SYNOPSIS

TITLE OF TRIAL

Multicentre, controlled, randomised, investigator-blinded, comparative study of oral **M**esalazine 4 g per day **O**nce daily versus 4 g per day in **T**wo divided doses in patients with active **U**lcerative coliti**S** (**MOTUS**)

SIGNATORY INVESTIGATOR(S)

[redacted]

TRIAL SITE(S)

44 centres in 4 countries: Belgium, France, Netherlands, United Kingdom.

PUBLICATION (REFERENCE)

Flourié B, Hagège H, Tucat G, Maetz D, Hébuterne X, Kuyvenhoven JP, et. al; MOTUS study investigators. Randomised clinical trial: once- vs. twice-daily prolonged-release mesalazine for active ulcerative colitis. Aliment Pharmacol Ther. 2013 Apr;37:767-75.

TRIAL PERIOD	**CLINICAL PHASE**
First patient first visit: 10-Nov-2008 Last patient last visit: 21-Jun-2010	Phase IIIb

OBJECTIVES

Primary Objective

To demonstrate that mesalazine per os (po) 4 g per day once daily (QD) was non-inferior to the reference regimen, mesalazine po 4 g per day in two divided doses (BID) (2 x 2 g per day), in patients with active ulcerative colitis (UC) treated for 8 weeks, in terms of remission evaluated with the Ulcerative Colitis Disease Activity Index [UC-DAI] score ≤1. Both treatment groups received a daily enema containing 1 g of mesalazine at bedtime during the initial 4 weeks.

Secondary Objectives

To compare the following between the two groups:

- Compliance
- Clinical remission at Week 4 and Week 8
- Clinical variables improvement (stool frequency and bloody stools) at Week 4, 8 and 12 separately
- Treatment failure rates at Week 4 and Week 8
- Time to remission according to patient's diary (normal stool frequency and cessation of bleeding)
- Time to cessation of bleeding
- Improvement at Week 4 and 8 based on UC-DAI score
- Endoscopic assessment at Week 0 and Week 8
- Acceptability of the treatment

- Safety
- Proportion of patients staying in clinical remission at Week 12.

ENDPOINTS

Primary Endpoint

Remission after 8 weeks of treatment, defined as UC-DAI score ≤1.

Secondary Endpoints

Comparison of the following items between the two groups:

- Compliance at Week 8
- Clinical remission at Week 4, Week 8 and Week 12
- Treatment failure rates at Week 4 and Week 8 defined as the need for other treatment (i.e steroids, immunosuppressive or immunomodulating drugs) than those allowed by the protocol. The need for other treatment was judged by investigators. Treatment failure was counted as non-remission.
- Clinical variables (stool frequency and bloody stools) at Week 4, 8 and 12 separately
- Time to remission according to patient's diary (normal stool frequency and cessation of bleeding).
- Time to cessation of bleeding
- Improvement at Week 4 and 8 based on UC-DAI score
- Endoscopic assessment at Week 0 and Week 8
- Acceptability of the treatment at Week 4 and 8
- Proportion of patients staying in clinical remission at Week 12
- Safety

METHODOLOGY

Randomised, investigator-blinded, controlled, parallel-group, multicentre, non-inferiority trial.

NUMBER OF SUBJECTS

A total of 398 patients (199 per treatment group) were planned for this non-inferiority trial. Patient disposition in the trial is shown below.

	QD		BID		Total	
	N	(%)	N	(%)	N	(%)
Screened patients					215	(100%)
Reason for screening failure						
- Patient is not fulfilling inclusion/exclusion criteria					5	(2.3%)
- Patient withdrew consent					1	(0.5%)
- Other					3	(1.4%)
Randomised patients	102	(49.5%)	104	(50.1%)	206	(100%)
Safety Analysis Set	102	(50.5%)	100	(49.5%)	202	(98.1%)
ITT Analysis Set	101	(50.0%)	101	(50.0%)	202	(98.1%)
mITT Analysis Set	89	(44.1%)	90	(44.6%)	179	(88.6%)
Per Protocol Set	79	(39.1%)	77	(38.1%)	156	(77.2%)
Reason for withdrawal before Visit 3:						
- Insufficient response	2	(2.0%)	1	(1%)	3	(1.5%)
- Worseneing of UC	1	(1.0%)	2	(1.9%)	3	(1.5%)
- AE	2	(2.0%)	3	(2.9%)	5	(2.4%)
- SAE	2	(2.0%)	1	(1.0%)	3	(1.5%)
- Patient lost to follow up	1	(1.0%)	1	(1.0%)	2	(1.0%)
- Other reasons	4	(4.0%)	5	(4.8%)	9	(4.4%)

MAIN CRITERIA FOR INCLUSION/EXCLUSION

The patient population was selected to include patients that were 18 years or over with relapsing mild to moderate UC. Patients with a newly diagnosed or relapsing disease, and with a disease extension beyond the rectum and a UC-DAI score between 3 and 8 in the 15 days before inclusion, were included.

Patients that in the previous year had failed to respond to steroids and were non-responsive to rectal 5-ASA therapy, or to oral 5-ASA therapy (>3 g/day for induction) were not to be included.

INVESTIGATIVE MEDICINAL PRODUCTS

Test regimen

Oral Mesalazine

Pentasa 2 g Sachet prolonged release granules (95% load granules) 4 g/day po once daily (QD), in the morning, for 8 weeks

Batch numbers BB0764C and BB0765C

Enema

1 g of mesalazine rectal suspension at bedtime during the initial 4 weeks

Reference regimen

Oral Mesalazine

Pentasa 2 g Sachet prolonged release granules (95% load granules) 4 g (2 x 2 g)/day po, (BID), once in the morning and once in the evening, for 8 weeks.

Batch number BC0554A

Enema

1 g of mesalazine rectal suspension at bedtime during the initial 4 weeks

DURATION OF TREATMENT

8 weeks.

STATISTICAL METHODS

The Screened Population

The Screened population included all patients who entered the trial.

The Randomised Population

The Randomised population included all patients who were randomised to investigational medicinal product (IMP).

The Safety Population

The Safety population included all patients who received at least one dose of IMP.

The Intention-To-Treat Efficacy Population

The Intention-To-Treat (ITT) efficacy population included all randomised patients who received at least one dose of IMP, evaluated for Last Observation Carried Forward (LOCF) and for Observed Cases (OC).

Modified ITT Analysis Set

The modified ITT (mITT) population included all patients in the ITT population having evaluable UC-DAI score at Visit 3 (Week 8)

The Per-Protocol Efficacy Population

The Per-Protocol (PP) efficacy population included all patients in ITT population without any major protocol deviation, evaluated for LOCF and for OC.

Quantitative variables were summarised in tables displaying sample sizes, means, standard deviations, medians and percentiles when appropriate, and extreme values. Qualitative variables were described in terms of frequencies and percentages of the number of individuals examined.

For the primary efficacy endpoint the non-inferiority of the 4 g/ day QD regimen was assessed by calculating the 95% two-sided Confidence Interval (CI) of the difference in remission rates between the QD and BID regimen for the ITT, mITT and PP; LOCF. CI was adjusted on country and computed using Mantel-Haenszel weights. The 4 g/day QD regimen would be non-inferior to the 4 g/day BID regimen if the lower limit of this CI was greater than –15%.

Secondary efficacy endpoints were summarised for the ITT (OC and LOCF) population using descriptive statistics and compared between treatment groups using Cochran-Mantel-Haenszel chi-square d tests adjusted on country (categorical variables) or analyses of variance with or without repeated measures with country as cofactor.

Time to remission according to patient’s diary and time to cessation of bleeding defined as the time between

the first dose of IMP and the first bleeding free day were compared between treatment groups using survival analysis adjusted by country (Cox model).

Clinical remission at Week 4, 8 and 12 (defined as normalization of stool frequency, disappearance of bleeding stools and no active disease at Physicians Global Assessment), endoscopic remission at Week 8, mucosal healing based on UC-DAI index (endoscopic sub-score ≤1) at Week 8 and complete remission (UC-DAI score=0) at Week 8 were submitted to the same analysis as the primary analysis computing a two-sided 95% CI of the difference between treatments after adjustment on country.

Correlation coefficients between compliance and other secondary efficacy variables were computed, both groups combined. To measure the strength of the association between the compliance level and quantitative variables, Spearman's rank correlation coefficient were computed. For qualitative variables, the correlation ratio was used.

EFFICACY RESULTS

The primary efficacy endpoint of the trial was the rate of remission (UC-DAI score ≤1) at Week 8 of treatment assessed in ITT, mITT and PP populations. Despite the actual sample size being smaller than that planned, non-inferiority was shown in the three statistical analysis subsets. With remission rates of:

- 52.1% in the QD group and 41.8% in the BID group, 95% CI: [-3.4 ; 24.1] in the ITT population
- 58.8% in the QD group and 46.8% in the BID group, 95%CI: [-2.6 ; 26.6] in the mITT population
- 61.0% in the QD group and 48.3% in the BID group, 95%CI: [-2.7 ; 28.2] in the PP population,

the analysis supported non-inferiority of the 4 g/day QD regimen, compared to the 4 g/day BID regimen.

PENTASA 4 g/day (QD) was non-inferior, as well as consistently numerically superior to PENTASA 4 g/day (BID) in all secondary efficacy analyses. The QD regimen was non-inferior for rates of patients achieving clinical remission at:

- Week 4 (clinical remission rate varied from 39.8% to 43.8% in QD group compared to 27.6% to 30.8% in BID group)
- Week 8 (clinical remission rate varied from 45.1% to 50.3% in QD group compared to 40.8% to 44.3% in BID group)

Furthermore, the QD regimen was non-inferior in:

- Rates of patients staying in clinical remission at Week 12 (92.4% in the QD group *versus* 79.4% in the BID group)
- Rates of complete remission at Week 8 (varied from 31.1% to 35.5% in QD group *versus* from 26.1% to 29.2% in BID group)
- Rate of endoscopic remission (Rachmilewitz score <4) at Week 8 (varied from 62.2% to 70.2% in QD group *versus* from 54.4% to 61.1% in BID group).

In some secondary efficacy analyses, the QD regimen was superior to the BID regimen:

- Normal stools were more frequent at Week 4 (p=0.0133),
- Improvement at Week 8 (decrease of the UC-DAI score of 2 points or more) was more frequent (p=0.0148),
- Time to remission was shorter (p=0.0416),

- Endoscopic Rachmilewitz score was improved at Week 8 (p=0.0300),
- Mucosal healing rates at Week 8 were higher according to UC-DAI index (p=0.0069)

Treatment compliance was similarly high in both treatment groups.

SAFETY RESULTS

Similar proportions of patients in both treatment groups - approximately one-third overall - had adverse events (AEs), and treatment-emergent adverse events (TEAE), during the trial (Safety population). The most frequently observed TEAEs were *mild* or *moderate* gastrointestinal disorders, in <10% of the patients.

No death occurred in the trial. Ten serious AEs (SAEs) were reported in 8 patients; 4 of these SAEs were considered *possibly* or *probably* related to IMP (one patient in each treatment group). Over the course of treatment, there were no meaningful differences between the treatment groups in mean clinical safety laboratory parameters, weight, and vital signs, as well as in the frequency of markedly abnormal changes in these safety variables. In conclusion, PENTASA 4 g/day (once-daily dosing) is considered safe and well tolerated.

CONCLUSIONS

In active, *mild* to *moderate* UC, oral PENTASA 4 g/day (once-daily dosing) was non-inferior to PENTASA 4 g/day (in two divided doses) in induction of remission, after 8 weeks of treatment.

Treatment compliance was similarly high with both the QD and the BID treatment regimen.

Both the QD and BID treatment regimens were safe and well tolerated.