treatment (Elseviers et al. 2004).

Safety in pregnancy and lactation

The safety and tolerability of 5-ASA preparations during pregnancy and lactation have already been comprehensively discussed in the Clinical Documentation on Salofalk® granules (Kruis 2000).

There are two recent clinical studies available evaluating the safety of 5-ASA treatment during pregnancy. No drug related increase in relevant risks of the treatment with 5-ASA during pregnancy was observed (Diav-Citrin et al. 1998, Marteau et al. 1998). A

large epidemiologic study in Denmark on the birth outcome in women exposed to 5-ASA during pregnancy did not find an increased risk of malformations. However women who had prescribed 5-ASA during pregancy had an increased risks of stillbirth and preterm birth. The authors reported that it was difficult to distinguish the specific effects of disease activity and 5-ASA drugs (Norgard et al. 2003).

Briggs et al. (2008), reviewing the use of drugs during pregnancy, concluded that the maternal benefits from therapy with 5-ASA outweigh the potential risk to the foetus.

There is only limited experience with the use of 5-ASA in lactation, but many reports suggest that 5-ASA treatment of the breast-feeding mother is considered as safe for the neonate (Silverman et al. 2005; Klotz & Harings-Kaim 1993; Jenss et al. 1990)

Nevertheless, single cases of hypersensitivity reactions like diarrhoea vs. 5-ASA were reported (Nelis 1989). Therefore, Salofalk® 4g/60ml enemas should only be used during breast-feeding if the potential benefit outweighs the possible risk. If the suckling neonate develops diarrhoea, breast-feeding should be discontinued.

In conclusion, 5-ASA seems to be relatively safe in pregnancy and lactation. Due to the lack of adequate and well-controlled trials in pregnant women and nursing mothers, 5-ASA should only be used in pregnancy or during lactation if the potential benefit outweighs the possible risk.

Safety in paediatrics

Rectal as well as oral 5-ASA formulations have also been successfully used in paediatric patients with IBD and have become well-established treatment options in both primary therapy of IBD and maintenance therapy in UC. According to the ECCO guidelines on management of UC, 5-ASA is the therapy of choice in the treatment of mild to moderate active UC in paediatric patients (Biancone et al. 2008).

The safe use and the favourable tolerability of 5-ASA in children has been further confirmed by Hadziselimovic et al. (2000) in a 5-year follow-up of continuous 5-ASA treatment (30 mg/kg bw/day), representing more than 250 patient years with no serious adverse reactions reported.

Ferry (2001) reported the treatment of 340 children with IBD in an age range between < 1 and 18 years. The mean initial dose in all age groups was in the range of 40 to 48 mg/kg bw/day. Only 4% (15 patients) stopped treatment due to adverse events; the authors concluded that 5-ASA was well tolerated.

Kirschner (1998) suggested an initial dose of 60 mg/kg bw/day and a maintenance dose of 20-30 mg/kg bw/day. According to the ECCO guidelines, the recommended dosage in the therapy of mild to moderate active UC is 50-75 mg/kg bw/day with a maximum of 4 g/day. (Biancone et al. 2008).

As result of an European harmonisation process on use of 5-aminosalicylates in paediatric patients mesalazine can be recommended for the treatment of paediatric UC in children of 6 years or older. Oral preparations like Salofalk® 500 mg tablets and Salofalk® granules are approved for the treatment of acute episodes and the maintenance of remission of UC in children with an age of 6 years and older in the EU. The recommended dosage for children older than 6 years is 30-50 mg/kg bw/day,

maximum 75 mg/kg bw/day in the therapy of acute attacks and 15-30 mg/kg bw/day for maintenance of remission. For rectal preparations of 5-aminosalicylic acid there is only limited experience in paediatric patients.

For practical reasons it is generally recommended to give half of the adult dose to children with a body weight of less than 40 kg and the full adult dose if the body weight exceeds 40 kg.

In conclusion, 5-ASA / Salofalk® rectal and oral delayed-release formulations, though not as extensively investigated as in adult IBD patients, are deemed as adequately safe in pediatric use. The available data reveal no specific safety risks or altered tolerability specific for a paediatric IBD patient population.

2.5.5.2 Safety in Studies with 5-ASA 500 mg Suppositories

The safety data of one biopharmaceutical / pharmacokinetic studies (SAS-2/BIO, SAS-5/BIO, see Section 2.5.2.1.1) and 4 clinical efficacy / safety studies in patients with ulcerative proctitis (Williams et al. 1987, Williams 1990, SAS-6/UCA, see Section 2.5.4.1.1) are summarized in the following.

The safety studies (Table 2.5-12) included a total of 687 subjects, 390 of whom received 5-ASA 500 mg suppositories, 200 received other suppositories and 97 patients received placebo.

Table 2.5-12: Studies evaluating the safety of 5-ASA 500 mg suppositories

	Number of subjects	**5-ASA 500 mg suppositories**	**Placebo / Comparator**
SAS-2/BIO	24	24	n.a. crossover*
SAS-5/BIO	48	48	n.a. three-way crossover*
Williams et al. 1987	39	14 12 (^{99m}Tc-labeled 5-ASA suppositories)	13
Williams 1990	173	39 (Study 1) 50 (Study 2)	40 (Study 1) 44 (Study 2)
SAS-6/UCA Publication by Andus et al. 2010	403	203	Salofalk® 1g suppositories 200
Total	**687**	390	**97 / 200**

* crossed-over patients were counted only once

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In Study SAS-2/BIO (n=24) where 5-ASA suppositories were administered for 5 days to healthy subjects, a total of 37 and 34 AEs were experienced by subjects whilst receiving Rowasa® and Salofalk®500 mg suppositories, respectively. A further event was recorded but the treatment could not be ascertained as the time of onset was not recorded. The most frequently reported AEs were headache (11 cases in the Rowasa® group and 5 cases in the Salofalk® group, respectively), peri-anal irritation (6 and 4), flatulence (4 and 5) and diarrhoea or loose stools (4 and 5).

The majority of cases of headache and flatulence were considered possibly related to the study medication, and most cases of diarrhoea were considered probably related. Seven out of 10 cases of peri-anal irritation, however, were classified as almost certainly related to study treatment.

No events were of particular note and similar events were recorded for Rowasa® and Salofalk®, suggesting that both are equally well tolerated.

During study SAS-5/BIO, three different 5-ASA suppositories were administered to healthy male subjects, each in a single dose. All 48 randomised subjects (aged between 19 and 55 years) completed the trial according to protocol. There was no drop-out.

During this trial, 18 non-serious AEs were reported by 16 subjects. No serious AE was reported.

The most frequently and possibly study drug-related AE was headache, which occurred 7 times in 5 subjects. All AEs were of mild intensity, with exception of one (moderate vomiting after Salofalk 1 g suppositories). All AEs resolved at the end of the trial.

No clinically significant abnormal laboratory parameters occurred in any subject during this trial.

The test medication (Salofalk® 1 g suppository) and both reference medications (Salofalk® 2 x 500 mg suppositories and Pentasa® 1 g suppository) were considered safe and well tolerated when given as single rectal dose to healthy, male, Caucasian subjects.

No side effects were reported in the study published by Williams 1987.

In the 2 studies compared by Williams (1990), AEs were few and insignificant in both trials. The incidence of AEs was similar in the 5-ASA and placebo groups with the most frequently reported AEs in both groups being headache (11%), flatulence (7%), diarrhoea (6%) and abdominal pain (6%).

Detailed information is available on AEs of Study 1 (Banks Statistical Report 1986). In this study, AEs occurred in 23 out of 39 (59%) patients in the 5-ASA group and in 22 out of 40 (55%) patients in the placebo group. The most frequently reported AEs were headache, abdominal pain and flatulence. There were no major treatment group differences with respect to the safety assessments.

No death, serious or significant AEs occurred in the studies.

In the phase III study SAS-6/UCA, comparing Salofalk® 1 g suppositories (OD) to Salofalk® 500 mg suppositories (TID) during 6 weeks in total, 48 treatment-emergent AEs occurred in 38/200 patients (19.0%) taking 1 g mesalazine OD, and 67 treatment-emergent AEs occurred in 43/203 patients (21.2%) taking 500 mg mesalazine TID. The most frequently reported treatment-emergent AEs were headache, nasopharyngitis, and ulcerative colitis. All other treatment-emergent AEs occurred in less than 2% of all patients. All treatment-emergent AEs were of mild (1 g mesalazine OD: 29 patients [14.5%], 500 mg mesalazine TID: 33 patients [16.3%]) or moderate (1 g mesalazine OD: 9 patients [4.5%], 500 mg mesalazine TID: 14 patients [6.9%]) intensity. In total, 6 treatment-emergent AEs in 5 patients (2.5%) in the 1 g mesalazine OD and 9 treatment-emergent AEs in 7 patients [3.4%] in the 500 mg mesalazine TID group were considered at least possibly drug related.

No patient died during the course of this study. In total, 2 serious AEs (SAEs) occurred in 2 patients: One patient in the 1 g mesalazine OD group experienced a subclavian artery embolism, one patient in the 500 mg mesalazine TID group experienced anxiety. None of these SAEs was related to the study medication. Both events were serious because the patient had been hospitalised.

Except for a decrease in ESR (-3.6 ± 9.5 mm vs. -4.1 ± 8.1 mm) and CRP (-1.0 ± 11.5 mg/l vs. -0.6 ± 12.3 mg/l), laboratory parameters did not show a relevant mean change in the 1 g mesalazine OD and 500 mg mesalazine TID group. The decrease in ESR and CRP can be attributed to the anti-inflammatory effect of mesalazine. Most deviations from the normal range were considered as not clinically relevant. Clinically relevant deviations occurred in 22 patients taking 1 g mesalazine OD and 16 patients taking 500 mg mesalazine TID. Most clinically relevant deviations were assessed as causally related to ulcerative colitis. One patient each in the 1 g mesalazine OD and 500 mg mesalazine TID group showed an increase in lipase activity (laboratory sign of pancreatitis) assessed as causally related to the study drug.

Body weight and vital signs remained virtually unchanged throughout the study in both groups.

Tolerability was assessed as "very good" or "good" in > 90% of the patients by both the patients and investigators. Patients rated tolerability of 1 g mesalazine OD slightly better than tolerability of 500 mg mesalazine TID ("very good": 50.0% vs. 44.8%). No such difference was observed in the investigators' ratings.

In summary, the clinical studies demonstrated that 5-ASA 500 mg suppositories are safe and well-tolerated with an AE profile similar to that of placebo.

2.5.5.3 Post-Marketing Experience

Salofalk® is available, by prescription only, as enteric-coated tablets (250 mg and 500 mg mesalazine), as sachets of gastro-resistant, prolonged-release granules (500 mg, 1000 mg and 1500 mg mesalazine), suppositories (250 mg, 500 mg and 1000 mg mesalazine), foam (1000 mg mesalazine), and enemas (2000 mg mesalazine/60 mL, 2000 mg/30 mL and 4000 mg/60 mL).

Salofalk® suppositories were first approved in Germany on 20 February 1984 (EU and international birth date). Approval for the tablets followed in December 1984, for enemas in 1986, and for granules and foam in 2001. Salofalk® granules (500 mg and 1000 mg) were first approved in October 2001.

Salofalk® preparations are registered in various countries worldwide (PSUR 2010), Attachment 1). The major current markets for Salofalk® preparations are Germany, Austria, Belgium, The Netherlands, Switzerland, Greece, Israel, Czech Republic, and Turkey (PSUR 2010, Section 2).

Two PSURs for Salofalk® preparations covering the periods from 1 January 2002 to 28 February 2007 (PSUR 2007) and from 1 March 2007 to 28 February 2010 (PSUR 2010), respectively, are presented in Module 5.

Patient exposure: From 01 January 2002 through 28 Februrary 2007 Salofalk® tablets were used for a total of 727,994 patient treatment years, Salofalk® suppositories for 414,352 treatment cycles, Salofalk® enemas for 344,699 treatment cycles, and Salofalk® 500 / 1000 gastro-resistant prolonged release granules (Granu-Stix) for 71,564 patient treatment years. Salofalk® foam enemas were used for 55,031 treatment cycles/year. One treatment cycle equals daily therapy for 6 weeks on an average daily 5-ASA dose of 1,500 mg (suppositories) and 4 g (enemas).

From 01 March 2007 through 28 Februrary 2010 Salofalk® tablets were used for a total of 582,118 patient treatment years, Salofalk® suppositories for 323,132 treatment cycles, Salofalk® enemas for 295,208 treatment cycles, and Salofalk® 500 / 1000 gastro-resistant prolonged release granules (Granu-Stix) for 85,052 patient treatment years. Salofalk® foam enemas were used for 210,763 treatment cycles/year. One treatment cycle equals daily therapy for 6 weeks on an average daily 5-ASA dose of 1,500 mg (suppositories) and 4 g (enemas).

Changes to reference safety information

In 2003 and 2004, the German authority (BfArM) approved new product information for Salofalk® tablets, suppositories, enemas and granules including dosing recommendations for children and detailed safety information (PSUR 2007, Section 4).

In 2005, the product information of all formulations of Salofalk® was updated to include cholestatic hepatitis as an undesirable side effect (PSUR 2007, Section 4).

In August 2006, the excipient dibutylphthalate was replaced by macrogol in Salofalk® tablets (PSUR 2007, Section 4).

In the period covered by PSUR 2010 (1 March 2007 to 28 February 2010), reversible oligospermia and peripheral neuropathy were included as side effects in the product information of Salofalk® granules and foam according to a request during the renewal of the marketing authorisations. The company decided to include these reactions into the product information of all mesalazine preparations.

The Summaries of Product Characteristics for Salofalk® tablets, granules, suppositories, enemas and foam are provided in PSUR 2010, Attachment 2.

Reports of suspected adverse drug reactions:

PSUR 2007

During the 5-year period under review in PSUR 2007, the marketing authorisation holder (MAH) received 80 cases regarding 104 ADRs associated with Salofalk® (PSUR 2007, Section 6). Nineteen of these reactions were classified as serious and unlisted, 49 as serious and listed; 7 reactions were non-serious and unlisted, 29 reactions non-serious and listed. (It has to be taken into account that the classification of cholestatic hepatitis was changed from unlisted to listed in 2004.)

Most frequent were gastrointestinal disorders with 19/104 ADRs. Pancreatitis, which is a known ADR of mesalazine, represents the most frequent reaction with 6 serious reactions. No increase in reporting frequency or severity as compared with the previous reporting period was observed. The second most frequently affected organ system was skin and subcutaneous tissue with 16/104 ADRs. Hepatobiliary disorders were reported in 10 cases, 8 reports were classified as musculoskeletal disorders, and 7 reports as renal and urinary disorders with nephritis (3 cases) representing the most frequent reaction.

The 19 serious unlisted ADRs included 3 deaths: 1 acute hepatic failure (reported by a consumer), 1 unexplained death, and 1 anaphylactic reaction with myocardial infarction.

One serious unlisted case of reversible oligospermia was received, as was 1 serious unlisted case of demyelinating polyneuropathy.

An analysis of serious unlisted cases by the MAH is provided in PSUR 2007, Section 6.3.

PSUR 2010

During the 3-year period under review in PSUR 2010, the MAH received 98 cases regarding 129 ADRs associated with Salofalk® (PSUR 2010, Section 6).

Thirteen of these reactions were classified as serious and unlisted, 33 as serious and listed; 27 were non-serious and unlisted and 56 were non-serious and listed.

The most frequent ADRs were gastrointestinal disorders and skin and subcutaneous tissue disorders. No specific signals or new safety issues were identified from the reports received during this period.

One new death was reported in PSUR 2010: a case of a fatal respiratory reaction following treatment with an unspecified dose and formulation of mesalazine. Causality could not be assessed due to insufficient information.

An analysis of serious unlisted cases by the MAH is provided in PSUR 2010, Section 6.3.

In the period under review, Dr. Falk Pharma received 2 case reports pertaining to drug exposure during pregnancy. Case No. SA-22/07 reported a congenital ventricular septal defect following maternal administration of mesalazine during pregnancy for UC. Case No. SA-04/10 concerned a 32-year-old woman who received Salofalk® 500 mg as treatment for Crohn's disease. She gave birth to a female baby with auricle anomaly on

both sides. Details are provided in the PSUR (PSUR 2010, Section 6.3.2). In addition, one case of overdose (suicide attempt, No. SA-14/07) was reported (PSUR 2010, Section 8.4). The ingestion of about 150 g mesalazine did not result in renal or hepatic toxicity, as documented by the laboratory values for creatinine and GGT.

Cummulative line listing

Since 1997, a total of 41 case reports with serious and unlisted ADRs have been reported to the MAH. [In 1997 the ICH E2C format for PSUR as adopted by the CPMP came into operation (CPMP/ICH/288/95). Therefore, reports since 1997 are provided in this format.].

Six unlisted deaths have been reported: hepatic failure, acute hepatic failure, pancreas carcinoma, unexplained death, anaphylactic reaction with myocardial infarction (therapeutic response unexpected with drug substitution), and respiratory failure (see PSUR 2010, Attachment 7).

Late breaking information

No late breaking information was available up to the date of PSUR 2010, i.e. 28 February 2010.

In summary, there are no new safety concerns arising from the latest post-marketing experience reports. The current product information adequately reflects the current knowledge and experience with Salofalk®.

In conclusion,

- The available safety data generated in controlled clinical studies and the most recent PSUR confirm the known favourable safety profile of all Salofalk® formulations. No Salofalk® formulation-specific type of adverse drug reaction was noted. No cases of 5-ASA intoxication have been reported to date. Product information on safety has been accordingly adapted to post-marketing experience.
- The experience with the long-standing use of Salofalk® (250 mg / 500 mg) suppositories, and more recently also Salofalk® 1 g suppositories in the treatment of acute exacerbation of distal ulcerative proctitis, in conjunction with the favorable safety profile observed in clinical trials, show that these rectal preparations are generally well tolerated.
- Salofalk® suppositories (250 mg / 500 mg) appear to be adequately safe in paediatric use.
- Several lines of evidence confirm that 5-ASA preparations do not seem to be associated with a specific inherent nephrotoxicity. However, hypersensitivity reactions which may affect also the kidneys may occur in isolated cases.

2.5.6 Benefits and Risks Conclusions

Irrespective of the maximum proximal extent of the mucosal inflammation, in ulcerative colitis (UC) nearly always the rectum and to a various extent - the distal parts of the colon are affected. As in UC the inflammation is largely restricted to the rectal and/or colonic mucosa, optimally, the therapeutic principle should be targeted directly to the sites of inflammation. With a topically acting agent, preparations releasing the active ingredient only locally, acting from the luminal side of the rectum and/or the colon, therapeutically effective mucosal drug concentrations should be achieved minimising the loss of the drug by absorption into the systemic circulation to ensure an optimally targeted treatment of UC.

Due to the local release and the topical action of the active ingredient, rectal 5-ASA preparations are considered the treatment of choice of inflammations in the distal parts of the large bowel in patients with UC and ulcerative proctitis.

Salofalk® 500mg suppositories provide the advantage of effectively delivering relatively high doses of 5-ASA directly to the rectum which is often the site of maximal inflammation.

Studies on its low systemic bioavailability and distribution from suppository formulations have shown that 5-ASA release is restricted to the mucosal areas affected in ulcerative proctitis, i.e. the rectum.

The efficacy of rectal 5-ASA preparations in the treatment of acute exacerbations of distal UC is well established and recommended as first-line and standard approach in all national and international guidelines on the treatment of UC.

It has been shown that there are no major differences in pharmacokinetics between adult and paediatric patient populations. As shown in clinical trials and reports on treatment experience, topical 5-ASA / Salofalk® preparations have been well tolerated in paediatric use.

The therapeutic efficacy of 5-ASA suppositories in the treatment of active ulcerative proctitis/distal UC has been demonstrated by various controlled clinical trials and is well established. In particular, the efficacy of 5-ASA 500 mg suppositories in ulcerative proctitis has been shown in the following clinical trials presented in this amendment of the Clinical Documentation:

- The bioequivalence / pharmacokinetic study SAS-2/BIO demonstrates that Salofalk® 500 mg suppositories and Rowasa® 500 mg suppositories can be regarded as bioequivalent.
- Study SAS-5/BIO on the bioavailability/pharmacokinetics of 5-ASA and its metabolite released by one Salofalk® 1g suppository and two Salofalk® 500 mg suppositories demonstrates the close similarity of plasma concentrations after both preparation even if formally bioequivalence was not shown.
- In the double-blind clinical trial by Williams et al. (1987), 5-ASA suppositories were shown to be more effective than placebo in patients with active distal proctitis. In addition, using ^{99m}Tc-labled 5-ASA suppositories restrction of the spread to the rectum was shown.

- Two studies presented in the publication by Williams (1990) confirmed the efficacy, safety and tolerance of 5-ASA suppositories (Rowasa®) in the treatment of ulcerative proctitis.
- A recent large phase III study, SAS-6/UCA (published by Andus et al. 2010), showed again high rates of clinical remission, therapeutical equivalence safety and tolerability of Salofalk® 500 mg suppositories and Salofalk® 1 g suppositories .

Extensive systematic analyses of published clinical trials provide further support for the effectiveness (and safety) of rectal 5-ASA suppository preparations in active distal UC, i.e. in ulcerative proctitis. In addition, these metaanalyses also indicated that in the treatment of distal ulcerative colitis rectal 5-ASA preparations were at least as or even more effective as than rectal preparations of corticosteroids.

The dose recommendation for the treatment of patients with active distal UC remains unaffected to be 500 mg 5-ASA t.i.d., that is three Salofalk® 500 mg suppositories daily.

The available safety data generated in controlled clinical studies and the most recent PSURs confirm the established favourable safety profile of all Salofalk® formulations. No Salofalk® formulation-specific type of adverse drug reaction was noted. No cases of 5-ASA intoxication have been reported to date. Product information on safety has been accordingly adapted to post-marketing experience.

The long-standing clinical use of Salofalk® 500 mg suppositories in the therapy of acute exacerbation of distal UC, together with the experience with this preparation in clinical trials, show that this rectal preparations is safe and well tolerated.

Salofalk® 250 and 500 mg suppositories appear to be adequately safe in paediatric use.

Several lines of evidence show that 5-ASA preparations do not have an inherent neprotoxic potential. However, hypersensitivity reactions may occur in single cases.

The available evidence indicates that 5-ASA seems to be relatively safe in pregnancy. Data on a limited number of exposed pregnant women indicate no specific adverse effect of 5-ASA on pregnancy or on the health of the foetus or the newborn child. However, due to the limitations of the experience with the use of 5-ASA during pregnancy and lactation, 5-ASA should only be used in pregnancy if the possible benefit outweighs the potential risk. Hypersensitivity reactions like diarrhoea in the breast-fed infant were described and cannot be excluded. Therefore, Salofalk® suppositories should only be used during breast-feeding if the possible benefit outweighs the potential risk. If the suckling neonate develops diarrhoea, breast-feeding should be discontinued.

In summary, based on the presented clinical data, and the post-marketing experience data, Salofalk® 500 mg suppositories are therapeutically rational and effective in the treatment of active distal UC / ulcerative proctitis. The product key characteristics, in particular with respect to safety, are adequately reflected in the current product information texts (SmPC / data sheet, PIL), which have recently been amended.

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