Synopsis of study report: 34/2001 K1
Location in Module 5:

Study Code:
BY217 FK1 007

Report Version:
3.0

Title of the study:

40 weeks treatment with 0.5 mg roflumilast in patients with asthma

Investigators:

A total of 59 investigators in 6 countries.

Study center(s):

A total of 60 centers participated, located in Austria (5), Germany (26), Hungary (9), Poland (5), South Africa (9), and Spain (6).

Publication (reference):

Not applicable.

Studied period (years):

30. Nov.1998 to 04. May 2000

Clinical phase:

II/III

Objectives:

The objective of the present study was to investigate the safety of a long-term treatment with roflumilast in patients with asthma. Furthermore, the study aimed to provide information on the long-term effect of roflumilast on both pulmonary function and asthma exacerbation rate.

Methodology:

This was an open, multi-center, multi-national phase II/III study. Patients with asthma who had completed the preceding study BY217/FK1 006 (see CSR No. 38/2001) according to the protocol (per-protocol), or who had dropped out due to an asthma exacerbation which could be treated according to the protocol of the present trial, were eligible. The trial consisted of a

40-week treatment period (treatment: 0.5 mg/day roflumilast), starting with visit T12 (last scheduled visit of study BY217/FK1 006) and visits scheduled after 4, 14, 27, and 40 weeks (visits T16, T26, T39, and T52, respectively), and a follow-up period, if applicable.

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

Intention-to-treat (0.5 mg roflumilast) n = 456

Diagnosis and criteria for inclusion:

Patients of either sex who had given written informed consent and who had completed the preceding study BY217/FK1 006 per-protocol were eligible. Furthermore, patients who had been drop-outs in the preceding study due to an asthma exacerbation, which could be treated according to the protocol of the present study were included.

Test product:

Roflumilast

Dose:

0.5 mg/tablet

Mode of administration:

One tablet once daily in the morning, oral administration.

Batch No.:

BY217-46-1-1 (Germany, Hungary, South Africa), BY217-46-5-1 (Austria, Hungary, Poland, South Africa, Spain).

Duration of treatment:

40 weeks

Reference product:

Not applicable.

Dose:

Not applicable.

Mode of administration:

Not applicable.

Batch No.:

Not applicable.

Criteria for evaluation:

Safety evaluation (primary):	laboratory values, physical examination, vital signs (ECG, BP, HR), and adverse event (AE) monitoring
Efficacy evaluation (secondary):	spirometric lung function tests (FEV_1, FVC, PEF), subjective effectiveness rating (patient/physician), asthma exacerbations

Statistical methods:

An ITT and extended ITT analysis (if applicable) were performed. Safety parameters and the subjective ratings of asthma control by patients and investigators were analyzed in a descriptive manner.

For the secondary lung function variables, the differences to T0 (start of acute study BY217/FK1 006) and to $T_{startLT}$ (start of present trial, for most patients T12) were calculated and an analysis of covariance (ANCOVA) was applied. In addition, analyses separated by treatment groups of the acute study were carried out. All tests were performed two-sided at the significance level $\alpha = 0.05$. The start value ($T_{startLT}$, usually T12) of the lung function variables was not included as a covariate with regard to the analysis of the differences to $T_{startLT}$ (e.g. T52- $T_{startLT}$). If applicable, the last observation was carried forward not to every visit but only to the last visit (endpoint).Center effects were not included in the statistical analysis, since the number of patients per center was limited.

SUMMARY - CONCLUSIONS

Summary:

Efficacy Results:

The lung function variables FEV_1, FVC and PEF were analyzed in comparison to T0 (the first measurement of the preceding study BY217/FK1 006) and to $T_{startLT}$ (the first measurement of the present long-term trial BY217/FK1 007).

Comparison to T0

The comparison to T0 revealed a statistically significant increase in all measured parameters. Thus, the efficacy of the drug already shown in study BY217/FK1 006 was at least maintained during the long-term trial.

Between-group comparison of differences to T0 (patients grouped according to their treatment in the acute study) showed no statistically significant differences.

FEV_1 (l): ITT last-value analysis FEV_1 vs. T0

Treatment group of acute study	T0		T_{lastLT}	Within treatment differences T_{lastLT} – T0		
	Mean % pred.	LS Mean	LS Mean	LS Mean ± Std Err	95% CI	p-value two-sided
0.1 mg roflumilast (n = 148)	2.47 74%	2.43	2.85	0.42 ± 0.05	0.33, 0.51	< 0.0001
0.25 mg roflumilast (n = 151)	2.40 73%	2.43	2.79	0.36 ± 0.05	0.27, 0.45	< 0.0001
0.5 mg roflumilast (n = 150)	2.42 73%	2.43	2.82	0.38 ± 0.05	0.29, 0.47	< 0.0001

CI = confidence interval.
T_{lastLT} = ITT last value of long term trial analysis.

Comparison to $T_{startLT}$

Using the measurements at $T_{startLT}$ as reference showed a statistically significant increase in all lung function variables for patients treated with 0.1 mg roflumilast in the preceding study BY217/FK1 006. In addition, a statistically significant increase in FVC was found in patients treated with 0.25 mg roflumilast in the acute study.

Analysis of the between-group differences (grouping by treatment in study BY217/FK1 006) revealed statistically significant differences between the 0.1 mg and 0.5 mg roflumilast group for all lung function variables. Furthermore, a statistically significant difference was found for PEF between the 0.1 mg and 0.25 mg roflumilast group.

The vast majority of patients and investigators rated the treatment “very effective” or “effective”. Most patients (57%) and investigators (60%) felt an improvement in comparison to T0. Furthermore, 20% patients (22% investigators) realized an improvement compared to the start of the long-term trial. There were no apparent differences between patients grouped by treatment of study BY217/FK1 006.

Safety Results:

During this trial, 221 (48%) patients experienced 509 AEs. Most frequently, AEs related to the respiratory system and thus mainlyto the underlying disease, were reported. Most AEs were mild to moderate in intensity.

Summary of adverse events and causality assessment[a] (ITT, n = 456)

Relation to study drug	No. (%) [b] of AE
Total no of AEs:	509
not related	388 (76)
unlikely related	62 (12)
likely related	54 (11)
definitely related	5 (1)

[a] According to the investigator.
[b] Percentages are calculated out of the total number of AEs.

The majority of AEs (88%) were rated "not" or "unlikely related" to the study medication. Investigators considered 11% of AEs "likely related" to the study drug (Sponsor's assessment: 7%), the most frequent being headache and gastrointestinal symptoms. According to the investigator, 5 AEs experienced by 4 patients were "definitely related" to the study medication. These were headache, nausea, diarrhea, asthenia, and dyspepsia. However, the Sponsor assessed only one case "definitely related" (mild dyspepsia).
No death occurred in the course of this trial. Overall, 16 serious AEs were reported for 16 patients. All of them were "not" or "unlikely related" to the study drug (investigators' assessment). Furthermore, 43 AEs experienced by 29 patients led to premature discontinuation. The investigators rated most of these "moderate" in intensity (74%) and "not related" (47%) to the study medication.
Routine laboratory tests revealed no apparent changes in laboratory parameters during the trial. However, there were individual clinically significant abnormalities in 22 (5%) patients.
Measurement of vital signs and physical examination did not reveal any apparent changes during the trial. Three clinically relevant ECG abnormalities detected at T52 were judged "unlikely" or "not related" to the roflumilast treatment.

Conclusions:

The present long-term trial showed a stable and consistent effectiveness of 0.5 mg roflumilast. For patients treated with 0.1 mg roflumilast during the preceding study BY217/FK1 006, the lung function further improved.
In total, 48% of patients experienced AEs. Most of these were judged "unlikely" or "not related" to the study medication. However, a relation to the roflumilast treatment was suspected for some cases of headache or gastrointestinal symptoms.
All AEs were easy to manage and did not bear any intolerable risk for the patients. Further, their pattern was expected from similar findings during earlier trials.
There was no apparent influence of the 40-week roflumilast treatment on laboratory parameters, vital signs, ECG or physical examination. Thus the study confirmed the good safety profile and good tolerability of roflumilast.