Disclaimer: This study was originally sponsored by ALTANA Pharma AG and was acquired from Takeda by AstraZeneca. For additional information regarding this study, please contact the AstraZeneca Clinical Study Information Center at information.center@astrazeneca.com.

1 Title Page — Clinical Study Report No. 15/2006 — Version 1.0

Title: Morning versus evening administration of 500 µg Roflumilast once daily for 6 weeks in patients with asthma. The MOVE-study		Version date:	09-Jun-2006
		INN:	Roflumilast
		Project No. / List No.:	BY217
		Compound No.:	B9302-107
		Batch No.: Roflumilast 500 µg Roflumilast placebo	 420210, 130220 130280
Study Protocol No.:	**BY217/M2-015**	Development phase:	IIIb
EudraCT No:	2004-001065-18	Indication studied:	Asthma
Study initiation date:	14-May-2004	Date of early termination:	Not applicable
Study completion date:	07-Jul-2005	Summary of modifications:	Not applicable

Name and country of investigators:
45 centers in Australia, Belgium, France, South Africa, Spain,
Coordinating investigator:
[redacted] ALTANA Pharma AG (RCD/C2), Konstanz, Germany (until 10-Jan-2005),
[redacted] UCT Lung Institute, George Street, 7925 Mowbray, Cape Town, South Africa (from 10-Jan-2005)

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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.

2 Synopsis

Title of the study:

Morning *versus* evening administration of 500 µg roflumilast once daily for 6 weeks in patients with asthma.
The MOVE-Study.

Investigators and study centers:

A total of 45 investigators at 45 centers in Australia (9), Belgium (6), France (12), South Africa (11), and Spain (7) participated in the study.

Coordinating investigator:

[redacted] UCT Lung Institute, Cape Town, South Africa

Publication (reference):

Not applicable

Studied period:

14-May-2004 (first patient in) to 07-Jul-2005 (last patient out)

Clinical phase:

IIIb

Objectives:

- to compare the effect of 500 µg roflumilast orally od (once daily) administered in the morning compared with the evening administration for 6 weeks on lung function, symptoms, and use of rescue medication in patients suffering from asthma;
- to investigate the safety and tolerability of roflumilast comparing morning vs (*versus*) evening administration;
- to investigate pharmacokinetics by determining plasma levels of roflumilast and its major metabolite roflumilast N-oxide.

Methodology:

Multicenter, double-blind, randomized, parallel group study (with a single-blind placebo baseline period).

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

It was planned to randomize 375 patients (1:1 randomization), with 298 patients assumed to be PP (per-protocol).

Analyzed sets:

	Enrolled	Randomized	Safety set	Full analysis set	Valid cases set
Rof500 am		201	201	201	161
Rof500 pm		202	201	201	173
Total	511	403	402	402	334

Rof500 am = roflumilast 500 µg once daily in the morning, Rof500 pm = roflumilast 500 µg once daily in the evening.

Diagnosis and main criteria for inclusion:

Patients meeting the following criteria were considered for inclusion in the baseline period:

- written informed consent was given;
- age 12 to 70 years old;
- diagnosis of persistent bronchial asthma (with reference to the GINA [Global Initiative for Asthma] guidelines 2002);
- baseline FEV_1 % of predicted had to be:
  a) 50 to 85 in patients either untreated or receiving any asthma medication except ICS (inhaled corticosteroids); eg (for example) short-acting bronchodilators, DSCG (disodium cromoglycate), nedocromil, anticholinergics, long-acting bronchodilators, theophylline or aminophylline, lipoxygenase inhibitors, leukotriene antagonists, alone or in combination;
  b) 60 to 90 in patients receiving not more than 500 µg BDP-CFC (beclomethasone dipropionate-chlorofluorocarbon; or equivalent) and/or in combination with any other asthma medication mentioned above, see a);
- no change in asthma treatment 4 weeks prior to baseline period;
- patients who, with the exception of asthma, were in good health.

Randomization criteria

Patients had to meet all of the following randomization criteria to be eligible for randomization into the double-blind treatment period at the last baseline visit (randomization visit):

- FEV_1 between 50 and 85 % of predicted at Randomization Visit T0, ie (*id est*) last baseline visit, when salbutamol (rescue medication) was withheld for at least 4 hours prior to the measurement;
- positive reversibility test during baseline, ie an increase of initial FEV_1 ≥12% and ≥200 mL, 15 to 30 min after inhalation of 200 to 400 µg salbutamol;
- ≥1 puff/day salbutamol (rescue medication) on average during the last week directly preceding the Randomization Visit T0. Visit Days B0 and T0 were not taken into account.

Test product dose, mode of administration, batch no.:

Roflumilast tablet, 500 µg od, orally, am or pm, 420210 and 130220

Duration of treatment:

Baseline period: 1 to 2 weeks; treatment period: 6 weeks

Reference product dose, mode of administration, batch no.:

Not applicable

Criteria for evaluation:

Efficacy evaluation (primary)

- FEV_1 [L] (repeated measurements ANCOVA including all visits from T0 to the final visit [T6 or early termination])

Efficacy evaluation (secondary):

- spirometric lung function parameters: FEV_1[1], FVC (forced vital capacity), PEF (peak expiratory flow), $MEF_{25-75\%}$ (mean expiratory flow between 25% and 75% of the vital capacity);
- morning and evening PEF (diary);
- diurnal PEF variability;
- ACQ (Asthma Control Questionnaire);
- asthma symptom score: daytime, nighttime and score sum;
- daily use of rescue medication (diary);
- proportion of symptom-free days and rescue medication-free days;
- severe asthma exacerbations.

Pharmacokinetic evaluation (secondary):

Trough plasma levels of roflumilast and roflumilast-N oxide at T6.

[1] Analyses other than the primary analysis.

Safety evalution (secondary):
AEs (adverse events), vital signs, ECG (electrocardiogram), changes in laboratory values and in physical examination findings.

Statistical methods:

The primary comparison was roflumilast 500 µg od am vs roflumilast 500 µg od pm; FEV_1 was the primary variable. The primary analysis of the primary and most of the secondary efficacy variables was a repeated measurements ANCOVA including all visits from T0 to the final visit (T6 or early termination).
The primary variable was tested in an a-priori order, so that non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm needed to be shown first before superiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was tested in a confirmatory manner. The non-inferiority acceptance limit for FEV_1 was set to –100 mL. The primary analysis for the test of non-inferiority was the PP analysis, whereas the ITT analysis was the primary analysis for the superiority test.
The secondary efficacy variables were analyzed in an exploratory manner. AEs were analyzed using descriptive statistics.

SUMMARY - CONCLUSIONS

Summary:

Demography and baseline characteristics
In total, 403 patients were randomized (1:1) and 402 patients were included in the FAS for the ITT analysis (201 patients per treatment group).
In general, the two treatment groups were well comparable with respect to patient disposition, demographic and other baseline characteristics (see Table below).

Demographic and other baseline characteristics by treatment

		FAS		VCS	
		Rof500 am (N = 201)	**Rof500 pm (N = 201)**	**Rof500 am (N = 161)**	**Rof500 pm (N = 173)**
Age [years]	Median (range)	41 (15, 68)	39 (12, 70)	40 (15, 68)	39 (12, 70)
Weight [kg]	Mean ± SD	77 ± 18.0	76 ± 17.1	78 ± 18.6	76 ± 16.8
Height [cm]	Mean ± SD	167 ± 10.1	168 ± 10.2	167 ± 10.3	168 ± 10.3
BMI [kg/m^2]	Mean ± SD	28 ± 6.2	27 ± 5.8	28 ± 6.4	27 ± 5.7
Sex [n (%)][a]	Female	118 (58.7)	107 (53.2)	94 (58.4)	89 (51.4)
	Male	83 (41.3)	94 (46.8)	67 (41.6)	84 (48.6)
Race [n (%)][a]	Asian	8 (4.0)	5 (2.5)	8 (5.0)	4 (2.3)
	Black	15 (7.5)	12 (6.0)	11 (6.8)	10 (5.8)
	Caucasian	166 (82.6)	165 (82.1)	132 (82.0)	143 (82.7)
	Other	12 (6.0)	19 (9.5)	10 (6.2)	16 (9.2)
Asthma severity (GINA)	Intermittent	3 (1.5)	1 (0.5)	1 (0.6)	1 (0.6)
[n (%)][a]	Mild persistent	4 (2.0)	6 (3.0)	2 (1.2)	5 (2.9)
	Moderate persistent	32 (15.9)	37 (18.4)	22 (13.7)	31 (17.9)
	Severe persistent	123 (61.2)	115 (57.2)	106 (65.8)	100 (57.8)
	Not available	39 (19.4)	42 (20.9)	30 (18.6)	36 (20.8)
Smoking status [n (%)][a]	Non-smokers	143 (71.1)	137 (68.2)	116 (72.0)	121 (69.9)
	Ex-smokers	38 (18.9)	40 (19.9)	28 (17.4)	32 (18.5)
	Current smokers	20 (10.0)	24 (11.9)	17 (10.6)	20 (11.6)
Pack years [n][b]	Mean ± SD	5 ± 2.7	5 ± 2.9	5 ± 2.6	5 ± 2.9
FEV_1 at T0 [L][c]	Mean ± SD	2.196 ± 0.621	2.276 ± 0.618	2.178 ± 0.614	2.269 ± 0.625
[% of predicted][c]	Mean ± SD	70.7 ± 9.8	71.6 ± 9.5	70.0 ± 9.4	71.3 ± 9.5
FEV_1 rev. at B0 [% increase][c]	Mean ± SD	18.6 ± 14.5	21.5 ± 14.5	19.0 ± 15.0	22.1 ± 15.1

[a] Percentages are based on the number of patients in a treatment group.
[b] Subset current and ex-smokers.
[c] The baseline lung function parameters did not necessarily include data from all patients in the analysis sets.
B0 = first baseline visit, BMI = body mass index, FAS = full analysis set, n = number of patients, rev. = reversibility, Rof500 am = roflumilast 500 µg once daily in the morning, Rof500 pm = roflumilast 500 µg once daily in the evening, SD = standard deviation, T0 = randomization visit, VCS = valid cases set.
Data source: Table 15.1.2.1, Table 15.1.2.5, Table 15.2.2.1, Table 15.1.3.1, and Table 15.2.2.4.

Efficacy

If not indicated otherwise, efficacy results are summarized for the repeated measurements analysis, which was the primary efficacy analysis. The analysis of change from baseline generally supported the results of the repeated measurements analysis.

Primary efficacy variable: FEV_1

FEV_1 increased statistically significantly with both roflumilast treatments (0.210 L with roflumilast 500 µg od am and 0.216 L with roflumilast 500 µg od pm; PP, confirmed by ITT; see Table below). The analysis of between-treatment differences demonstrated non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm (one-sided p = 0.0048, PP, confirmed by ITT). Superiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was not shown (one-sided p = 0.5353, ITT, confirmed by PP).

Change from T0 in FEV_1 [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN				Mean	Within-treatment difference		
		n	n obs	at T0	LSMean ± SE	95% CI	p-value[a]
PP	Rof500 am	155	421	2.188	0.210 ± 0.028	0.154, 0.265	<0.0001
	Rof500 pm	167	444	2.282	0.216 ± 0.028	0.161, 0.270	<0.0001
ITT	Rof500 am	200	552	2.196	0.209 ± 0.026	0.158, 0.259	<0.0001
	Rof500 pm	199	557	2.276	0.212 ± 0.026	0.161, 0.262	<0.0001

BETWEEN					Difference Test - Ref			
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value non-inf.[b]	p-value sup.[c]
PP	Rof500 am	Rof500 pm	155	167	-0.006 ± 0.036	-0.077, 0.065	0.0048	0.5682
ITT	Rof500 am	Rof500 pm	200	199	-0.003 ± 0.033	-0.068, 0.062	0.0019	0.5353

[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for non-inferiority, significance level 2.5%, non-inferiority margin = -100 mL.
[c] One-sided p-value for superiority, significance level 2.5%.
CI = confidence interval, FEV_1 = forced expiratory volume in 1 second, LS = least squares, n = number of patients with data available, n obs = number of observations, Rof500 am = roflumilast 500 µg once daily in the morning, Rof500 pm = roflumilast 500 µg once daily in the evening, SE = standard error of the LSMean, T0 = randomization visit.
Data source: Table 15.2.1.1 and Table 15.2.1.2.

Secondary efficacy variables

Lung function parameters

A statistically significant within-treatment increase was found for FVC, PEF, and $MEF_{25-75\%}$ (PP, ITT). The differences between the regimens were not statistically significant for any of the three secondary lung function variables (PP, ITT).

Morning and evening PEF (diary)

The results for PEF derived from patients' diary were different from the results obtained by spirometry: In the repeated measurements analysis morning PEF did not change statistically significantly over the treatment period in both groups (PP, ITT). When analyzing the change from baseline, morning PEF improved statistically significantly within the roflumilast 500 µg od am group (PP). Evening PEF decreased during the study in both treatment groups. The decrease was statistically significant in the roflumilast 500 µg od pm group (PP, ITT). For both morning and evening PEF the differences between treatments were in favor of roflumilast 500 µg od am but did not reach statistical significance (PP, ITT).

Diurnal PEF variability (diary)

PEF variability decreased in both treatment groups (PP, ITT). The decrease was statistically significant for roflumilast 500 µg od am in the ITT analysis. The differences between treatments were not statistically significant (PP, ITT).

Daily use of rescue medication (diary)

A statistically significant decrease in the daily use of rescue medication was seen for the roflumilast 500 µg od am group and the roflumilast 500 µg od pm group (PP, ITT). The between-treatment differences were not statistically significant (PP, ITT).

Asthma symptom score (diary)

The asthma symptom scores (daytime, nighttime, and score sum) decreased statistically significantly during the study in both treatment groups, indicating an improvement in asthma symptoms (PP, ITT). The differences between roflumilast 500 µg od am and roflumilast 500 µg od pm were not statistically significant.

Asthma symptom- and rescue medication-free days (diary)

No differences between the treatment groups were detected for the percentage of asthma symptom- and rescue medication-free days.

Asthma Control Questionnaire

A statistically significant improvement in asthma control (corresponding to a decrease in ACQ score) was observed in the two treatment groups (PP, ITT). Non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was demonstrated (PP, confirmed by ITT). Furthermore, there were no statistically significant differences between the treatment groups with regard to the number of patients with or without an improvement in ACQ.

Number of patients with severe asthma exacerbations

The number of patients experiencing a severe asthma exacerbation was comparable between the roflumilast 500 µg od am group (9 out of 201 patients [4.5%]) and the roflumilast 500 µg od pm group (10 out of 201 patients [5%], ITT). There were no statistically significant differences between the treatment groups with regard to the number of patients experiencing a severe asthma exacerbation (Fisher's exact test, PP and ITT). Furthermore, the two-sample log-rank test revealed no statistically significant differences between the treatment groups for the time to onset of the first severe asthma exacerbation (PP, ITT).

Study discontinuation

The median time to study discontinuation was 43 days in both treatment groups (PP, ITT). The two-sample log-rank test revealed no statistically significant differences between the treatment groups for the time to study discontinuation (PP, ITT).

Subgroup analyses by smoking status

Statistically significant improvements in FEV_1 could be seen with the two roflumilast treatments in both (ex-)smokers and non-smokers (PP, ITT). Non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was demonstrated in non-smokers (PP, confirmed by ITT). In (ex-)smokers, non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was not shown (PP, confirmed by ITT). However, this result has to be interpreted with caution due to the small sample size. Superiority of roflumilast 500 µg od am to roflumilast 500 µg od pm was not demonstrated for any of the two subgroups (ITT, confirmed by PP).

Pharmacokinetic evaluation

Blood samples were taken approximately 25 and 13 h (median time intervals) after the morning and evening administration, respectively. Trough plasma levels for the metabolite were similar in patients receiving roflumilast in the morning and in the evening, whereas roflumilast trough plasma levels after evening administration were 33.9% higher compared to trough plasma levels after morning administration.

Safety

A summary of AEs is given in the following table:

Frequency of treatment-emergent AEs (SAF)

	Rof500 am (N = 201)	Rof500 pm (N = 201)	Total (N = 402)
Number of patients (%)[a] with:			
AEs	109 (54.2)	129 (64.2)	238 (59.2)
SAEs: all	0 (0.0)	2 (1.0)	2 (0.5)
deaths	0 (0.0)	0 (0.0)	0 (0.0)
AEs with causality[b] suggested			
- by the investigator	49 (24.4)	63 (31.3)	112 (27.9)
- by the sponsor	49 (24.4)	68 (33.8)	117 (29.1)
AEs leading to discontinuation	27 (13.4)	27 (13.4)	54 (13.4)
AEs not yet known to be recovered	10 (5.0)	4 (2.0)	14 (3.5)
Changes in study medication due to AEs	16 (8.0)	19 (9.5)	35 (8.7)
Changes in conc. medication due to AEs	74 (36.8)	91 (45.3)	165 (41.0)

[a] Percentages are based on the total number of patients in a treatment group.
[b] AEs assessed as 'likely' or 'definitely' related to the study medication.
Conc. = concomitant, N = number of patients in each treatment group, Rof500 am = roflumilast 500 µg once daily in the morning, Rof500 pm = roflumilast 500 µg once daily in the evening.
Data source: Table 15.3.1.3 and Table 15.3.2.1.

The overall incidence of AEs was higher in patients taking roflumilast 500 µg od pm (64.2%) than in patients taking roflumilast 500 µg od am (54.2%). The most frequently reported AEs were related to the gastrointestinal tract (such as diarrhoea and nausea). These AEs occurred more frequently in patients taking roflumilast 500 µg od pm (25.9%) than in patients taking roflumilast 500 µg od am (18.4%). Furthermore, AEs relating to nervous system disorders showed higher incidences in the roflumilast 500 µg od pm group (21.4%) than in the roflumilast 500 µg od am group (16.4%), largely due to a difference in the incidence of headache.

The frequency of AEs considered to be causally related to study medication (assessed as 'likely' or 'definitely' related by the investigator) was higher in the roflumilast 500 µg od pm group (31.3%) than in the roflumilast 500 µg od am group (24.4%). The most frequent 'likely' or 'definitely' related AE was headache, followed by diarrhoea and nausea.

The majority of patients with AEs experienced events with mild or moderate severity. Over 95% of AEs in each treatment group resolved during the study.

There were no deaths during the treatment period of this study. One patient who was enrolled in the baseline period, but not randomized, died.
Two SAEs were reported during the treatment period for 2 (1.0%) of patients in the roflumilast 500 µg od pm group, none were reported in the roflumilast 500 µg od am group.
The percentage of patients who were withdrawn from the study due to AEs was 13.4% in both treatment groups. The most common reason for study discontinuation was asthma followed by headache and nausea.
Overall, for all clinical chemistry and hematology parameters analyzed, the mean changes from baseline were small and not clinically relevant. There were no major differences in the incidence of clinically significant abnormalities between the two treatment groups and most of these were considered 'not' or 'unlikely' related to study medication by the investigator.
Vital signs and ECG did not reveal any clinically significant changes due to study drug administration.
These results were comparable to those observed in previous studies and support a favorable safety profile for roflumilast.

Conclusion

This study demonstrated that roflumilast 500 µg administered in the morning was of comparable efficacy as roflumilast 500 µg administered in the evening in improving lung function, symptoms, and use of rescue medication in patients with asthma. Non-inferiority of roflumilast 500 µg od am to roflumilast 500 µg od pm for the primary efficacy variable FEV_1 was demonstrated. No statistically significant differences between the two regimens were found for all secondary efficacy variables.
In total, 54.2% of patients treated with roflumilast 500 µg od am and 64.2% of patients treated with roflumilast 500 µg od pm experienced AEs. Overall, the number and type of AEs were not unexpected for the patient population under investigation. The majority of patients with AEs experienced events that were judged 'not related' or 'unlikely related' to the study medication. Most of the AEs were of mild or moderate severity and resolved during the study. There was no apparent clinically relevant influence on laboratory parameters, vital signs, ECG or physical examination.
Overall, the safety results obtained from this study confirm the known tolerability profile of roflumilast. Furthermore, roflumilast was equally efficacious regardless of the time of administration. The evening administration provides an additional option and flexibility in dosing which adds to patients' convenience and might facilitate compliance in a clinical setting. However, there was a tendency of a higher tolerability of the morning administration suggesting that morning administration may provide a small difference in patients reporting side effects.

Date of report: 09-Jun-2006