Synopsis of study report: 187/2002
Location in Module 5:

Study Code:
BY217/FHP030

Report Version:
Version 2.0 (dated 02 March 2005)

Title of the study:

Anti-inflammatory activity of roflumilast. Study on the efficacy of oral roflumilast (500 µg/d) over 4 weeks on sputum neutrophils in chronic obstructive pulmonary disease (COPD) patients. A double-blind, randomized, placebo-controlled, 2-period, crossover study (BY217/FHP030)

Study center(s): monocenter study:
Leiden University Medical Center, NL-2300 RC Leiden, the Netherlands

Publication (reference): Not applicable

Studied period (years): 23 January 2001 (first patient in) –21 June 2002 (last patient out)

Clinical phase: IIa

Objectives: To investigate the anti-inflammatory effects of a 4-week treatment with roflumilast 500 µg once daily (od) as versus placebo (2-period crossover design) in patients with COPD

Methodology: Randomized, double-blind, placebo-controlled, 2-period crossover design. Amongst others, all steroids were withdrawn 4 weeks and long-acting β_2-agonists 14 days prior to study start. After the single-blind baseline period (placebo), patients who met the randomization criteria (visit V0) were randomly assigned to one of the following treatment sequences:

Sequence	n	Treatment period 1	Treatment period 2
Sequence 1:	21	Roflumilast 500 µg od (Test)	Placebo od (Reference)
Sequence 2:	20	Placebo od (Reference)	Roflumilast 500 µg od (Test)

Od = Once daily

The 2 treatment periods were divided by a washout period of 4-6 weeks.

The following measurements were performed during baseline and both treatment periods:

Activities	Baseline (2 weeks)			Period 1 (4 weeks)					Washout Period	Period 2 (4 weeks)					F
	B0 d -14	B1 d -7	B2 d 0	V0 d 0	V1 d 7	V2 d 14	V3 d 21	V4 d 28		V5 d 0	V6 d 7	V7 d 14	V8 d 21	V9 d 28	
Written informed consent	X														
Physical examination/ Medical history	X													X	X*
Random to treatment				X											
Medication distribution	X			X	X	X	X			X	X	X	X		
ECG, BP, HR, laboratory	X	X*	X					X		X				X	X*
Lung funkt.: pre-bronchodil. Lung funkt.: post-bronchodil.	X X		X X		X	X	X	X X		X X	X	X	X	X X	
Bronchodilation-Test/ Reversibility documentation	X														
Induced sputum	X		X			X		X		X		X		X	
Blood withdrawal (biochem. marker)			X[1]		X[2]	X[2]	X[2]	X[2]		X[1]	X[2]	X[2]	X[2]	X[2]	
PK (1 sample)			X[1]		X[2]	X[2]	X[2]	X[2]		X[1]	X[2]	X[2]	X[2]	X[2]	
Med. intake at study center					X	X	X	X			X	X	X	X	
Compliance check		X*	X		X	X	X	X			X	X	X	X	
Questions on AEs	X	X*	X		X	X	X	X		X	X	X	X	X	
Evaluation excape criteria		X*	X		X	X	X	X		X	X	X	X	X	
Diary card/instruction sheet	X	X*		X	X	X	X	X		X	X	X	X	X	
Current smoking status	X	X*	X		X	X	X	X		X	X	X	X	X	

B0 : at least 4 weeks before V0
PK = single pharmacokinetic measurement for compliance check
X* if applicable

Between Period 1 and 2: Washout-period: 28 ? x ? 42 days
[1] pre-dose value
[2] 1 h after drug intake

Baseline period (2 weeks) visits B0 – if applicable B1 – and B2; Treatment period 1 (4 weeks) visit V0 – V4; Washout (4-6 weeks); Treatment period 2 (4 weeks) visit V5 – V9; Post study follow-up (F), if necessary

No. of subjects (total and for each treatment):

In total, 44 COPD patients were enrolled into the study, 41 of them were randomized.

Dataset	Total	Number of patients per sequence	
		Sequence 1	Sequence 2
		Roflumilast 500 µg od-Placebo	Placebo-Roflumilast 500 µg od
Full analysis set	41	21	20
Valid cases set	34	20	14

Diagnosis and criteria for inclusion and randomization:

Inclusion criteria

- History of COPD
- Age 45 to 75 years
- Pre-bronchodilator FEV1/FVC ≤ 70% and 35% ≤ FEV1%predicted ≤ 75% post-bronchodilator when salbutamol was withheld ≥ 6 hours and anticholinergics ≥ 8 hours
- Fixed airways obstruction, defined by < 12% or < 200 ml increase of initial values after administration of salbutamol (400 µg via MDI) within 3 months prior to B0 or at least at B0. Measurements of reversibility could slightly deviate from 200 ml (e.g. 220 ml) but not in the percentage criterion (< 12 %)
- Smoking history (≥ 10 pack years) and current smokers or ex-smokers (stable for at least 6 months prior to visit B0)
- Inflammatory status as determined by the evaluation of neutrophils in the sputum (sputum neutrophilia at baseline ≥ 45% of total non-squamous cells at B0)
- No change in the treatment in the last 4 weeks
- Patients in a stable clinical state (no exacerbation or history of upper airway infection 4 weeks prior to baseline visit)
- With the exception of COPD, patients were in good health

Randomization criteria

- Sputum neutrophilia at B0 and B2/V0 ≥ 45% of total non-squamous cells
- 35% ≤ FEV1%predicted ≤ 75% post-bronchodilator at visit B2/V0 (= time range reference value for the following visits) when salbutamol was withheld for ≥ 6 hours and anticholinergics for ≥ 8 hours
- FEV1 value pre-bronchodilator at visit B2/V0 was within a range of ± 15% of visit B0 value.

Test product: Roflumilast

Dose: 500 µg/tablet

Mode of administration: oral administration, once daily, in the morning

Batch No.: Batch 1: 499110 (S02330338); Batch 2: 101160 (S02330338)

Duration of treatment: 4 weeks

Reference product: Placebo

Dose: Not applicable

Mode of administration: oral administration, once daily, in the morning

Batch No.: Batch 1: 199110 (S02330169); Batch 2: 101160 (S02330169)

Criteria for evaluation:

Efficacy

The primary variable was the reduction in the proportion of sputum neutrophils of total non-squamous cell count after a 4-week treatment with roflumilast 500 µg od versus placebo.

Primary variable:

- Sputum neutrophils: period 1 (V4 vs B2/V0) versus period 2 (V9 vs V5)

Secondary variables were analyzed in analogy to the primary variable:

- Other sputum cells: eosinophils, macrophages, lymphocytes, bronchial epithelial cells
- Sputum neutrophils after a 2-week treatment (V2 vs B2/V0) and (V7 vs V5)
- Biochemical markers in sputum supernatant: neutrophil elastase, interleukin-8 (IL-8)
- Biochemical markers in blood: tumor necrosis factor alpha (TNFα), E-selectin
- Lung function variables: FEV1, FVC, FEF25-75%, PEF
- Use of rescue medication (descriptive)

Pharmacokinetics

- Evaluation of roflumilast as compliance check
- Evaluation of roflumilast N-oxide as compliance check

Safety

- Adverse Events (AEs)
- Laboratory work-up (clinical chemistry, hematology, urine analysis)
- Physical examination
- ECG (PQ-, QRS-, QT-, QTc, QTc(Bazett)- interval and Heart Rate)
- Blood pressure, Pulse rate

Statistical methods:

The primary variable was the proportion of sputum neutrophils of total non-squamous cells (%neutrophils). To evaluate the primary variable the log-transformed ratios (post/pre) were calculated per patient for both treatment periods: period 1 (V4/V0) and period 2 (V9/V5). Subsequently, the ratio of both treatment periods (Roflumilast/Placebo) was calculated and tested for superiority of roflumilast 500 µg od over placebo in an intention-to-treat analysis (ITT-analysis).

The assessment of superiority of a 4-week treatment of roflumilast 500 µg od over placebo was performed by a non-parametric intention-to-treat analysis with point estimate (Hodges-Lehmann) for the ratio of both treatment periods (Roflumilast/Placebo), and nonparametric 95%-confidence interval. In order to investigate the robustness of results a non-parametric per-protocol analysis was performed.

The ITT-analysis of the secondary efficacy variables was performed in an exploratory manner, and analyzed in the same way as the primary variable. For all markers of anti-inflammatory activity (sputum cells and biochemical markers in sputum supernatant and blood) the data were log transformed, and a multiplicative model was used.

The proportion of sputum neutrophils of total non-squamous cells (%neutrophils) after two weeks of treatment was evaluated in the same way as the primary variable, the log-transformed ratios (post/pre) were calculated per patient for both treatment periods: period 1 (V2/V0) and period 2 (V7/V5).

Lung function variables were analyzed using a parametric analysis and was based on the differences of both treatment period differences: period 1 (V4-V0) and period 2 (V9-V5).

Pharmacokinetic analyses of roflumilast and roflumilast N-oxide in plasma were performed using selective turbo ion spray liquid chromatography/tandem mass spectrometry assay (LC/MS/MS).

All safety variables were analyzed in a descriptive manner.

SUMMARY – CONCLUSIONS

In this 2-period crossover study the efficacy of a 4-week treatment with roflumilast 500 µg od versus placebo was investigated with respect to the reduction in the proportion of sputum neutrophils of total non-squamous cells (primary variable), other sputum inflammatory cells, biochemical markers in sputum supernatant and blood as well as lung function variables.

Pharmacokinetic results

Pharmacokinetic analysis of roflumilast and roflumilast N-oxide showed that with the exception of in total 2 study visits in 2 patients, all patients took the study drug according to the Study protocol. This was the same visit number (V6) for 2 patients (CRF Id #339 and #341), who attended the study center at the same date (25 April 2002). A possible explanation could be that the tubes were exchanged at the investigational site.

Efficacy results

Since neutrophils are the predominant inflammatory cells in the sputum of COPD patients, the effect of treatment with roflumilast 500 µg od versus placebo was evaluated using the proportion of sputum neutrophils of total non-squamous cells as a primary variable (%neutrophils).

The primary variable, %neutrophils, was not statistically significantly reduced after a 4-week treatment with roflumilast 500 µg od versus placebo. In ITT analysis there was no difference between roflumilast 500 µg od and placebo as evaluated by the point estimate with non-parametric 95% confidence interval 0.99 (0.89-1.13). This was confirmed by the PP-analysis.

Statistical analysis of proportion of sputum neutrophils of total non-squamous cells (%neutrophils) after a 4-week treatment with roflumilast 500 µg od versus placebo

Variable	Analysis	Roflumilast 500 µg od		Placebo		Non-parametric analysis Roflumilast/Placebo		
		Vstart	Vlast	Vstart	Vlast	N	Point estimate	95% CI
%neutrophils		N = 31	N = 31	N = 35	N = 35			
	ITT	75.00	73.40	74.20	74.80	30	0.99	0.89, 1.13
		N = 29	N = 29	N = 32	N = 32			
	PP	75.00	73.40	73.60	75.40	29	0.99	0.88, 1.14

Vstart, Vlast: paired start (V0 resp. V5) and end point visits (V4 resp. V9), summary statistics: medians
Point estimate (Hodges-Lehmann) with nonparametric 95%-CI (Moses)
Note: data have been log-transformed
ITT = Intention-to-treat analysis; PP = Per-protocol analysis; CI = Confidence Interval

The other sputum inflammatory cells (eosinophils, macrophages, lymphocytes, bronchial epithelial cells) were not statistically significantly reduced after a 4-week treatment with roflumilast 500 µg od as versus placebo.

The secondary variable sputum neutrophils after a 2-week treatment with roflumilast 500 µg od was not significantly reduced: point estimate 0.94 (95% CI 0.86-1.03).

The biochemical markers in sputum supernatant (neutrophil elastase, IL-8) and biochemical markers in blood (TNFα, E-selectin) were not statistically significantly reduced after a 4-week treatment with roflumilast 500 µg od as versus placebo.

Note that the point estimate for TNFα (0.78) points numerically in the direction indicating a reduction by roflumilast, and that the upper limit of the 95% confidence interval was with 1.02 only slightly above 1. This suggests that the level of TNFα was reduced after a 4-week treatment with roflumilast 500 µg od versus placebo.

Statistical analysis of biochemical markers in sputum supernatant after a 4-week treatment with roflumilast 500 µg od versus placebo (ITT)

Biochemical marker in sputum supernatant	Roflumilast 500 µg od		Placebo		Non-parametric analysis Roflumilast/Placebo		
	Vstart	Vlast	Vstart	Vlast	N	Point estimate	95% CI
Neutrophil elastase (µg/ml)	N = 34	N = 34	N = 35	N = 35			
	2.51	2.78	2.64	3.06	31	0.97	0.52, 1.74
IL-8 (pg/ml)	N = 33	N = 33	N = 37	N = 37			
	6813	7532	12034.60	9062.60	32	0.84	0.50, 1.36

Vstart, Vlast: paired start (V0 resp. V5) and end point visits (V4 resp. V9), summary statistics: medians
Point estimate (Hodges-Lehmann) with nonparametric 95%-CI (Moses)
Note: data have been log-transformed
IL-8 = Interleukin-8; CI = Confidence Interval; ITT = Intention-to-treat analysis

Statistical analysis of biochemical markers in blood after a 4-week treatment with roflumilast 500 µg od versus placebo (ITT)

Biochemical marker in blood	Rofumilast 500µg od		Placebo		Non-parametric analysis Roflumilast/Placebo		
	Vstart	Vlast	Vstart	Vlast	N	Point estimate	95% CI
TNFα (pg/ml)	N = 34	N = 34	N = 38	N = 38			
	8024.83	7633.25	8966.17	10030.83	31	0.78	0.57, 1.02
E-selectin (ng/ml)	N = 35	N = 35	N = 39	N = 39			
	48.55	48.60	51.90	47.55	34	1.01	0.94, 1.09

Vstart, Vlast: paired start (V0 resp. V5) and end point visits (V4 resp. V9), summary statistics: medians
Point estimate (Hodges-Lehmann) with nonparametric 95%-CI (Moses)
Note: data have been log-transformed
CI = Confidence Interval; ITT = Intention-to-treat analysis

The lung function variables FEV1 (post- and pre-bronchodilator), but not FVC, FEF25-75%, and PEF (all post-bronchodilator), showed a statistically significant improvement after a 4-week treatment with roflumilast 500 µg od versus placebo. The increase was 62 ml for post-bronchodilator FEV1, and 78 ml for pre-bronchodilator FEV1.

Statistical analysis of lung function variables after a 4-week treatment with roflumilast 500 µg od versus placebo (ITT)

Lung function variable	Roflumilast 500 µg od		Placebo		Parametric analysis Roflumilast – Placebo		
	Vstart	Vlast	Vstart	Vlast	N	Point estimate	95% CI
Post-bronchodilator	N = 34	N = 34	N = 38	N = 38			
FEV1 (L)	1.72	1.80	1.73	1.65	31	0.062	0.0063, 0.1170
Pre-bronchodilator	N = 36	N = 36	N = 39	N = 39			
FEV1 (L)	1.60	1.59	1.62	1.61	31	0.078	0.0156, 0.1411
Post-bronchodilator	N = 34	N = 34	N = 38	N = 38			
FVC (L)	3.55	3.57	3.37	3.39	31	0.087	-0.0194, 0.1931
Post-bronchodilator	N =34	N = 34	N = 38	N = 38			
FEF25-75% (L/s)	0.66	0.75	0.68	0.64	31	0.031	-0.0327, 0.0943
Post-bronchodilator	N = 34	N = 34	N = 38	N = 38			
PEF (L/min)	329.7	315.6	331.2	332.1	31	- 4.68	-22.207, 12.844

Vstart, Vlast: paired start (V0 resp. V5) and end point visits (V4 resp. V9), summary statistics: medians
Point estimates and two-sided 95%-CI (analysis of variance for the 2-period crossover design)
CI = Confidence Interval; ITT = Intention-to-treat analysis

Safety results:

During treatment, 36 out of 41 randomized patients reported a total of 164 AEs. Twenty-three patients reported AEs during both treatment periods. In total, twice as many AEs (109 AEs) were reported during treatment with roflumilast 500 µg od as versus placebo (55 AEs).

The most frequently reported AE in the total population were diarrhea (9%) and flu syndrome (9%), followed by headache (7%), cough increased (7%), and dyspnea (6%). The severity of diarrhea varied from mild to severe, and of flu syndrome from mild to moderate intensity.

The incidence rate of diarrhea, headache, nausea, and abnormal stools was higher during treatment with roflumilast 500 µg od versus placebo. These are recognized AEs associated with roflumilast and are already described in the Investigator's Brochure.

The incidence rate of respiratory related symptoms (flu syndrome, cough increased, upper respiratory infection, sputum increased and bronchitis) was higher during treatment with placebo versus roflumilast 500 µg od.

Frequency of AEs (≥ 4 AEs in one of the treatment periods), sorted by number of AEs during treatment with roflumilast 500 µg od

Adverse events (AEs) (symptoms according to Harts code)	Number (%) of AEs					
	Total		Roflumilast 500 µg od		Placebo	
Number of randomized patients	41		38		39	
Number of AEs	164		109		55	
Diarrhea	15	(9%)	13	(12%)	2	(4%)
Headache	12	(7%)	12	(11%)	-	
Flu syndrome	15	(9%)	8	(7%)	7	(13%)
Nausea	6	(4%)	6	(6%)	-	
Dizziness	8	(5%)	6	(6%)	2	(4%)
Cough increased	11	(7%)	6	(6%)	5	(9%)
Dyspnea	10	(6%)	6	(6%)	4	(7%)
Vomiting	6	(4%)	4	(4%)	2	(4%)
Abnormal stools	4	(2%)	4	(4%)	-	
Upper respiratory infection	9	(5%)	3	(3%)	6	(11%)
Sputum increased	8	(5%)	3	(3%)	5	(9%)
Bronchitis	7	(4%)	2	(2%)	5	(9%)

Most AEs during roflumilast 500 µg treatment (83%) were assessed by the investigator as 'unrelated' or 'unlikely' related to the study drug.

In total, the investigators assessed 18 AEs as 'likely' or 'definitely' related to roflumilast 500 µg od. Amongst them, the most frequent AEs were diarrhea (n = 5), headache (n = 3), and nausea (n = 3). The sponsor assessed another 6 AEs in 5 patients as 'likely' or 'definitely' related to the study drug, whereas the investigator assessed these AEs as 'unrelated' or 'unlikely' related to the study drug. Amongst them the most frequent AE was dizziness (n = 2). Diarrhea, headache, nausea, and dizziness are all recognized side effects of roflumilast (Investigator's Brochure).

There were no deaths and no other serious AEs. There were 11 AEs that led to premature discontinuation of the study experienced by 5 randomized patients (4 patients treated with roflumilast 500 µg od and 1 patient treated with placebo). Five of these 11 AEs (diarrhea twice, abdominal pain, dizziness and headache) were assessed as 'likely' or 'definitely' related to roflumilast by the investigator. These are all known side effects of roflumilast (see Investigator's Brochure).

Routine laboratory investigations, physical examination, ECG, blood pressure, and heart rate, measured during treatment, were not affected by the study medication.

Overall Conclusions:

Superiority of roflumilast 500 µg over placebo in reducing sputum neutrophils (primary variable) in this 2-period crossover study could not be demonstrated. There were no statistically significant between-treatment differences with regard to the other markers of anti-inflammatory activity: sputum inflammatory cells, and biochemical markers in sputum supernatant and blood.

Lung function FEV1 (pre- and post-bronchodilator) was statistically significantly improved after a 4-week treatment with roflumilast 500 µg od.

No major safety problems were seen during treatment with roflumilast 500 µg od in patients with COPD.

Addendum for Public Disclosure

Please note that this study result synopsis is presenting the results as pre-specified in the initial analyses plan of 2001. The same data set was also re-analysed evaluating all sputum inflammatory cells expressed as absolute numbers per gram of sputum and using current appropriate standard analyses methods applying a repeated measurements model including all measurements.