Pharma

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1 Title Page Clinical Study Report No. 296/2005 Version 1.0

Title: A 24-week, placebo-controlled, randomized, parallel-group study comparing roflumilast 500 mcg daily versus placebo on pulmonary function and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD).		Version date:	27-Jul-2006
		INN:	Roflumilast
		Project No. / List No.:	BY217
		Compound No.:	B9302-107
		Batch Nos.: Roflumilast 500 mcg Roflumilast placebo	 105302, 091102 103302, 104302
Study Protocol No.:	**BY217/M2-110**	Development phase:	III
EudraCT No:	not applicable	Indication studied:	COPD
Study initiation date:	10 June 2003	Date of early termination:	not applicable
Study completion date:	10 Mar 2005	Summary of modifications:	not applicable

Name and country of investigators:
One-hundred forty-two (142) investigators in 6 countries (Argentina, Canada, Columbia, Mexico, Peru, and the United States).
Coordinating investigator:
[redacted] Canada.

Name of sponsor's responsible medical officer:
Dr Dirk Bredenbröker, ALTANA Pharma AG (RC2/P2), Konstanz, Germany

Person(s) responsible for study report:
Dr Annette Rempel, ALTANA Pharma AG (RCS/P2), 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 RCD/C2 at ALTANA Pharma AG, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

SYNOPSIS

Title of the study:

A 24-week, placebo-controlled, randomized, parallel-group study comparing roflumilast 500 mcg daily versus placebo on pulmonary function and respiratory symptoms in patients with chronic obstructive pulmonary disease (COPD).

Investigators:

One-hundred forty-two Investigators.

Study center(s):

One-hundred forty-two sites in 6 countries (Argentina, Canada, Columbia, Mexico, Peru, and the United States) grouped into 10 regions.

Publication (reference): Not yet published.

Studied period (years): 10 June 2003 to 10 March 2005.

Clinical phase: Phase III.

Objectives:

The primary objective of this study was to compare the effects of roflumilast 500 mcg once daily (QD) and placebo on postbronchodilator FEV_1 (forced expiratory volume in 1 second) in subjects with COPD.

The secondary objectives of this study were as follows:

- Compare the effects of roflumilast and placebo on pulmonary symptomatology (as measured by the St. George's Respiratory Questionnaire [SGRQ]) in subjects with COPD.
- Evaluate the effects of roflumilast on additional symptoms of COPD, including symptoms as collected on electronic diaries (cough, sputum, breathlessness) use of supplemental (short-acting) bronchodilators as rescue medication, number of exacerbations, and other Health Outcome Measures (EuroQoL [EQ-5D] and Treatment Satisfaction Questionnaire [TS3]).
- Evaluate the effects of roflumilast on other measures of lung function as assessed by spirometry.
- Evaluate the safety and tolerability of roflumilast in subjects with COPD.
- Characterize the pharmacokinetics of roflumilast and roflumilast-N-oxide in subjects with COPD (the full pharmacokinetic [PK] methodology and results of the PK analyses will be presented in another report).

Methodology:

Study Design: This was a Phase III, placebo-controlled, double-blind, randomized, parallel-group study with a single-blind Run-in period.

The study was divided into the following components:

- **Screening**: Subjects evaluated for study eligibility.
- **Single-blind Run-In period**: Four-week study period with visits at -4 weeks (relative to Baseline), -2 weeks (relative to Baseline) and 0 weeks (Baseline), during which excluded respiratory medications (including inhaled corticosteroids, long-acting beta-agonists, and long-acting anticholinergics) were withdrawn.
- **Randomization at Baseline**: Eligible subjects randomized in a double-blind manner to either placebo or roflumilast 500 mcg QD.
- **Double-blind 24-week treatment period**: Clinic visits scheduled to occur at 4-week intervals (Weeks 4, 8, 12, 16, 20, and 24). Pulmonary function testing occurred at every visit; the SGRQ was administered at Week 4 (Visit 4), Week 12 (Visit 6), and Week 24 (Visit 10)/Final visit. COPD exacerbations were documented at each visit. Patients recorded symptom-related information in an electronic diary throughout the study. Health outcomes assessments, including EQ-5D, TS3, and Healthcare Resource Utilization Questionnaire, were assessed at intervals throughout the study. Adverse events (AEs) were documented at each visit.

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

	Enrolled	**Randomized**
Roflumilast 500 mcg		449
Placebo		460
Total	**1304**	**909**

Diagnosis and criteria for inclusion:

- Primary Inclusion Criteria:
  - Diagnosis of COPD by a physician based on American Thoracic Society (ATS) criteria.
  - Postbronchodilator $FEV_1/FVC \leq 70\%$.
  - Postbronchodilator $FEV_1 \geq 30\%$ and $\leq 80\%$ predicted.
  - Postbronchodilator FEV_1 increase $\leq 12\%$ or ≤ 200 mL compared to prebronchodilator value.
  - Score of Grade ≥ 1 on the Medical Research Council (MRC) Dyspnea Scale.
  - Currently stable COPD.

- Randomization Criteria at Baseline:
  - Postbronchodilator FEV_1 ≥30% and ≤80% predicted; FEV_1/FVC ≤70%.
  - Medication compliance of 80% to 100% during the run-in period.
  - Stable COPD during the Run-in period.
  - Score of grade ≥1 on the MRC Dyspnea Scale.

Test product: roflumilast

Dose: one tablet of 500 mcg QD in the morning
Mode of administration: oral administration
Batch Nos.: 105302, 091102
Duration of treatment: 24 weeks

Reference product: placebo

Dose: one tablet QD in the morning
Mode of administration: oral administration
Batch No.: 103302, 104302
Duration of treatment: 24 weeks

Criteria for evaluation:

Efficacy evaluations:

- Pulmonary Function Tests:
  - FEV_1: Forced expiratory volume in the first second
  - FVC: Forced Vital Capacity (expiratory)
  - FEF_{25-75}: Forced Expiratory Flow between 25% and 75% of vital capacity
  - PEF: Peak expiratory flow
  - FIV_1: Forced inspiratory volume in the first second
  - FVC_{in}: Forced Vital Capacity (inspiratory)
- Subject's Daily Electronic Diary:
  - COPD symptom scores
  - Rescue medication usage
  - Study medication usage
  - Lung function measurements
  - COPD Exacerbations

- Patient-Reported Outcomes
  - SGRQ
  - TS3
  - EQ-5D
- MRC Dyspnea Scale
- Healthcare Resource Utilization Questionnaire

Pharmacokinetic, pharmacodynamic, and/or other evaluations: Evaluate the pharmacokinetics of roflumilast and its metabolite, roflumilast-N-oxide in subjects with COPD and to determine which cofactors (eg, age, gender, etc) affect the PK.

Safety evaluations:

- Adverse Events
- COPD Symptoms
- Gastrointestinal (GI) Events
- Laboratory Evaluations
- Physical Examinations and Vital Signs
- 12-Lead electrocardiogram (ECG)

Statistical methods:

All statistical testing was 2-sided using a 5% significance level (Type I error rate of 0.05). To control the overall Type I error rate, the key secondary endpoint was tested only after a statistically significant finding for the primary efficacy endpoint could be concluded. No adjustments were made for multiple comparisons. A general linear model (analysis of covariance, ANCOVA) was used to evaluate between-treatment differences for the in-clinic postbronchodilator change in FEV_1 from Baseline to Final Visit.

- Change from Baseline to Final Visit in the SGRQ Total score was analyzed in a manner similar as the primary efficacy endpoint.
- The in-clinic spirometry endpoints were summarized and analyzed in a similar manner as the primary efficacy endpoint.
- The total number of exacerbations per subject was analyzed using the van Elteren extension of the Wilcoxon Rank Sum test with smoking status and center as the strata. The proportion of subjects with exacerbations was analyzed using both logistic regression and the Cochran-Mantel-Haenszel (CMH) test controlling for smoking status and center.
- Most electronic diary endpoints were analyzed using the Wilcoxon Rank Sum test. Daily mean diary endpoints were analyzed using ANCOVA.

- The overall and domain scores from the SGRQ were analyzed in a similar manner as the primary efficacy endpoint.
- Changes from Baseline to postrandomization visits were summarized descriptively by treatment group for the EQ-5D Index (utility score) and EQ-5D visual analog scale (VAS).
- The categorical responses to the TS3 were summarized by treatment group at Baseline and all postrandomization visits.

SUMMARY - CONCLUSIONS

Summary

Subject Disposition and Demography: Sixty-seven percent of roflumilast-treated subjects completed the study, versus approximately 77% of placebo-treated subjects. The most frequent reasons for which roflumilast-treated subjects withdrew from the study were AEs (15.4%), consent withdrawn (10.5%), and lack of efficacy (2.9%). The most frequent reasons for which placebo-treated subjects withdrew from the study were consent withdrawn (8.5%), AEs (7.6%), and protocol violations (3.0%).

Most subjects were between 55 and 74 years of age, with a mean age of 64.2 years in the roflumilast treatment group (range: 25 to 93 years) and 64.6 years in the placebo treatment group (range: 40 to 88 years). Most subjects were white (approximately 88%) and male (51.4% roflumilast-treated subjects and 55.4% placebo-treated subjects).

Efficacy Results:

- The least squares mean (LS mean) difference between treatment groups for the change from Baseline to Final visit (last observation carried forward [LOCF]) in postbronchodilator FEV_1 was 70 mL; this difference was statistically significant in favor of roflumilast (p-value <0.001).
- The LS mean difference between treatment groups for the change from Baseline to Final visit (LOCF) in SGRQ Total score was 0.53 (p-value = 0.473).
- The LS mean differences between treatment groups for the changes from Baseline to each visit in postbronchodilator pulmonary function tests were statistically significantly different at an alpha = 0.05 level in favor of roflumilast at the following time points and for the following pulmonary function tests:
  - All weeks for FEV_1;
  - All weeks except Week 16 for FVC;
  - Weeks 4, 8, and Final visit (LOCF) for FEF_{25-75};
  - Weeks 4, 8, 20, and Final visit (LOCF) for FEV_1/FVC;
  - Weeks 4 and 8 for PEF; and

- Week 8 and Final visit (LOCF) for $FVC_{inspiratory}$.

- There were no differences between treatment groups in the mean number of prorated COPD exacerbations of any severity, or in the mean number of moderate or severe prorated COPD exacerbations during the double-blind treatment study period.
- There were no statistically significant differences between treatment groups in the proportion of subjects with at least 1 COPD exacerbation of any severity, or in the proportion of subjects with at least 1 moderate or severe COPD exacerbation during the double-blind treatment period.
- There were no statistically significant differences between treatment groups in the time to the first COPD exacerbation of any severity, or in the time to the first moderate or severe COPD exacerbation.
- There were statistically significant differences between treatment groups for the changes from Baseline to Weeks 16, 20, and 24 in the number of puffs/day of rescue medication used. The observed changes however, were not clinically meaningful (all within-treatment mean differences were ≤0.60 puffs).
- There were no statistically significant differences between treatment groups in the changes from Baseline to any of the postrandomization time points in Cough Scores, Breathlessness Scores, Sputum Production Scores, or COPD Summary Symptom Scores.
- Roflumilast-treated subjects demonstrated statistically significantly greater changes in PEF_{am} and FEV_{1am} values (collected via the electronic diary) from Baseline to all time points than did placebo-treated subjects. The observed mean PEF_{am} and FEV_{1am} values in roflumilast-treated subjects increased relative to Baseline, while the observed mean PEF_{am} and FEV_{1am} values in placebo-treated subjects decreased.
- There were statistically significant differences between treatment groups in the daily LS mean electronic diary values over the full 24-week double-blind treatment period for FEV_{1am} and PEF_{am}, but not for the other diary parameters.
- There were no statistically significant differences between treatment groups in the mean percent of Rescue Medication-Free Days, Symptom-Free Days, or Healthy Days during the double-blind treatment period.
- Except for the SGRQ Total score at Week 4 and the Impacts Component score at Week 4, there were no statistically significant differences between treatment groups in the LS mean changes from Baseline in SGRQ component scores.
- There was no statistically significant difference between treatment groups in the percent of subjects who were SGRQ Responders.
- There were no notable changes from Baseline, nor were there notable trends or differences between treatment groups in EQ-5D scores.

- There were no notable differences or trends between treatment groups in responses to the TS3.

Pharmacokinetic, pharmacodynamic, and/or other results: The results of the population PK analysis in COPD patients are described in a separate report.

Safety Results:

- A total of 297 placebo-treated subjects (65%) and 317 roflumilast-treated subjects (71%) reported at least 1 AE during the course of the study. The most frequently-reported adverse events by roflumilast-treated subjects were diarrhea (15%), nausea (11%), nasopharyngitis (9%), and headache (7%). These same events were reported by 4%, 3%, 7%, and 2% of placebo-treated subjects, respectively.
- A total of 35 placebo-treated subjects (8%) and 67 roflumilast-treated subjects (15%) withdrew from the study due to least 1 AE. AEs resulting in withdrawal in ≥2.0% subjects in either treatment group were diarrhea in 11 roflumilast-treated subjects (2.4%) and in 1 placebo-treated subject (0.2%) and nausea in 9 roflumilast-treated subjects (2.0%) and in 1 placebo-treated subject (0.2%).
- Five deaths were reported during the study including 3 roflumilast-treated subjects and 2 placebo-treated subjects. The 3 deaths in the roflumilast-treated subjects were due to (investigator terms) cardiac arrest and gross hematuria (both in 1 subject), lung mass, and small-cell lung cancer. None of these events were considered by the investigator to be related to study medication. No cause of death was available for 1 of the placebo-treated subjects who died. The causes of death in the other placebo-treated subject were (investigator terms) congestive heart failure exacerbation, hypertension, and ischemic heart disease. None of these events were considered by the investigator to be related to study medication.
- There were 127 SAEs reported by 78 subjects during the study; of these, 41 were reported by placebo-treated subjects (8.9%) and 37 by roflumilast-treated subjects (8.2%). The most frequently reported SAE in either treatment group was COPD exacerbation in 7 roflumilast-treated subjects and in 11 placebo-treated subjects.
- There were no meaningful differences between treatment groups in the mean changes from Baseline in laboratory values.
- There were no meaningful within treatment group changes from Baseline to Final visit, nor were there any meaningful between-group differences in the changes from Baseline to Final visit, in systolic blood pressure, diastolic blood pressure, or pulse.

Conclusion(s):

- The primary efficacy endpoint for the study, change from Baseline to Final visit in postbronchodilator FEV_1, is statistically significant with a between-treatment difference of

70 mL, favoring roflumilast. Secondary lung function measurements are supportive of the observed between-treatment differences in FEV_1.

- Results from the analysis of the key secondary endpoint, change from Baseline to Final visit in SGRQ Total score, do not demonstrate a treatment-effect of roflumilast on health-related quality of life.
- There are no significant treatment differences observed in the analysis of exacerbation endpoints, which is not unexpected due to the small number of exacerbations that were reported during the course of the study.
- There are no observed treatment differences for symptom-related endpoints, as evaluated by electronic diaries or subject-reported outcome tools (EQ-5D and TS3).
- There are no observed treatment differences for health outcomes, as assessed by the Health Resource Utilization Questionnaire.
- The AE profile is consistent with other roflumilast studies, with diarrhea, nausea, and headache among the most common AEs reported by roflumilast-treated subjects. There is no evidence in this study to suggest that treatment with roflumilast results in gastrointestinal bleeding.
- Overall, these results are consistent with other roflumilast studies.