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Clinical Report of Phase I Trial

Title	An open, single centre, single and repeated dose trial to investigate the pharmacokinetic profile of roflumilast and roflumilast N-oxide after administration of 500 µg dose of roflumilast in healthy Chinese subjects		
Trial Approval Letter ID:	**2010L04972**		
Trial ID:	**RO-2455-101-EC**		
Sponsor:	Nycomed: a Takeda company/ Nycomed GmbH	(Seal)	
Sponsor Contact:	Nycomed: a Takeda company Bernhard Scheibe (Germany)		
	Phone: +49 7531/84-0 Fax: +49 7531/84-2474		
Trial Phase:	Phase I, Human pharmacology		
Date of Trial Initiation:	16 May 2011	**Date of Trial completion:**	26 June 2011
Principal Investigational Unit/Institution:	Peking Union Medical College Hospital		
Principal Investigator:	[redacted]		
Lead Biostatistician:	Xianyi Kong		
Responsible Company of Statistical Analysis:	PPD, Inc		
Date of Report:	26 April 2012		
Site of Source Data Storage:	Peking Union Medical College Hospital, Clinical Pharmacology Research Center, Phase I unit		

1 Synopsis

Sponsor:	Nycomed：a Takeda company Nycomed GmbH
Investigational Medicinal Product:	Roflumilast Tablet

Title of the Trial:

An open, single centre, single and repeated dose trial to investigate the pharmacokinetic profile of roflumilast and roflumilast N-oxide after administration of 500 µg dose of roflumilast in healthy Chinese subjects

Principal Investigator and Trial Site:

This trial was conducted at Peking Union Medical College Hospital, Clinical Pharmacology Research Centre, Phase I unit (address: No. 41 Damucang Lane, Xicheng District, Beijing, 100032) in China, and the Principal Investigator was [redacted]

Publication (reference):

Not applicable.

Studied Period:

16 May 2011 (first subject in) to 26 June 2011 (last subject out).

Objectives:

The primary objective was to assess the pharmacokinetics of roflumilast and roflumilast N-oxide after single and repeated oral administrations of roflumilast 500 µg in healthy Chinese subjects. The secondary objectives were to investigate the safety and tolerability of roflumilast in Chinese subjects. In addition other pharmacokinetic (PK) characteristics of roflumilast and roflumilast N-oxide were assessed.

Methodology:

This was an open, single centre trial. Eligible subjects received a single dose in Period I and repeated doses in Period II with a one sequence trial design and a washout interval of at least 7 days (≥7 days) and not more than 14 days (≤14 days) between the two periods. The Investigator or deputy administered the investigational medicinal product to subjects and documented all necessary information. Following administration of the trial medication, the

Investigator or deputy performed a hand- and mouth check.

Plasma samples for the PK profile assessment were collected on Days 1 to 8 (Period I) at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after administration of a single dose of roflumilast 500 μg and on Days 14 to15 at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of a repeated dose of roflumilast 500 μg in Period II.

Plasma analysis method: high performance liquid chromatography - mass spectrometry/ mass spectrometry method.

Number of Subjects (Total and for Each Treatment) Enrolled and Analysed:

A total of 152 subjects were enrolled. Among which, 120 subjects were screening failures, 32 subjects were included in the safety analysis set and in the per-protocol set. 1 subject prematurely discontinued during the Period II, and 31 subjects completed this trial (23 male subjects, 8 female subjects).

Diagnosis and Criteria for Inclusion and Exclusion:

Inclusion Criteria:

1. Subject has been informed both verbally and in writing about the objectives of the trial, the methods, the anticipated benefits and potential risks and the discomfort to which he or she may be exposed, and has given written consent to participation in the trial prior to trial start and any trial-related procedure.
2. Healthy male or female (24 males and 8 females) Chinese ethnic origin subjects, aged 40 years and older.
3. Assessed as healthy based on a screening examination including medical history, physical examination, blood pressure, pulse rate, electrocardiogram (ECG) assessment, and clinical laboratory results.
4. Body weight according to a body mass index (BMI) between 19 and 28 kg/m^2, (both inclusive) and a body weight ≥50 kg.
5. Females with childbearing potential using a medically acceptable and reliable method of contraception for the entire trial duration, such as tubal ligation, hysterectomy, or intrauterine device without hormones, or post-menopausal females, the latter is defined as females who have had no menstrual period for at least 2 years.

Exclusion Criteria:

1. History or current evidence of clinically relevant allergies or idiosyncrasy to drugs or food.
2. History of allergic reactions to roflumilast or any inactive ingredients of the trial medication.
3. History or current evidence of any clinically relevant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematological, endocrinological, metabolic, neurological, psychiatric, or other disease (within the last 2 years).
4. History of malignancy within the past 5 years.
5. Electrocardiogram abnormalities of clinical relevance (e.g. QTc according to Bazett's formula: QTc >450 msec [male], QTc >470 msec [female], PQ ≥220 msec).
6. Blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic.
7. Elevated transaminases >2 x upper limit of normal range and/or increased total bilirubin >1.5 x upper limit of normal range.
8. Clinically relevant abnormalities in clinical chemical, hematological, or any other laboratory variables.
9. Chronic or clinically relevant acute infections.
10. Proneness to orthostatic dysregulation, fainting, or blackouts.
11. Positive results in any of the virology tests of acute or chronic infectious human immunodeficiency virus (HIV) and hepatitis A, B, and C virus infections.
12. Positive drug screen.
13. Abuse of alcohol or drugs.
14. Positive beta-HCG pregnancy test (female).
15. Pregnant or lactating females.
16. Lack of suitability for the trial:
    a) Treatment with any known enzyme inducing or inhibiting agents (St. John's wort, barbiturates, phenothiazines, cimetidine, ketoconazole etc.) within 30 days prior to or during the trial.
    b) Use of any medication (e.g. over-the-counter medication including herbal products and Chinese traditional medicines) within two weeks prior to trial drug administration or within less than 10 times the elimination half-life of the respective

drug, or anticipated concomitant medication during the treatment period (single intake of a drug may be accepted if judged by the investigators to have no clinical relevance and no relevance for the trial objectives).

c) Consumption of any enzyme inducing or inhibiting aliments and beverages (broccoli, brussel sprout, grapefruit, grapefruit juice, star fruit etc.) within 14 days prior to the start of the trial.

d) Consumption of any caffeine- or theophylline-containing product 48 hours prior to the first administration of trial medication.

e) Vegetarian diet or other peculiar dietary habits that would preclude the subject's acceptance of standardized meals.

f) Surgery of the gastrointestinal tract that may interfere with drug absorption (note: this was not applicable for minor abdominal surgery such as appendectomy and herniotomy).

g) Anticipated donation of spermatocytes or oocytes for medically assisted reproduction techniques during the trial and within 3 months after the last dose of the present trial.

h) Participation in drug trials within the last 3 months before start of the trial.

i) Blood donation within the last 30 days before start of the trial.

j) Smoking (non-smoker was defined in this trial when the subject has never smoked or stopped smoking at least 3 months before the start of screening).

k) Positive cotinine test.

17. Administrative reasons:

a) Lack of ability or willingness to give informed consent.

b) Anticipated non-availability for trial visits/procedures.

c) Anticipated lack of willingness or inability to cooperate adequately.

d) Vulnerable subjects (e.g. persons kept in detention).

e) Anticipated lack of ability or willingness to apply safe contraception without using hormonal contraceptives.

Investigational Medicinal Product, Dose and Mode of Administration, Batch No.:

Day 1 (Period I): single oral dose of roflumilast 500 µg in the morning.

Days 1 to 14 (Period II): repeated oral dose of roflumilast 500 µg in the morning.

Each dose was administered after an overnight fast along with 240 mL of non-carbonated water (e.g. tap water).

Batch Number: 10605949

Reference Product, Dose, Mode of Administration, Batch No.:

Not applicable.

Duration of Treatment:

- Trial Period I (single dose): 8 days (1 dose of 500 µg roflumilast, administered on Day 1)
- Wash-out Period: ≥7 days and ≤14 days
- Trial Period II (repeated dose): 15 days (14 doses of 500 µg roflumilast each, administered on Day 1 through Day 14)

Criteria for Evaluation:

Primary Variables:

The primary variables were AUC_{inf} (area under the plasma concentration-time curve extrapolated to infinity) and C_{max} (maximum plasma concentration) of roflumilast and its N-oxide based on plasma levels determined on Days 1 to 8 (Period I) at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, and 168 hours after administration of a single dose of roflumilast 500 µg, and AUC_{tau} (area under the plasma concentration-time curve during 24 hours) and C_{max} of roflumilast and its N-oxide based on plasma levels determined on Day 14 at the following time points: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours after administration of a repeated dose of roflumilast 500 µg in Period II.

Secondary Variables:

The secondary variables were $AUC_{0\text{-}tlast}$ (area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantification), $t_{1/2}$ (terminal elimination half-life), T_{max} (time to reach C_{max}) and λ_z (apparent first order terminal elimination rate constant) of roflumilast and its N-oxide as well as the accumulation ratio of AUC_{tau} and C_{max}. In addition, protein binding of roflumilast on Day 1 at 1 hour after dosing and of roflumilast N-oxide at 4 hours after administration of a single dose of roflumilast 500 µg in Period I was determined.

Safety Variables:

The safety of single and repeated dose of Roflumilast 500 µg was assessed by evaluation of the following variables: Treatment-emergent adverse events (AEs); Clinical laboratory variables as described in the trial protocol (hematology [at screening and final check], blood

chemistry [at screening and final check], coagulation [at screening and final check], serology [only at screening], pregnancy test [urine: on Day –1 in Period I and Day 13 in Period II; serum: at screening and final check], urine drug screen [at screening, on Day –1 in Period I and Day 13 in Period II], urine cotinine test [at screening, on Day –1 in Period I and Day 13 in Period II], alcohol breath test [at screening, on Day –1 in Period I and Day 13 in Period II] and urinalysis [at screening and final check]); Vital signs (at screening and final check; on treatment days [Day 1 and Day 2 in Period I, and Day 14 and Day 15 in Period II]); 12-lead electrocardiogram (ECG) (at screening and final check); physical examination (at screening and final check); body weight measurements (at screening and final check).

Statistical Methods:

The calculation of PK parameters (PK analysis) was performed for all subjects who had been exposed to roflumilast 500 µg and for whom any PK parameters could be calculated. The PK parameters were calculated using the validated WinNonlin software, Version 5.2 - (Pharsight, Cary, North Carolina, USA).

The roflumilast plasma concentration data were analysed using non-compartmental analysis (NCA Model 200). AUC_{inf} was calculated by the trapezoidal rule up to the last measured concentration above lower limit of quantification (LLOQ), and was extrapolated to infinity using standard techniques. $AUC_{0\text{-tlast}}$ was calculated by the trapezoidal rule up to the last measured concentration above LLOQ. C_{max} and T_{max} were obtained directly from the measured concentrations. The elimination half-life was to be calculated as $t_{1/2}=\ln(2) / \lambda_z$.

Exploratory subgroup analyses with respect to sex (male/female) were performed for AUC_{inf} and C_{max} using the WinNonLin analysis of variance. Data were presented as geometric means and 90% confidence intervals (90% CI).

Unscheduled measurements of safety data (for example unscheduled laboratory data or unscheduled ECG measurements) were not considered in the statistical analyses. Unscheduled measurements were included in subjects' listings.

Adverse events were categorized as being either baseline or treatment-emergent. All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 14.0. Incidences of AEs were summarized by preferred term and system organ class.

Descriptive summary statistics were calculated for clinical laboratory variables, vital signs, and ECG parameters. Scatter plot for each hematology, blood chemistry and coagulation variable by visit (screening visit and end of trial visit) were provided to analyse the outlier values.

Summary - Conclusions:

Demography and Baseline Characteristics

In the safety analysis set, the mean age was 44.7 years (ranging from 40 to 61 years). The mean values of height, weight and BMI were 162.4 cm (ranging from 145.0 to 178.5 cm), 63.6 kg (ranging from 52.0 to 88.4 kg) and 24.1 kg/m^2 (ranging from 20.0 to 27.9 kg/m^2), respectively. Only 2 of the 32 subjects were former smokers of 12.5 cigarettes per day averagely (ranging from 10 to 15 cigarettes per day). All of the 32 subjects were Chinese in ethnicity, and 24 subjects were male and 8 subjects were female.

Pharmacokinetic Results

Roflumilast

Mean roflumilast PK parameter estimates following single and multiple doses of 500 µg roflumilast are presented in the following table.

Roflumilast: Mean Pharmacokinetic Parameter Estimates (Geometric Mean, 68%-range) Following Single and Multiple Doses of 500 µg Roflumilast

	Single Dose			Multiple Dose		
	Geometric Mean	68% Range		Geometric Mean	68% Range	
AUC_{inf} [µg/L*h]	54.86	39.96	75.33	–	–	–
AUC_{tau} [µg/L*h]	–	–	–	56.48	41.42	77.00
C_{max} [µg/L]	10.55	7.94	14.00	12.45	9.93	15.61
t_{max} [a] [h]	0.75	0.25	2.50	0.75	0.50	2.50
$t_{1/2}$ [h]	21.84	11.96	39.89	–	–	–

[a] t_{max} displayed as median and minimum/maximum

The median accumulation of roflumilast after multiple as compared to single doses of 500 µg roflumilast is 1.5-fold for the systemic exposure (AUC) and 1.2-fold for the peak concentration (C_{max}). The mean AUC_{tlast} and C_{max} are 2% and 21% lower in female as compared to male subjects following a single dose. The mean AUC_{tau} and C_{max} values were 4% higher and 9% lower, respectively, in female as compared to male subjects following multiple doses of 500 µg roflumilast. The mean fraction unbound roflumilast in healthy Chinese subjects is 0.3%.

Roflumilast N-Oxide

Mean roflumilast N-oxide PK parameter estimates following single and multiple doses of 500 µg roflumilast are presented in the following table.

Roflumilast N-oxide: Mean Pharmacokinetic Parameter Estimates (Geometric Mean, 68%-range) Following Single and Multiple Doses of 500 µg Roflumilast

	Single Dose			Multiple Dose		
	Geometric Mean	68% Range		Geometric Mean	68% Range	
AUC_{inf} [µg/L*h]	610.75	478.95	778.83	–	–	–
AUC_{tau} [µg/L*h]	–	–	–	640.62	501.22	818.79
C_{max} [µg/L]	12.62	10.45	15.22	37.67	29.67	47.83
t_{max} [a] [h]	4.00	2.50	24.00	3.00	1.00	4.00
$t_{1/2}$ [h]	26.72	20.17	35.42	–	–	–

[a] t_{max} displayed as median and minimum/maximum

The median accumulation after multiple as compared to single doses of 500 µg roflumilast is 2.6-fold for the systemic exposure (AUC) and 2.9-fold for the peak concentration (C_{max}). The mean AUC_{tlast} value was 12% higher in female as compared to male subjects following a single dose. The mean C_{max} value was 7% higher in female as compared to male subjects following a single dose. Mean AUC_{tlast} and C_{max} values were 16% and 21% higher in female as compared to male subjects following multiple doses of 500 µg roflumilast. The mean fraction unbound roflumilast N-oxide in healthy Chinese subjects is 2%.

Safety Results

Eleven AEs were reported in 7 out of 32 subjects (21.9%) during Period I (single dose) and 10 of the AEs were judged by the investigator to be related to the trial treatment. No serious AEs (SAEs) were reported during Period I. All AEs reported by these 7 subjects were considered as mild in intensity.

One hundred and five AEs were reported in 29 out of 32 subjects (90.6%) during Period II (repeated dose) and 102 of the AEs were judged by the investigator to be related to the trial treatment. The majority of the AEs were considered as mild (97 AEs in 23 out of 32 subjects, 71.9%) or moderate (6 AEs in 5 out of 32 subjects, 15.6%) in intensity. For 1 subject 2 severe AEs were reported, 1 of the 2 AEs also met the criteria for a SAE (deafness neurosensory). The event started as a non-serious AE of tinnitus 3 days after repeated dose of roflumilast in Period II. This was the only SAE reported in the trial. The Investigator considered the deafness neurosensory to be related to roflumilast, and described the temporal relationship and no respective medical history as the explanations. The causal relationship was assessed by the sponsor as not related to roflumilast, since alternative explanations for the occurrence of this SAE are available.

None of the subjects reported AEs related to trial specific procedures. One subject prematurely discontinued from this trial due to an AE (skin infection) that was unrelated to

trial treatment. Adverse events were continuing in 3 subjects at the end of this trial. The outcome of one AE for 1 subject was unknown at the end of this trial. Most of the AEs (111 AEs; 95.7%) recovered or resolved during the course of the trial.

Among subjects with normal values of laboratory parameters at Screening, only 1 subject was detected with values below the lower limit of the alert range in haemoglobin. No subject had laboratory values higher than the upper limit of the alert range in laboratory parameters at the last measurement (End of Trial Visit).

There was no clinical relevant finding observed in vital signs, physical examination (including body weight) and ECGs examination.

Conclusions:

Pharmacokinetic Conclusions

After the administration of single and multiple doses of 500 µg roflumilast to healthy Chinese subjects, roflumilast and roflumilast N-oxide exhibited typical mean concentration-time profiles. After the application of roflumilast once daily for 14 days, steady state was reached. Roflumilast and roflumilast N-oxide showed a typical mean accumulation ratio when systemic exposures (compared with single dose, 1.5-fold after multiple dose for roflumilast and 2.6-fold for roflumilast N-oxide) and peak concentrations (compared with single dose, 1.2-fold after multiple dose for roflumilast and 2.9-fold for roflumilast N-oxide) were compared after single and multiple applications of the trial drug. As in other populations, mean systemic exposures and peak concentrations of roflumilast N-oxide are slightly higher in female as compared to male healthy Chinese subjects. Mean free concentrations of roflumilast and roflumilast N-oxide are similar in healthy Chinese as compared to other ethnic groups, which will be documented in a separate report.

Safety Conclusions

A total of 116 AEs were reported in 29 out of 32 subjects included in this study. All AEs were of mild or moderate intensity with the exception of 1 subject who reported 2 AEs of severe intensity. Almost all AEs resolved during the trial and only 1 subject prematurely discontinued from this trial due to an AE (skin infection) that was unrelated to the trial treatment. One event was classified as an SAE. No deaths were reported.

Laboratory values did not show any clinically relevant changes between the screening and post-trial examination. After intake of the trial medication, no clinically relevant alterations were observed during physical examination (including ECG, vital signs and body weight).

Assessments of AEs, laboratory investigations, vital signs and ECG measurements, and

physical examinations (including body weight) did not reveal any safety concerns. Overall, safety data indicate that daily oral doses of 500 µg roflumilast were safe and well tolerated in healthy Chinese subjects.
Date of Report: 26 April 2012