2 Synopsis

Title of the study:

Effects of a 4-week treatment with 500 µg roflumilast on exhaled nitric oxide, pulmonary function and other inflammation indices in patients with asthma

Study center(s):

Pulmonary Research Institute, Grosshansdorf, Germany
INSAF GmbH, Wiesbaden, Germany

Publication (reference): Not applicable

Studied period (years): 03-Dec-2002 (first patient in) to 20-Dec-2004 (last patient out)

Clinical phase: III

Objectives:

The aim of this study was to investigate the effect of a 4-week treatment with roflumilast 500 µg od vs placebo on exhaled NO (nitric oxide, primary variable), BHR (bronchial hyperresponsiveness) to AMP (adenosine 5'-monophosphate), eosinophils in sputum, other specific inflammatory markers and lung function. Further, safety and tolerability was studied in patients with asthma.

Methodology:

This study was designed as a double-blind, placebo-controlled, randomized, two-period crossover study with a single-blind placebo baseline period in patients with asthma.

The study consisted of the following study periods:

- baseline period (1 to 3 weeks), Visit B0, B1 (B2, B3 were optional visits);
- treatment period 1 (4 weeks), Visit T0 and T4 (T0, randomization visit);
- single-blind wash-out period to separate the treatment sequences (2 to 4 weeks);
- treatment period 2 (4 weeks), Visit T8 and T12;
- follow up visit (F, if necessary).

Patients with stable asthma who met the inclusion criteria entered the single-blind baseline period. All asthma controller medication was withdrawn at study entry. After the baseline period (placebo), patients who met the randomization criteria were randomly assigned to one of the following treatment sequences:

- Sequence 1: roflumilast 500 µg od – washout– placebo;
- Sequence 2: placebo – washout – roflumilast 500 µg od.

Throughout the baseline and the treatment period, exhaled NO, inflammatory markers, lung function tests including BHR to AMP and safety assessments were performed at site visits. Morning and evening PEF (peak expiratory flow), use of salbutamol as rescue medication, and asthma related symptoms were assessed using an electronic patient's diary. On site visit days, all lung function measurements in an individual patient were performed at the same time of the day (within ±2 h of the time of measurement at Visit T0) after a resting period of 15 min. Patients had to withhold their rescue medication salbutamol for at least 6 h prior to lung function measurements.

No. of patients (total and for each treatment sequence):

	Number of patients		
	Rof500-Placebo	**Placebo-Rof500**	**Total**
Full analysis set	28	24	52
Valid cases set	24	20	44

Rof500 = roflumilast 500 µg od

Diagnosis and criteria for inclusion:

Patients of either sex with asthma who gave their informed consent and who met the following criteria could be included into the baseline period:

- diagnosis of bronchial asthma as defined by NIH (National Institute of Health) guideline criteria;
- 18 to 70 years old;

- written informed consent;
- baseline FEV_1 (forced expiratory volume in 1 second) had to be $FEV_1 \geq 60\%$ of predicted at B0 (see Amendment No. 1);
- positive reversibility test (FEV_1 increase of ≥ 15 %, 15 to 30 min after inhalation of max. salbutamol 400 µg) within the last 6 months prior to B0;
- positive skin prick test to at least one common allergen:
  a) documented within the last 12 months prior to B0 or
  b) to be performed within baseline period (if has to be checked in baseline, test will be performed after all investigations);
- patients who, with the exception of asthma, were in good health;
- clinically stable patients with no major changes in asthma treatment.

Randomization criteria:
After the baseline period (1 to 3 weeks), patients were randomized if they fulfilled the following criteria:

- exhaled NO level ≥ 30 ppb and reproducible values between B0 and T0 within ±75%;
- $PC_{20}FEV_1$ reproducible within the limit of 1.5 doubling doses between visit B0 and T0;
- FEV_1 value reproducible within the limits of ±15% between visits B0 and T0.

Test product: roflumilast

Dose: 1 tablet, 500 µg

Mode of administration: oral administration, once daily, in the morning

Batch No.: 101160, 130220

Duration of treatment: 4 weeks roflumilast followed by 4 weeks placebo or *vice versa*

Reference product: placebo

Dose: 1 tablet

Mode of administration: oral administration, once daily, in the morning

Batch No.: 410190, 130280

Criteria for evaluation:

Efficacy variables

- exhaled NO (change from baseline as primary analysis of primary variable);

- exhaled NO (at the endpoint as secondary analysis of primary variable);
- $PC_{20}FEV_1$ and doubling concentration to AMP;
- sputum differential cell count including sputum eosinophils;
- inflammatory markers in sputum supernatant (IL-8 [interleukin-8] and ECP [eosinophilic cationic protein]);
- inflammatory markers in serum (ECP and E-selectin);
- inflammatory markers in blood (differential blood cell count, WBC [white blood cell count]);
- inflammatory markers in urine (9α,11β-PGF2 [9α,11β-prostaglandin F2] and LTE_4 [leukotriene E4]);
- lung function (FEV_1 [forced expiratory volume in one second], FVC [forced vital capacity], $MEF_{25-75\%}$ [mean expiratory flow between 25% and 75% of vital capacity], PEF [peak expiratory flow]);
- PEF, asthma symptoms and use of rescue medication (from electronic diary recordings);
- pharmacokinetics for compliance check.

Safety variables

Report of AEs (adverse events), laboratory values (hematology, clinical chemistry, urine analysis), physical examination, electrocardiogram, BP (blood pressure) and HR (heart rate).

Statistical methods:

Efficacy variables

The primary variable was change from baseline in exhaled NO, assuming a normal distribution, and was analyzed with ANCOVA (analysis of covariance) adopted for the crossover design. The dependent variable was the change from baseline (or washout) to endpoint. Besides the treatment, the following fixed factors and covariables were included in the model: baseline respective washout value of exhaled NO, age, sex and center. Additionally the random factor subject nested in sequence was included. Secondary variables were analyzed in an exploratory manner with the same ANCOVA model, except for exhaled NO at the endpoint, $PC_{20}FEV_1$, and the inflammatory markers. For the variables $PC_{20}FEV_1$, exhaled NO at the endpoint, and the inflammatory markers a lognormal distribution was assumed and these variables were analyzed with a multiplicative model.

Safety variables

For safety and tolerability variables descriptive statistics were given.

SUMMARY - CONCLUSIONS

Efficacy results

The results below are given for the ITT analysis.

Primary variable: change from baseline in exhaled NO assuming a normal distribution
The analysis of the primary variable exhaled NO, calculated as the difference from start to endpoint, showed a statistically significant decrease with roflumilast 500 µg (-10.576 ppb, two-sided p = 0.0220) and essentially unchanged levels of exhaled NO with placebo (-0.729 ppb, two-sided p = 0.8722). Superiority of roflumilast 500 µg to placebo could not be demonstrated although the between-treatment difference was in favor of roflumilast and almost reached statistical significance (-9.847 ppb, one-sided p = 0.0257).

Change from baseline in exhaled NO [ppb]: additive model (ITT)

WITHIN			Start	Endpoint	Difference Endpoint – Start		
		N	Mean	Mean	LSMean ± SE	95% CI	p-value[a]
	Rof500	50	77.820	66.880	-10.576 ± 4.452	-19.554, -1.598	0.0220
	Pbo	46	79.696	77.783	-0.729 ± 4.505	-9.814, 8.355	0.8722
BETWEEN					**Difference Test - Ref for Endpoint - Start**		
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	p-value sup.[b]
	Rof500	Pbo	50	46	-9.847 ± 4.916	-19.760, 0.066	0.0257

[a] Two-sided p-value for within-treatment differences, significance level 5%.
[b] One-sided p-value for superiority, significance level 2.5%.
CI = confidence interval, Endpoint = T4 or T12 (paired values), LS = least squares, n = number of patients with data available, Pbo = placebo od, Ref = reference, Rof500 = roflumilast 500 µg od, SE = standard error, Start = T0 or T8 (paired values).

Secondary variables
Treatment with roflumilast vs placebo resulted in a 11% reduction in exhaled NO at the endpoint assuming a lognormal distribution (ratio 0.890, one sided p = 0.0301).

The between treatment comparisons statistically significantly improved for both variables associated with the BHR to AMP: $PC_{20}FEV_1$ at the endpoint was increased by 61% (ratio 1.61, one-sided p = 0.0009) and the doubling concentration factor increased with 0.766 (one-sided p = 0.0025) after a 4-week treatment with roflumilast vs placebo.

Treatment with roflumilast vs placebo decreased sputum eosinophil % by 9% (ratio 0.908). In contrast, treatment with roflumilast vs placebo increased sputum neutrophils % by 12% (ratio 1.124) and sputum lymphocytes % by 20% (ratio 1.203). Except for the reduction in

absolute number of squamous cells (ratio 0.603, one-sided p = 0.0120), none of the between-treatment comparisons for the sputum cells analyzed as sputum cell % or absolute number of sputum cells (expressed in cells/mL) reached statistical significance.

For the inflammatory markers in sputum supernatant, treatment with roflumilast vs placebo reduced ECP by 25% (ratio 0.748, one-sided p = 0.1025). IL-8 was statistically significantly decreased by 33% after a 4-week treatment with roflumilast vs placebo (ratio 0.668, one-sided p = 0.0214).

For the inflammatory markers in serum, treatment with roflumilast vs placebo reduced ECP by 18% (ratio 0.823, one-sided p = 0.0714) and reduced E-selectin by 6% (ratio 0.939, one-sided p = 0.0592). Both decreases did not reach statistical significance, but were numerically in favor of roflumilast.

Treatment with roflumilast vs placebo reduced blood eosinophil % by 10% (ratio 0.901, one-sided p = 0.0862) and the absolute number of eosinophils by 8% (ratio 0.923, one-sided p = 0.1704). Both reductions did not reach statistical significance, but were numerically in favor of roflumilast. In contrast, treatment with roflumilast vs placebo slightly increased blood neutrophils % by 3% (ratio 1.031, one-sided p = 0.9096) and the absolute number of neutrophils by 2% (ratio 1.019, one-sided p = 0.6527). The WBC count was essentially unchanged after treatment with roflumilast vs placebo (ratio 0.992, one-sided p = 0.4140).

For the inflammatory markers in urine, treatment with roflumilast vs placebo statistically significantly decreased LTE_4 assessed pre- and post-challenge. Treatment with roflumilast vs placebo statistically significantly decreased LTE_4 assessed post-challenge by 15% (ratio 0.849, one-sided p = 0.0077) and LTE_4 assessed pre-challenge by 14% (ratio 0.862, one-sided p = 0.0090). Treatment with roflumilast vs placebo reduced the level of 9α,11β-PGF2 (post-challenge) by 7% (ratio 0.925, one-sided p = 0.1838), whereas the level of 9α,11β-PGF2 (pre-challenge) was essentially unchanged (ratio 1.015, one-sided p = 0.5711).

None of between-treatment differences for the lung function variables were statistically significant.

Post-hoc analysis

In a post-hoc analysis, change from baseline in exhaled NO assuming a lognormal distribution was analyzed based on newly published literature. The between-treatment ratio was statistically significant (ratio 0.865, one-sided p = 0.0189), indicating a decrease in exhaled NO of 13% for a 4-week treatment with roflumilast vs placebo.

Safety results

During the study, 43 patients experienced 103 treatment-emergent AEs. Of these, 32 [62%] patients experienced 66 AEs with roflumilast 500 µg and 23 [49%] patients experienced 37 AEs with placebo. There were in total four SAEs. During treatment with roflumilast 1 [2%] patient experienced 3 SAEs and 1 [2%] patient reported 1 SAE with placebo. There were no deaths during the study. The percentage of patients who discontinued the study due to AEs was higher with roflumilast (4 [8%] patients) than with placebo (0 patients).

Nasopharyngitis was the most common AE (reported by 9 patients with roflumilast and by 5 patients with placebo) and is considered as part of the background noise in patients with asthma. Headache was the second most common AE (reported by 9 patients with roflumilast and by 3 patients with placebo). The third most frequently reported AE was diarrhea (reported by 8 patients with roflumilast and by 0 patients with placebo). AEs that occurred more frequently (difference of ≥5% of patients) with roflumilast than with placebo were except for the AEs nasopharyngitis, headache and diarrhoea, the AEs nausea and dizziness. Three patients reported nausea and 4 patients reported dizziness with roflumilast, whereas none of the patients reported these AEs with placebo.

The majority of AEs were mild and moderate in intensity with roflumilast and placebo treatment. AEs that were assessed by the investigator as at least likely related to the study medication were experienced by 17 [33%] patients treated with roflumilast and by 1 [2%] patient treated with placebo. One patient reported the AE nausea with roflumilast that was assessed by the investigator as definitely related to study medication. There was no rechallenge performed for this patient. Nausea is a gastrointestinal complaint that is in line with the known safety profile of roflumilast. AEs associated with abnormal laboratory values were experienced by 2 patients with roflumilast and by 4 patients with placebo. The investigator assessed none of these laboratory AEs as definitely or likely related to the study medication.

No clinically relevant changes in hematology, biochemistry, and urine values were observed with both treatments during the course of the study. There were 6 AEs associated with abnormal laboratory values: 2 AEs with roflumilast and 4 AEs with placebo. Physical examination, BP, and ECG measured during treatment with roflumilast and placebo did not reveal any influence of both treatments.

No new safety signal could be detected.

Conclusions:

This study showed that the change from baseline in exhaled NO assuming a normal distribution (primary variable) was decreased during a 4-week treatment with roflumilast 500 µg od and with placebo od. The between-treatment difference almost reached statistical significance (one-sided $p = 0.0257$). Superiority of roflumilast vs placebo could be demonstrated for the variables that assessed BHR to AMP ($PC_{20}FEV_1$ and the doubling concentration). The change from baseline for sputum cells, inflammatory markers in serum and blood as well as lung function were not statistically significant after treatment with roflumilast vs placebo, whereas statistical significant changes from baseline were found for the inflammatory markers IL-8 in sputum supernatant and LTE_4 in urine.

In a post-hoc-analysis, change from baseline in exhaled NO assuming a lognormal distribution showed a statistically significant superiority of roflumilast 500 µg vs placebo (one sided $p = 0.0189$).

Overall, levels of exhaled NO decreased significantly with roflumilast, which indicates an anti-inflammatory effect of roflumilast. Anti-inflammatory properties of roflumilast were also shown in terms of reduction of BHR to AMP ($PC_{20}FEV_1$ AMP; change in $PC_{20}FEV_1$ during treatment in terms of doubling concentrations) in this study population. However, sputum eosinophils were not statistically significantly reduced with roflumilast or placebo, but levels of IL-8 in sputum supernatant were significantly reduced as compared to baseline as well as placebo. The observed safety data of roflumilast within this study were in line with the known safety profile of roflumilast.