2 Synopsis

Title of the study:

Pharmacokinetics of 250 µg, 375 µg and 500 µg roflumilast in children and adolescents with mild to moderate asthma and healthy adult subjects – an open, one-period, three parallel group design with repeated oral doses of once daily roflumilast for 14 days

study center(s):

Northeast Medical Research Associates, Inc., North Dartmouth, MA 02747, USA and Sneeze, Wheeze & Itch Associates, LLC, Normal, IL 61761, USA

Children's Mercy Hospitals and Clinics, Kansas City, MO 64108, USA

Publication (reference):

Not applicable

Studied period:

18-Jul-2005 (first patient in) to 14-Sep-2005 (last patient out)

Clinical phase:

Phase I

Objectives:

The primary objective of the study was to characterize dose-corrected AUC_{TAU} and C_{max} of roflumilast and roflumilast N-oxide at steady-state on Day 14 in pediatric and adolescent patients with mild to moderate asthma and in healthy adults.

When the study was planned, the above primary objectives seemed to be appropriate. However, when the results of the study were evaluated, and especially during discussions with Prof Kearns, it became clear that the primary objectives of the study needed to be modified. Hence, AUC_{TAU} and C_{max} of roflumilast and roflumilast N-oxide were not only corrected for body weight but for the body weight and applied dose of roflumilast, i.e. body

weight- and dose-corrected AUC_{TAU} and C_{max}. These changes were viewed as uncritical, due to the entirely exploratory nature of the study.

The secondary objectives were to assess

- Body weight-corrected CL_{ss}/F, t_{max}, dose-corrected C_{avg}, λ_z, $t_{1/2}$ and PTF of roflumilast
- t_{max}, dose-corrected C_{avg}, λ_z and $t_{1/2}$ of roflumilast N-oxide
- AUC ratio of roflumilast N-oxide/roflumilast
- Safety and tolerability

Methodology:

This study was conducted according to an open, one-period, three parallel group design with repeated doses of once daily roflumilast for 14 days. It consisted of a screening examination, a treatment period (14 days), and a post-study examination. Children and adolescents were allocated to treatment groups according to body weight.

Children (aged 6 to 8, and 9 to 11 years) were assigned to the following treatment groups:

- 250 µg roflumilast for < 40 kg body weight
- 375 µg roflumilast for ≥ 40 kg to < 60 kg body weight

Adolescents (aged 12 to 14, and 15 to 17 years) were assigned to the following treatment groups:

- 375 µg roflumilast for ≥ 40 kg < 60 kg body weight
- 500 µg roflumilast for ≥60 kg body weight

Healthy adults (aged 18 to 40 years) received 500 µg roflumilast.

Blood samplings for pharmacokinetic purposes were performed on Day 14 at the following time points:

- At pre-dose (within 5 min prior to study drug administration) and 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, 14 h, and 24 h (10 samples) after oral administration of roflumilast once daily for 14 days.
- Trough levels of roflumilast and roflumilast N-oxide were determined using only the samples collected at pre-dose and 24 h post-dosing.

Analytical Method: Plasma concentrations of roflumilast and roflumilast N-oxide were measured using a validated high performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS/MS) detection. The calibration ranges were 0.1 to 20 µg/L for roflumilast and 0.1 to 40 µg/L for roflumilast N-oxide using a sample volume of 400 µL.

No. of patients/ subjects planned and analyzed:

Due to the exploratory nature of the study, no formal sample size calculation was performed. The sample size of 36 patients/ subjects was chosen due to feasibility.

	Full analysis set	Valid cases set
Children	12	12
Adolescents	12	12
Adults	14	12
Total	38	36

Diagnosis and criteria for inclusion:

Patients/ subjects were eligible for the study, if they met the following inclusion criteria:

- Patients/ subjects and/or parent(s)/legal guardian(s) had been fully informed verbally and in writing about objective, nature, significance, implications, and risks of the clinical study.
- Patients/ subjects and/or parent(s)/legal guardian(s) had given written consent to participation in the study prior to protocol specific procedures.
- Patients/ subjects were willing to adhere to dose and visit schedule.

A **pediatric/ adolescent patient** was eligible for the study, if all of the following inclusion criteria were met:

- History or current evidence of stable persistent mild to moderate bronchial asthma as defined by the following signs and symptoms:

  a. Patient was in a stable clinical state (no exacerbation or history of acute sinus or upper/lower airway infection four weeks prior to first drug administration)

  b. Stable asthma concomitant medication for at least four weeks. The following asthma medications were allowed:

     i. Inhaled glucocorticosteroids (estimated equipotent doses of inhaled glucocorticosteroids):

        - Beclomethasone dipropionate ≤ 1000 µg/day or

        - Budesonide ≤ 800 µg/day or

        - Flunisolide ≤ 2000 µg/ day or

        - Fluticasone ≤ 500 µg/ day or

        - Triamcinolone acetonide ≤ 2000 µg/ day

     ii. Short acting β2-agonists: albuterol ≤ 600 µg/ day

     iii. Leukotriene modifiers:

        - Montelukast sodium: 5 mg qpm (6 to 14 years), 10 mg qpm (> 14 years)

        - Zafirlukast: 10 mg bid (5 to 11 years), 20 mg bid (≥ 12 years);

c. Patient with stable, seasonal allergic rhinitis concomitant medication for at least four weeks. The following allergic rhinitis medications were allowed:

i. Nasal and ophthalmic steroids

ii. Short-acting antihistamines

- Fexofenadine: 60 mg or 180 mg tablet twice daily (children ≥ 12 years and adults); 30 mg tablet twice daily (children 6 to 11 years)
- Loratadine: 10 mg tablet once daily or 10 mg syrup once daily (children ≥ 6 years)
- Desloratadine: 5 mg tablet once daily (children ≥ 12 years and adults)
- Azelastine: 2 sprays per nostril twice daily (children ≥ 12 years and adults); 1 spray per nostril twice daily (children 5 to 11 years)
- Cetirizine: 5 mg or 10 mg tablet once daily (children ≥ 12 years and adults), 5 mg or 10 mg syrup 1 or 2 teaspoons once daily (children 6 to 11 years)

- Male or female patient, between 6 and 17 years (inclusive) at the time of study medication intake.
- Suitably simplified (according to age and intellectual maturity) study related information was made available to pediatric or adolescent study participant. Patient was willing to give written informed consent and/ or assent (between 6 and 17 years [inclusive]), and of parent(s)/legal guardian(s) and is able to provide informed consent and adhere to dose and visit schedules.

An **adult subject** was eligible for the study, if the following inclusion criteria were met:

- Healthy male or female subject, between 18 and 40 years (inclusive) at the time of study medication intake.
- Assessed as healthy, based on a screening examination including medical history, physical examination, pulse rate, blood pressure, electrocardiogram (ECG) and clinical laboratory results.

A **pediatric/ adolescent patient or adult subject** had to comply with all of the following inclusion criteria:

- Non-smoker or ex-smoker (defined as smoking cessation of at least one year, and a smoking history <10 pack years).
- Normal body weight as evidenced by a Body Mass Index (BMI) ≥ 18 and ≤ 28 kg/m².
- ECG at screening within normal limits or clinically acceptable to the investigator/sponsor.
- Willing to be confined to the research clinic from at least 1 hour prior to Day 14 until 24 hours after the roflumilast dose.
- On Day 14, willing to fast from 2 hours prior to dosing, until 2 hours after the roflumilast dose
- Birthday did not occur during the study in cases where it would affect substratification according to age.

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

- Roflumilast tablet, 125 µg, once daily, oral administration, 430170
- Roflumilast tablet, 250 µg, once daily, oral administration, 330200

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

- Roflumilast tablet, 500 µg, once daily, oral administration, 130220

Duration of treatment:

14 days

Criteria for evaluation:

Pharmacokinetic parameters, their definition and methods of estimation are summarized in the following table. Parameters, either modified or added to the original set in the study protocol, are marked in **bold**. Primary pharmacokinetic parameters are marked with an asterisk (*).

Parameter estimate	Definition	Method of Estimation/ Units
***AUC_{TAU} (=AUC_{τ})**	'Observed' area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ) within the dosing interval of 24 h (TAU = τ)	Linear trapezoidal method [hr•µg/L]
AUC_{BW}	Area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ) within the dosing interval of 24 h (TAU = τ), *corrected for body weight of the individual participant*	AUC_{TAU} [hr•µg/L]/ body weight [kg]
AUC_D	Area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ) within the dosing interval of 24 h (TAU = τ), *corrected for the applied dose of roflumilast*	AUC_{TAU} [hr•µg/L]/ dose [µg]
***AUC_{corr}**	'Corrected' AUC_{TAU}: Area under the plasma concentration-time curve up to the last sampling time with a concentration above the limit of quantitation (LOQ) within the dosing interval of 24 h (TAU = τ), *corrected for body weight of the individual participant and the applied dose of roflumilast*	AUC_{TAU} [hr•µg/L]/ dose [µg]/ body weight [kg]
***C_{max}**	'Observed' maximum plasma concentration	Observed [µg/L]

Parameter estimate	Definition	Method of Estimation/ Units
C_{maxBW}	Maximum plasma concentration *corrected for body weight of the individual participant*	Observed C_{max} [µg/L]/ body weight [kg]
C_{maxD}	Maximum plasma concentration *corrected for the applied dose of roflumilast*	Observed C_{max} [µg/L]/ dose [µg]
***$C_{max\ corr}$**	'Corrected' maximum plasma concentration: Maximum plasma concentration *corrected for body weight of the individual participant and the applied dose of roflumilast*	C_{max} [µg/L]/ dose [µg]/ body weight [kg]
C_{min}	Minimum plasma concentration	Observed [µg/L]
$t_{1/2}$	Half-life	$\ln(2)/\lambda_z$ [hr]
λ_z	Terminal rate constant	Absolute value of the slope of the linear regression line during the observed elimination phase of the concentration-time curved, displayed on the natural logarithm (ln) concentration scale [1/hr]
t_{max}	Time to reach C_{max}	Observed [hr]
C_{avg}	Average plasma concentration	AUC_{TAU} [hr•µg/L]/dosing interval TAU [hr] = [µg/L]
$C_{avg\ D}$	Average plasma concentration *corrected for the applied dose of roflumilast*	AUC_{TAU} [hr•µg/L]/dosing interval TAU [hr]/ dose [µg]
CL_{ss}/F	'Observed' apparent plasma clearance at steady state, after oral administration of roflumilast	$Dose_{po}$ [µg]/AUC_{TAU} [hr•µg/L] = [L/hr]
$CL_{ss}/F/BW$	'Corrected' apparent plasma clearance at steady state, after oral administration of roflumilast: Apparent plasma clearance at steady state, *corrected for body weight of the individual participant*	CL_{ss}/F [L/hr]/body weight (=BW) [kg] = [L/hr/kg]
PTF	Peak-Trough Fluctuation as fluctuation index	Computed as $100 \bullet (C_{max}-C_{min})/C_{avg}$, where C_{min} and C_{max} were obtained between 0 and τ.
tPDE4i - activity	Total PDE4 inhibitory activity	$(AUC_{roflumilast} \bullet CF_{roflumilast}) + (AUC_{roflumilast\ N\text{-}oxide} \bullet CF_{roflumilast\ N\text{-}oxide})$, where $CF_{roflumiast} = fu_{roflumilast}/(IC_{50\ roflumilast} \bullet 24hr)$ and $CF_{roflumilast\ N\text{-}oxide} = fu_{roflumilast\ N\text{-}oxide}/(IC_{50\ roflumilast\ N\text{-}oxide} \bullet 24hr)$
Metabolic ratio (= AUC ratio of roflumilast N-oxide/roflumilast)	The ratio of areas under the plasma concentration-time curve within the dosing interval of 24 h of roflumilast N-oxide and roflumilast	$AUC_{TAU\ roflumilast\ N\text{-}oxide}/AUC_{TAU\ roflumilast}$
$fu_{roflumilast}$	Fraction of roflumilast concentration in plasma, not bound (unbound) to plasma proteins = free fraction of roflumilast in plasma	Observed
$fu_{roflumilast\ N\text{-}oxide}$	Fraction of roflumilast N-oxide concentration in plasma, not bound (unbound) to plasma proteins = free fraction of roflumilast N-oxide in plasma	Observed

Parameter estimate	Definition	Method of Estimation/ Units
V_z/F	'Observed' apparent volume of distribution	$V_z = \frac{Dose}{\lambda_z * AUC_0^{\tau}}$ [L]
$V_z/F/BW$	'Corrected' apparent volume of distribution: Apparent volume of distribution, *corrected for body weight of the individual participant*	$V_z = \left(\frac{Dose}{\lambda_z * AUC_0^{\tau}} \right) / BW$ [L/kg]

Safety variables: Adverse events, vital signs (non-invasive blood pressure, pulse rate), ECG, clinical laboratory.

Statistical methods:

The pharmacokinetic parameter estimates (AUC_{corr}, AUC_{TAU}, $C_{max\ corr}$ and C_{max}) for plasma roflumilast and roflumilast N-oxide were calculated by a non-compartmental analysis using WinNonlin. Prior to analysis, the primary pharmacokinetic parameter estimates were log-transformed and an analysis of variance (ANOVA) model was used where appropriate using the 90% confidence interval (90%CI) for the ratio of the least-squares means (LSM) with the bioequivalence wizard module in WinNonlin.

Confidence intervals of 90% for the ratio of the LSM were performed. For each log-transformed parameter, a 90% CI was computed for the difference (Test-Reference) between the LSMs (Test (children < 40 kg, adolescents ≥ 40 kg to < 60 kg, and adolescents ≥ 60 kg, respectively)) and Reference (adults) on Day 14). The endpoints (points estimates and confidence limits) of the intervals were then exponentiated resulting in approximate 90% CI in the natural scale for the ratios of geometric means.

No difference in primary pharmacokinetic parameter estimates of roflumilast and roflumilast N-oxide between the populations was concluded, if the 90% CI for the ratio of geometric mean of the AUC_{corr}, AUC_{TAU}, $C_{max\ corr}$ and C_{max} values for a given parameter were entirely contained within 80% to 125%.

Summary statistics of primary and secondary pharmacokinetic parameter estimates are presented as mean, geometric mean, median, min/max, standard deviation (SD) or standard error of the mean (SEM) and geometric 68% range, where appropriate.

SUMMARY

Demography and baseline characteristics:

Demographic and anthropometric data are summarized in the following:

Characteristic	Children (N=12)	Adolescents (N=12)	Adults (N=12)
Age [years]			
Mean ±SD	9 ±1.8	15 ±1.4	25 ±6.3
Median (min, max)	9 (6, 11)	15 (12, 17)	24 (18, 34)
Gender			
Male, n (%)	6 (50)	6 (50)	6 (50)
Female, n (%)	6 (50)	6 (50)	6 (50)
Height [cm]			
Mean ±SD	139 ±12.8	166 ±9.6	170 ±11.5
Median (min, max)	135 (124, 163)	162 (155, 183)	168 (155, 196)
Body weight [kg]			
Mean ±SD	39.7 ±8.7	61.4 ±11.1	73.3 ±16.3
Median (min, max)	39 (28, 57)	59 (46, 86)	68.5 (52, 107)
Body mass index [kg/m^2]			
Mean ±SD	20.5 ±2.7	22.3 ±2.7	25.0 ±2.8
Median (min, max)	19.9 (18.2, 27.1)	22.2 (19.1, 28.1)	24.7 (20.9, 28.7)
Smoking			
Ex-smokers, n (%)	0 (0)	0 (0)	2 (17)
Non-smokers, n (%)	12 (100)	12 (100)	10 (83)
Race			
White, n (%)	5 (42)	8(67)	11 (92)
Black or African American, n (%)	2 (17)	2 (17)	0 (0)
American Indian or Alaska native, n (%)	1 (8)	0 (0)	0 (0)
Other, n (%)	4 (33)	2 (17)	1 (8)

Pharmacokinetic results:

In order to determine the appropriate dose for children and adolescents, FDA and EMEA guidelines recommend to obtain AUC and C_{max} values in children and adolescents, similar to those, associated with effectiveness and safety in adults. It is assumed that a dose of 500 µg roflumilast renders these effects in adults. In order to avoid undue overexposure to roflumilast and roflumilast N-oxide (safety) but also to achieve similar systemic exposures and peak plasma concentrations, as achieved in adults (effectiveness), children and adolescents received age- and body weight-adjusted doses of roflumilast, assuming that age and body weight were the main factors that influence the systemic exposure of roflumilast.

A total of 12 children (6 to 11 years), 12 adolescents (12 to 17 years) and 12 adults (18 to 34 years) completed this study, following a three parallel group design. Children and adolescents were stratified by age and body weight (children < 40 kg, children ≥ 40 to < 60 kg, adolescents ≥ 40 to < 60 kg, adolescents ≥ 60 kg) and received once daily 250 µg, 375 µg, 375 µg and 500 µg roflumilast for 14 days, respectively. Adults were included as a direct comparison and received the standard dose of 500 µg roflumilast for 14 days. Primarily, body weight- and dose-corrected AUC and C_{max} were assessed for each pediatric and adolescent subpopulation and compared with those of the adults.

Extent of systemic exposure

AUC values at steady state, as a measurement for systemic exposure, were 'corrected' for body weight and applied dose, to compare these values across different age groups. 'Observed' AUC values were also presented to demonstrate the robustness of the conclusions. In general, 'observed' and 'corrected' values were similar. For **roflumilast**, body weight and dose corrected systemic exposures were 9%, 29%, 12% and 22% lower in children < 40 kg, children ≥ 40 kg to < 60 kg, adolescents ≥ 40 kg to < 60 kg and adolescents ≥ 60 kg, respectively, when compared to adults. For **roflumilast N-oxide**, body weight and dose corrected systemic exposures were similar in children < 40 kg, and 12%, 19% and 32% lower in children ≥ 40 kg to < 60 kg, adolescents ≥ 40 kg to < 60 kg and adolescents ≥ 60 kg, respectively, when compared to adults.

Peak plasma concentrations

C_{max} values at steady state, as a measurement for peak plasma concentrations, were simultaneous corrected for body weight and applied dose, to compare these values across different age groups. 'Observed' C_{max} values were also presented to demonstrate the robustness of the conclusion. In general, 'observed' and 'corrected' values were similar. For **roflumilast**, body weight and dose corrected peak plasma concentrations were similar in children < 40 kg, children ≥ 40 kg to < 60 kg and adolescents ≥ 60 kg but 13% lower in adolescents ≥ 40 kg to < 60 kg, when compared to adults. For **roflumilast N-oxide**, body weight and dose corrected peak plasma concentrations were similar in children ≥ 40 kg to < 60 kg, and 8% higher in children < 40 kg but 11% and 30% lower in adolescents ≥ 40 kg to < 60 kg and adolescents ≥ 60 kg, respectively, when compared to adults.

Additional pharmacokinetic parameters

Body weight corrected dose of roflumilast

The mean applied roflumilast dose, corrected for body weight, was about 8 µg/kg (ranging from about 7 to 9 µg/kg) in children < 40 kg, about 8 µg/kg (ranging from about 7 to 9 µg/kg) in children ≥ 40 to < 60 kg, about 7 µg/kg (ranging from about 6 to 8 µg/kg) in adolescents ≥ 40 to < 60 kg, about 7 µg/kg (ranging from about 6 to 8 µg/kg) in adolescents ≥ 60 kg, and about 7 µg/kg (ranging from about 6 to 9 µg/kg) in adults.

Metabolic ratio

Metabolic ratios were similar in adolescents and adults (about 13) but slightly higher in children (between about 15 and 16), when compared to adults, indicating that the metabolic turn-over from roflumilast to roflumilast N-oxide is similar in adolescents and adults but slightly higher in children, when compared to adults.

Total PDE4 inhibitory activity of roflumilast

The total PDE4 inhibitory activity of roflumilast was similar in children < 40 kg and adolescents ≥ 40 kg to < 60 kg but 13% and 30% lower in children ≥ 40 kg to < 60 kg, and adolescents ≥ 60 kg, respectively, when compared to adults.

Dosing recommendations

In order to illustrate the rational for dosing recommendations, the main pharmacokinetic results of each treatment group are summarized in the following table:

Treatment group	**Daily Dose***	**Body Weight Corrected Dose****	**AUC_{corr} Roflumilast N-oxide*****	**$C_{max\ corr}$ Roflumilast N-oxide*****	**tPDE4i Activity*****
		Geom Mean (68% ranges)	Ratio (90%CIs)	Ratio (90%CIs)	Ratio (90%CIs)
Children <40kg	250	8 (7, 9)	102 (80, 132)	108 (81, 145)	96 (76, 122)
Children ≥40kg to <60kg	375	8 (7, 9)	88 (68, 113)	96 (71, 128)	87 (68, 110)
Adolescents ≥40kg to <60kg	375	7 (6, 8)	81 (63, 105)	89 (66, 119)	95 (75, 121)
Adolescents ≥60kg	500	7 (6, 8)	68 (53, 88)	70 (52, 93)	70 (55, 89)
Adults (Reference)	**500**	**7 (6, 9)**	**100**	**100**	**100**

* [µg], ** [µg/kg], *** [% Ref]

In order to determine the appropriate dose for children and adolescents, FDA and EMEA guidelines recommend to obtain AUC and C_{max} values in children and adolescents, similar to those, associated with effectiveness and safety in adults. It is assumed that a dose of 500 µg roflumilast renders these effects in adults. Hence, data of this study suggest that 250 µg roflumilast in children < 40 kg is similar to 500 µg roflumilast in adults. However,

equivalence was not statistically proven. Also, present data suggest that a dose of 375 µg roflumilast in children ≥ 40 kg to < 60 kg and adolescents ≥ 40 kg to < 60 kg result in a slight underexposure and that these groups should have received a dose of 500 µg roflumilast. However, the apparent underexposure of about 30% after a dose of 500 µg roflumilast in adolescents ≥ 60 kg might be explained by a lack of compliance of roflumilast intake. The examination of individual plots of this group showed that adolescent #50047 had a concentration-time profile that strongly resembled a 'single dose' profile with considerably lower roflumilast N-oxide concentrations at Day 14 than at Day 15. This might indicate, that not all subject in the adolescents ≥ 60 kg have fully complied with the assigned roflumilast intake. An increase of the dose in this group would bare the risk of overexposure with a lack of tolerability and safety. Therefore, a dose of 500 µg roflumilast in adolescents ≥ 60 kg might lead to exposure levels, comparable to those in adults. Overall, the above results should be interpreted with caution, since this study is entirely exploratory in nature and has not been powered for inferential conclusions.

Safety results:

Frequency of treatment-emergent AEs are summarized in the following:

	Number (%)[a] of Patients/ Subjects with AE				
	Children		**Adolescents**		**Adults**
	250 µg (N=6)	375 µg (N=6)	375 µg (N=6)	500 µg (N=6)	500 µg (N=14)
AEs	5 (83)	3 (50)	4 (67)	4 (67)	10 (71)
Serious AEs	0	0	0	0	0
Deaths	0	0	0	0	0
AEs with suggested causality[b]	1 (17)	1 (17)	2 (33)	1 (17)	6 (43)
AEs leading to study discontinuation	0	0	0	0	0

[a] Percentages are based on the total number of patients/ subjects in a treatment group.
[b] AEs assessed as likely or definitely related to the study medication according to the investigator.
N = number of subjects in each treatment.

None of the AEs was classified as serious AE. Although none of the treatment-related AEs led formally to study discontinuation, it seems likely that adults #50007 (nausea, headache, diarrhea and felt lethargic) and #50011 (loss of appetite, vertigo, nausea and anxiety) discontinued the study during the treatment period due to AE. One adult discontinued the study during baseline prior to the first intake of study medication due to the occurrence of an AE. During the 14-day treatment period, 8 children reported a total of 21 AEs, 8 adolescents reported a total of 13 AEs and 10 adults reported a total 39 AEs. Five [83%] children who received 250 µg roflumilast reported 15 AEs, and 3 [50%] children who received 375 µg roflumilast reported 6 AEs. Four [67%] adolescents received 375 µg roflumilast reported 7 AEs and 4 [67%] adolescents who received 500 µg roflumilast reported 6 AEs. The reported

AEs were in general of mild or moderate intensity. The most frequently reported treatment-emergent AEs were gastrointestinal disorders experienced by 6 adults, 5 children and 4 adolescents. They included vomiting, diarrhea, and nausea. Nervous system disorders were experienced by 7 adults, 3 children and 3 adolescents. The most frequent AE in this system organ class was headache. Physical examination, BP, and ECG and laboratory values did not reveal any clinically relevant changes during the course of the study neither in children and adolescents nor in adults.

CONCLUSIONS

Pharmacokinetics:

A dose of 250 µg roflumilast in children < 40 kg seemed to be comparable to 500 µg roflumilast in adults, although no equivalence was statistically proven. A dose of 375 µg roflumilast in children ≥ 40 kg to < 60 kg and adolescents ≥ 40 kg to < 60 kg resulted in a slight underexposure suggesting that these groups should have received a dose of 500 µg roflumilast. The apparent underexposure of about 30% after a dose of 500 µg roflumilast in adolescents ≥ 60 kg might be explained by a lack of compliance with roflumilast intake. A dose of 500 µg roflumilast in adolescents ≥ 60 kg might lead to exposure levels, comparable to those in adults.

Safety and Tolerability:

None of the AEs was classified as serious AE. Although none of the treatment-related AEs led formally to study discontinuation, it seems likely that adults #50007 (nausea, headache, diarrhea and felt lethargic) and #50011 (loss of appetite, vertigo, nausea and anxiety) discontinued the study due to AE. No age or dose related trend was discernible with respect to the kind, causality or intensity of adverse events. The most frequently reported treatment-emergent adverse events in all groups were gastrointestinal disorders, including vomiting, diarrhea, and nausea. Treatment with roflumilast in age- and dose-dependent manner, as applied in this exploratory study, did not reveal any risk not already identified in the previous clinical program. Overall, roflumilast was safe and well tolerated in children and adolescents with asthma between 6 and 17 years of age, and adults.

Date of report: **27-Feb-2007**