Pharma

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1 Title Page — Clinical Study Report No. 36/2007 — Version (1.0)

Title: Pharmacokinetic Evaluation of Study BY217/ M2-034: A Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of Roflumilast on Airway Inflammation and Function Following Allergen Challenge in Subjects with Allergic Asthma		Version date:	05-Jun-2007
		INN:	Roflumilast
		Project No. / List No.:	BY217
		Compound No.:	B9302-107
		Batch No.: Roflumilast 500 µg: 120180, 320200 Roflumilast Placebo: 130290	
Study Protocol No.:	**BY217/M2-034**	Development phase:	II
EudraCT No:	not applicable	Indication studied:	Asthma
Study initiation date:	08-Dec-2004	Date of early termination:	not applicable
Study completion date:	08-Jul-2005	Summary of modifications:	not applicable

Name and country of investigators:

[redacted] McMaster University, Hamilton, Canada; [redacted] Laval Hospital, Quebec, Canada

Name of sponsor's responsible medical officer:

Dr Dirk Bredenbröker, ALTANA Pharma AG (RCS/P2), Konstanz, Germany

Person(s) responsible for study report:

Dr Andreas Hünnemeyer, ALTANA Pharma AG (RPR/PK), 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:

Pharmacokinetic Evaluation of Study BY217/ M2-034: A Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of Roflumilast on Airway Inflammation and Function Following Allergen Challenge in Subjects with Allergic Asthma

Investigators and study centers:

Two centers in Canada:

[redacted] St. (Joseph's Hospital – McMaster University, 50 Charlton Avenue, East, CA-L8N4A6, Hamilton)

[redacted] (Hospital Laval, 2725 Chemin Sainte-Foy, Pav. U 1er Etage G1V 4G5 Sainte Foy Québec, Canada)

Coordinating investigator:

Not applicable

Publication (reference):

Not applicable

Studied period:

08-Dec-2004 (first patient in) to 08-Jul-2005 (last patient out).

Clinical phase:

Phase II

Objectives:

Primary Objective:

- to compare the effect of roflumilast to placebo treatment on allergen-induced airway eosinophilia in patients with allergic asthma.

Secondary Objectives:

- to evaluate the allergen-induced EAR (early asthmatic response) and LAR (late asthmatic response) in patients with allergic asthma following repeated dosing of roflumilast;
- to evaluate the effect of roflumilast on allergen-induced AHR (airway hyperreactivity);
- to characterize the steady-state PK (pharmacokinetics) of roflumilast and roflumilast N-oxide in patients with allergen-induced asthma;

- to evaluate the safety and tolerability of roflumilast in patients with asthma;
- to evaluate the effect of roflumilast on allergen-induced airway MCC (metachromatic cells, ie mast cells and basophils) and sputum ECP (eosinophilic cationic protein) levels.

Methodology:

The study was a double-blind, placebo-controlled, crossover study to evaluate the efficacy of roflumilast on airway inflammation and function in patients with allergen-induced asthma.

Individuals with stable, mild to moderate allergic asthma, with a history of episodic wheeze and shortness of breath, were eligible for enrollment.

The study was divided into 4 phases: Screening, Pre-Randomization Evaluation, Randomization/Treatment Period 1, and Treatment period 2/Final Evaluation.

Patients received one tablet (roflumilast 500 µg or placebo) orally each morning after the morning meal with at least 200 mL (6 ounces) of fluid daily for the first 14 consecutive days in each of the 15-d treatment periods. There was a washout period between treatment periods (approximately 3 to 5 weeks).

Pharmacokinetic methods:

At one trial site ([redacted]), blood specimens were collected from subjects for pharmacokinetic (PK) assessments on Day 14 of each treatment period (Visits 7 and 11). A pre-dose blood specimen was collected. The dose of study drug was to be administered at the Investigator site with 200 ml of water after the morning meal. Following administration of the dose, blood specimens were collected at 15 min, 30 min, 60 min, 90 min, 2h, 3h, 4h, 6h, 8h, 12h, and 24h post-dose. The 24h post-dose blood sample was collected in the absence of any dosing of study drug on that Day 15 (Visits 8 and 12) of each treatment period.

Concentration of roflumilast and roflumilast N-oxide were analyzed using validated high performance liquid chromatographic (HPLC) methods coupled with tandem mass spectrometric (MS/MS) detection.

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

The sample size was planned to be at least 22 evaluable patients (11 in each treatment sequence), with a maximum of 24 patients.

A total of 47 patients were enrolled; 25 patients were randomized and took at least one dose of study medication (thus the SAF (safety set) was identical to the FAS (full analysis set). All received roflumilast 500 µg, while only 23 patients crossed over and started treatment with placebo. A similar number of patients was allocated to each of the treatment sequences:

13 patients were allocated to roflumilast 500 µg/placebo while 12 patients were allocated to placebo/roflumilast 500 µg. Following the exclusion of 3 patients with major protocol violations, the VCS (valid cases set) included 12 patients from the roflumilast 500 µg/placebo treatment sequence and 10 patients from the placebo/roflumilast 500 µg treatment sequence.

Diagnosis and main criteria for inclusion:

Patients who met the following criteria were included into the study:

- 18 to 55 years of age;
- male; or a female of non-childbearing potential (greater than or equal to 2 years postmenopausal or documented as surgically incapable of conception); or a non-lactating female of childbearing potential who agreed not to become pregnant during the study. When sexually active, females of childbearing potential had to already be using either oral contraceptives, IUD (intrauterine device), Norplant®, or Depo-Provera® injections or agree to use at least any two of the following: a cervical barrier (diaphragm), spermicide, or condom. Females who were not sexually active had to agree to use at least two of the above barrier methods if they became sexually active during the course of the study;
- the patient was an outpatient;
- had to have a negative (quantitative) serum pregnancy test for female patients of childbearing potential at Phase 1 Screening (Visit 1), a negative urine pregnancy test for female patients of childbearing potential at Phase 3 Randomization/Treatment Period 1 (Visit 5), and Phase 4 Treatment Period 2/Final Evaluation (Visit 9) prior to double-blind treatment;
- had symptoms of asthma for the last 6 months that satisfied the American Thoracic Society definition of asthma, ie episodic wheezing, coughing, shortness of breath, and chest tightness associated with airflow limitation that was at least partially reversible, either spontaneously, or with medication;
- had an unmedicated (no inhaled short-acting bronchodilator for at least 8 h) FEV_1 (forced expiratory volume in 1 s) of ≥70% of the predicted normal value for age, height, and sex (using the standards of Crapo) with a 12% downward adjustment applied for individuals of African descent;
- positive MCh (methacholine) inhalation challenge at Pre-Randomization Evaluation Visit 2 (MCh $_{PC20FEV1}$ (methacholine provocative concentration resulting in a 20% reduction in FEV_1) <16 mg/mL) reflecting AHR;
- had a documented allergy to a common aeroallergen (animal, dust mite, mold, and pollen allergens) as confirmed by a recognized skin prick test wheal ≥2 mm in diameter; Note: In practice, all randomized patients had a documented allergy to one of these allergens, but this cannot be confirmed by the results of skin testing at screening as this evaluation was omitted from the CRF;
- positive allergen-induced early and late airway bronchoconstriction. The EAR was defined by an acute fall in FEV_1 ≥20% within 2 h following allergen challenge. The LAR was defined by a fall in FEV_1 ≥15% between 3 h and 7 h following allergen challenge;
- the patient was someone from whom the investigator or study personnel would expect conscientious cooperation over the duration of the study;

- the patient was able to execute or obtain written informed consent at Visit 1.

Randomization criteria:

In addition to the inclusion and exclusion criteria, patients had to have a documented EAR and LAR in inhaled incremental allergen challenge and positive MCh inhalation challenge at the Pre-Randomization Evaluation visits, to be eligible for entry into the double-blind treatment periods of the study.

The Pre-Randomization Evaluation MCh inhalation challenge test was considered positive if a decrease of at least 20% in the FEV_1 occurred at a concentration of <16 mg/mL. An EAR was defined by an acute fall in FEV_1 ≥20% within 2 h after allergen challenge. A positive LAR was defined by a reduction in FEV_1 of at least 15% from the pre-allergen value between 3 h and 7 h after allergen challenge.

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

Roflumilast 500 µg, one tablet od (once daily), orally, 120180 and 320200.

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

Placebo, one tablet od, orally, 130290 and 130290.

Duration of treatment:

Two 15 d treatment periods (14 d with treatment and day 15 without treatment) separated by a washout period (approximately 3 to 5 weeks).

Criteria for evaluation:

For efficacy and safety variables, please refer to the clinical report of study BY217/M2-034 (Report No. 52/2006)

Pharmacokinetic variables, their definition and methods of estimation are summarized in the following table:

Parameter estimate	Definition	Method of Estimation/ Units
AUC_T	'Observed' area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ) within the dosing interval of 24 h (= T)	Linear trapezoidal method [hr•µg/L]
C_{max}	Maximum plasma concentration	Observed [µg/L]
C_{avg}	Average plasma concentration	AUC_τ [hr•µg/L]/dosing interval τ [hr] = [µg/L]
t_{max}	Time to reach C_{max}	Observed [hr]

Parameter estimate	Definition	Method of Estimation/ Units
$t_{1/2}$	Half-life	$\ln(2)/\lambda_z$ [1/hr]
λ_z	Terminal rate constant	Absolute value of the slope of the linear regression line during the observed elimination phase of the concentration-time curved, displayed on the natural logarithm (ln) concentration scale [1/hr]
PTF, Fl	Peak-Trough Fluctuation as fluctuation index	Computed as $100 \bullet (C_{max}-C_{min})/C_{avg}$, where C_{min} and C_{max} were obtained between 0 and τ.

Statistical methods:

For statistical methods of efficacy and safety variables, please refer to the clinical report of study BY217/M2-034 (Report No. 52/2006).

The pharmacokinetic variables were estimated from plasma concentration-time data, tabulated and summarized.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Demographic data and baseline characteristics of patients with pharmacokinetic data are summarized in the following table:

	N	Mean	SD	SE	Min	Median	Max	CV%
Age [years]	15	29.0	11.8	3.05	19	23	54	40.7
Weight [kg]	15	77.5	16.1	4.17	55	73	106	20.8
Height [m]	15	169	9.02	2.33	155	170	183	5.31
PC20 FEV_1 [mg/mL]	15	3.34	3.53	0.91	0.52	2.82	14.3	105
Asthma duration [years]	15	15.1	9.68	2.50	5.50	12.0	42.3	63.9

For 15 patients, pharmacokinetic profiles could be obtained. All of these patients were non-smokers. Of these 15 patients, one was Black, the others Caucasian. Ten patients were female.

Efficacy and safety results

For efficacy and safety results, please refer to the clinical report of study BY217/M2-034 (Report No. 52/2006).

Pharmacokinetic results

Pharmacokinetic variables of roflumilast and roflumilast N-oxide are summarized in the following table:

	AUC_T (µg•hr/L)	C_{max} (µg/L)	t_{max} (hr)	$t_{1/2}$ (hr)	C_{ave} (µg/L)	λ_z (1/hr)	Fl (%)
Roflumilast							
N	15	15	15	14	15	14	15
Mean	55.8	7.04	1.83	16.3	2.32	0.058	319
SD	29.0	2.55	1.05	11.7	1.21	0.027	176
Geometric Mean	49.2	6.64	1.52	13.6	2.05	0.0507	269
Lower_68%	29.1	4.66	0.77	7.58	1.21	0.028	141
Upper_68%	83.1	9.46	2.99	24.6	3.46	0.091	511
Roflumilast N-oxide							
N	15	15	15	14	15	14	15
Mean	473	26.8	4.37	38.0	19.7	0.0283	68
SD	194	10.0	1.95	29.7	8.09	0.0177	35
Geometric Mean	440	25.1	3.76	29.9	18.3	0.0231	60
Lower_68%	298	17.0	1.92	14.8	12.4	0.011	35.1
Upper_68%	648	36.9	7.36	60.3	27.0	0.047	101

Conclusions:

In this asthma population, pharmacokinetic profiles as well as pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide resemble those known from previous pharmacokinetic studies in healthy volunteers.

Date of report: 05-Jun-2007