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Title: A 24 Week, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Oral Roflumilast (250 mcg or 500 mcg) Daily in Patients with Asthma		Version date:	02-Jan-2007
		INN:	Roflumilast
		Project No. / List No.:	BY217
		Compound No.:	B9302-107
		Batch No.: Roflumilast 500 mcg Roflumilast 250 mcg Placebo	 130220 330200 130280
Study Protocol No.:	**BY217/M2-012**	Development phase:	III
EudraCT No:	not applicable	Indication studied:	Asthma
Study initiation date:	27-Oct-2003	Date of early termination:	not applicable
Study completion date:	15-Sep-2005	Summary of modifications:	not applicable

Name and country of investigators:

171 centers in Argentina, Columbia, Mexico, Peru, and United States of America (USA) participated

Coordinating investigator:

[redacted] University of Wisconsin Medical School, Madison, WI 53792, USA (from 26-Jun-2006).

Name of sponsor's responsible medical officer:
Dr Dirk Bredenbröker, ALTANA Pharma AG (RCS/P2), Konstanz, Germany

Person(s) responsible for study report:
Dr Klaus Fichtner, ALTANA Pharma AG (RCO/R3), Konstanz, Germany

Sponsors contact persons:

See accompanying letter of the regulatory approval application

Statement of GCP compliance:

This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

Archiving responsibility for essential documents:
Department RCO/CT at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

2 Synopsis

Title of the study:
A 24 Week, Double-Blind, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Efficacy and Safety of Oral Roflumilast (250 mcg or 500 mcg) Daily in Patients with Asthma.

Investigator(s) and study center(s):
171 centers in Argentina (10), Columbia (3), Mexico (8), Peru (6), and United States of America (144).

Coordinating investigator(s):
[redacted] (as of 26-June-2006), University of Wisconsin Medical School, 600 Highland Avenue, Madison, WI, 53792, USA

Publication (reference): Not applicable.

Studied period: The study started (first patient enrolled) on 27-Oct-2003 and ended (last patient completed) on 16-Sep-2005.

Clinical phase: Phase III

Objectives:
Primary objective
The main objective of this study was to compare the effects of oral roflumilast od (once daily) with placebo on lung function in patients with asthma.

Secondary objectives
- to evaluate the effects of roflumilast od on symptoms of asthma including morning and evening peak expiratory flow, asthma symptoms severity score, and use of supplemental short-acting β-agonists (as recorded in electronic diaries), the number of exacerbations and health outcome measures;
- to evaluate the effects of roflumilast on other measurements of lung function as measured by spirometry;
- to investigate the safety and tolerability of roflumilast in patients with asthma;
- to characterize the pharmacokinetics of roflumilast and roflumilast-N-oxide in patients with asthma.

Methodology:
This was a multi-center, double-blind, placebo-controlled, randomized, three-arm, parallel-group comparison of roflumilast 500 µg od and roflumilast 250 µg od versus placebo od. The duration of the double-blind treatment period was 24 weeks after a single-blind run-in phase of 2 or 4 weeks in duration.

Patients who met screening criteria entered the single-blind run-in phase. All asthma controller medications were withdrawn following the Screening Visit and patients were

provided with roflumilast placebo. Patients received supplies of rescue medication (inhaled albuterol/salbutamol) for use as required during the run-in period.

At the Screening Visit, each patient was given an e-diary (electronic diary) to collect daily the daytime asthma symptom score, the nighttime asthma symptom score, the amount of rescue medication used, the PEF_{am} (morning peak expiratory flow) and PEF_{pm} (evening peak expiratory flow), the morning and evening FEV_1 (forced expiratory volume in one second), and study drug compliance.

Eligible patients were randomized within 2 or 4 weeks of screening in a 1:1:1 ratio to receive either, roflumilast 250 µg, roflumilast 500 µg or placebo, od. Patients continued to use albuterol/salbutamol rescue medication as needed following randomization.

During the 24-week double-blind treatment period, patients were evaluated at the investigator's clinic at regular intervals (at weeks 2, 4, 8, 12, 18, and 24). At each clinic visit, patients completed QoL (quality of life) questionnaires, spirometry was performed, e-diary entries were reviewed, and laboratory procedures and AE (adverse event) assessment were performed.

No. of patients (total and for each treatment) planned and analyzed:
It was planned to randomize 819 patients into the three treatment groups (273 patients allocated per treatment arm). The actual number of patients enrolled, randomized and included in the analysis is shown in the following table:

	Enrolled	Randomized	Safety set	Full analysis set	Valid cases set
Rof500		285	285	285	154
Rof250		284	284	284	168
Placebo		280	280	280	154
Total	2153	849	849	849	476

Rof250 = roflumilast 250 µg once daily, Rof500 = roflumilast 500 µg once daily.

Diagnosis and main criteria for inclusion:
Inclusion into baseline period
Patients had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

- men and women aged 18 through 70 years of age;
- the patient had received verbal and written study information, all questions had been answered satisfactorily and a consent form had been personally signed and dated by the patient and the investigator or designated study staff;
- the patient had a diagnosis of persistent bronchial asthma with reference to the GINA [Global Initiative for Asthma] guidelines (for Argentina only, this was modified by protocol amendment to "**mild** persistent bronchial asthma");
- the patient had a FEV_1 between 60 and 90% predicted at Visit 1 when albuterol/salbutamol (rescue medication) was withheld for at least 4 h prior to the measurement;

- there had been no change in asthma treatment within 4 weeks prior to Visit 1;
- patient was a non-smoker or ex-smoker (for 12 months or longer);
- in the investigator's judgment, the patient was able and willing to comply with study visits and procedures (including laboratory tests, lung function tests), plus accurate and timely completion of an electronic daily study diary;
- patients formerly (ie before implementation of protocol amendment #5) enrolled in the study but withdrawn without being randomized and allocated double-blind medication could be considered for re-entry in the study provided that they satisfied the modified randomization criteria resulting from protocol amendment #5.

Inclusion into the treatment period (randomization criteria)

Patients had to meet all of the following randomization criteria to be eligible for randomization into the double-blind treatment period at Visit 3:

- FEV_1 was between 60 and 80% predicted when albuterol/salbutamol (rescue medication) was withheld for at least 4 h prior to the measurement. To allow for variability in the lung function tests, patients who met all entrance criteria except for FEV_1 between 60 and 80% of the predicted value when albuterol/salbutamol (rescue medication) was withheld for at least 4 h prior to the measurement, could repeat Visit 3 within 3 d. If repeat spirometry demonstrated FEV_1 between 60% and 80% predicted then the patient could enter the study;
- the patient had a positive reversibility test at Visit 1 or Visit 2 defined as an increase of initial FEV_1 ≥12% from 15 to 30 min after inhalation of 2 to 4 puffs of an albuterol/salbutamol MDI (metered dose inhaler);
- the patient had used ≥2 puffs/d and <8 puffs/d albuterol/salbutamol, rescue medication, on at least 6 of 14 d (42%) immediately prior to randomization;
- the patient's asthma summary symptom total score (daytime and nighttime) was ≥2 (out of a maximum of 8) on at least 6 of 14 d (42%) immediately prior to randomization;
- there had been no exacerbation during run-in requiring additional therapy beyond the run-in period from the date of screening;
- there had been at least 14 d in the run-in period from the date of screening;
- the patient had been compliant in completing the e-diary during the single-blind run-in period. A minimum of at least 10 of 14 d of complete and accurate diary data had to be present immediately prior to randomization;
- the patient had been compliant with taking run-in study medication (roflumilast placebo). Patient had been at least 80% compliant during the 14 d immediately prior to randomization with reference to information recorded in the electronic diary;
- the patient still met all other relevant inclusion and exclusion criteria.

Test product, dose, mode of administration, batch no.: roflumilast, one tablet of 500 µg od in the morning**,** oral administration, batch no. 130220 **or** roflumilast, one tablet of 250 µg od in the morning, oral administration, batch no. 330200.

Reference product, dose, mode of administration, batch no.: placebo, one tablet od in the morning, oral administration, batch no.130280.

Duration of treatment: 4 weeks in baseline period, followed by 24 weeks in the double-blind treatment period.

Criteria for evaluation:

Primary efficacy variable

- the primary efficacy variable was FEV_1 [L] (mean change in FEV_1 from baseline during the treatment period).

Key secondary efficacy variables

- PEF_{am};
- rescue medication intake;
- total asthma symptom score;
- time to first severe exacerbation during treatment period.

Other secondary efficacy variables

- lung function assessments from on-site spirometry: FVC (forced vital capacity), $FEF_{25-75\%}$ (forced expiratory flow over 25% to 75% of vital capacity), PEF (peak expiratory flow);
- lung function assessments from e-diary: PEF_{pm}, PEF_{dv} (diurnal variability of PEF);
- asthma e-diary assessments: daytime and nighttime asthma symptom score, symptom-free days, rescue medication-free days;
- exacerbation variables: time to first exacerbations requiring oral or parenteral steroid treatment (EROS), proportion of patients with severe exacerbations, proportion of patients with EROS, overall number of severe exacerbations, overall number of EROS;
- quality of life questionnaires: AQLQ(S) (Asthma Quality of Life Questionnaire, standardized version: overall, activity limitation, symptoms, emotional function, environmental stimuli scores), ACQ (Asthma Control Questionnaire: overall score).

Safety variables

- AEs;
- laboratory assessments (biochemistry, hematology and urinalysis);
- vital signs and ECG (electrocardiogram).

Statistical methods:

A hierarchical testing was applied; therefore no multiplicity adjustment was necessary. The primary comparison was a test for superiority of roflumilast 500 µg od vs placebo with respect to the primary variable FEV_1, followed by a test for superiority of the key secondary variables in a hierarchical order. After superiority of the highest dose was shown for these variables, testing was continued for roflumilast 250 µg od vs placebo, and also for roflumilast 500 µg od vs roflumilast 250 µg, for the same parameters.

The primary analysis was performed using a repeated measurement ANCOVA (analysis of covariance). This model included all observed measurements from the scheduled visits of the treatment period. The dependent variable was the change from baseline at each scheduled visit. Treatment, pooled region/country, sex, time, baseline smoking status, baseline asthma severity class according to GINA, treatment-by-time interaction, baseline age, baseline FEV_1) were included as factors and covariables in the ANCOVA model. The correlation structure in the visit timepoints was specified to be unstructured, allowing for the greatest flexibility in estimation.

The repeated measurements analysis ANCOVA including all visits/weeks after the randomization visit/week to the final visit/week (or early termination) was performed for FEV_1, PEF_{am}, total asthma symptom score, rescue medication intake, FVC, $FEF_{25-75\%}$, PEF, PEF_{pm}, PEF_{dv}, daytime and nighttime asthma symptom score, overall AQLQ, AQLQ domain scores and ACQ overall score.

The Mann-Whitney U-Test was used to test the between-treatment differences of PEF diurnal variability, percent of rescue-medication-free days, and percent of symptom-free days. Wilcoxon's signed-rank test was used to analyze the within-treatment differences of PEF_{dv}.

The log-rank test was used to test time to first severe asthma exacerbation, and time to first EROS. The Cochran-Armitage test for trend was used to test for the proportion of patients with at least one severe exacerbation and at least one EROS. The number of severe exacerbations and EROS was analyzed using the Wilcoxon rank-sum test.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

The demographic data of patients in the full analysis set are summarized below. There were no major differences between the three treatment groups.

Demographic and other baseline characteristics by treatment (full analysis set)

		Full analysis set		
		Rof500 (N = 285)	**Rof250 (N = 284)**	**Placebo (N = 280)**
Age [years]	Median (range)	40.0 (18, 69)	40.0 (18, 69)	39.0 (18, 70)
Weight [kg]	Mean ± SD	81.34 ± 22.45	80.07 ± 21.47	80.78 ± 21.73
Height [cm]	Mean ± SD	167.12 ± 9.94	166.04 ± 10.50	165.87 ± 10.44
Sex [n (%)][a]	Female	169 (59.3)	183 (64.4)	173 (61.8)
	Male	116 (40.7)	101 (35.6)	107 (38.2)
Race [n (%)][a]	Asian	4 (1.4)	3 (1.1)	2 (0.7)
	Black	27 (9.5)	18 (6.3)	20 (7.1)
	White	174 (61.1)	177 (62.3)	168 (60.0)
	Other	80 (28.1)	85 (29.9)	90 (32.1)
	Not assessed	0 (0.0)	1 (0.4)	0 (0.0)
Asthma severity (GINA) [n (%)]	Intermittent	0 (0.0)	0 (0.0)	0 (0.0)
	Mild persistent	0 (0.0)	0 (0.0)	0 (0.0)
	Moderate persistent	13 (4.6)	19 (6.7)	12 (4.3)
	Severe persistent	262 (91.9)	256 (90.1)	259 (92.5)
	Missing	10 (3.5)	9 (3.2)	9 (3.2)
ICS pre-treatment [n (%)]	Not pre-treated with ICS	214 (75.1)	209 (73.6)	229 (81.8)
	Pre-treated with ICS	71 (24.9)	75 (26.4)	51 (18.2)
Smoking status [n (%)][a]	Non-smoker	231 (81.1)	225 (79.2)	222 (79.3)
	Ex-smoker	54 (18.9)	59 (20.8)	58 (20.7)
Pack years [n]	Mean ± SD	6.4 ± 8.0	7.7 ± 10.4	8.6 ± 11.9
FEV_1 [L]	Mean ± SD	2.353 ± 0.555	2.311 ± 0.559	2.358 ± 0.617
FEV_1 predicted [%]	Mean ± SD	69.9 ± 7.4	70.1 ± 6.8	70.6 ± 7.3
FEV_1 reversibility [%]	Mean ± SD	23.0 ± 13.8	23.0 ± 12.8	22.1 ± 13.2
FEV_1 reversibility [mL]	Mean ± SD	529.3 ± 294.9	534.6 ± 294.7	523.7 ± 316.0
PEF_{am} [L/min]	Mean ± SD	345.7 ± 112.2	336.3 ± 117.2	331.1 ± 115.3
Asthma symptom score	Median (range)	2.667 (0.86, 6.00)	2.857 (0.57, 7.00)	2.714 (0.83, 7.00)
Rescue medication intake [puffs/d]	Median (range)	3.714 (0.86, 8.86)	3.429 (0.57, 9.00)	3.667 (0.29, 11.43)

[a] Percentages are based on the number of patients in a treatment group.
FEV_1 = forced expiratory volume in 1 second, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroids, PEF_{am} = morning PEF, Rof250 = roflumilast 250 µg od, Rof500 = roflumilast 500 µg od, n = number of patients with data available, SD = standard deviation.

Efficacy results

If not indicated otherwise, results of the ITT analysis, which was the primary analysis in this superiority study, are reported.

Primary efficacy variable

Mean change from baseline for FEV_1 (repeated measurements analysis)

The analysis of the primary variable, mean change from baseline in FEV_1 during the double-blind treatment period, showed improvements in all three treatment groups (0.186 L with roflumilast 500 µg, 0.203 L with roflumilast 250 µg and 0.135 L with placebo, ITT). For the difference between treatment groups for change in FEV_1 during 24-weeks of treatment,

roflumilast 500 µg was not shown to be statistically significantly superior to placebo (0.051 L, 95% CI: -0.016, 0.118 L, one-sided p-value = 0.0661, ITT). For the PP analysis, however, the difference was statistically in favor of roflumilast 500 µg over placebo.

Change from baseline in FEV_1 [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN				Mean at Baseline	Within-treatment difference	
		n	n obs		LSMean ± SE	95% CI
ITT	Rof500	257	1188	2.341	0.186 ± 0.038	0.112, 0.260
	Rof250	257	1296	2.302	0.203 ± 0.037	0.131, 0.276
	Placebo	256	1232	2.348	0.135 ± 0.038	0.060, 0.209
PP	Rof500	140	629	2.364	0.160 ± 0.045	0.072, 0.248
	Rof250	156	762	2.300	0.155 ± 0.042	0.073, 0.236
	Placebo	141	634	2.365	0.049 ± 0.043	-0.036, 0.134

BETWEEN					Difference Test - Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	1-sided p-value[a]	2-sided p-value[b]
ITT	Rof500	Placebo	257	256	0.051 ± 0.034	-0.016, 0.118	0.0661	0.1323
	Rof250	Placebo	257	256	0.069 ± 0.034	0.002, 0.135	0.0211	0.0423
	Rof500	Rof250	257	257	-0.017 ± 0.034	-0.084, 0.049	0.6958	0.6084
PP	Rof500	Placebo	140	141	0.111 ± 0.042	0.029, 0.194	0.0042	0.0085
	Rof250	Placebo	156	141	0.106 ± 0.040	0.027, 0.186	0.0045	0.0090
	Rof500	Rof250	140	156	0.005 ± 0.041	-0.075, 0.085	0.4491	0.8982

[a] One-sided p-value, significance level 2.5%
[b] Two-sided p-value, significance level 5%
Superiority can be concluded if the lower bound of the 95% confidence interval is greater than 0.
Baseline was defined as technically acceptable value at Visit 3.
CI = confidence interval, Rof500 = roflumilast 500 µg od, Rof250 = roflumilast 250 µg od, FEV_1 = forced expiratory volume in 1 s, LS = least squares, n = number of patients with data available, n obs = number of observations, SE = standard error of the LSMean.

Since FEV_1 was not proven to be statistically superior for roflumilast 500 µg compared with placebo, the hypothesis testing cascade was stopped, and all further hypotheses of key secondary and secondary variables were conducted in an exploratory manner.

The difference between treatment groups for change in FEV_1 was statistically significant in favor of roflumilast over placebo for roflumilast 250 µg (0.069 L, 95%CI: 0.002, 0.135 L, one-sided p-value = 0.0211, ITT). This was confirmed by the PP analysis.

Secondary variables

Key secondary variables

Mean change from baseline for PEF_{am} (repeated measurements analysis)

There was a worsening in PEF_{am} in all treatment groups (-0.370 L/min, -2.044 L/min, -5.378 L/min, for roflumilast 500 µg, roflumilast 250 µg, and placebo, respectively). The worsening of PEF_{am} for roflumilast 500 µg and roflumilast 250 µg compared with placebo was not statistically significant.

Mean change from baseline for rescue medication intake (repeated measurements analysis)

There were reductions in rescue medication intake in all three treatment groups. The magnitude of the changes was greater for both roflumilast treatment groups (-0.560 puffs/d, -0.545 puffs/d for roflumilast 500 µg and 250 µg, respectively) than for the placebo group (-0.200 puffs/d). Statistically significant between-treatment differences were seen for both roflumilast treatments compared with placebo (roflumilast 500 µg vs placebo: -0.360, one-sided p-value = 0.0204; roflumilast 250 µg vs placebo: -0.345, one-sided p-value = 0.0237). For the PP analysis, the roflumilast 250 µg vs placebo comparison was statistically significant in favor of roflumilast over placebo.

Mean change from baseline for total asthma symptom score (repeated measurements analysis)

There were large within-treatment reductions (improvements) in total asthma symptom score in all three treatment groups. The magnitude of the changes was similar for all treatment groups (-0.826, -0.833, -0.803, for roflumilast 500 µg, roflumilast 250 µg and placebo, respectively). There were no statistically significant between-treatment differences for total asthma symptom score during 24 weeks of treatment.

Time to first severe exacerbation (log-rank test)

The numbers and percentages of patients experiencing severe asthma exacerbations were similar in all three treatment groups (98 [34.4%] in the roflumilast 500 µg group, 103 [36.3%] in the roflumilast 250 µg group, and 111 [39.6%] patients in the placebo group). The median time to onset of the first severe asthma exacerbation was longer in patients treated with roflumilast (52.5 d and 50.0 d for roflumilast 500 µg and 250 µg, respectively) than in patients treated with placebo (31.0 d). There were no statistically significant differences between roflumilast treatments and placebo in time to first severe exacerbation. For the PP analysis, the time to first severe exacerbation following treatment with roflumilast 500 µg was significantly longer than after treatment with placebo.

Other secondary variables

Mean change from baseline for FVC, PEF, and $FEF_{25-75\%}$ (spirometry, repeated measurements analysis)

There were large within-treatment increases in PEF in all three treatment groups. FVC and $FEF_{25-75\%}$ also increased during the treatment period, with greater increases in the roflumilast groups. There were no statistically significant between-treatment differences for PEF, FVC or $FEF_{25-75\%}$. For the PP analysis, the increases in PEF and FVC were significantly different for the comparisons of roflumilast 500 µg and placebo, and roflumilast 250 µg and placebo.

Mean change from baseline for PEF_{pm} and PEF_{dv} (diary, repeated measurements analysis)

Similar to the results for PEF_{am}, there was a worsening in PEF_{pm} in all treatment groups, except for roflumilast 250 µg where an improvement in PEF_{pm} was shown. There was little change in PEF_{dv} during the study for any of the treatment groups. There were no statistically significant differences between roflumilast treatments and placebo in PEF_{pm} or PEF_{dv}.

Mean change from baseline for individual asthma symptom scores (repeated measurements analysis)

There were large reductions (improvements) in both daytime and nighttime asthma symptom score in all three treatment groups. The magnitude of the changes was similar for all treatment groups. There were no statistically significant differences between roflumilast treatments and placebo for either daytime or nighttime asthma symptom scores.

Percentage of asthma symptom-free and rescue medication-free days (Mann-Whitney U-Test)

The median percentage of asthma symptom-free days and rescue medication-free days was higher in the roflumilast treatment groups than in the placebo group. The between-treatment difference for roflumilast 500 µg and placebo was not statistically significant. There was a statistically significant between-treatment difference for rescue medication-free days in favor of roflumilast 250 µg over placebo (one-sided p-value = 0.0128). Results were generally similar for the PP analysis although there were no statistically significant between-treatment differences.

Time to first EROS (log-rank test)

During the treatment period, fewer patients in the roflumilast treatment groups experienced an EROS than patients in the placebo group. The median time to onset of the first EROS was longest in patients treated with roflumilast 500 µg (43.0 d); roflumilast 250 µg (35.0 d) also showed an improvement over placebo (30.0 d). There were no statistically significant differences between roflumilast treatments and placebo in time to first EROS.

Mean change from baseline for quality of life (assessed by AQLQ(S), repeated measurements analysis)

There were improvements for AQLQ(S) overall score and individual domain scores in all three treatment groups with placebo generally showing the smallest increases. The improvements were numerically small and most did not reach the minimum important difference of 0.5. There were no statistically significant between-treatment differences for AQLQ(S) overall score or any of the individual domain scores.

Mean change from baseline for quality of life (assessed by ACQ, repeated measurements analysis)

There were within-treatment reductions (improvements) for ACQ overall score in all three treatment groups. The magnitude of the changes was similar for all treatment groups, but numerically small and unlikely to be clinically relevant. There were no statistically significant between-treatment differences for ACQ overall score.

Safety results:

Adverse events

The following table summarizes the treatment-emergent AEs reported during the double-blind treatment period:

Treatment-emergent adverse events (safety set)

	Rof500 (N = 285)	Rof250 (N = 284)	Placebo (N = 280)	Total (N = 849)
Number of patients (%)[a] with:				
AEs	185 (64.9)	181 (63.7)	172 (61.4)	538 (63.4)
SAEs	10 (3.5)	8 (2.8)	6 (2.1)	24 (2.8)
AEs with causality[b] suggested by the investigator	62 (21.8)	35 (12.3)	28 (10.0)	125 (14.7)
AEs leading to discontinuation	39 (13.7)	28 (9.9)	25 (8.9)	92 (10.8)
AEs not yet known to be recovered	20 (7.0)	31 (10.9)	20 (7.1)	71 (8.4)
Changes in study medication due to AEs	8 (2.8)	6 (2.1)	0 (0.0)	14 (1.6)

[a] Percentages are based on the total number of patients in a treatment group.
[b] AEs assessed as 'related' to the study medication by the investigator.
AE = adverse event, N = number of patients in each treatment group, %: percent of patients n with at least one event in the category based on N, Rof500 = roflumilast 500 µg od, Rof250 = roflumilast 250 µg od, SAE = serious adverse event.

During the double-blind treatment period, 185 (64.9%) patients in the roflumilast 500 µg group, 181 (63.7%) patients in the roflumilast 250 µg group, and 172 (61.4%) patients in the placebo group experienced AEs. Most frequently, AEs were from the 'infections and infestations', 'gastrointestinal disorders', and 'nervous system disorders' SOCs, with the latter two categories showing a trend for a reduction in the frequency of associated AEs with reducing dose of roflumilast. In all treatment groups the most frequently reported AE was headache. The percentage of patients with AE headache, diarrhoea, nausea, dizziness, insomnia and fatigue tended to decrease as the dose of roflumilast decreased. This in line with the known safety profile of roflumilast as outlined in the Investigator's Brochure. Most other AEs were distributed evenly over the three treatment groups.

Most AEs were moderate in intensity in all three treatment groups. AEs which were related to the study medication according to the investigator were experienced by 62 (21.8%) patients treated with roflumilast 500 µg, by 35 (12.3%) patients treated with roflumilast 250 µg, and by 28 (10.0%) patients treated with placebo. The median time to onset of AEs increased from 25 d in the roflumilast 500 µg group, through 49 d in the roflumilast 250 µg group, to 56 d in the placebo group. The median duration of AEs was similar and most patients (>92%) recovered from their AEs without sequelae in all three treatment groups.

During the treatment period 10 patients in the roflumilast 500 µg group experienced 16 SAEs, 8 patients in the roflumilast 250 µg group experienced 10 SAEs, and 6 patients in the placebo group experienced 7 SAEs (including a death). One patient in the placebo group was diagnosed with glioma, 93 d after first intake of double-blind study medication. The patient died approximately 2 months after onset of this SAE. This fatal SAE was assessed as 'not related' to study medication by the investigator. Most of the 24 SAEs were assessed as 'not related' to the study medication by the investigator; two AEs (convulsion [roflumilast 250 µg] and ventricular arrhythmia [placebo]) were assessed as 'related'.

More patients discontinued due to AEs in the roflumilast 500 µg group (39 [13.7%] patients) than in the roflumilast 250 µg group (28 [9.9%] or in the placebo group (25 [8.9%] patients). Of these, seven patients in the roflumilast 500 µg group, four patients in the roflumilast

250 µg group, and three patients in the placebo group (including the patient who died) discontinued due to SAEs.

Clinical laboratory assessments

Overall, no clinically relevant changes in hematology, biochemistry, urinalysis values, and hemoccult findings were observed in any of the three treatment groups during the course of the study. During the double-blind treatment period, 20 patients in the roflumilast 500 µg group, 20 patients in the roflumilast 250 µg group, and 19 patients in the placebo group experienced AEs associated with abnormal laboratory values. All laboratory AEs assessed by the investigator as 'related' to study medication occurred in the placebo group.

Vital signs

BP and HR measured during the study period did not reveal any influence of the two different treatments. ECG findings were similar for all treatment groups.

In conclusion, the observed safety data for roflumilast in this study were generally in line with the known safety profile of this drug.

Conclusions:

In conclusion, following roflumilast 500 µg treatment for 24 weeks, the improvement in the primary efficacy parameter of FEV_1 was not significantly different to placebo. For the roflumilast 250 µg treatment, the improvement in FEV_1 was statistically significant in favor of roflumilast over placebo. Although there were clear trends towards improvement in the roflumilast treatment groups for a variety of key secondary and secondary variables, these did not achieve clinically relevant effects compared with placebo. The small improvements in efficacy variables compared with placebo were countered by a higher incidence of AEs in the roflumilast treated groups.

Date of report: 02-Jan-2007