Synopsis of study report: 80/2002
Location in Module 5:

Study Code:
BY217/FHP032

Report Version:
Version 2.0 (dated 10 December 2004)

Title of the study: Study on the pharmacokinetics of single oral doses of 100 µg and 250 µg roflumilast in children with mild to moderate asthma

Study centers: National Jewish Medical and Research Center, Department of Pediatrics, 1400 Jackson Street, Denver, Colorado 80206, USA; Children's Mercy Hospital, Department of Pediatrics, 2401 Gillham Road, Kansas City, MO 64108, USA.

Publication (reference): not applicable

Study period (years): 27 December 2000 – 25 June 2001 **Clinical Phase:** I

Objectives:
- Primary: To determine the pharmacokinetic characteristics of roflumilast and its main metabolite (roflumilast N-oxide) after single oral doses of 100 µg and 250 µg roflumilast in children (6-10 years old) and adolescents (11-16 years old) with mild to moderate asthma.
- Secondary: To assess the safety and tolerability of oral roflumilast.

Methodology: The study was conducted according to an open, two-period design. Each patient received 100 µg roflumilast during Period 1 of the study, and 250 µg roflumilast during Period 2 of the study.

Blood samples for the determination of the pharmacokinetics of roflumilast (B9302-107) and the metabolite (B9502-044) were taken pre-dose and at 0.5h, 1h, 1.5h, 2h, 3h, 4h, 6h, 9h, 12h, 24h, 32h, 48h, and 60h post-dose in the 100 µg group. Patients receiving 250 µg roflumilast had an additional blood sample taken at 72 hours post-dose.

No. of subjects: Twenty-five patients were included in the study: 13 children (median age: 7 years) and 12 adolescents (median age: 12 years). Twenty-four of these patients completed the study according to the protocol (pp-population).

Blood pressure and pulse rate were measured at screening, at pre-dose as well as 1h, 2h, 4h, 12h, 24h post-dose and at the post-study examination. Resting ECG (12-lead), clinical laboratory (clinical chemistry, hematology, urinalysis) were determined at the screening and the post-study examination. Adverse events were monitored continuously during the study.

Diagnosis and criteria for randomization and inclusion into treatment:
Patients with mild to moderate asthma, in the following two age groups: 6-10 years for children and 11-16 years of age for adolescents.

Test product: Roflumilast

Dose: Single dose of 100 µg (Period 1) and 250 µg (Period 2)

Mode of administration: Oral administration with 180 ml water in the morning

Batch No.: BY217-44-1-1 (tablets of 100 µg) and
BY217-45-4-1 (tablets of 250 µg)

Duration of treatment: One day for each of the two Periods.

Reference product: None

Criteria for evaluation:

- Pharmacokinetics: Primary variables were the area under the curve (AUC) and the plasma concentration (C_{max}) for roflumilast and roflumilast N-oxide measured in plasma samples after single oral administration of 100 µg or 250 µg roflumilast. In addition, the terminal elimination half-life ($t_{1/2}$) and the time of maximum plasma concentration (t_{max}) for roflumilast and roflumilast N-oxide were determined.
- Safety and tolerability: Physical examination including vital signs (blood pressure, pulse rate) as well as a 12-lead-ECG, and clinical laboratory investigations (clinical chemistry, hematology, urinalysis) were used as safety variables. In addition, adverse events were monitored during the entire study.

Statistical methods:
The primary variable $AUC_{(0\text{-inf.})}$ was calculated by the trapezoidal rule and extrapolated techniques, whereas C_{max} was obtained directly from the serum concentration-time profiles. The biostatistical analysis was performed using the 'BIOQPC' program (Version 1.2.2). Point

estimates and 90% confidence intervals for the $AUC_{(0\text{-inf.})}$ and C_{max} ratios were evaluated in patients of the two age groups. When calculating the Test/Reference ratios, the 250 µg dose (test) was referenced to the 100 µg dose (reference) to test dose proportionality; to generate a measure of metabolic activity, roflumilast N-oxide (test) was referenced to roflumilast (reference).

The comparison with the historical pharmacokinetic data obtained from adults was done in an exploratory manner and is presented descriptively, giving mean (SEM, SD), median (min, max) or geometric mean (68% range). In addition, point estimates were generated from the ratios of $AUC_{(0\text{-inf.})}$, whereby roflumilast N-oxide (test) was referenced to roflumilast (reference).

The pharmacokinetic variables $t_{1/2}$ and t_{max} were analyzed for roflumilast and roflumilast N-oxide in an exploratory manner. The safety variables were analyzed in a descriptive manner using summary statistics (e.g. median, 68%-range, mean, SD) where appropriate.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

The following tables show the pharmacokinetics of roflumilast in children and adolescents; they also present the comparison to adults from historical data.

Roflumilast: Summary of mean pharmacokinetic characteristics following one single oral dose of 100 µg of roflumilast (Period 1) or one single oral dose of 250 µg of roflumilast (Period 2) in children and adolescents. Pharmacokinetic characteristics presented for adults following one single oral dose of 500 µg of roflumilast were evaluated in the study FHP010 (CSR 11/98). [geom. mean, 68% range; tmax: median (min, max)].

Pharmacokinetic Characteristic	**Children** Period 1 (100 µg)	**Children** Period 2 (250 µg)	**Adolescents** Period 1 (100 µg)	**Adolescents** Period 2 (250 µg)	**Adults FHP010 (500 µg)** historical comparison
$AUC_{(0\text{-inf.})}$ [µg/lxh]	**9.0** (6.2, 13.1)	**26.1** (17.1, 39.8)	**5.8** (3.9, 8.7)	**16.4** (11.4, 23.6)	**31.25** (24.69, 39.54)
C_{max} [µg/l]	**2.76** (1.84, 4.12)	**7.41** (5.81, 9.47)	**1.85** (1.27, 2.69)	**4.39** (3.34, 5.77)	**6.517** (4.979, 8.531)
t_{max} [h]	**0.50** (0.50, 1.50)	**0.50** (0.50, 1.00)	**0.50** (0.50, 2.00)	**0.50** (0.50, 1.50)	**0.75** (0.25, 2.00)
$t_{1/2}$ [h]	**8.54** (3.04, 23.95)	**8.32** (3.76, 18.42)	**7.44** (4.95, 11.19)	**10.80** (5.82, 20.04)	**10.30** (6.44, 16.45)

Assessment of dose proportionality in children: Point estimates and 90%-confidence limits for the Test/Reference ratios of roflumilast and roflumilast N-oxide $AUC_{(0\text{-inf.})}$ and C_{max} values

following one single oral dose of 100 µg of roflumilast (reference) and one single oral dose of 250 µg of roflumilast (test). Data were adjusted to the reference dose (100 µg).

Pharmacokinetic Characteristic	Roflumilast		Roflumilast N-oxide	
	Point estimate	90% confidence limit	Point estimate	90% confidence limit
$AUC_{(0\text{-inf.})}$	1.15	1.01 – 1.32	1.06	0.97 – 1.16
C_{max}	1.05	0.87 – 1.27	1.07	0.98 – 1.16

Data indicate that there is an overproportional increase in the AUC of roflumilast by 15% when the dose is increased from 100 µg to 250 µg in children. This increase is less pronounced for roflumilast N-oxide.

Assessment of dose proportionality in adolescents: Point estimates and 90%-confidence limits for the Test/Reference ratios of roflumilast and roflumilast N-oxide $AUC_{(0\text{-inf.})}$ and C_{max} values following one single oral dose of 100 µg of roflumilast (reference) and one single oral dose of 250 µg of roflumilast (test). Data were adjusted to the reference dose (100 µg).

Pharmacokinetic Characteristic	Roflumilast		Roflumilast N-oxide	
	Point estimate	90% confidence limit	Point estimate	90% confidence limit
$AUC_{(0\text{-inf.})}$	1.16	0.95 – 1.42	1.07	0.97 – 1.18
C_{max}	0.95	0.79 – 1.14	0.99	0.92 – 1.06

Safety results:

Two single doses of 100 µg roflumilast and 250 µg roflumilast were safe and well tolerated in children and adolescents. Overall, six adverse events occurred in 24 patients. Two of these adverse events were injection site pain (one reported as pain in extremity). All events were considered unrelated or unlikely related to treatment with study medication. Twelve-lead ECG recording revealed normal findings. The duration of the QTc interval was not prolonged by treatment with roflumilast. Laboratory values were unaffected by treatment with roflumilast. Vital signs remained stable over the 24 hours post-dosing during both treatment periods.

Conclusions:

Both in children and in adolescents, the point estimates for the $AUC_{(0\text{-inf.})}$ and for the C_{max} Test/Reference ratios (Test: 250 µg roflumilast; Reference: 100 µg roflumilast) were within their equivalence ranges for roflumilast and roflumilast N-oxide. However, for the $AUC_{(0\text{-inf.})}$ of roflumilast, the upper limit of the 90% confidence interval was outside the equivalence range in children and adolescents. Therefore, dose proportionality could not be found for roflumilast in any of these two groups. In contrast, dose proportionality was found for roflumilast N-oxide, as the 90% confidence intervals for $AUC_{(0\text{-inf.})}$ and for C_{max} were inside the respective equivalence ranges.

The systemic exposure of roflumilast adjusted by dose and body weight in children and adolescents was below the systemic exposure observed in adults. AUC Test/Reference ratios of the systemic exposures found for roflumilast N-oxide (Test) and roflumilast (Reference) indicated an increased metabolic activity in children and adolescents, explaining the lower systemic exposure of roflumilast found in children and adolescents.

The pharmacokinetic parameters $t_{1/2}$ and t_{max} were found to be independent from the administered dose and were similar in children and adolescents. Elimination half lives ($t_{1/2}$) for roflumilast and roflumilast N-oxide were similar to those found in adults. The pharmacokinetic parameter t_{max} was similar to that investigated in adults for roflumilast; in contrast, t_{max} for roflumilast N-oxide was 2 h in children and adolescents as compared to 13 h in adults. In adults, C_{max} was reached in a second maximum after a prolonged distribution phase which was not observed in children and adolescents.

In the present study, 100 µg roflumilast and 250 µg roflumilast, each administered as single dose, were safe and well tolerated in children and adolescents.