SYNOPSIS

TITLE OF STUDY: Pentasa® once daily in ulcerative colitis for maintenance of remission: A European multi-centre investigator blinded randomised controlled study of mesalazine (Pentasa® Sachet) comparing one gram twice with two gram once daily
INVESTIGATOR(S): CO-ORDINATING INVESTIGATOR: [redacted]
STUDY CENTRE(S): Belgium, Czech republic, Denmark, Finland, Germany, the Netherlands, Norway and Sweden
PUBLICATION (REFERENCE): The study results are intended for publication in a peer reviewed journal

STUDIED PERIOD (YEARS):	**PHASE OF DEVELOPMENT:**
Q1 2005 Q2 2007	III

OBJECTIVES:

Primary Objective:

To demonstrate that 2 grams mesalazine once daily is non-inferior to 1 gram mesalazine twice daily in terms of remission rate in patients with mild to moderate ulcerative colitis.

Secondary Efficacy Objectives:
To compare between the two groups

1 Compliance
2 Time to relapse
3 Severity of relapse
4 Endoscopic evaluation
5 Average of UC-DAI* at each visit
6 Acceptability

*abbreviated at visit 2 and 3

Secondary Safety Objectives:
To compare between the two groups

- Incidence of Adverse Events

METHODOLOGY:

Multi-centre, randomised controlled, investigator blinded study.
The randomisation will be done centrally.
The patients will be treated for 1 year, with clinical and laboratory assessments at 0, 4, 8 and 12 months.
Endoscopic examinations at enrolment and on completion of the study (at relapse or after 12 months).

NUMBER OF SUBJECTS:

Planned were 360 patients for demonstration of non-inferiority of once daily treatment; 326 to be analysed in PP analyses and 360 in ITT analyses.

A total of 378 patients were screened (ASS sample), 362 patients were randomised and treated (ASR and AST sample). The ITT and PP1 sample comprised 353 patients; the PP2 sample comprised 296 patients.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Adult subjects (age > than 18 years) with established diagnosis of ulcerative colitis in clinical remission with an UC-DAI <2 at enrolment but who have had a clinical relapse within the past year.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Mesalazine, granules 2 grams orally, in a once daily dose regime, Batch numbers: PA 352D, PK 889D, and PL 028D.

DURATION OF TREATMENT:

1 year

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

Mesalazine, granules 1 gram orally, in a twice daily dose regime, Batch numbers: PA 351D, PK 890D, and PK 889D.

CRITERIA FOR EVALUATION:

Efficacy:

• Primary efficacy variable:
Remission rate

• Secondary efficacy variables:
1 Compliance
2 Time to relapse
3 Severity of relapse
4 Endoscopic evaluation
5 Average of UC-DAI* at each visit
6 Acceptability
* abbreviated at visit 2 and 3

Safety:

• Secondary safety variables:
Occurrence of adverse events

STATISTICAL METHODS:

Primary objective of this trial was to compare Kaplan-Meier estimated remission rate until 1 year based on the UC-DAI score. If the 95% confidence interval for the treatment difference OD minus TD was completely above -10%, OD was considered to be non-inferior to TD.

The sample size of 360 patients was based on a non-inferirioty limit (delta) of 10%, assuming 10% drop-outs and a remission rate of 60% and 65% in the control and experimental arm respectively.

The following secondary efficacy parameters were to be tested using Wilcoxon's 2-sample test stratified by centre: % compliance, compliance using VAS scores, change from baseline of the mucosal appearance score, UC-DAI total score, and acceptability of treatment using VAS scores.

Time-to-relapse was to be tested using the log-rank test stratified by centre. A 95% confidence interval for the hazard ratio was to be calculated using Cox regression stratified by centre.

Overall relapse rate, rate of mild to moderate UC, and rate of severe relapse were to be tested using conditional logistic regression stratified by centre.

The number of patients with at least one (S)AE was to be tested using Fisher's Exact test 2-sided.

The All-Subjects-Screened (ASS) sample consisted of all screened patients, whether or not admitted to the trial.
The All-Subjects-randomized (ASR) sample consisted of all screened patients who were randomized.
The All-Subjects-Treated (AST) sample consisted of all randomized patients who took study medication at least once.
The Intention-to-Treat (ITT) sample consisted of all randomized and treated patients who had at least one post-baseline efficacy assessment, minus deviators from major entry criteria.
ITT analysis was to be repeated with two different Per-Protocol (PP) populations:
PP1: this population comprised all ITT patients, but no data on relapse collected after the time of dropout were used.

PP2: in this population all patients discontinuing or lost to follow-up were excluded. Major protocol violators erroneously completing the study were excluded as well.

EFFICACY RESULTS:

Primary parameter:

Kaplan-Meier estimated UC-DAI remission rates

	Kaplan-Meier remission rate (%)		Difference in Kaplan-Meier remission rate (%)	95% CI	P-value*
	2 g mesalazine OD	1 g mesalazine TD			
ITT sample	70.9	58.9	11.9	1.4-22.5	0.0236
PP1 sample	71.3	58.7	12.5	1.8-23.3	0.0212
PP2 sample	71.5	57.1	14.4	3.5-25.3	0.0089

* Log-rank test

Summary of the UC-DAI remission rate at End-of-Study

	2 g mesalazine OD		1 g mesalazine TD	
	n/N (%)	95% CI	n/N (%)	95% CI
ITT sample				
Patients in remission	121/164 (73.8)	67.0-80.6	110/173 (63.6)	56.4-70.8
PP1 sample				
Patients in remission	106/146 (72.6)	65.3-79.9	95/157 (60.5)	52.8-68.2
PP2 sample				
Patients in remission	102/140 (72.9)	65.5-80.3	89/151 (58.9)	51.0-66.8

n: number of patients with remission; N: total number of patients with data available

The primary efficacy endpoint, which was the Kaplan-Meier estimated UC-DAI remission rate until 1 year, showed that treatment with 2 g mesalazine OD was non-inferior to treatment with 1 g mesalazine TD. The difference in Kaplan-Meier estimated remission rates even reached statistical significance in favour of the 2 g mesalazine OD treatment group compared to the 1 g mesalazine TD treatment group.

Secondary parameters:

The superior effect of the 2 g mesalazine OD dose regimen was supported by the analysis of the secondary efficacy parameters.
Compliance measured by the percentage of sachets used was slightly better for the 2 g mesalazine OD treatment group (ITT and PP1: 78.8-80.3%; PP2: 80.5-82.6%) than for the 1 g mesalazine TD treatment group (ITT and PP1: 74.6-79.8%; PP2: 77.1-79.3%). The differences were not statistically significant.

Compliance measured by the VAS score was better for the 2 g mesalazine OD treatment group (ITT and PP1: 94.5-96.5%; PP2: 95.6-96.7%) than for the 1 g mesalazine TD treatment group (ITT and PP1: 93.1-94.0%; PP2: 92.9-93.8%). The differences were numerically small but at almost all time points statistically significant.

The difference in subjectively experienced compliance between the OD and TD regime particularly appeared from the answers to the questions 'forgot to take medication?' and 'careless at times about medication?'.

The time-to-relapse was longer after treatment with 2 g mesalazine OD (ITT: 202.0 days (median)) than after treatment with 1 g mesalazine TD (ITT: 148.0 days (median)). However, the clinical relevance of a difference of this magnitude is absent. The difference was statistically significant for the PP2 analysis only.

Also the relapse rate was lower after treatment with 2 g mesalazine OD (ITT: 25.4%) than after treatment with 1 g mesalazine TD (ITT: 34.2%). The differences were only statistically significant in PP2 analysis. In addition, the rate of mild to moderate UC was lower after treatment with 2 g mesalazine OD (ITT: 16.6%) than after treatment with 1 g mesalazine TD (ITT: 25.5%), but the difference was not statistically significant.

Endoscopic evaluation of mucosal appearance revealed a lower mean mucosa score after treatment with 2 g mesalazine OD (0.70) than after treatment with 1 g mesalazine TD (0.75). The difference was not statistically significant.

The UC-DAI subscores 'stool frequency', 'rectal bleeding', and 'physician's global assessment' were more frequently categorised as 'normal' during treatment with 2 g mesalazine OD (ITT: 81.5, 79.6 and 72.3%, respectively) than with 1 g mesalazine TD (ITT: 67.7, 70.7 and 62.5%, respectively). In addition, the UC-DAI total score at End-of-Study was lower after treatment with 2 g mesalazine OD (1.74) than after treatment with 1 g mesalazine TD (2.33) (the difference was not statistically significant).

The acceptability of treatment was significantly better for the 2 g mesalazine OD dose regimen, which was most pronounced at End-of-Study (ITT: 96.3 vs 85.6 for 2 g mesalazine OD and 1 g mesalazine TD, respectively).

SAFETY RESULTS:

Overall, 42.9% of the patients in the 2 g mesalazine OD treatment group and 36.4% of the patients in the 1 g mesalazine TD group reported on or more (S)AEs during the study. The difference in overall incidence was not statistically significant (P=0.2368). There was no clear difference between the treatments with respect to individual preferred terms.
One patient in the 2 g mesalazine OD treatment group died during the study due to severe cerebral haemorrhage. This SAE was considered to be unlikely related to the study medication. An additional 5 patients from the 2 g mesalazine OD treatment group and 4 patients from the 1 g mesalazine TD treatment group experienced an SAE. All SAEs were not or unlikely related to the study medication. Five patients from the 2 g mesalazine OD treatment group and 1 patient from the 1 g mesalazine TD treatment group discontinued the study due to the experience of one or more AEs.
Overall, the most frequently reported treatment-emergent adverse events (TEAEs) were gastrointestinal disorders (abdominal pain, abdominal pain upper, diarrhoea and flatulence) and infections and infestations (bronchitis, gastroenteritis, nasopharyngitis and sinusitis).
The majority of the TEAEs was mild or moderate in intensity and considered by the investigator to be unrelated or unlikely related to the study medication. Per preferred term there was no clear difference between the treatment groups with respect to severity and relatedness to study medication.
With respect to the clinical laboratory parameters, vital signs and physical examination, no clinically relevant abnormalities were observed.

CONCLUSIONS:

The 2 g mesalazine OD dosing regimen was associated with a higher efficacy and a higher acceptability compared to the 1 g mesalazine TD dosing regimen. Compliance differences in the advantage of the OD regimen were small and did not reach statistical significance when objectively measured. VAS score differences were also small, but statistically significant at all time points. With regard to the primary efficacy outcome, remission rate, the 2 g mesalazine OD dosing regimen was not only non-inferior, but even significantly better than the 1 g mesalazine TD dosing regimen.

The oral administration of 2 g mesalazine OD as well as 1 g mesalazine TD for 12 months was safe and well tolerated by male and female adult patients diagnosed with mild to moderate quiescent UC.