Disclaimer: This study was originally sponsored by Nycomed and was acquired from Takeda by AstraZeneca. For additional information regarding this study, please contact the AstraZeneca Clinical Study Information Center at information.center@astrazeneca.com.

1 Title Page

Clinical Study Report No. 174/2008

Version (2.0)

Title: Efficacy of 500 µg Roflumilast once daily versus placebo over 12 weeks in patients with diabetes mellitus type 2. The FORTUNA study		Version date:	14-Jan-2009
		INN:	Roflumilast
		Program/Project No.:	BY217
		Compound No.:	B9302-107
		Batch No.:	BY217-268
Study Protocol No.:	**BY217/M2-401**	Development phase:	IIb
EudraCT No:	2005-005702-23	Indication studied:	diabetes mellitus type 2
Study initiation date:	09-Aug-2006	Date of early termination:	not applicable
Study completion date:	08-Nov-2007	Summary of modifications:	1

Name and country of investigators: 55 centers located in Germany, Ukraine, Romania, Argentina, Mexico and Chile.

Coordinating investigator: [redacted] Department of Internal Medicine II, Großhadern, Ludwigs-Maximilians-University, Munich, Germany

Name of sponsor's responsible medical officer:

Gabriele Hecker-Barth, MD, Nycomed GmbH, Konstanz, Germany
Dirk Bredenbroeker, MD, Nycomed GmbH, Konstanz, Germany
Udo-Michael Goehring, MD, Nycomed GmbH, Konstanz, Germany
Armella Escher, PhD, Nycomed GmbH, Konstanz, Germany

Person(s) responsible for study report:

Dr Claudia Gruss, Nycomed GmbH, Konstanz, Germany

Sponsors contact persons:

See accompanying letter of the regulatory approval application

Statement of GCP compliance:

This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

Archiving responsibility for essential documents: Department RDM/CP at Nycomed GmbH, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

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2 Synopsis

Title of the study:

Efficacy of 500 µg Roflumilast once daily versus placebo over 12 weeks in patients with diabetes mellitus type 2. The FORTUNA study.

Investigator(s) and study center(s):

55 investigators in 55 centers located in Germany, Ukraine, Romania, Argentina, Mexico and Chile.

Coordinating investigator:

[redacted] Department of Internal Medicine II, Großhadern, Ludwigs-Maximilians-University, Munich, Germany

Publication (reference): Not applicable

Studied period: 9-Aug-2006 (first patient in) to 08-Nov-2007 (last patient out)

Clinical phase: Phase IIb

Objectives:

The study objectives were:

- to investigate and compare the effect of 500 µg roflumilast once daily (od) versus placebo on HbA1c over 12 weeks in patients with diabetes mellitus type 2;
- to investigate and compare the safety and tolerability of roflumilast in patients with diabetes mellitus type 2.

Methodology:

This study was a 12-week, randomized, double-blind, multi-center study including two parallel treatment arms (placebo and 500 µg roflumilast od).

Patients with confirmed diabetes type 2 diagnoses that were eligible for participation entered the single-blind baseline period. The patients had to be naïve for diabetes mellitus type 2 medications. During the baseline period, the patients received placebo. On completion of the baseline period, patients were re-evaluated and those who met all randomization criteria were randomized in a 1:1 ratio to receive once-daily roflumilast 500 µg, or placebo.

After 2, 4, 8 and 12 weeks (V3, 4, 5 and Vend) of the treatment period further diabetes specific laboratory tests and safety assessments were performed at clinic visits. Visits had to

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be scheduled in the morning (between 6.00 am and 12.00 pm) and within a specific time-frame (±1.5 h compared with the randomization visit V2).

The timing of one or more follow-up visits required to adequately monitor ongoing AEs depended on the AE, but was scheduled no later than 30 d after the treatment period ended.

Blood samples were collected at V3 and Vend to determine roflumilast and roflumilast N-oxide at pre-specified investigational sites in Romania only and from a total of 50 randomly selected patients. The samples were used to obtain pharmacokinetic and pharmacodynamic parameter estimates of roflumilast and roflumilast N-oxide in the patient population.

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

Originally, it was planned to enroll 375 patients and to randomize 250 patients (125 patients in each group).

With Amendment No. 2 to the Study Protocol the number of patients to be enrolled was changed to 465 and the expected number of patients eligible for randomization after the single blind baseline period was reduced to 190 (95 patients in each group).

Analyzed sets

	Enrolled	Safety set	Full analysis set	Valid cases set
Rof500		107	107	88
Pbo		98	98	89
Total	487	205	205	177

Pbo = placebo, Rof500 = roflumilast 500 µg qd.
Data source: Table 15.1.1.2

Diagnosis and main criteria for inclusion:

Patients meeting the following criteria were considered for inclusion in the baseline period:

- given written informed consent;
- age >35 and ≤70 years;
- patients with diagnosis of type 2 diabetes according to ADA criteria (American Diabetes Association) and inadequately controlled on diet and exercise alone;
- HbA1c at baseline: ≥7.5 to 8.5 % (up to 9% in Mexico, Ukraine and Romania)[1] ;
- BMI between ≥26 and ≤35 kg/m^2;
- willingness of patient to check his/her blood glucose with equipment provided by the sponsor during the treatment phase in case of hypo-/hyperglycemia episodes;
- willingness to adhere to the physician's advise to comply with diet and exercise.

[1] Originally, it was allowed to include patients with HbA1c values of ≥7.5% to 9% at baseline. This range was narrowed to ≥7.5% to 8.5% as per Amendment No. 1 of the Study Protocol. However, in some countries (Mexico, Ukraine and Romania) the original limit of 9% was reinstated with Amendment No. 3.

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Patients were randomized after 2 weeks of the baseline period, if the following criteria were fulfilled:

- judged to be clinically stable;
- tablet compliance ≥80% and ≤125%;
- HbA1c in the range of 7.5% to 8.5 % (up to 9% in Mexico, Ukraine and Romania)[2] tested at V0 by the central laboratory.

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

Roflumilast, one 500 µg tablet, once daily, oral administration in the morning after breakfast, batch number BY217-268.

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

Placebo, one tablet, once daily, oral administration in the morning after breakfast, batch number BY217-268.

Duration of treatment:

2 weeks baseline (placebo) and 12 weeks treatment (randomized 1:1 to roflumilast or placebo)

Criteria for evaluation:

Primary efficacy variable

- mean change in HbA1c [%] from baseline to last study visit (Vlast) with 500 µg roflumilast od versus placebo.

Secondary efficacy variables

- the clinical relevance of the effect size observed for the primary efficacy endpoint was further evaluated by a responder analysis;
- mean change in HbA1c from baseline to each scheduled post-randomization visit;
- mean change from baseline to each scheduled post-randomization visit and Vlast in serum lipids (high-density-lipoprotein-cholesterol [HDL], low-density-lipoprotein-cholesterol [LDL], and triglycerides [TG]), fasting plasma glucose (FPG), fructosamine, glycerol, free fatty acids (FFA), plasma insulin, fasting pro-insulin, c-reactive protein (CRP),

[2] Originally, it was allowed to include patients with HbA1c values of ≥7.5% to 9% at baseline. This range was narrowed to ≥7.5% to 8.5% as per Amendment No. 1 of the Study Protocol. However, in some countries (Mexico, Ukraine and Romania) the original limit of 9% was reinstated with Amendment No. 3.

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interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), intercellular adhesion molecule 1 (ICAM-1), E-selectin, plasminogen activator inhibitor 1 (PAI-1), adiponectin, and leptine;

- mean change from baseline to each scheduled post-randomization visit and Vlast based on a 5-hour period post meal area under the curve (AUC) for FFA, glycerol, glucose, glucagon, insulin, and C-peptide;
- mean change in body weight, waist and hip circumference, waist to hip ratio, and body mass index (BMI) from baseline to each scheduled post-randomization visit and Vlast;
- Time to event (study withdrawal, time to study withdrawal due to an AE and time to lack of efficacy (LOE)[3].

Safety variables

- incidence of hypo- and hyperglycemic episodes;
- incidence of AEs;
- changes in laboratory values;
- changes in physical examination findings including electrocardiograms (ECG);
- changes in vital signs (blood pressure [BP] and heart rate [HR]).

Statistical methods:

The primary efficacy variable was the mean change in HbA1c level (expressed as % of total Hb) from baseline value at randomization (V2) to the endpoint/last value obtained (Vlast).

The confirmatory analysis to show a statistically significant difference of roflumilast 500 µg versus placebo was performed on the full analysis set (FAS) using an analysis of covariance model (ANCOVA) with the mean change as the dependent variable. The last measurement after start of study medication intake in the treatment period was used for the endpoint analysis, ie the last observation was carried forward (LOCF). The following factors and co-variables were included in the model: value at V2 (ie baseline value of the dependent variable), BMI (at baseline), age, sex, and geographical region. The primary statistical test for the primary endpoint was two-sided, using a significance level of 5.0%.

Additional exploratory analyses were performed for each geographical region separately and for subgroups of patients stratified by HbA1c value at baseline (≤8% *vs* >8%), changes in diet or exercise, and country. A repeated measurement analysis to analyze changes over time in more detail was performed as well.

Finally, the clinical relevance of the effect size observed for the primary efficacy variable was evaluated by a responder analysis. A relevant improvement was defined as a patient reaching

[3] LOE was defined in Amendment No. 1 to the Study Protocol as any FPG measurement ≥220 mg/dL (measured at any visit) or any blood glucose (BG) measurement ≥12 mmol/L (ie 220 mg/dL, measured by the patient during a self monitoring test), if that measurement was confirmed in a second test to be scheduled within one week

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a HbA1c level ≤7.0% or showing an absolute decrease in HbA1c level of 0.7% between the baseline value at randomization (V2) and Vlast. The response rates were compared between treatment groups with a log-binomial model including the factors and covariables treatment, HbA1c value at V2, BMI (at baseline), sex, age and region. The calculation was performed based on all patients and for the subgroups of patients.

The secondary efficacy variables were analyzed in an exploratory manner, ie no corrections for multiplicity were performed. AEs were analyzed using descriptive statistics.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

In total, 205 patients were randomized (1:1). 205 patients took at least one dose of the study medication, and were included in the FAS (full analysis set) for ITT analyses. As summarized in the table below, patients in the two treatment groups were well comparable with respect to demographic and other baseline characteristics.

Demographic and other baseline characteristics (FAS and VCS)

		FAS		VCS	
Treatment variable[a]		**Rof500 (N = 107)**	**Pbo (N = 98)**	**Rof500 (N = 88)**	**Pbo (N = 89)**
Age [years]	Median (range)	55 (35, 71)	54 (35, 69)	55 (38, 71)	54 (35, 69)
Height [cm]	Mean ± SD	166 ± 9	166 ± 9	165 ± 9	166 ± 9
Weight [kg]	Mean ± SD	84 ± 11	84 ± 11	84 ± 11	84 ± 10
BMI [kg/m^2]	Mean ± SD	30.34 ± 2.7	30.56 ± 3.0	30.52 ± 2.5	30.52 ± 2.9
Sex [n (%)][a]	Male	48 (44.9)	49 (50.0)	41 (46.6)	46 (51.7)
	Female	59 (55.1)	49 (50.0)	47 (53.4)	43 (48.3)
Race [n (%)][a]	Asian	1 (0.9)	0 (0.0)	1 (1.1)	0 (0.0)
	White	92 (86.0)	86 (87.8)	77 (87.5)	78 (87.6)
	Other	14 (13.1)	12 (12.2)	10 (11.4)	11 (12.4)
Waist circumference [cm] at V2	Mean ± SD	100 ± 11	102 ± 11	101 ± 11	102 ± 11
Hip circumference [cm] at V2	Mean ± SD	108 ± 10	107 ± 10	108 ± 9	107 ± 10
Waist to hip ratio at V2	Mean ± SD	0.93 ± 0.1	0.95 ± 0.1	0.94 ± 0.1	0.95 ± 0.1
HbA1c [%] at V2	Mean ± SD	7.9 ± 0.5	7.9 ± 0.6	7.9 ± 0.5	7.9 ± 0.6
HbA1c at V2	≤8%	72 (67.3)	65 (66.3)	58 (65.9)	59 (66.3)
	≥8%	35 (32.7)	33 (33.7)	30 (34.1)	30 (33.7)
Change in diet or exercise	No	97 (90.7)	85 (86.7)	79 (89.8)	76 (85.4)
	Yes	10 (9.3)	13 (13.3)	9 (10.2)	13 (14.6)

[a] Percentages are based on the number of patients in the respective treatment group.
BMI = body mass index, FAS = full analysis set, HbA1c = Hemoglobin A1c, N = number of patients in the respective treatment group, n = number of patients in the respective category, Pbo = placebo, Rof500 = roflumilast 500 µg od, SD = standard deviation, VCS = valid cases set.
Data source: Table 15.1.2.1 and Table 15.1.2.2.

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Efficacy results

The present study compared the effects of 500 µg roflumilast od versus placebo in patients suffering from diabetes mellitus type 2. The primary efficacy endpoint was the mean change in HbA1c level (expressed as % of total Hb) from baseline (V2) to the last value obtained (Vlast).

Statistical testing of the primary endpoint was performed in a confirmatory manner. HbA1c decreased from baseline to Vlast in both treatment groups. The decrease was more pronounced for patients in the roflumilast 500 µg group than in the placebo group. A statistically significant between-treatment difference in change of HbA1c levels was shown in favor of roflumilast (LSMean: -0.45 ± 0.11 %, p-value: <0.0001, two-sided; ITT). The ITT analysis was strongly supported by the PP analysis. A statistically significant difference in favor of roflumilast was demonstrated by both the ANCOVA model including the LOCF method and the repeated measurements analysis. Subgroup analyses by geographic region, by HbA1c, and by diet and exercise status yielded results comparable to those for the overall population. Responder analysis of HbA1c revealed that the majority of the roflumilast-treated patients were responders (62.6%), whereas only 36.7% of patients in the placebo group were responders. A statistically significant risk ratio of 1.727 (p-value: 0.0003, two-sided) indicated a greater benefit for roflumilast compared with placebo treatment.

The tests for all secondary endpoints were exploratory and performed at a significance level of 5.0%, two-sided.

The change in HbA1c from baseline to each post-randomization visit was defined as secondary variable. For patients in the roflumilast group, HbA1c levels decreased continuously during the course of the study. In consequence, the largest decrease compared to baseline was seen at Vend. HbA1c levels in patients treated with placebo decreased to a smaller extent throughout the study, as compared to patients treated with roflumilast.

A further secondary variable was the difference from baseline to the last post-randomization visit for diabetes specific blood parameters. Most diabetes specific blood parameters decreased, ie improved, during the course of the study. Generally, decreases were more pronounced in the roflumilast compared with the placebo group.

Statistically significant between-treatment differences in favor of roflumilast were found for glucose (p-value: 0.0006) and fructosamine (p-value: 0.0010).

Most metabolic and inflammatory parameters showed trends towards an improvement with roflumilast therapy as compared to placebo treatment, but the differences were too small to reach statistical significance and are not suitable to draw solid conclusions.

Further secondary variables were derived from the mixed meal evaluations: Absolute AUCs[4] decreased from V2 to Vlast for the parameters FFA, glycerol, glucose, and glucagon, while

[4] According to the analysis originally planned in the SAP, excess AUCs were to be calculated with reference to the pre-meal value for each respective parameter. However, this analysis was found post-hoc to be not suitable.

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they increased for insulin and C-peptide in the roflumilast 500 µg group. In the placebo group, decreases in AUCs for FFA, glycerol and glucose were smaller than in the roflumilast group, and in contrast to roflumilast-treated patients, the glucagon AUC increased in placebo-treated patients, while the insulin and C-peptide AUCs decreased. Between-treatment analysis revealed statistically significant differences in favor of roflumilast for glycerol, glucose and C-peptide (ITT and PP analyses). In the PP analysis, a statistically significant between-treatment difference in favor of roflumilast was also shown for glucagon.

With regard to the secondary variable LOE, the vast majority of patients in both treatment groups did not experience LOE. However, in agreement with the lack of diabetes therapy in the placebo group, the incidence of LOE was higher under placebo (7 patients, 7.1%) than under roflumilast (2 patients, 1.9%). The mean time to onset of LOE was 5.5 days for roflumilast-treated and 16.4 days for placebo-treated patients. The risk of experiencing LOE was markedly decreased in the roflumilast group compared to the placebo group (as indicated by a hazard ratio of 0.252). However, the between-treatment difference did not reach statistical significance.

The mean time to study discontinuation or study discontinuation due to AE was shorter for roflumilast-treated patients (50.7 days ± 31.2 days and 35.7 days ± 30.1 days, respectively, ITT analysis) than for placebo-treated patients (60.8 days ± 33.3 days and 54.7 days ± 39.1 days, respectively, ITT analysis). No statistically significant between-treatment differences were observed with regard to have study discontinuation or study discontinuation due to AE.

In both treatment groups mean body weight decreased during the study. The decrease was more pronounced in the roflumilast compared with the placebo group. Likewise, mean waist and hip circumference decreased during the study in both treatment groups. Among placebo-treated patients the decreases were comparably lower than in roflumilast-treated patients. The change in waist to hip ratio was comparable for both treatment groups. However, the results had not been stratified for males and females. Between-treatment comparisons of roflumilast and placebo were statistically significant in favor of roflumilast for waist and hip circumference, but not for weight, BMI and waist/hip ratio.

Safety results:

The majority of patients in each treatment group took double-blind study medication for more than 12 weeks (with the maximum duration of study medication intake being 121 days for the roflumilast-treated patient 80239, for whom an extended time interval of approximately 6 weeks between V2 and V3 was documented).

The overall incidence of treatment-emergent AEs was slightly higher in the roflumilast 500 µg group (47.7%) than in the placebo group (44.9%).

Therefore, it was decided post-hoc to also analyze time-averaged 5-hour AUCs based on absolute values measured. Results of the excess AUC analysis can be found in Section 15.2.

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Frequency of treatment-emergent AEs (SAF)

	Rof500 (N = 107)	Pbo (N = 98)	Total (N = 205)
Number of patients (%)[a] with at least one:			
AE	51 (47.7)	44 (44.9)	95 (46.3)
SAE: all	3 (2.8)	1 (1.0)	4 (2.0)
deaths	0 (0.0)	0 (0.0)	0 (0.0)
AE with causality[b] suggested			
- by the investigator	23 (21.5)	9 (9.2)	32 (15.6)
- by the sponsor	21 (19.6)	5 (5.1)	26 (12.7)
AE leading to discontinuation	9 (8.4)	3 (3.1)	12 (5.9)

[a] Percentages are based on the number of patients in the respective treatment group.
[b] Assessed as likely or definitely related to the study medication.
N = number of patients in the respective treatment group, Pbo = placebo, Rof500 = roflumilast 500 µg od, SAF = safety set.
Data source: Table 15.3.1.4 and Listing 16.2.6.11.

On the system organ class (SOC) level investigations were the most frequent treatment-emergent AEs among patients in the roflumilast 500 µg group. Weight decrease was the most commonly documented AE in this class, followed by C-reactive protein increase. However, weight decrease in diabetic patients constitutes generally a rather beneficial effect, unless accompanied by other AEs. In the placebo group, metabolism and nutrition disorders were the most frequent treatment-emergent AEs. In this SOC, hyperglycaemia was most common, which is in agreement with the lack of diabetes therapy in the placebo group. Compared to placebo-treated patients, patients in the roflumilast 500 µg group also had higher rates of treatment-emergent AEs with regard to infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and psychiatric disorders. In the placebo group, metabolism and nutrition disorders were more frequently reported than in the roflumilast group.

The frequency of patients with AEs assessed as likely or definitely related to the study medication was higher among patients in the roflumilast 500 µg group (20.6% likely and 0.9% definitely related) compared with patients in the placebo group (9.2% likely and 0.0% definitely related). In the roflumilast 500 µg group the likely related treatment-emergent AE documented in the highest number of patients was weight decrease (which is considered as a positive effect in diabetes patients), followed by asthenia, nausea, arthralgia, and headache. Compared with the roflumilast-treated patients, fewer placebo patients experienced the AEs weight decrease, asthenia, and headache. No placebo-treated patient experienced nausea or arthralgia. Adverse events assessed as definitely related to the study medication by either the investigator or the sponsor were headache, asthenia, arthralgia, and nausea. Except for nausea, the AEs were severe in intensity, and all led to study discontinuation.

Treatment-emergent AEs in both treatment groups were primarily mild to moderate in intensity. The vast majority of AEs in both treatment groups resolved during the study.

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No patients died during the study.

A total of 4 non-fatal SAEs (depression, convulsion, abortion spontaneous and deep vein thrombosis) occurred in 3 patients in the roflumilast 500 µg group (2.8%), and 1 non-fatal SAE (lumbar vertebral fracture) was documented in 1 patient in the placebo group (1.0%). All of the SAEs were assessed by the investigator as not related or unlikely related to the study medication.

The percentage of patients who withdrew due to AEs was higher in the roflumilast 500 µg group (9 patients, 8.4%) compared with the placebo group (3 patients, 3.1%). The most frequent AE leading to withdrawal among patients in both groups was hyperglycaemia. All other AEs leading to withdrawal did not occur in more than 1 patient in either treatment group.

With regard to events of special interest, decreased weight was documented in 7 patients in the roflumilast 500 µg group (6.5%), but in only 2 patients in the placebo group. Of the 7 roflumilast cases, none were severe in intensity, but all 7 cases were assessed by the investigator as likely related to the study medication. The 2 cases of decreased weight documented in the placebo-treated patients were both mild in intensity and assessed by the investigator as likely related to the study medication. Of the 7 patients who experienced weight loss in the roflumilast group the majority did not have any concurrent AEs. Only one case of concurrent dyspepsia and nasopharyngitis was reported. Of the 2 placebo-treated patients who experienced weight loss, for 1 patient the concurrent AE cough was documented.

No cases of mesenteric vasculitis or tumors were documented as AEs in patients treated with either roflumilast 500 µg or placebo. With regard to infections related to TNF-α inhibition three AEs (gastroenteritis, pyelonephritis and herpes virus infection), were documented for three patients in the roflumilast treatment group only. While the pyelonephritis and herpes virus infection were considered unrelated to the study medication, the investigator assessed the AE gastroenteritis as likely related to study medication intake.

With regard to cardiac safety, two episodes of decreased heart rate were documented in the roflumilast group for patient 80051. Both episodes were moderate and not serious. While the patient recovered from the first episode, the outcome of the second episode was unknown. Both AEs were assessed as unrelated to the study medication by the investigator and the sponsor. In the placebo group, the AE sinus bradycardia was reported for patient 80355. The AE was mild in intensity and not serious. The patient had recovered from the AE at the end of the study and the AE was assessed as unrelated to study medication by the investigator and the sponsor. For patient 80399 in the placebo group two episodes of tachycardia were documented. The AEs were mild in intensity and not serious. The patient had recovered from the tachycardia at the end of the study and the AEs were assessed as unlikely related to study medication by the investigator and the sponsor.

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During the treatment period only one hypoglycemic episode (defined as blood glucose [BG] <2.8 mmol/L (<50 mg/dL) or reported symptoms [sweatening, jittery feeling, dizziness, and tremor] confirmed by measurement of BG <2.8 mmol/L [<50 mg/dL]) occurred in 1 roflumilast-treated patient. It should be noted, however, that on the onset day of the episode discrepant glucose levels were observed for this patient. While the glucose level recorded in the patient's diary was 2.1 mmol/L, the level measured during the study visit taking place approximately 2 hours later was notably higher (7.5 mmol/L). According to the diary, the patient did not show any hypoglycemic symptoms. The same patient experienced a pronounced weight decrease during the study. No hypoglycemic episode occurred in placebo-treated patients. With regard to hyperglycemic events (defined as BG ≥12 mmol/L [≥220 mg/dL] or reported symptoms [polyuria, polydipsia, and fatigue] confirmed by measurement of BG ≥12 mmol/L [≥220 mg/dL]), the number of patients experiencing at least one episode was higher in the placebo group (14 patients, 14.3%) compared with the roflumilast group (6 patients, 5.6%), which is in agreement with the lack of diabetes therapy among the placebo-treated patients. The time to onset of the single hypoglycemic episode in the roflumilast-treated patients was 15.0 days. With regard to the hyperglycemic episodes, a longer median time to onset was observed among the placebo-treated patients (18.0 days) compared with the roflumilast-treated patients (13.0 days).

In both treatment groups, median changes from baseline to end of treatment in hematology and clinical chemistry values were generally small and not clinically relevant. The frequency of individual laboratory values that reached alert values was low in both treatment groups. One roflumilast-treated patient presented with a positive serum pregnancy test at Vend. Except for the AE hyperglycaemia, which was more frequent among patients in the placebo group, there was no difference in the frequency of laboratory AEs in the two treatment groups. Most laboratory AEs occurred in single patients only. Hyperglycaemia was most frequently assessed by the investigator as laboratory abnormality likely related to study medication.

Both blood pressure and heart rate were generally stable in patients of both treatment groups throughout the study. One roflumilast-treated patient had a systolic blood pressure below the lower alert limit at one study visit. Another patient in the same treatment group had a diastolic blood pressure above the upper alert limit at one study visit. In the placebo group, the AE blood pressure increase was documented for one patient. Hypertension and hypotension were documented as an AE in 1 patient each in the roflumilast 500 μg treatment group. Neither AE was attributed to study medication by the investigator.

The majority of the ECG evaluations performed was assessed by the investigator as normal. Of all abnormal ECG assessments, none were assessed by the investigator to have any clinical relevance. In the placebo group, the AEs sinus bradycardia and tachycardia were documented for one patient each. The AEs were assessed by the investigator to be unrelated and unlikely related to study medication, respectively.

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Physical examinations did not reveal any clinically relevant changes due to administration of study medication.

No new safety findings beyond those already listed in the Investigator Brochure arose from this study. The results are consistent with those of previous studies, and support a favorable risk-benefit assessment for roflumilast 500 µg.

Conclusions:

Overall, the results show a clear anti-diabetic effect of roflumilast treatment in patients with diabetes mellitus type 2, based on statistically significant and clinically relevant reductions in HbA1c, fructosamine and FPG. Treatment with roflumilast was generally safe and well tolerated in this patient population.

Date of report: 14-Jan-2009

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