2 Clinical Trial Synopsis

Title of the clinical trial:

Pharmacokinetic parameters of roflumilast and its active metabolite roflumilast N-oxide after a single 500-µg dose of roflumilast in healthy Mexican subjects

Short Title / Acronym: PK-MX029

Trial Site:

CINDETEC (*Centro de Investigación y Desarrollo Tecnológico en Enfermedades Cronicas/* Research and Technological Development Center on Chronic Diseases)

Studied period:

19-Jul-2011 (FSFV) to 30-Oct-2011 (database lock)

Phase of Development:

Phase I

Objectives:

- **Primary objective:**

To determine the pharmacokinetic parameters (PkP) of roflumilast and roflumilast N-Oxide after a single dose of roflumilast 500µg in healthy Mexican population.

- **Secondary objective:**

To determine the safety and tolerability profile of roflumilast 500µg in healthy Mexican population and the total PDE4 inhibitory (tPDE4i) activity of roflumilast.

Methodology:

- Open-label, single-dose, single-centre clinical trial performed to study the PkP of roflumilast and roflumilast N-oxide in a group of 26 healthy Mexican volunteers of both sexes, between 18 and 47 years.
- The clinical trial (CT) was divided in three main stages: analytic phase, clinical phase and evaluation phase. During the analytic phase, the validation of analytical procedures was developed. The clinical phase included volunteer screening, clinical intervention and 15 days follow-up. Finally, during documentation phase, the CT report (Spanish) was prepared and delivered to Local Sanitary Authorities, full CT documentation and closing were carried out.
- Roflumilast and roflumilast N-oxide were quantified in plasma by ultra-performance liquid chromatography (UPLC) coupled with mass spectrometry.
- The primary pharmacokinetic variables were $AUC_{0-\infty}$ and C_{max} of roflumilast and roflumilast N-oxide.
- Sampling times during clinical intervention:

Sample number	Time after drug administration (h)	Schedule example
1	0	7:50 am
2	0.25	8:15 am
3	0.5	8:30 am
4	0.75	8:45 am
5	1	9:00 am
6	1.25	9:15 am
7	1.5	9:30 am
8	2	10:00 am
9	4	12:00 pm
10	6	14:00 pm
11	8	16:00 pm
12	10	18:00 pm
13	12	20:00 pm
14	14	22:00 pm
15	24	8:00 am day 2
16	48	8:00 am day 3
17	96	8:00 am day 5
18	120	8:00 am day 6
19	168	8:00 am day 8
20	216	8:00 am day 10

No. of patients planned and analyzed:

- Planned sample size: 26 healthy volunteers
- Analysed sets:

	N
Screened	80
Entered	26
Treated w/Roflumilast 500 µg	26
Discontinued	0

Diagnosis and main criteria for inclusion:

- Signing of the informed consent form prior to the performance of any procedure.
- Subjects of both sexes, between 18 and 55 years of age.
- Clinically healthy.
- Body Mass Index (BMI) between 18.5 and 24.9 kg/m^2.
- Women with effective or definitive contraceptive methods (bilateral tubal occlusion, hysterectomy or postmenopausal, defined as the absence of menstruation for at least 2 years).
- Availability to attend the visits and comply with all the study requirements.

IMP, dose and mode of administration, batch no(s).:

Active ingredient: roflumilast

Pharmaceutical form: Tablets

Administration route: Oral

Dose: 500 □g

Manufacturer: Nycomed GmbH (Konstanz, Germany; Oranienburg GmbH, Germany).

Batch number: 10635137

Expiry date: September 2012

Duration of treatment:

Each subject underwent one single-dose of roflumilast 500 µg administered orally.

Criteria for evaluation:

Pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide following oral administrations was obtained by a non-compartmental analysis approach.

Statistical methods:

- Plasma C_{max} and T_{max} were obtained by graphical analysis, directly from the data. The terminal plasma half time ($T_{½}$) was calculated as $\ln 2/\lambda_Z$, where λ_Z is the individual elimination constant.

Summary-Conclusions

Demography and baseline characteristics

Demographic Data (n=26)		
Age (years)	Mean ± SD	26.0 ± 7.22
	Range	18-47
Age groups	18-20	4
	21-30	17
	31-55	5
	Female	10
	Male	16
BMI*	Mean ± SD	21.81 ± 1.90
	Range	18.51 - 24.98

Pharmacokinetic parameters

- Arithmetic means of roflumilast pharmacokinetic parameters were as follows: $AUC_{0-\infty}$ 69.5 µg·h/L (SEM±5.5, min. 36.5 and max. 151.3); C_{max} 11.4 µg/L (SEM±0.74, min. 5.5 and max. 25.5); $T_{½}$ 11.32 h (SEM±1.28, min. 5.6 and max. 38.5); T_{max} median was 0.73 h (min. 0.25 and max. 1.98).
- Arithmetic means of N-oxide pharmacokinetic parameters were as follows: $AUC_{0-\infty}$ 715.1 µg·h/L (SEM±44.8, min. 413.1 and max. 1474.0); C_{max} 13.1 µg/L (SEM±0.54, min. 5.9 and max. 18.4); $T_{½}$ 45 h (SEM±2.1, min. 30.6 and max. 78.3); T_{max} median was 3.98 h (min. 1.5 and max. 24).
- The exposure to roflumilast and roflumilast N-oxide observed in this study was found to be higher when compared to historical data from the Caucasian subjects, but within the range of other Non-Caucasian populations such as Black, USA Hispanics and Asian subjects.

Pharmacokinetic parameter estimates of roflumilast in Mexican Healthy Volunteers

Roflumilast				
	T_{max} (h)	C_{max} (µg/L)	$AUC_{0-\infty}$ (µg•h/L)	$t_{1/2}$ (h)
N	26	26	26	26
Mean	0.778	11.402	69.537	11.317
Standard Deviation	0.426	3.79	28.101	6.559
Standard Error	0.084	0.743	5.511	1.286
Variance	0.181	14.365	789.643	43.016
Minimum	0.25	5.555	36.471	5.596
Median	0.733	11.05	62.805	12.119
Maximum	1.983	25.495	151.311	38.501
Variation Coefficient	54.722	33.241	40.411	57.955
Geometric Mean	0.692	10.9	65.101	10.097
Skewness	1.528	1.876	1.486	2.728
Kurtosis	1.765	5.48	1.984	9.459
Kolmogorov S P Value	0.166	0.675	0.463	0.073

Pharmacokinetic parameter estimates of roflumilast N-oxide in Mexican Healthy Volunteers

Roflumilast N-oxide				
	T_{max} (h)	C_{max} (µg/L)	$AUC_{0-\infty}$ (µg•h/L)	$t_{1/2}$ (h)
N	26	26	26	26
Arithmetic Mean	4.72	13.14	715.09	40.90
Standard Deviation	4.18	2.73	228.69	9.38
Standard Error	0.82	0.54	44.85	1.84
Variance	17.50	7.43	52297.30	87.99
Minimum	1.48	5.86	413.15	28.79
Median	3.98	12.53	664.53	41.13
Maximum	23.97	18.38	1474.02	67.93
Variation Coefficient (%)	88.56	20.75	31.980	22.93
Geometric Mean	4.00	12.83	685.48	39.92
Skewness	4.00	-0.46	1.50	0.70
Kurtosis	15.76	0.35	2.78	0.71
Kolmogorov S P Value	0.00	0.83	0.41	0.91

Safety

- Adverse events reported during the study were known roflumilast adverse events, of mild or moderate severity and of transient duration.
- No subjects discontinued the study because of AEs
- No serious adverse events or deaths occurred during or after the trial.
- According to the observed safety profile, administration of roflumilast in healthy Mexican population was tolerable and no further significant influences on safety are expected. Roflumilast 500 mcg is considered an acceptable dose for Mexican subjects.