Clinical Study Report Synopsis

Version/Date: Final report v. 1.0 / 14 Mar 2008

Randomised, single-blind, multicentre 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

Project No.:	SAS-6/UCA
EudraCT No.:	2004-005018-35
Short title:	OD vs. TID dosing with mesalazine suppositories in acute ulcerative proctitis
Investigational drug:	Salofalk® 1000 mg suppositories (1 g mesalazine once daily [OD])
Reference drug:	Salofalk® 500 mg suppositories (0.5 g mesalazine three times daily [TID])
Indication:	Acute ulcerative proctitis
Phase of study:	III
First patient enrolled:	09 Jun 2005
Last patient completed:	06 Jun 2007
Date of final report:	14 Mar 2008

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GCP Statement: This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

SYNOPSIS

Name of Sponsor/Company **Dr. Falk Pharma GmbH**	*Individual Study Table Referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product: **Salofalk® 1000 mg suppositories**	*Volume:*	
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Title of Study:
Randomised, single-blind, multicentre 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

Study Centres:
35 centres enrolled patients: Five centres in Germany, 10 centres in Israel, 13 centres in Russia, and 7 centres in Ukraine.

Study Period:	**Phase of Development:**
First patient enrolled: 09 Jun 2005 Last patient completed: 06 Jun 2007	III

Objectives:
Primary objective:
- To prove the therapeutic equivalence of once daily (OD) 1.0 g mesalazine suppositories versus three times daily (TID) 0.5 g mesalazine suppositories in patients with active ulcerative proctitis.

Secondary objectives:
- 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.

Methodology:
This was a single-blind (investigator-blind), randomised, multicentre, comparative, phase-III clinical trial. The study was conducted with two arms in the form of a parallel group comparison and had to serve to compare two different dosing regimens (1.0 g OD vs. 0.5 g TID) of mesalazine suppositories:

Group A (investigational drug): 1.0 g mesalazine suppositories OD
Group B (reference drug): 0.5 g mesalazine suppositories TID

The study was planned to be performed according to a 3-stage group sequential adaptive design with possible sample size adjustments after the 2 planned interim analyses.

Number of Patients (Total and for Each Treatment):
Planned/Adapted during Interim Analyses:

A 3-stage group sequential adaptive design was used. The first interim analysis was planned to be performed after 2 x 85 per-protocol (PP) evaluable patients had finished the trial. The second and the final analysis were planned to be performed after further 2 x 43 PP evaluable patients each had finished the trial. The estimated sample size, without sample size adaptation, was 344 evaluable patients.

The 1st interim analysis was performed on 145 PP evaluable patients. It did not yield a significant result. The study was continued and the number of patients to be evaluable for PP analysis at the second stage was increased from 2 x 43 patients to 2 x 60 patients.

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The 2nd interim analysis was performed on 270 PP evaluable patients. It yielded a significant result. Recruitment of the study was stopped after the result of the interim analysis was available. However, as recruitment continued during the time the interim analysis was performed, another 93 patients were included. The study was carried on in these patients. In total, 408 patients were randomised.

The final analysis was performed on a total of 354 PP evaluable patients.

Analysed in the Final Analysis:

Number of patients	1 g mesalazine OD	0.5 g mesalazine TID	Total
Randomised	201	207	408
Safety	200	203	403
ITT	200	203	403
PP	182	172	354

In total, 403 patients received study medication and were included in the safety and intention-to-treat (ITT) analysis set. Nineteen patients treated with 1 g mesalazine OD and 35 patients treated with 0.5 g mesalazine TID were excluded from the PP analysis set. Primary reason for exclusion from PP analysis was major protocol deviations occurring in 14 patients in the 1 g mesalazine OD and 23 patients in the 1 g mesalazine TID group.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion Criteria:	Main Exclusion Criteria:
• Signed informed consent, • Men or women aged 18 to 75 years,	• Crohn's disease, • Proctitis of a different origin,
• Active ulcerative proctitis, i.e. inflammation/lesions maximal 15 cm of rectum, • Diagnosis confirmed by endoscopy and histological examination, • Established or new diagnosis, • Mildly to moderately active disease ($3 < DAI < 11$).	• Prior bowel resection leading to diarrhoea and/or pouch formation, • Toxic megacolon, • Hemorrhagic diathesis, • Symptomatic gastrointestinal disease, • Present or past colorectal cancer, • Serious secondary disease(s), • Serum transaminase (ALT and/or AST), and/or alkaline phosphatase ≥ 2 x ULN, • Serum creatinine > 1.5 mg/dl or > 133 µmol/l, • Regular oral or rectal treatment with 5-ASA, olsalazine or sulfasalazine within the last 4 weeks. • Immunosuppressants within 3 months and/or corticosteroids within 1 month prior to baseline, • Existing or intended pregnancy or breast-feeding.

Duration of Treatment: Six weeks

Test Drug, Dose and Mode of Administration, Batch Number:

1.0 g mesalazine (Salofalk® 1000 mg suppositories) once daily (OD).

Patients were to administer rectally one suppository containing 1.0 g mesalazine at bedtime.

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Batch numbers: 04 D 32, 06 L 25 Expiry date: Apr 2007, Dec 2008
See Appendix 8.1.6 *List of Patients by Batch Numbers of Study Medications*

Reference Drug, Dose and Mode of Administration, Batch Number:
0.5 g mesalazine (Salofalk® 500 mg suppositories) three times daily (TID).
Patients were to administer rectally one suppository containing 0.5 g mesalazine each in the morning, at noon and at bedtime.
Batch numbers: 04 I 02, 06 K 22 Expiry date: Sep 2007, Nov 2009
See Appendix 8.1.6 *List of Patients by Batch Numbers of Study Medications*

Criteria for Evaluation:
Primary Efficacy Variable:
- Clinical remission, defined as Disease Activity Index (DAI) < 4 at the final visit week 6/withdrawal visit.

Secondary Efficacy Variables:
- Improvement of disease,
- Remission (defined by DAI_{FDA}),
- Individual items of the DAI/DAI_{FDA},
- Presence of clinical symptoms,
- Endoscopic remission (DAI/DAI_{FDA}),
- Change of DAI/DAI_{FDA} from baseline to final/withdrawal visit,
- Time to first symptomatic remission,
- Rate of clinical remission (defined by CAI ≤ 4) at the final/withdrawal visit,
- Clinical improvement (CAI),
- Clinical Activity Index (CAI) in the course of the study,
- Individual items of the CAI in the course of the study,
- Presence of rectal mucus in the course of the study,
- Presence of tenesmus in the course of the study,
- Number of stools in the course of the study,
- Number of bloody stools in the course of the study,
- Change of ESR from baseline to final/withdrawal visit,
- Physician's global assessment (PGA),
- Histological Index (HI),
- Endoscopic Index (EI),
- Change of SIBDQ from baseline to final/withdrawal visit,
- Patient's acceptance of study drug,
- Patient's preference regarding administration frequency of study drugs.

Safety:
- Adverse events (AEs),
- Standard haematology, blood chemistry, urinalysis,
- Vital signs (blood pressure, heart rate, body weight),
- Assessment of tolerability by investigator and patient.

Statistical methods:

Primary efficacy evaluation:	
Clinical remission (DAI 1)	Three-stage group-sequential adaptive design; shifted asymptotic χ^2-test for comparing two rates; non-inferiority margin: 15%.
	Absolute and relative frequencies of remission by country, centre, smoking status, duration of

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	the disease, gender, CAI at baseline, DAI at baseline and extraintestinal disease symptoms at baseline.
Secondary efficacy evaluation:	
DAI 1&2, CAI, number of stools, number of bloody stools, ESR and change in ESR, EI and change in EI, SIBDQ and SIBDQ subscores; time to first resolution of clinical symptoms (acc. to Löfberg)	Summary statistics incl. 95%-confidence interval (CI)
Change in DAI 1&2, CAI, number of stools, number of bloody stools, SIBDQ and SIBDQ subscores	Summary statistics incl. 95%-CI; difference between treatment groups with 95%-CI and t-test
Remission, improvement, no change and deterioration of DAI 1&2 and EI; normalisation, improvement, no change and deterioration of DAI 1&2 subscores, CAI subscores; no confirmation of UC, remission, improvement, no change and deterioration of HI; presence of rectal tenesmus, mucus	Absolute and relative frequencies
Categories of PGA, HI and patient's acceptance and preference of study drug	Absolute and relative frequencies
Improvement of disease acc. to DAI 1; clinical remission acc. to DAI 2	Absolute and relative frequencies incl. 95%-CI; difference in relative frequencies between treatment groups with 95%-CI
Endoscopic remission acc. to DAI 1&2; clinical remission acc. to CAI; clinical improvement acc. to CAI	Absolute and relative frequencies; difference in relative frequencies between treatment groups with 95%-CI
DAI 1&2 subscores	Shift tables comparing frequencies of patients in categories of DAI 1&2 subscores between visits
Time to first resolution of clinical symptoms (acc. to Löfberg)	Time to event analysis: median time to event incl. 95%-CI; hazard ratio incl. 95%-CI; survival distribution function

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Safety evaluation:	
Adverse events, tolerability	Absolute and relative frequencies
Laboratory parameters	Summary statistics incl. 95%-CI; absolute and relative frequencies of deviations from the normal range and of investigator assessments
Vital signs	Summary statistics incl. 95%-CI
Physical examination	Absolute and relative frequencies of changes and findings
Others (e.g. baseline characteristics):	
Categorical variables	Absolute and relative frequencies
Continuous variables	Summary statistics

DAI 1 = original DAI acc. to Sutherland; DAI 2 = DAI acc. to FDA definition.
Summary statistics include mean, standard deviation, minimum, maximum, upper and lower quartile, median.

Summary:
Patient disposition:
A total of 408 patients were randomised to treatment with study medication; 386 patients completed the study; 22 patients were prematurely withdrawn (1 g mesalazine OD: 9 patients [4.5%]; 0.5 g mesalazine TID: 13 patients [6.3%]). Primary reason for premature withdrawal was lack of patient's co-operation (11 patients). Three patients were withdrawn due to intolerable AEs. In 2 patients, lack of efficacy was the reason for premature withdrawal. Six patients were withdrawn due to other reasons.

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Demographic and baseline characteristics (ITT analysis set)		**1 g mesalazine OD (n = 200)**	**0.5 g mesalazine 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)
BMI [kg/m^2]	Mean (SD)	24.1 (4.0)	24.1 (3.8)
Smoking history			
Non-smoker	n (%)	155 (77.5%)	161 (79.3%)
Ex-smoker	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)
Stool frequency in (complete) remission [per day]	Mean (SD)	1.3 (0.6)	1.2 (0.5)
Patients with extraintestinal disease symptoms	n (%)	32 (16.0%)	29 (14.3%)
Course of the disease (established 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 acute episode [months]	Median (Range)	1.0 (0.0 – 142.0) [n = 142]	1.0 (0.0 – 13.0) [n = 161]
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)			
DAI 1**	Mean (SD)	6.2 (1.6) [n = 200]	6.2 (1.5) [n = 201]
DAI 2**	Mean (SD)	6.3 (1.5) [n = 200]	6.3 (1.4) [n = 201]
Clinical Activity Index (CAI)	Mean (SD)	6.7 (2.2) [n = 198]	6.7 (1.9) [n = 197]
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)
Short Inflammatory Bowel Disease Questionnaire (SIBDQ) total score	Mean (SD)	4.5 (1.1) [n = 196]	4.3 (1.1) [n = 199]

* New diagnosis is defined as 'duration of disease < 6 months' and 'course of the ulcerative proctitis' = 'continuous'.
** DAI 1 = original DAI acc. to Sutherland; DAI 2 = DAI acc. to FDA definition.

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The two treatment groups showed no relevant differences with regard to demographic and anamnestic characteristics at baseline in the ITT analysis set. Only some minor imbalances were found: The duration of the disease, the number of previous acute episodes and the proportion of patients with a recurrent disease was higher in patients taking 0.5 g mesalazine TID than in patients taking 1 g mesalazine OD. The proportion of patients with a new diagnosis and with a continuous disease was higher in the 1 g mesalazine OD than in the 0.5 g mesalazine TID group.
Based on the anamnestic characteristics at baseline, no difference in the severity of acute ulcerative proctitis can be concluded between patients in both treatment groups.

Efficacy Results:

Primary Efficacy Evaluation:

Clinical remission rates at the interim analyses and at the final analysis in the PP and ITT analysis set each:

		Number (%) of patients with clinical remission at the final/withdrawal examination		Difference between proportions* [95%-CI]	Shifted asymptotic χ^2-test for comparing two rates**
		1 g mesalazine OD	0.5 g mesalazine TID		
1st interim analysis	PP	60 (82.2%) n = 73	64 (88.9%) n = 72	-6.7% [-18.1%, 4.7%]	0.0819***
	ITT	65 (79.3%) n = 82	66 (80.5%) n = 82	-1.2% [-13.5%, 11.1%]	0.0150***
2nd interim analysis	PP	121 (86.4%) n = 140	117 (90.0%) n = 130	-3.6% [-11.2%, 4.1%]	2.692****
	ITT	131 (83.4%) n = 157	129 (83.2%) n = 155	0.2% [-8.1%, 8.5%]	3.436****
Final analysis	PP	160 (87.9%) n = 182	156 (90.7%) n = 172	-2.8% [-9.2%, 3.6%]	3,463****
	ITT	168 (84.0%) n = 200	172 (84.7%) n = 203	-0.7% [-7.8%, 6.4%]	3,790****

* Difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID]; asymptotic CI;
** 'Effect' = difference between proportions [1 g mesalazine OD – 0.5 g mesalazine TID] + 0.15);
*** observed p-value (one-sided);
**** inverse normal.

At the 2nd interim analysis, the inverse normal for the non-inferiority test of H_0 ($\pi_{mesalazine}$ (1.0 g OD) $\leq$ $\pi_{mesalazine}$ (0.5 g TID) - 0.15) exceeded the critical value of 2.337 for the PP analysis set. This provided confirmatory evidence that the proportion of patients with clinical remission in patients taking 1 g mesalazine OD was not more than 15% (absolute difference) lower than in patients taking 0.5 g mesalazine TID. Thus, therapeutic equivalence of once daily 1.0 g mesalazine suppositories versus three times daily 0.5 g mesalazine suppositories in patients with active ulcerative proctitis was proven.
At the final analysis, the result of the second interim analysis was confirmed, however, the result of the final analysis was only exploratory in nature.
95%-CIs did not show a statistically relevant difference in clinical remission rates between treatment groups at the interim analyses and at the final analysis.

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Secondary Efficacy Evaluation (PP analysis set):

Number (%) of patients with a change in DAI 1, CAI and EI from baseline to LOCF:

Change	DAI 1*		CAI		EI**	
	1 g mesalazine OD n = 182	0.5 g mesalazine TID n = 172	1 g mesalazine OD n = 182	0.5 g mesalazine TID n = 172	1 g mesalazine OD n = 176	0.5 g mesalazine 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.

* Patients with (DAI 1) > 3 at baseline; ** patients with EI ≥ 4 at baseline.

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 in indices and sub-scores should be mentioned:

- Normalisation rates of the DAI 1 sub-scores stool frequency (62.7% vs. 53.8%) and disease activity (66.5% vs. 62.8%) were higher in the 1 g mesalazine OD than in the 0.5 g mesalazine TID group. The normalisation rate of the rectal bleeding sub-score (87.3% vs. 91.1%) turned out in favour of the 0.5 g mesalazine TID group.
- The proportion of patients with clinical remission according to CAI was slightly higher in the 0.5 g mesalazine TID (92.4%) than in the 1 g mesalazine 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 0.5 g mesalazine TID group.
- The proportion of patients with remission of EI was slightly higher in the 0.5 g mesalazine TID (89.6%) than in the 1 g mesalazine OD group (84.7%).

Differences in remission/normalisation rates in favour of one group are nearly always balanced by differences in improvement rates in favour of the other group.

The majority of patients showed an improvement of HI from baseline to final examination. There was no difference in the proportion of patients with improvement of HI (62.6% vs. 60.5%) between groups.

The median time to first resolution of clinical symptoms did not show any difference between the 1 g mesalazine OD (5.0 days) and 0.5 g mesalazine TID group (7.0 days) (hazard ratio: 0.850).

The median decrease in ESR after the 1st hour from baseline to LOCF did not show any differences between the 1 g mesalazine OD (-2.0 mm) and 0.5 g mesalazine TID group (-3.0 mm).

In the majority of patients, complete relief or at least a marked improvement of symptoms (therapeutic

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success) was indicated by PGA at final visit (1 g mesalazine OD: 162 patients [89.0%], 0.5 g mesalazine TID: 153 patients [89.0%]).
According to the SIBDQ and its sub-scores, quality of life improved from baseline to the final visit in both treatment groups.

Acceptance and preference results (PP analysis set):

Administration of the study drug was assessed as "easy" in about 85% of the patients in both treatment groups, and only about 10% of the patients reported a "considerable" interference of administration with daily routine, however, the comparison between groups showed a clear preference for 1 g mesalazine OD treatment. The percentage of patients considering administration of the study drug as "easy" (91.8% vs. 79.7%), reporting "almost no" interference of administration with daily routine (69.2% vs. 44.8%) and indicating "preference to apply 1 supp./day in the evening" (93.4% vs. 81.4%) was higher in the 1 g mesalazine OD than in the 0.5 g mesalazine TID group.

Safety results:

In total, 48 treatment-emergent AEs occurred in 38 patients [19.0%] taking 1 g mesalazine OD, and 67 treatment-emergent AEs occurred in 43 patients [21.2%] taking 0.5 g 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 patients experienced treatment-emergent AEs of mild (1 g mesalazine OD: 29 patients [14.5%], 0.5 g mesalazine TID: 33 patients [16.3%]) or moderate (1 g mesalazine OD: 9 patients [4.5%], 0.5 g 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 0.5 g mesalazine TID group were considered at least possibly drug related.
No patient died during the course of this study. In total, 2 serious adverse events (SAEs) occurred in 2 patients: One patient in the 1 g mesalazine OD group experienced a subclavian artery embolism, one patient in the 0.5 g 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 (-3.57 (9.47) mm vs. -4.11 (8.14) mm) and CRP (-1.00 (11.53) mg/l vs. -0.59 (12.31) mg/l), laboratory parameters did not show a relevant mean change in the 1 g mesalazine OD and 0.5 g 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 0.5 g mesalazine TID. Most clinically relevant deviations were assessed as causally related to ulcerative colitis. One patient each in the 1 g mesalazine OD and 0.5 g 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 0.5 g mesalazine TID ("very good": 50.0% vs. 44.8%). No such difference was observed in the investigators' ratings.

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Conclusions:

- Both 1 g mesalazine OD and 0.5 g mesalazine TID were highly efficacious in patients with active ulcerative proctitis, and once daily 1 g mesalazine suppositories proved to be therapeutically equivalent to three times daily 0.5 g mesalazine suppositories.
- Rectal mesalazine treatment induced a prompt cessation of clinical symptoms.
- Both 1 g mesalazine OD and 0.5 g mesalazine TID were safe and well tolerated, and no differences in terms of safety and tolerability between treatment groups could be observed.
- Both 1 g mesalazine OD and 0.5 g mesalazine TID were very well accepted, but patients preferred to take suppositories once daily.

Date of the report:	14 Mar 2008

Added information

Publication:	Andus T, Kocjan A, Müser M, Baranovsky A, Mikhailova TL, Zvyagintseva TD, et al. 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. Inflamm Bowel Dis. 2010;16(11):1947-56