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Title of the study:

Pharmacokinetics and safety of roflumilast after once-daily repeated oral administration of 250 µg to patients with liver cirrhosis Child-Pugh A and B in comparison to healthy subjects

Study center:

Drug Research Centre Ltd, 8230 Balatonfüred, Ady E. U. 12, Hungary

Publication (reference):

Not applicable

Studied period (years):

24 August 2004 – 02 November 2004

Clinical phase: I

Objectives:

The aim of this study was to evaluate the steady-state pharmacokinetics of roflumilast and roflumilast N-oxide after repeated oral doses of 250 µg roflumilast administered once-daily for 14 days in patients with impaired hepatic function, i.e. liver cirrhosis Child-Pugh stage A and B as compared to matched healthy controls. Further, the study provided information on the safety and tolerability of this roflumilast treatment.

Methodology:

The study was conducted in a single center and had an open, non-randomized, one-period, repeated dose parallel group study design stratified according to hepatic function. It consisted

of a screening examination, a treatment period (Study Day -2 to 15 with a morning administration of 250 µg roflumilast on Study Days 1-14), and a post-study examination.

Subjects were assigned to 3 groups: healthy subjects (Group 1), patients with liver cirrhosis Child-Pugh stage A (Group 2), patients with liver cirrhosis Child-Pugh stage B (Group 3). Healthy subjects were matched to patients with liver cirrhosis Child-Pugh A according to sex, age and body weight.

Blood samplings for pharmacokinetic purposes were performed on the following days for roflumilast and roflumilast N-oxide:

- Study Day 14 (steady state): at pre-dose, 0.25 h, 0.5 h, 0.75 h 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 4 h, 5 h, 6 h, 8 h, 10 h, 12 h, 16 h and 24 h after morning dosing
- Study Days 12, 13, and 14: sampling within 30 min before dosing for determination of trough values. The trough plasma concentration on Study Day 14 served as pre-dose value.

Plasma protein binding: The blood samples taken 1 h, 4 h, 12 h, and 24 h after dosing were also used to determine protein binding i.e. the fraction of roflumilast and roflumilast N-oxide bound to plasma protein.

Monoethylglycinexylidide (MEGX) test: In the morning of Study Day –1, the MEGX-test was performed. Serum samples for determination of lidocaine and its metabolite(s) were taken 15 and 30 minutes after i.v. administration of lidocaine (1 mg/kg body weight).

Analytical Method:
Plasma concentrations of roflumilast and roflumilast N-oxide were determined by using a validated High Performance Liquid Chromatography with tandem Mass Spectrometry (HPLC-MS/MS) assay. For measurements of pharmacokinetic samples, the lower limit of quantitation (LLOQ) was 0.04 µg/L for both compounds, using a sample volume of 0.5 mL. For measurements of plasma protein binding samples, the LLOQ was 0.00499 µg/L for both compounds, using a sample volume of 0.5 mL.

Serum concentrations of MEGX and lidocaine were also determined using a validated HPLC-MS/MS assay. The LLOQ was 2 µg/L and 20.0 µg/L for MEGX and lidocaine, respectively, using a sample volume of 0.1 mL.

No. of subjects:

A total of 25 subjects (8 healthy subjects, 17 patients with liver cirrhosis) were enrolled in this study. All subjects were of Caucasian origin. One patient was withdrawn due to a

prolongation of the QTc-interval already present at screening, so that 24 subjects (8 per group) were available for the analysis of the primary pharmacokinetic variables.

Diagnosis and criteria for inclusion:

Eligible subjects were male or female Caucasians, aged 18 to 75 years, who gave their written informed consent. Patients with mild or moderate hepatic impairment as assessed by Child-Pugh classification (stage A and B, respectively) were included in this study together with healthy controls.

Test product:

Roflumilast

Dose:

250 µg once daily (in the morning)

Mode of administration:

Oral

Batch No.:

120190

Duration of treatment:

14 days

Reference product:

None

Criteria for evaluation:

In the pharmacokinetic evaluation, the apparent oral clearance normalized for body weight (CLssFBW) of roflumilast, and the area under the plasma concentration-time curve [$AUC_{(0\text{-}24h)}$] as well as the maximum plasma concentration (C_{max}) of roflumilast and its N-oxide metabolite served as primary pharmacokinetic parameter estimates. The time to reach maximum concentration (t_{max}), the terminal half-life ($t_{1/2}$), the minimum plasma concentration (C_{min}) and the peak-to-trough fluctuations (PTF) for roflumilast and roflumilast N-oxide were evaluated as secondary variables.

The safety and tolerability data were also analyzed as secondary variables.

Statistical methods:

The primary pharmacokinetic parameter estimates ($AUC_{(0-24h)}$, C_{max}, CLssFBW) of analytes were compared between groups with the WinNonLin linear mixed effects modeling (bioequivalence wizard) to perform an analysis of variance (ANOVA) using the 90% confidence interval (CI) for the ratio of the least-squares means (LSM). Each pharmacokinetic parameter estimate was log-transformed prior to analysis and a 90% CI was computed for the difference (Test-Reference) between the LSMs. Point estimates and confidence limits were then exponentiated resulting in approximate 90% CIs in the natural scale for the ratios of geometric means.

CLssFBW, $AUC_{(0-24h)}$ and C_{max} of roflumilast as well as $AUC_{(0-24h)}$ and C_{max} of roflumilast N-oxide were compared between the groups, giving point estimates together with the respective 90% confidence intervals (CI) for the ratios of Group 2/Group 1 and of Group 3/Group 1. A multiplicative model with a parametric analysis was to be used unless substantial deviations from this model would call for a non-parametric analysis.

Lack of difference in the pharmacokinetics of roflumilast and roflumilast N-oxide between patients with liver cirrhosis and healthy controls was concluded when the 90% CIs were entirely within the equivalence range of 0.80 to 1.25 for $AUC_{(0-24h)}$ and CLssFBW, and of 0.75 to 1.33 for C_{max}.

The safety variables were analyzed descriptively, including summary statistics (e.g. median, min and max, 68%-range, mean, SD) where appropriate.

SUMMARY – CONCLUSIONS

Demographic data:

Demographic characteristics for the study population (full analysis set)

Characteristic	Healthy Subjects (n=8)	Liver Cirrhosis Child-Pugh A (n=8)	Liver Cirrhosis Child-Pugh B (n=9)
Age [years]			
median (min, max)	52 (43, 67)	51 (44, 63)	52 (43, 66)
Height [cm]			
median (min, max)	164 (145, 180)	166 (162, 175)	165 (156, 171)
Weight [kg]			
median (min, max)	69 (54, 92)	69 (52, 102)	68 (52, 80)
Sex, n (%)			
Male	3 (37.5%)	5 (62.5%)	6 (66.7%)
Female	5 (62.5%)	3 (37.5%)	3 (33.3%)

Pharmacokinetic results:

Primary pharmacokinetic parameter estimates of roflumilast following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N[a]	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	**30.018**	**45.279**	**57.711**
(hr*µg/L)		19.907, 45.265	32.435, 63.211	29.953, 111.191
CLssFBW	8	**0.119**	**0.075**	**0.066**
(L/hr/kg)		0.077, 0.183	0.050, 0.113	0.031, 0.140
C_{max}	8	**4.705**	**4.828**	**5.950**
(µg/L)		3.822, 5.791	3.693, 6.311	4.149, 8.531

[a]There were 8 observations in each of the 3 groups

Primary pharmacokinetic parameter estimates of roflumilast N-oxide following a 14-day oral administration of roflumilast (250 µg once daily) in patients with liver cirrhosis Child-Pugh A and B as compared with healthy subjects; geometric mean, 68% range

Parameter	N[a]	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
$AUC_{(0-24h)}$	8	**308.69**	**382.66**	**436.13**
(hr*µg/L)		210.35, 453.02	283.27, 516.94	309.55, 614.47
C_{max}	8	**17.61**	**22.12**	**24.65**
(µg/L)		12.71, 24.39	16.89, 28.96	17.55, 34.63

[a]There were 8 observations in each of the 3 groups

The peak exposure of roflumilast (C_{max}) was similar in patients with liver cirrhosis Child-Pugh A and in healthy subjects, whereas a statistically significant increase of 26% was observed in the Child-Pugh B patient population. With respect to the total exposure [$AUC_{(0-24h)}$] of roflumilast, results indicated an increase of 51% in Child-Pugh A patients and of 92% in Child-Pugh B patients when compared with healthy subjects.

The disease-related changes in AUC are reflected by the changes in CLssFBW of roflumilast which showed a decrease of about 37% and 45% in Child-Pugh A and Child-Pugh B patients, respectively, when compared with healthy subjects following multiple daily doses of 250 µg roflumilast.

Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast primary pharmacokinetic parameter estimates following 14-day oral administration of roflumilast (250 µg once daily)

Compound	Dependent	Reference (N=8)	Test (N=8)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast	$AUC_{(0-24h)}$ [hr*µg/L]	Healthy	Child-Pugh A	30.018	45.279	150.84	99.24	229.27
		Healthy	Child-Pugh B	30.018	57.711	192.25	126.49	292.21
	CLssFBW [L/hr/kg]	Healthy	Child-Pugh A	0.119	0.075	63.37	39.38	101.97
		Healthy	Child-Pugh B	0.119	0.066	55.45	34.46	89.22
	C_{max} [µg/L]	Healthy	Child-Pugh A	4.705	4.828	102.62	80.26	131.22
		Healthy	Child-Pugh B	4.705	5.950	126.47	98.9	161.71

Test/Reference ratios refer to Group 2/Group 1 and Group 3/Group 1 as defined in the study protocol
i.e. Child-Pugh A (Test)/Healthy Subjects (Reference) and Child-Pugh B (Test)/Healthy Subjects (Reference)

For roflumilast N-oxide, the pharmacokinetic parameter estimates related to the disease status. In Child-Pugh A patients, total exposure [$AUC_{(0-24h)}$] of roflumilast N-oxide was 24% higher and C_{max} 26% higher than in healthy subjects. In Child-Pugh B patients, total exposure and C_{max} were respectively 41% and 40% higher than in healthy subjects.

Point estimate and 90%-confidence limits for the Test/Reference ratios of roflumilast N-oxide primary pharmacokinetic parameter estimates following 14-day oral administration of roflumilast (250 µg once daily)

Compound	Dependent	Reference (N=8)	Test (N=8)	Ref Geo LSM	Test Geo LSM	Ratio [%Ref]	CI 90 Lower	CI 90 Upper
Roflumilast N-Oxide	$AUC_{(0-24h)}$ [hr*µg/L]	Healthy	Child-Pugh A	308.694	382.668	123.96	92.2	166.68
		Healthy	Child-Pugh B	308.694	436.135	141.28	105.08	189.97
	C_{max} [µg/L]	Healthy	Child-Pugh A	17.609	22.124	125.64	95.95	164.51
		Healthy	Child-Pugh B	17.609	24.656	140.02	106.93	183.34

Test/Reference ratios refer to Group 2/Group 1 and Group 3/Group 1 as defined in the study protocol
i.e. Child-Pugh A (Test)/Healthy Subjects (Reference) and Child-Pugh B (Test)/Healthy Subjects (Reference)

The mean free fraction of roflumilast N-oxide was approximately 38% higher in patients with moderate liver cirrhosis (Child-Pugh B patient population) than in patients with mild liver cirrhosis (Child-Pugh A) and healthy subjects.

Free fraction of roflumilast and roflumilast N-oxide expressed as percentage in healthy subjects and patients with liver cirrhosis Child-Pugh stage A and B on Study Day 14 following once-daily administration of 250 µg roflumilast

Compound	% free fraction, mean (standard deviation)		
	Healthy Subjects	Liver Cirrhosis Child-Pugh A	Liver Cirrhosis Child-Pugh B
Roflumilast	0.61 (0.45)	0.41 (0.33)	0.49 (0.22)
Roflumilast N-oxide	1.51 (0.21)	1.47 (0.22)	2.03 (0.37)

MEGX-test: There was substantial between-subject variance with regard to the concentrations of lidocaine and MEGX within each group and considerable overlap between the groups. On average, the subjects with liver cirrhosis Child-Pugh stage B tended to have a lower MEGX/lidocaine concentration ratio, especially after 15 min, with a distinctly lower linear slope between the MEGX-concentrations.

Safety results:

A total of three AEs were reported in this study, one prior to the intake of study drug and two during treatment. None of the events were classified as serious AEs and none of them led to study discontinuation. No unexpected AEs or deaths were reported.

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

Conclusions:

Results obtained in this study are essentially in line with those of the single-dose study performed in patients with mild liver cirrhosis (Research Report 263/2000, ALTANA Pharma Konstanz, Germany), but the increase in plasma AUCs of roflumilast and roflumilast N-oxide observed in this patient population (Child-Pugh stage A) after oral intake of 250 µg roflumilast at steady-state was not as pronounced as in the previous single-dose study. In both studies, patients with mild liver cirrhosis had a maximal plasma concentration (C_{max}) of roflumilast which was similar to that of healthy controls.

The observed differences in $AUC_{(0-24h)}$ increased with the severity of liver disease (51% increase in Child-Pugh A patients and 92% increase in Child-Pugh B patients for roflumilast; 24% increase in Child-Pugh A patients and 41% increase in Child-Pugh B patients for roflumilast N-oxide) when compared with healthy subjects following multiple daily doses of 250 µg roflumilast. These findings also suggest that the total exposure of the active metabolite, roflumilast N-oxide, was generally less affected by liver impairment than that of roflumilast.

For roflumilast, the alterations in peak exposure (C_{max}) by liver impairment were not as pronounced as those in total exposure [$AUC_{(0-24h)}$]; a statistically significant increase in C_{max} values (26% increase) occurred only in the Child-Pugh B patient population. For roflumilast N-oxide, the changes in C_{max} were proportional to those in total exposure and a statistically significant increase in C_{max} values was observed in all patients with liver cirrhosis (26% increase in Child-Pugh A patients and 40% increase in Child-Pugh B patients).

In summary, results indicate a broad overlap of the pharmacokinetic parameter estimates C_{max} and $AUC_{(0-24h)}$ across the groups. When comparing patients with liver cirrhosis to healthy subjects a gradual increase in exposure was observed in patients with liver cirrhosis Child-Pugh stage A and B for both roflumilast and roflumilast N-oxide. Interindividual variability with regard to the pharmacokinetic parameter estimates increased with disease severity, an important finding with regard to safety when roflumilast is administered to patients with liver impairment.

Overall, safety data indicate that daily oral doses of 250 µg roflumilast in patients with mild-to-moderate liver cirrhosis were safe and well tolerated.