2 Synopsis

Title of the study: Relative bioavailability of new Roflumilast formulations

One study site in Germany.

Publication (reference): Not applicable

Studied period: 26-Jun-2006 (first subject in) to 18-Sep-2006 (last subject out)

Clinical phase: Phase I

Objectives:

The primary objective was to assess the relative bioavailability of Roflumilast Dry Syrup (Treatment B)-, Roflumilast Pellets (Treatment C)-, and Roflumilast Spheres (Treatment D) formulation, as compared with the Roflumilast Standard (Treatment A) formulation.

The secondary objectives were to assess quantitatively and qualitatively the possible gustatory change after the oral administration of the tablet/suspensions, containing the Roflumilast Standard (Treatment A) formulation, and Roflumilast Dry Syrup (Treatment B)-, Roflumilast Pellets (Treatment C)-, and Roflumilast Spheres (Treatment D) formulation, assuming a 'neutral' taste before the administration of the study medication; and to assess safety and tolerability.

Methodology:

This was a randomized, open-label, single-centre, four-period changeover, single-dose study conducted in healthy male subjects. The study started with the screening examination within 21 days prior to the first administration of the study medication. Subjects were randomized and hospitalized on the day before study medication administration. After an overnight fasting period of at least 10 h the subjects entered the first of four treatment periods (7 days each) and received a single dose of the respective study medication in the morning of Day 1 of each treatment period. The subjects were discharged 24 h p.a. if medically appropriate. After a washout period of at least 10 days subjects returned to the study site for the next treatment period. The study was completed with a post-study examination that was performed within 6 to 14 days after the last administration of study medication.

For pharmacokinetic analyses blood samples were drawn on Day 1 to 6 of the respective treatment period at pre-dose, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 14 h, 24 h, 48 h, 72 h, 96 h, and 120 h p.a. Pharmacodynamic assessment by visual analogue scale and description of gustatory sensations were performed on Day 1 of each treatment period at 5 min, 15 min, and 60 min p.a.

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

As the pharmacokinetic characteristics were only known for the Roflumilast Standard formulation but not for the new formulations, no formal sample size calculation was done. In order to obtain reliable results, 16 subjects were recruited for this four-period changeover study.

Diagnosis and main criteria for inclusion:

To be eligible, a subject complied with all of the following criteria:

- subject was informed both verbally and in writing about the objectives of the clinical study, the methods, the anticipated benefits and potential risks and the discomfort to which he may be exposed, and gave written consent to participation in the study prior to study start and any study-related procedure;
- healthy male subjects of Caucasian ethnic origin, aged between 18 and 50 years (inclusive). Assessed as healthy based on a screening examination including medical history, physical examination, blood pressure, pulse rate, ECG assessment, and clinical laboratory results;
- intact tongue and oral cavity;
- normal body weight as evidenced by BMI (Body Mass Index) between ≥ 18 and ≤ 28 kg/m², and body weight > 50 kg.

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

Roflumilast Standard, 500 µg, tablet, single dose, per os, Batch No 00000609;

Roflumilast Dry Syrup, 500 µg, granules, single dose, per os, Batch No 00001094;

Roflumilast Pellets, 500 µg, granules, single dose, per os, Batch No 00001076;

Roflumilast Spheres, 500 µg, granules, single dose, per os, Batch No 00000974.

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

Not applicable.

Duration of treatment:

One single dose of Roflumilast 500 µg (different formulations) was administered on Day 1 of each treatment period.

Criteria for evaluation:

Primary pharmacokinetic parameters

$AUC_{0\text{-}tlast}$ and C_{max} of Roflumilast and Roflumilast N-oxide

Secondary pharmacokinetic parameters

$AUC_{0\text{-}inf}$, $AUC_{0\text{-}tmax}$, t_{max}, $t_{½}$, MRT, and CL/F of Roflumilast and $AUC_{0\text{-}inf}$, $AUC_{0\text{-}tmax}$, t_{max}, and $t_{½}$ of Roflumilast N-oxide as well as safety and tolerability of the treatment.

Statistical methods:

For comparison of the primary pharmacokinetic parameter estimates of analytes, calculation of the ratio for the medians for Test vs Reference and corresponding 90% confidence intervals based on a multiplicative model was performed. Equivalence was concluded, if the confidence interval lay entirely within the equivalence range (0.80 – 1.25 for C_{max} and $AUC_{0\text{-}tlast}$). All analyses were interpreted in an exploratory manner. The statistical model was an ANOVA, addressing the changeover design with period, treatment, and sequence as fixed effects and subject nested in the sequence as random effect.

Secondary pharmacokinetic and pharmacodynamic parameter estimates were analyzed in a descriptive manner, including summary statistics, such as median, 68%-range, mean, SD or SEM, and geometric mean and geometric 68%-range, where appropriate. A coding of the description of gustatory sensations (qualitative assessment) was performed according to appropriate terms. Descriptive analyses were performed on these terms.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

All subjects were of male Caucasian origin. Eight subjects were non-smokers, four were current smokers, and one ex-smoker (valid cases set). The mean age was 29 years, mean height 182 cm, mean weight 82 kg, and mean BMI 25 kg/m^2.

Pharmacokinetic results

For Roflumilast, ratios of $AUC_{0\text{-tlast}}$ indicated a similar systemic exposure after the application of Roflumilast Dry Syrup and Roflumilast Pellets when compared with Roflumilast Standard (with their 90% confidence intervals entirely included in the equivalence range of 80% to 125%) but a 28% lower systemic exposure after the application of Roflumilast Spheres.

Ratios of C_{max} indicated a 48%, 10%, and 77% lower peak concentration after the application of Roflumilast Dry Syrup, Roflumilast Pellets, and Roflumilast Spheres, respectively, when compared with Roflumilast Standard.

Roflumilast: $AUC_{0\text{-tlast}}$ and C_{max} ratios of geometric least square means and 90% CI of the formulations Roflumilast Dry Syrup vs Roflumilast Standard, Roflumilast Pellets vs Roflumilast Standard, and Roflumilast Spheres vs Roflumilast Standard

	Ref (N = 13)	Test (N = 13)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
$AUC_{0\text{-tlast}}$	Standard	Dry Syrup	42.40	38.93	91.83	85.04	99.17
	Standard	Pellets	42.40	44.22	104.31	96.59	112.64
	Standard	Spheres	42.40	30.73	72.48	67.12	78.26
C_{max}	Standard	Dry Syrup	6.90	3.59	52.00	43.79	61.75
	Standard	Pellets	6.90	6.18	89.54	75.41	106.32
	Standard	Spheres	6.90	1.60	23.16	19.50	27.50

$AUC_{0\text{-tlast}}$ = area under the plasma concentration time curve up to the last sampling with a concentration above the LLOQ, CI 90 = 90% confidence interval estimate expressed as percentage of Reference mean (100×Test/Reference), C_{max} = maximum plasma concentration; Geo LSM = geometric least square mean, LLOQ = lower limit of quantification, N = number of subjects in a specified analysis set, Ratio = Ratio (Test/Reference) of treatment mean values expressed as a percentage of reference mean (100×Test/Reference), Ref = reference.

For Roflumilast N-oxide, ratios of $AUC_{0\text{-tlast}}$ indicate a similar systemic exposure after the application of Roflumilast Dry Syrup and Roflumilast Pellets when compared with Roflumilast Standard (with their 90% confidence intervals entirely included in the equivalence range of 80% to 125%) but a 35% lower systemic exposure after the application of Roflumilast Spheres.

Ratios of C_{max} indicate a similar peak concentration after the application of Roflumilast Pellets (with the 90% confidence intervals entirely included in the equivalence range of 80% to 125%) but a 25% and 51% lower peak concentration after the application of Roflumilast Dry Syrup and Roflumilast Spheres, respectively, when compared with Roflumilast Standard.

Roflumilast N-oxide: $AUC_{0\text{-}tlast}$ and C_{max} ratios geometric least square means and 90% CI of the formulations Roflumilast Dry Syrup vs Roflumilast Standard, Roflumilast Pellets vs Roflumilast Standard, and Roflumilast Spheres vs Roflumilast Standard

	Ref (N = 13)	Test (N = 13)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
$AUC_{0\text{-}tlast}$	Standard	Dry Syrup	435.39	391.71	89.97	84.87	95.37
	Standard	Pellets	435.39	447.53	102.79	96.97	108.95
	Standard	Spheres	435.39	280.86	64.51	60.86	68.38
C_{max}	Standard	Dry Syrup	8.77	6.62	75.45	69.52	81.88
	Standard	Pellets	8.77	8.26	94.15	86.76	102.17
	Standard	Spheres	8.77	4.29	48.93	45.09	53.1

$AUC_{0\text{-}tlast}$ = area under the plasma concentration time curve up to the last sampling with a concentration above the LLOQ, CI 90 = 90% confidence interval estimate expressed as percentage of Reference mean (100×Test/Reference), C_{max} = maximum plasma concentration; Geo LSM = geometric least square mean, LLOQ = lower limit of quantification, N = number of subjects in a specified analysis set, Ratio = Ratio (Test/Reference) of treatment mean values expressed as a percentage of reference mean (100×Test/Reference), Ref = reference.

Roflumilast Dry Syrup, Pellets and Spheres were bioavailable to a different extent in humans. If standard bioequivalence criteria were applied, as defined by FDA guidance on bioequivalence and bioavailability, all three formulations would have failed when compared with Roflumilast Standard. However, a great similarity was observed between Roflumilast Pellets and Roflumilast Standard, only failing to reach bioequivalence with respect to C_{max} of Roflumilast.

Pharmacodynamic results

For all four formulations, the gustatory sensation ‘neutral’ was reported by the majority of subjects.

Safety results

During treatment, 14 subjects (93.3%) experienced a total of 41 AEs. The most frequently reported AEs were gastrointestinal disorders and nervous system disorders. The majority of the reported AEs were of mild intensity and most of them resolved completely. None of the AEs led to study discontinuation. No SAEs or deaths were reported.

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

Conclusions

Roflumilast Dry Syrup, Pellets and Spheres were bioavailable to a different extent in humans. If standard bioequivalence criteria were applied, as defined by FDA guidance on bioequivalence and bioavailability, all three formulations would have failed when compared with Roflumilast Standard. However, a great similarity was observed between Roflumilast Pellets and Roflumilast Standard, only failing to reach bioequivalence with respect to C_{max} of Roflumilast. For all four formulations, the gustatory sensation 'neutral' was reported by the majority of subjects. The safety data obtained in this study indicated, that treatment with Roflumilast 500 µg tested in different formulations was safe and well tolerated.

Date of report: 19-Jul-2007