2 Synopsis

Title of the study: A pilot study to investigate the bioequivalence of two Roflumilast 500 µg tablet formulations (B and E) in healthy volunteers. A single-centre, single-dose, open label, randomized, four-period change-over phase I study with two replicated treatment sequences and a washout interval of at least 7 days between periods.

study center:

AAIPharma Deutschland GmbH & Co. KG, Wegenerstr. 13, 89231 Neu-Ulm, Germany

Publication (reference): Not applicable

Studied period: 23-Jul-2007 (first patient in) to 01-Oct-2007 (last patient out)

Clinical phase: phase I

Objectives:

Primary objectives

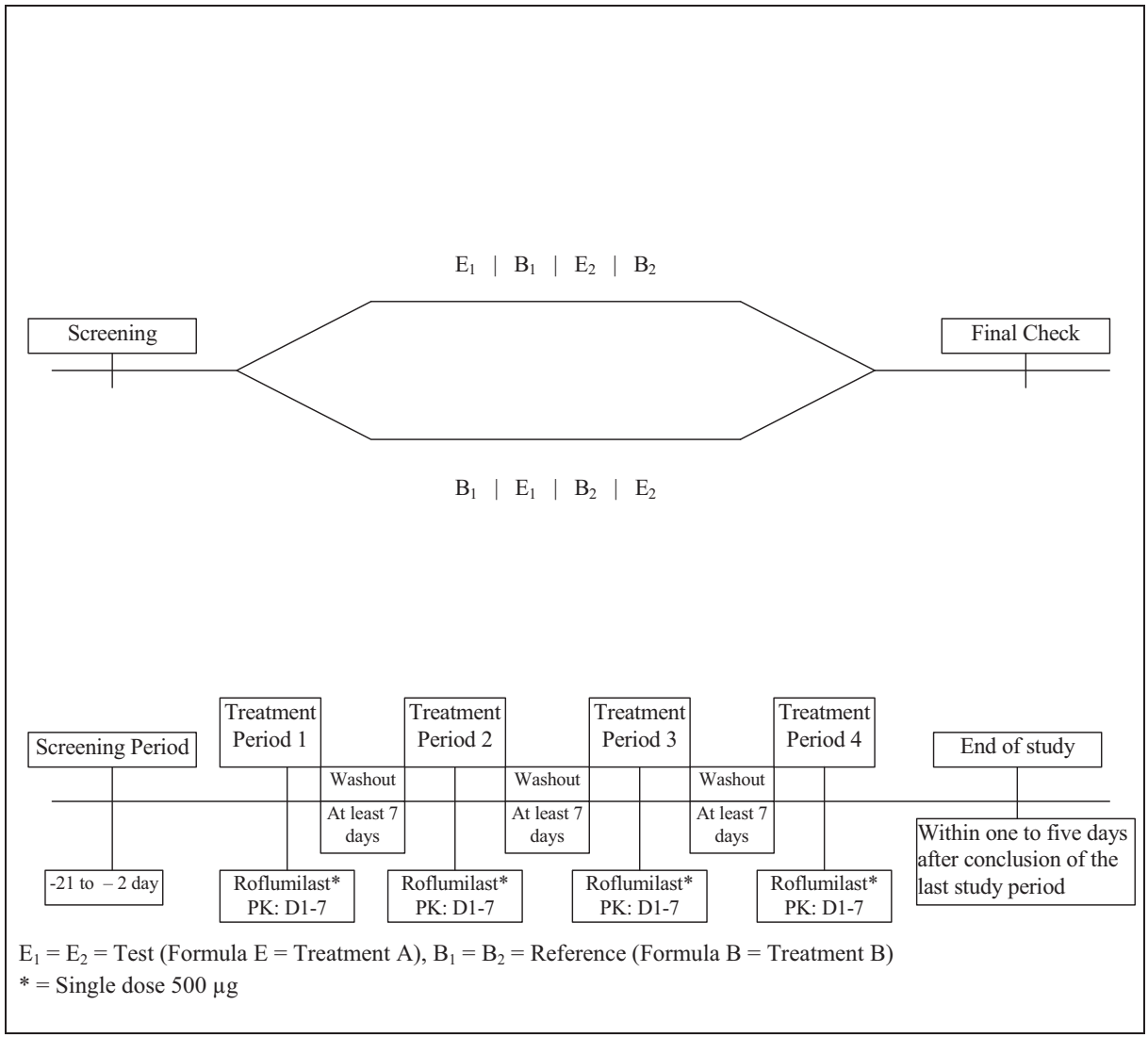
To investigate the bioequivalence of a large yellow D-shaped roflumilast-500 µg tablet (TEST; Formula E) and the current roflumilast-500 µg small round white tablet (REFERENCE; Formula B) by assessing the roflumilast and the roflumilast N-oxide exposure (extent [AUC_{tlast} and AUC_{inf}] of exposure and rate [C_{max}] of absorption) from plasma samples.

Secondary objectives

- To assess and compare other pharmacokinetic characteristics of roflumilast and roflumilast N-oxide of the two formulations from plasma samples
- To assess safety and tolerability
- To evaluate the total PDE4 inhibitory activity (tPDE4i) of both formulations

Methodology:

Study design: A single-centre, single-dose, open label, randomized, four-period change-over phase I study with two replicated treatment sequences and a washout interval of at least 7 days between periods.



$E_1 = E_2$ = Test (Formula E = Treatment A), $B_1 = B_2$ = Reference (Formula B = Treatment B)
* = Single dose 500 µg

Treatment sequences:

	Period 1	Period 2	Period 3	Period 4
Sequence 1	E_1	B_1	E_2	B_2
Sequence 2	B_1	E_1	B_2	E_2

B_1/B_2: Formula B of 500 µg roflumilast (B_1/B_2: Treatment B) = Reference
E_1/E_2: Formula E of 500 µg roflumilast (A_1/A_2: Treatment A) = Test

Description of methods and assay performance:

Method Description	
Matrix	**Lithium-heparin plasma**
Type of method	Validated HPLC-MS/MS detection method
Validation reports	73/2001 and 188/2007
Department or CRO	Department of Bioanalytics (Nycomed GmbH Konstanz)
Deviations from validated method	None
Sample volume	200 µL
Internal standards	BYK199199 (D_5-roflumilast) BYK199244 (D_5-roflumilast N oxide)

Study Assay Performance

	Calibration Range		Quality Control Samples	
Analyte	Lower Limit (LLOQ)	Upper Limit (ULOQ)	Inter-day Precision (%CV)	Inter-day Accuracy (%)
Roflumilast	0.100 µg/L	50.0 µg/L	2.25 to 5.61	99.6 to 101.8
Roflumilast N-oxide	0.100 µg/L	50.0 µg/L	2.36 to 3.85	98.9 to 100.7

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

A formal sample size calculation was not performed because treatment-specific within-subject variance and subject-by-formulation variance data were not available. Previous bioequivalence studies were all non-replicated studies and therefore, estimates of variance from these trials were not considered appropriate for sample size calculation in this trial.

However, to get reliable estimates 24 subjects were planned for inclusion such that the trial achieved at least 18 subjects for the per-protocol set and pharmacokinetic analysis set.

Diagnosis and main criteria for inclusion:

Healthy male and female subjects of any ethnic origin, age 45 years and older, with a Body Mass Index (BMI) between ≥ 18 and ≤ 29.9 kg/m², and a body weight ≥ 50 kg female / ≥ 60 kg male were included. Women were without childbearing potential (e.g. surgically sterile or post-menopausal females, the latter being defined as having had no menstrual period for at least 2 years).

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

Treatments:

Treatment	Dose	Description	Dosage Form	Frequency	Route	Duration	Batch No.
Formula E (Test)	500 µg	Yellow, D-shaped (267.7 mg)	Tablet	Once daily	Oral	1 day	170060
Formula B (Reference)	500 µg	White, round (65.5 mg)	Tablet	Once daily	Oral	1 day	170300

Washout interval: At least 7 days between periods

Duration of treatment: see above table

Criteria for evaluation:

Primary variables

- AUC_{tlast}, AUC_{inf} and C_{max} of roflumilast and roflumilast N-oxide

Secondary variables

- T_{max} and $t_{1/2}$ of roflumilast and roflumilast N-oxide and CL/F of roflumilast
- Safety and tolerability: adverse events, vital signs (blood pressure, pulse rate), body weight, ECG and safety laboratory
- Total PDE4 inhibitory activity (tPDE4i) for both formulations

Pharmacokinetic variables, their definition and methods of estimation are summarized below:

Pharmacokinetic variables:

Parameter estimate	Definition	Method of Estimation/ Units
AUC_{tlast}	Area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ)	Linear trapezoidal method [hr•µg/L]
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinity	$AUC_{tlast} + C_{last}/\lambda_z$ [hr•µg/L]
C_{max}	Maximum plasma concentration	Observed [µg/L]
λ_z	Terminal rate constant	Slope (rate constant) of log-linear regression of the terminal phase of the concentration-time profile
$t_{1/2}$	Half-life	$\ln(2)/\lambda_z$ [1/hr]
t_{max}	Time to reach C_{max}	Observed [hr]
CL/F	Apparent plasma clearance, after oral administration of roflumilast	Dosepo [µg]/AUC_{inf} [hr•µg/L] = [L/hr]
tPDE4i - activity	Total PDE4 inhibitory activity	($AUC_{roflumilast}$•$CF_{roflumilast}$) + ($AUC_{roflumilast\ N\text{-}oxide}$•$CF_{roflumilast\ N\text{-}oxide}$), where $CF_{roflumiast} = fu_{roflumilast}/(IC50_{roflumilast}$•24hr) and $CF_{roflumilast\ N\text{-}oxide} = fu_{roflumilast\ N\text{-}oxide}/(IC50_{roflumilast\ N\text{-}oxide}$•24hr)

Estimation of pharmacokinetic parameter estimates were based on the actual time and calculated by a non-compartmental analysis (NCA) using WinNonlin Enterprise, Version 4.1, Pharsight North Carolina (NCA Model 200, extra vascular). Mean plasma concentration plots and tables were based on nominal times.

Statistical methods:

Primary variables and their statistical analysis

The primary variables are the extent (AUC_{tlast} and AUC_{inf}) of exposure and the rate (C_{max}) of absorption of roflumilast and roflumilast N-oxide.

Bioequivalence can be concluded if the two-sided 90% confidence interval of the point estimate for the difference of means of the primary variables falls within the bioequivalence margins ln θ_1 = ln (0.8) and ln θ_2 = ln (1.25). In addition to this statistical test – displayed by the ln-mean of Reference and Test and the ratio of the geometric means with its 90% confidence interval – , the primary parameters were summarized descriptively by treatment for each period, separately reporting geometric mean and its 68%-range.

Secondary variables and their statistical analysis

The estimated t_{max} and $t_{1/2}$ of roflumilast and roflumilast N-oxide, the oral clearance as well as the total PDE4 inhibitory activity are summarized descriptively by treatment for each period separately reporting mean (SE, SD), median (min, max) and geometric mean (68%-range).

SUMMARY - CONCLUSIONS

Demography characteristics

Mean (SD, SE) and median (min/max) values of age, height, weight and BMI

Subject	N	Mean	SD	SE	Median	Min	Max
Age [years]	24	63.2	8.86	1.81	66.0	47.0	78.0
Height [cm]	24	170	10.1	2.07	172	149	187
Weight [kg]	24	74.2	11.9	2.43	74.4	57.5	101
BMI [kg/m^2]	24	25.4	1.97	0.403	25.6	22.1	29.8

A total of 24 Caucasian healthy subjects (12 male, 12 female), with an age between 47 and 78 years completed the study.

Pharmacokinetic results:

Roflumilast: Mean pharmacokinetic parameter estimates (geometric mean, 68%-range) following a single dose of 500 µg roflumilast of Formula B = Reference – Treatments B_1&B_2, and Formula E = Test – Treatments A_1&A_2

	Formula B (B_1&B_2)			Formula E (E_1&E_2)		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{tlast}	51.3	33.0	79.8	51.1	33.5	78.0
AUC_{inf}	56.9	36.7	88.2	56.6	37.3	85.8
C_{max}	8.21	6.45	10.4	9.59	7.43	12.4
$t_{1/2}$	26.9	18.2	39.7	26.6	18.4	38.6
t_{max} *	0.75	0.50	3.00	0.75	0.50	1.50
CL/F	8.79	5.67	13.6	8.83	5.83	13.4

*t_{max} displayed as median and min, max

For roflumilast, the mean pharmacokinetic parameter estimates after Formula B and E were comparable. The mean value of peak concentration after Formula B was lower when compared with that after Formula E.

Roflumilast: AUC_{tlast}, AUC_{inf} and C_{max} mean ratios (90% CI) following a single dose of 500 µg roflumilast of Formula B = Reference, and Formula E = Test

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
AUC_{tlast}	Formula B	Formula E	51.35	51.12	99.55	95.12	104.20
AUC_{inf}	Formula B	Formula E	56.85	56.61	99.57	95.34	103.99
C_{max}	Formula B	Formula E	8.21	9.59	116.85	110.77	123.25

Ratio: Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test /Reference).

For roflumilast, 90% confidence intervals of AUC_{tlast}, AUC_{inf} and C_{max} mean ratios were within the bioequivalence range of 80 to 125%.

Roflumilast N-oxide: Mean pharmacokinetic parameter estimates (geometric mean, 68%-range) following a single dose of 500 µg roflumilast of Formula B = Reference – Treatments B_1&B_2, and Formula E = Test – Treatments A_1&A_2

	Formula B – (B_1&B_2)			Formula E – (E_1&E_2)		
	Geo. Mean	68% Range		Geo. Mean	68% Range	
AUC_{tlast}	528	375	744	527	375	740
AUC_{inf}	574	386	855	568	387	832
C_{max}	9.53	7.47	12.2	9.78	7.53	12.7
$t_{1/2}$	32.6	22.6	47.0	31.2	22.4	43.5
t_{max} *	4.00	2.02	48.0	4.00	1.00	48.0

*t_{max} displayed as median and min, max

For roflumilast N-oxide, the mean pharmacokinetic parameter estimates after Formula B and E were similar.

Roflumilast N-oxide: AUC_{tlast}, AUC_{inf} and C_{max} mean ratios (90% CI) following a single dose of 500 µg roflumilast of Formula B = Reference and Formula E = Test

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
AUC_{tlast}	Formula B	Formula E	528.35	526.89	99.72	96.02	103.57
AUC_{inf}	Formula B	Formula E	574.33	567.53	98.82	94.77	103.04
C_{max}	Formula B	Formula E	9.53	9.78	102.67	99.03	106.45

Ratio: Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test /Reference).

For roflumilast N-oxide, 90% confidence intervals of AUC_{tlast}, AUC_{inf} and C_{max} mean ratios were within the bioequivalence range of 80 to 125%.

Total PDE4 Inhibitory Activity: Mean ratios (90% CI) following a single dose of 500 µg roflumilast of Formula B = Reference and Formula E =Test

	Ref	Test	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast AUC	Formula B	Formula E	56.85	56.61	99.57	95.34	103.99
Roflumilast N-oxide AUC	Formula B	Formula E	574.33	567.53	98.82	94.77	103.04
tPDE4i	Formula B	Formula E	1.11	1.09	98.85	94.86	103.00

Ratio: Ratio (Test/Reference) of treatment mean values, expressed as a percentage of Reference mean (100 x Test/Reference).

For the total PDE4 inhibitory activities, 90% confidence intervals of the mean ratios were within the bioequivalence range of 80 to 125%.

Safety results:

Twenty-four (24) subjects, 12 men and 12 women were dosed and completed the trial as planned. The study was performed according to the study protocol in all relevant parts. Overall, eighteen (18) subjects (75.0%) experienced adverse events (AE) in the present study.

There was no withdrawal due to AE. No death and no SAE or other significant AE was reported. The percentage of subjects who experienced at least one AE was similar in both treatment groups. After having received Treatment A (new yellow D-shaped roflumilast 500 µg tablet), 14 subjects out of 24 reported AEs and after having received Treatment B (current white round roflumilast 500 µg tablet), 12 subjects out of 24 reported AEs.

The most frequently reported AEs in both treatment groups were headaches. This was followed by back pain and nausea. Considering the intensity, most of the AEs experienced by subjects after Treatment A as well as after Treatment B were considered mild or moderate. One (1) subject experienced 6 AEs, 3 after either treatment that were considered as being severe. All 6 AEs that were considered severe were reported from the SOC gastrointestinal disorders, under the preferred term ‘vomiting’.

Clinically relevant laboratory values which occurred in the course of the study were back to non-clinically relevant values at the follow-up examination. None of these changes was considered drug-related. Mean systolic and diastolic blood pressure values and pulse rates did not show any clinically relevant changes during the study.

Conclusions:

Roflumilast 500 µg tablet formulation B that has been used in most parts of the clinical development program and formulation E that is intended to be marketed are bioequivalent in accordance with FDA and EMEA guidance documents. Bioequivalence was established in a middle aged and elderly study population (47 to 78 years) of male and female healthy subjects. Both formulations were equally safe and well tolerated.

Date of report: 18-Jun-2009