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Clinical Study Report No. 313/2006

Version (2.0)

Title: A 24-Week, Double-Blind, Parallel Group, Placebo and Active Controlled Study to Investigate the Efficacy and Safety of Daily Oral Roflumilast Taken with Low Dose Inhaled Corticosteroids in Patients with Chronic Asthma.	Version date: 21-Jan-2008
	INN: Roflumilast
	Program/Project No.: BY217
	Compound No.: B9302-107
	Batch No.: Roflumilast 500 µg: 120180; Placebo: 420240, 130280
Study Protocol No.: **BY217/M2-013**	Development phase: III
EudraCT No: not applicable	Indication studied: Asthma
Study initiation date: 30-Apr-2003	Date of early termination: not applicable
Study completion date: 03-Nov-2005	Summary of modifications: No. 1

Name and country of investigators: 174 centers in Austria, Croatia, Czech Republic, Finland, France, Greece, Hungary, India, Ireland, Italy, New Zealand, Norway, Pakistan, Philippines, Poland, Portugal, Russia, Singapore, South Africa, Spain, Taiwan, Thailand, United Kingdom.

Coordinating investigator: [redacted] UCT Lung Institute, George Street, 7700 Mowbray, Cape Town, South Africa.

Name of sponsor's responsible medical officer:

Dr Dirk Bredenbröker, Nycomed GmbH (RDM/MR), Konstanz, Germany

Person(s) responsible for study report:

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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/K2 at Nycomed GmbH, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

2 Synopsis

Title of the study:
A 24-Week, Double-Blind, Parallel Group, Placebo and Active Controlled Study to Investigate the Efficacy and Safety of Daily Oral Roflumilast Taken with Low Dose Inhaled Corticosteroids in Patients with Chronic Asthma.

Investigator(s) and study center(s):
174 centers in Austria (2), Croatia (6), Czech Republic (10), Finland (7), France (14), Greece (6), Hungary (5), India (8), Ireland (2), Italy (10), New Zealand (6), Norway (6), Pakistan (4), Philippines (3), Poland (6), Portugal (5), Russia (8), Singapore (4), South Africa (18), Spain (11), Taiwan (7), Thailand (7), United Kingdom (19).

Coordinating investigator(s):
[redacted] UCT Lung Institute, George Street, 7700 Mowbray, Cape Town, South Africa.

Publication (reference): Not applicable.

Studied period: The study started (first patient enrolled) on 30-Apr-2003 and ended (last patient completed) on 03-Nov-2005.

Clinical phase: Phase III

Objectives:
Primary objectives
- to establish superior efficacy of daily treatment with roflumilast taken with LDICS (low dose inhaled corticosteroids) versus placebo (LDICS alone) in patients with chronic asthma, and;
- if superiority to placebo (LDICS alone) was shown, to evaluate non-inferiority versus treatment with HDICS (high dose inhaled corticosteroids) in patients with chronic asthma.

Secondary objective
To investigate the safety and tolerability of roflumilast in patients with chronic asthma.

Methods:

This was a multi-center, double-blind, placebo-controlled, randomized, three-arm, parallel-group comparison of roflumilast 500 µg with LDICS vs placebo with LDICS, and roflumilast 500 µg with LDICS vs placebo with HDICS. The duration of the double-blind treatment period was 24 weeks after a single-blind run-in phase of 2, 4 or 6 weeks in duration.

Patients who met screening criteria entered the single-blind run-in phase. All asthma controller medications were withdrawn following the Screening Visit and patients were provided with placebo and LDICS. Patients received supplies of rescue medication (inhaled salbutamol) for use as required during the run-in period.

At the screening visit, each patient was given an e-diary (electronic diary) to collect daily the daytime asthma symptom score, the nighttime asthma symptom score, the amount of rescue medication used, the PEF_{am} (morning peak expiratory flow) and PEF_{pm} (evening peak expiratory flow), the morning and evening FEV_1 (forced expiratory volume in one second), and study drug compliance.

Eligible patients were randomized within 2, 4 or 6 weeks of screening in a 1:1:1 ratio to receive either, roflumilast 500 µg od plus LDICS, placebo od plus LDICS or placebo od plus HDICS. Patients continued to use salbutamol rescue medication as needed following randomization.

During the 24-week double-blind treatment period, patients were evaluated at the investigator's clinic at regular intervals (at weeks 2, 4, 8, 12, 18, and 24). At each clinic visit, patients completed QoL (quality of life) questionnaires, spirometry was performed, e-diary entries were reviewed, and laboratory procedures and AE (adverse event) assessments were performed.

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

It was planned to randomize 1014 patients into the three treatment groups (338 patients allocated per treatment arm). The actual number of patients enrolled, randomized and included in the analysis is shown in the following table:

	Enrolled	Randomized	Safety set	Full analysis set	Valid cases set
Rof + LDICS		388	388	388	275
Placebo + LDICS		385	385	385	282
Placebo + HDICS		398	398	398	296
Total	2049	1171	1171	1171	853

HDICS = high dose inhaled corticosteroids, LDICS = low dose inhaled corticosteroids, Rof = roflumilast 500 µg once daily.

Diagnosis and main criteria for inclusion:

Inclusion into baseline period

Patients had to meet all of the following inclusion criteria to be eligible for enrollment into the study:

- the patient was aged between 18 and 70 years of either sex (aged between 12 and 70 years in selected countries);
- for patients aged 18 to 70 years (for Singapore only, the applicable age range was 21 to 70 years): the patient had received verbal and written study information, all questions had been answered satisfactorily and a consent form had been personally signed and dated by the patient and the investigator;
- for patients aged 12 to 17 years in selected countries (for Singapore only, applicable age range was 12 to 20 years and the criterion was slightly modified): the parent/legal guardian had signed the parent/guardian informed consent form and the patient had signed the patient assent form after full discussion of the research nature of the treatment and its risks and benefits;
- the patient had a diagnosis of persistent bronchial asthma (with reference to the GINA [Global Initiative for Asthma] guidelines);
- the patient had been receiving BDP–CFC (BDP-chloroflurocarbons) ≤1000 µg/d or equivalent for the previous 4 weeks;
- the patient had a FEV_1 between 60 and 90% predicted at V1;
- there had been no change in asthma treatment within 4 weeks prior to V1;
- in the investigator's judgment, the patient was able and willing to comply with study visits and procedures (including laboratory tests, lung function tests), and accurate and timely completion of an electronic daily study diary;
- female patients aged 12-17 years who had started menstruation, and who were willing to have pregnancy tests as scheduled in the protocol. In Singapore only, patients in this age range who enrolled in the study after implementation of protocol amendment no. 9 had to provide a record of menstrual and sexual history at each study visit and be counseled on the risks of conceiving during their participation in the study;
- patients enrolled in the study but withdrawn without being randomized and allocated double-blind medication, before implementation of protocol amendment no. 8, could be considered for re-entry in the study, provided that they satisfied the modified randomization criteria of protocol amendment no. 8 (eg conditions on asthma summary symptom score and rescue medication use).

Inclusion into the treatment period (randomization criteria)

Patients had to meet all of the following randomization criteria to be eligible for randomization into the double-blind treatment period at V3:

- FEV_1 was between 50 and 80% predicted when salbutamol (rescue medication) was withheld for at least 4 h prior to the measurement;
- the patient had a positive reversibility test at V1 or V2 (or at V3 if test not performed or not correctly performed at V1 and V2), defined as an increase of initial FEV_1 ≥12% and/or ≥200 mL from 15 to 30 min after inhalation of 400 µg salbutamol;
- the patient had used ≥1 puff/d salbutamol (rescue medication) on average during the last week directly preceding randomization;

- the patient's asthma summary symptom score was ≥2 (out of a maximum of 8) on at least 4 of 7 d prior to randomization;
- there had been no exacerbation during run-in requiring additional therapy beyond prescribed run-in medication;
- there had been at least 14 d run-in period from the date of screening;
- the patient had been compliant in completing the e-diary during the single-blind run-in period. A minimum of 5 out of 7 d per week of complete and accurate diary data had to be present for at least 2 weeks prior to randomization;
- the patient had been compliant with taking study medication [roflumilast/placebo and ICS MDIs (metered dose inhalers)]. Between 80% and 100% study drug compliance had to be noted with reference to information recorded in the e-diary;
- the patient still met all other relevant inclusion and exclusion criteria.

Test product, dose, mode of administration, batch no.: roflumilast, one tablet of 500 µg od in the morning**,** oral administration, batch no. 120180 and BDP (beclomethasone dipropionate), 200 µg in the morning and evening, 100 µg/puff by inhalation, batch no. E063, E070, E164 or E267.

Reference product, dose, mode of administration, batch no.: placebo, one tablet od in the morning, oral administration, batch no. 420240, and either BDP, 200 µg in the morning and 200 µg in the evening, 100 µg/puff by inhalation, batch no. E063, E070, E164 or E267 or BDP, 400 µg in the morning and 400 µg in the evening, 200 µg/puff by inhalation, batch no. D031613, E024 or E080.

Duration of treatment: 2, 4 or 6 weeks in baseline period, followed by 24 weeks in the double-blind treatment period.

Criteria for evaluation:

Primary efficacy variable

- the primary efficacy variable was FEV_1 [L] (mean change in FEV_1 from baseline during the treatment period).

Key secondary efficacy variables

- PEF_{am};
- total asthma symptom score;
- rescue medication intake;
- time to first severe exacerbation during treatment period.

Other secondary efficacy variables

- lung function assessments from on-site spirometry: FVC (forced vital capacity), $FEF_{25-75\%}$ (forced expiratory flow over 25% to 75% of vital capacity), PEF (peak expiratory flow);
- lung function assessments from e-diary: PEF_{pm}, PEF_{dv} (diurnal variability of PEF);
- asthma e-diary assessments: daytime and nighttime asthma symptom score, symptom-free days, rescue medication-free days;
- exacerbation variables: time to first exacerbations requiring oral or parenteral steroid treatment (EROS), overall number of severe exacerbations, overall number of EROS;
- quality of life questionnaires: AQLQ(S) (Asthma Quality of Life Questionnaire, standardized version: overall, activity limitation, symptoms, emotional function, environmental stimuli scores), ACQ (Asthma Control Questionnaire: overall score).

Safety variables

- AEs;
- laboratory assessments (biochemistry, hematology and urinalysis);
- vital signs and ECG (electrocardiogram).

Statistical methods:

A hierarchical testing was applied; therefore no multiplicity adjustment was necessary. The primary comparison was a test for superiority of roflumilast + LDICS vs placebo + LDICS with respect to the primary variable FEV_1. After superiority of roflumilast + LDICS was shown, the non-inferiority test for the primary variable was performed. If non-inferiority of roflumilast + LDICS vs placebo + HDICS was shown, testing was continued for superiority of roflumilast + LDICS vs placebo + HDICS for the primary variable. If these tests led to a significant result, they were followed by a test for superiority of roflumilast + LDICS vs placebo + LDICS for the key secondary variables in a hierarchical order. After superiority of roflumilast + LDICS was shown for these variables, testing was continued for roflumilast + LDICS vs placebo + HDICS for the same parameters.

The primary analysis was performed using a repeated measurement ANCOVA (analysis of covariance). This model included all observed measurements from the scheduled visits of the treatment period. The dependent variable was the change from baseline at each scheduled visit. Treatment, pooled region/country, sex, time, baseline smoking status, baseline asthma severity class according to GINA, treatment-by-time interaction, baseline age, baseline FEV_1 were included as factors and covariables in the ANCOVA model. The correlation structure in the visit timepoints was specified to be unstructured, allowing for the greatest flexibility in estimation.

The repeated measurements analysis ANCOVA including all visits/weeks after the randomization visit/week to the final visit/week (or early termination) was performed for FEV_1, PEF_{am}, total asthma symptom score, rescue medication intake, FVC, $FEF_{25-75\%}$, PEF,

PEF_{pm}, PEF_{dv}, daytime and nighttime asthma symptom score, overall AQLQ, AQLQ domain scores and ACQ overall score.

The Mann-Whitney U-Test was used to test the between-treatment differences in PEF diurnal variability, percent of rescue-medication-free days and percent of symptom-free days. Wilcoxon's signed-rank test was used to analyze the within-treatment differences of PEF_{dv}. Cox-proportional hazards regression models and log-rank tests were used to analyze the time to first severe asthma exacerbation and time to first EROS. The number of severe exacerbations and EROS was analyzed using the Wilcoxon rank-sum test.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

There were no major differences in demographic data between the three treatment groups.

Demographic and other baseline characteristics by treatment (full analysis set)

		Full analysis set		
		Rof + LDICS (N = 388)	**Placebo + LDICS (N = 385)**	**Placebo + HDICS (N = 398)**
Age [years]	Median (range)	43 (12, 69)	44 (12, 70)	44 (12, 70)
Weight [kg]	Mean ± SD	73 ± 18	72 ± 18	72 ± 16
Height [cm]	Mean ± SD	166 ± 10	165 ± 10	165 ± 11
Sex [n (%)][a]	Female	224 (57.7)	238 (61.8)	245 (61.6)
	Male	164 (42.3)	147 (38.2)	153 (38.4)
Race [n (%)][a]	Asian	121 (31.2)	121 (31.4)	119 (29.9)
	Black	3 (0.8)	3 (0.8)	3 (0.8)
	White	249 (64.2)	245 (63.6)	254 (63.8)
	Other	9 (2.3)	8 (2.1)	10 (2.5)
	Not assessed	6 (1.5)	8 (2.1)	12 (3.0)
Asthma severity (GINA)	Intermittent	1 (0.3)	0 (0.0)	1 (0.3)
[n (%)]	Mild persistent	0 (0.0)	2 (0.5)	1 (0.3)
	Moderate persistent	18 (4.6)	16 (4.2)	14 (3.5)
	Severe persistent	363 (93.6)	354 (91.9)	374 (94.0)
	Missing	6 (1.5)	13 (3.4)	8 (2.0)
Smoking status [n (%)][a]	Non-smoker	299 (77.1)	301 (78.2)	302 (75.9)
	Current + ex-smoker	89 (22.9)	84 (21.8)	96 (24.1)
Pack years [n]	Mean ± SD	4.6 ± 3.1	5.4 ± 4.0	5.0 ± 3.1
FEV_1 [L]	Mean ± SD	2.086 ± 0.558	2.022 ± 0.555	2.029 ± 0.575
FEV_1 predicted [%]	Mean ± SD	69.5 ± 8.8	69.6 ± 9.5	69.0 ± 8.8
FEV_1 reversibility [%]	Mean ± SD	22.2 ± 15.4	23.3 ± 13.8	22.0 ± 10.7
FEV_1 reversibility [mL]	Mean ± SD	47.7 ± 33.5	47.5 ± 28.2	45.3 ± 24.0
PEF_{am} [L/min]	Mean ± SD	312 ± 110	305 ± 106	300 ± 118
Asthma symptom score	Median (range)	3.351 (0.00, 7.17)	3.412 (0.00, 7.25)	3.303 (0.00, 7.20)
Rescue medication intake [puffs/d]	Median (range)	3.662 (1.00, 11.00)	3.775 (1.00, 14.43)	3.626 (1.00, 12.29)

[a] Percentages are based on the number of patients in a treatment group.

FEV_1 = forced expiratory volume in 1 second, GINA = Global Initiative for Asthma, HDICS = high dose inhaled corticosteroids, LDICS = low dose inhaled corticosteroids, n = number of patients with data available, PEF_{am} = morning PEF, Rof = roflumilast 500 µg od, SD = standard deviation.

Efficacy results

If not indicated otherwise, results of the ITT analysis are reported which were the primary efficacy analysis for the test of superiority between roflumilast and placebo. The results of the PP analysis are reported for the primary efficacy analysis of non-inferiority.

Primary efficacy variable

Mean change from baseline for FEV_1 (repeated measurements analysis)

The analysis of the primary variable, mean change from baseline in FEV_1 during the double-blind treatment period, showed improvements in all three treatment groups (0.099 L with roflumilast + LDICS, 0.028 L with placebo + LDICS and 0.053 L with placebo + HDICS).

A statistically significant difference between roflumilast + LDICS and placebo + LDICS for change in FEV_1 during 24 weeks of treatment was shown (0.071 L, 95% CI: 0.021 L, 0.122 L, one-sided p-value = 0.0026, ITT), with the lower bound of the 95% CI greater than zero. Hence, superiority of roflumilast + LDICS over placebo + LDICS was proven.

For the non-inferiority test of roflumilast + LDICS vs placebo + HDICS, a statistically significant difference for change in FEV_1 was demonstrated in favor of roflumilast + LDICS (0.057 L, 95% CI: 0.000 L, 0.113 L, one-sided p-value = <0.0001, PP). The lower bound of the 95% CI was greater than -0.1 L. Hence non-inferiority of roflumilast + LDICS compared with placebo + HDICS was shown.

For the superiority test of roflumilast + LDICS vs placebo + HDICS for FEV_1, the difference was still in favor of roflumilast + LDICS; however the lower bound of the 95% CI was not greater than zero (0.046 L, 95% CI: -0.004 L, 0.096 L, one-sided p-value = 0.0343, ITT) and, hence, superiority of roflumilast + LDICS over placebo + HDICS was not proven.

Change from baseline in FEV_1 [L]: within- and between-treatment differences, repeated measurements analysis (ITT, PP)

WITHIN				Mean at Baseline	Within-treatment difference	
		n	n obs		LSMean ± SE	95% CI
ITT	Rof + LDICS	374	1920	2.089	0.099 ± 0.087	-0.071, 0.270
	Pbo + LDICS	366	1925	2.023	0.028 ± 0.087	-0.142, 0.198
	Pbo + HDICS	384	2063	2.024	0.053 ± 0.087	-0.116, 0.223
PP	Rof + LDICS	256	1227	2.016	0.315 ± 0.131	0.057, 0.573
	Pbo + LDICS	269	1276	1.999	0.222 ± 0.130	-0.033, 0.478
	Pbo + HDICS	282	1407	1.972	0.258 ± 0.131	0.001, 0.516

BETWEEN					Difference Test - Ref				
							1-sided p-value[a]		2-sided
	Test	Ref	n Test	n Ref	LSMean ± SE	95% CI	non-inf.	sup.	p-value[b]
ITT	Rof + LDICS	Pbo + LDICS	374	366	0.071 ± 0.026	0.021, 0.122		0.0026	0.0053
	Rof + LDICS	Pbo + HDICS	374	384	0.046 ± 0.025	-0.004, 0.096	<0.0001	0.0343	0.0686
PP	Rof + LDICS	Pbo + LDICS	256	269	0.093 ± 0.029	0.035, 0.150		0.0008	0.0016
	Rof + LDICS	Pbo + HDICS	256	282	0.057 ± 0.029	0.000, 0.113	<0.0001	0.0247	0.0494

[a] One-sided p-value, significance level 2.5%
[b] Two-sided p-value, significance level 5%
Non-inferiority margin(s): FEV1: -100 mL
Superiority can be concluded if the lower bound of the 95% confidence interval is greater than 0.
Baseline was defined as technically acceptable value at V3.
CI = confidence interval, HDICS = high dose inhaled corticosteroids, LDICS = low dose inhaled corticosteroids, non-inf = non-inferiority, Pbo = placebo, Rof = roflumilast 500 µg od, FEV_1 = forced expiratory volume in 1 s, LS = least squares, n = number of patients with data available, n obs = number of observations, SE = standard error of the LSMean, sup. = superiority.

Since FEV_1 for roflumilast + LDICS was not proven to be statistically superior compared with placebo + HDICS, the hierarchy of hypothesis testing was stopped, and all further hypotheses of key secondary and secondary variables were conducted in an exploratory manner.

Secondary variables

Key secondary variables

Mean change from baseline for PEF_{am} (repeated measurements analysis)

There was an increase (improvement) in PEF_{am} in all treatment groups (13.957 L/min, 8.083 L/min, 13.851 L/min, for roflumilast + LDICS, placebo + LDICS, and placebo + HDICS, respectively). The between-treatment differences for roflumilast + LDICS compared with placebo + LDICS and placebo + HDICS showed improvements for roflumilast + LDICS (roflumilast + LDICS vs placebo + LDICS: 5.874 L/min, 95% CI: -1.112 L/min, 12.859 L/min, one-sided p-value = 0.0496; roflumilast + LDICS vs placebo + HDICS: 0.106 L/min, 95% CI: -6.775 L/min, 6.988 L/min, one-sided p-value = 0.4879). The PP analysis differed from the results of the ITT analysis, with greater PEF_{am}

improvement for roflumilast + LDICS compared with placebo + LDICS, but less improvement of PEF_{am} for roflumilast + LDICS compared with placebo + HDICS.

Mean change from baseline for total asthma symptom score (repeated measurements analysis)
There were large within-treatment reductions (improvements) in total asthma symptom score in all three treatment groups. The magnitude of the changes was similar for all treatment groups (-1.723, -1.687, -1.794, for roflumilast + LDICS, placebo + LDICS and placebo + HDICS, respectively). The between-treatment differences for total asthma symptom score during 24 weeks of treatment showed greater improvement for roflumilast + LDICS when compared with placebo + LDICS (-0.036, 95% CI: -0.216, 0.143, one-sided p-value = 0.3456), but less improvement when compared with placebo + HDICS (0.071, 95% CI: -0.107, 0.248, one-sided p-value = 0.7831).

Mean change from baseline for rescue medication intake (repeated measurements analysis)
There were increases in rescue medication intake (worsening of condition) in all three treatment groups. The magnitude of the changes was greater for the roflumilast + LDICS (0.208 puffs/d) and placebo + LDICS (0.174 puffs/d) treatment groups than for the placebo + HDICS group (0.090 puffs/d). The between-treatment differences for roflumilast + LDICS compared with placebo + LDICS and placebo + HDICS showed greater deteriorations with roflumilast + LDICS (roflumilast + LDICS vs placebo + LDICS: 0.033 puffs/d, 95% CI: -0.143 puffs/d, 0.209 puffs/d, one-sided p-value = 0.6437; roflumilast + LDICS vs placebo + HDICS: 0.118 puffs/d, 95% CI: -0.056 puffs/d, 0.291 puffs/d, one-sided p-value = 0.9087). The PP analysis indicated reductions in rescue medication intake (improvement) during the study; the between-treatment differences for roflumilast + LDICS vs placebo + LDICS showed greater improvement for roflumilast + LDICS, but less improvement for roflumilast + LDICS vs placebo + HDICS.

Time to first severe exacerbation (Cox proportional hazards test)
Fewer patients experienced severe asthma exacerbations in the roflumilast + LDICS and placebo + HDICS groups compared with the placebo + LDICS group (roflumilast + LDICS: 107 [27.6%], placebo + LDICS: 133 [34.5%] and placebo + HDICS: 112 [28.1%]) The median time to onset of the first severe asthma exacerbation was longest in patients treated with roflumilast + LDICS (51.0 d) than in patients treated with either placebo + LDICS (36.0 d) or placebo + HDICS (40.0 d). Analysis of the time to first severe exacerbation indicated a lower hazards ratio for roflumilast + LDICS compared with placebo + LDICS (0.775, one-sided p-value = 0.0259) and comparable results when compared with placebo + HDICS (0.990, one-sided p-value = 0.4700). The PP analysis confirmed the results from the ITT analysis.

Other secondary variables

Mean change from baseline for FVC, PEF, and $FEF_{25-75\%}$ (spirometry, repeated measurements analysis)

There were large within-treatment increases in PEF in all three treatment groups. FVC also increased, with a greater increase in the roflumilast + LDICS group. $FEF_{25-75\%}$, however, reduced (worsened) in all three treatment groups. The between-treatment differences for roflumilast + LDICS compared with placebo + LDICS and placebo + HDICS showed improvements for roflumilast + LDICS for PEF (roflumilast + LDICS vs placebo + LDICS: 2.24 L/min, one-sided p-value = 0.3352; roflumilast + LDICS vs placebo + HDICS: 3.19 L/min, one-sided p-value = 0.2699) and FVC (roflumilast + LDICS vs placebo + LDICS: 0.092 L, one-sided p-value = 0.0015; roflumilast + LDICS vs placebo + HDICS: 0.065 L, one-sided p-value = 0.0165), with less deterioration for $FEF_{25-75\%}$, (roflumilast + LDICS vs placebo + LDICS: 0.106 L/s, one-sided p-value = 0.0037; roflumilast + LDICS vs placebo + HDICS: 0.053 L/s, one-sided p-value = 0.0877).

Mean change from baseline for PEF_{pm} and PEF_{dv} (diary, repeated measurements analysis)

Similar to the results for PEF_{am}, there was an increase (improvement) in PEF_{pm} in all three treatment groups. The between-treatment difference for PEF_{pm} showed greater improvement for roflumilast + LDICS when compared with placebo + LDICS (3.767 L/min, one-sided p-value = 0.1380), but less improvement when compared with placebo + HDICS (-0.153 L/min, one-sided p-value = 0.5179). There was a reduction (improvement) in PEF_{dv} for all of the treatment groups. The between-treatment difference for PEF_{dv} showed greater improvement for roflumilast + LDICS when compared with placebo + LDICS (-0.21%, one-sided p-value = 0.2434), but less improvement when compared with placebo + HDICS (0.15%, one-sided p-value = 0.6928).

Mean change from baseline for individual asthma symptom scores (repeated measurements analysis)

There were within-treatment reductions (improvements) in both daytime and nighttime asthma symptom score in all three treatment groups. The magnitude of the changes was similar for all treatment groups.

The between-treatment differences showed less improvement for roflumilast + LDICS in both daytime and nighttime asthma symptom score when comparing roflumilast + LDICS vs placebo + HDICS (daytime score: 0.004, one-sided p-value = 0.5309; nighttime score: 0.051, one-sided p-value = 0.8571). When comparing roflumilast + LDICS vs placebo + LDICS, daytime asthma symptom score showed greater improvement for roflumilast + LDICS (-0.065, one-sided p-value = 0.0866), while nighttime asthma symptom score showed less improvement (0.023, one-sided p-value = 0.6854). Results were similar for the PP analysis except for daytime asthma symptom score favoring roflumilast + LDICS for the comparison of roflumilast + LDICS vs placebo + HDICS.

Percentage of asthma symptom-free and rescue medication-free days (Mann-Whitney U-Test)
The median percentage of asthma symptom-free days was higher in the roflumilast + LDICS treatment group than in either the placebo + LDICS or placebo + HDICS groups. The median percentage of rescue medication-free days was the same for all three treatment groups. No relevant between-treatment differences for asthma symptom-free days and rescue medication-free days were seen.

Time to first EROS (Cox proportional hazards test)
During the treatment period, fewer patients in the roflumilast + LDICS treatment group (14) experienced an EROS than patients in the placebo + LDICS group (25) or placebo + HDICS group (17). The median time to onset of the first EROS was longer in patients treated with roflumilast + LDICS (78.5 d) than in patients treated with either placebo + LDICS (50.0 d) or placebo + HDICS (62.0 d). Analysis of the time to first EROS indicated a lower hazards ratio for roflumilast + LDICS, compared with both placebo + LDICS (0.598, one-sided p-value = 0.0659) and placebo + HDICS (0.897, one-sided p-value = 0.3826).

For the PP analysis, the comparison for roflumilast + LDICS vs placebo + HDICS indicated a higher hazards ratio for roflumilast + LDICS (1.303, one-sided p-value = 0.7264).

Mean change from baseline for quality of life (assessed by AQLQ(S), repeated measurements analysis)
There were improvements for AQLQ(S) overall score and individual domain scores in all three treatment groups, with placebo + HDICS generally showing the largest increases and placebo + LDICS showing the smallest increases. The improvements were numerically small and none reached the MCID of 0.5. The between-treatment differences for AQLQ(S) overall score or any of the individual domain scores showed greater improvement for roflumilast + LDICS when compared with placebo + LDICS, but less improvement when compared with placebo + HDICS.

Mean change from baseline for quality of life (assessed by ACQ, repeated measurements analysis)
There were within-treatment reductions (improvements) for ACQ overall score in all three treatment groups. The magnitude of the changes was similar for all treatment groups, but numerically small (none achieved the MCID of 0.5) and unlikely to be clinically relevant. The between-treatment comparisons of roflumilast + LDICS vs placebo + LDICS and roflumilast + LDICS vs placebo + HDICS for ACQ overall score showed improvements for the roflumilast + LDICS treatment group.

Safety results:
Adverse events
The following table summarizes the treatment-emergent AEs reported during the double-blind treatment period:

Treatment-emergent adverse events (safety set)

	Rof + LDICS (N = 388)		Pbo + LDICS (N = 385)		Pbo + HDICS (N = 398)		Total (N = 1171)	
Number of patients (%)[a] with:								
AEs	220	(56.7)	176	(45.7)	201	(50.5)	597	(51.0)
SAEs	17	(4.4)	11	(2.9)	11	(2.8)	39	(3.3)
AEs with causality[b] suggested by the investigator	53	(13.7)	17	(4.4)	20	(5.0)	90	(7.7)
AEs leading to discontinuation	45	(11.6)	23	(6.0)	17	(4.3)	85	(7.3)
AEs not yet known to be recovered	24	(6.2)	24	(6.2)	19	(4.8)	67	(5.7)
Changes in study medication due to AEs	7	(1.8)	2	(0.5)	0	(0.0)	9	(0.8)

[a] Percentages are based on the total number of patients in a treatment group.

[b] AEs assessed as 'related' to the study medication by the investigator.

AE = adverse event, N = number of patients in each treatment group, %: percent of patients n with at least one event in the category based on N, HDICS = high dose inhaled corticosteroids, LDICS = low dose inhaled corticosteroids, Pbo = placebo, Rof = roflumilast 500 µg od, SAE = serious adverse event.

During the double-blind treatment period, 220 (56.7%) patients in the roflumilast + LDICS group, 176 (45.7%) patients in the placebo + LDICS group, and 201 (50.5%) patients in the placebo + HDICS group experienced AEs. Most frequently, AEs were from the 'infections and infestations', 'gastrointestinal disorders', and 'nervous system disorders' SOCs. The latter two categories, however, showed a lower frequency of associated AEs for the placebo + LDICS and placebo + HDICS groups, compared to the roflumilast + LDICS group. For individual AEs, headache, diarrhoea, nausea, rhinitis, and myalgia occurred most frequently in the roflumilast + LDICS treatment group, and at a reduced rate in the placebo + LDICS and placebo + HDICS groups. This is in line with the known safety profile of roflumilast. Other AEs were distributed evenly over the three treatment groups.

Most AEs were mild or moderate in intensity in the three treatment groups. AEs which were related to the study medication according to the investigator were experienced by 53 (13.7%) patients treated with roflumilast + LDICS, by 17 (4.4%) patients treated with placebo + LDICS, and by 20 (5.0%) patients treated with placebo + HDICS. The median time to onset of AEs was 33 d in the roflumilast + LDICS group, 56 d in the placebo + LDICS group, and 61 d in the placebo + HDICS group. The median duration of AEs was similar and most patients (>90%) recovered from their AEs without sequelae in all three treatment groups.

During the treatment period 17 patients in the roflumilast + LDICS group experienced 21 SAEs, 11 patients in the placebo + LDICS group experienced 13 SAEs, and 11 patients in the placebo + HDICS group experienced 15 SAEs. No patient died during the study. Most of the SAEs were assessed as 'not related' to the study medication by the investigator. Four SAEs in the placebo + LDICS group (cholelithiasis, cholecystitis, blood creatine phosphokinase increased, dermatitis allergic) and two SAEs in the placebo + HDICS group (headache and asthma) were assessed as 'related'. No SAEs in the roflumilast + LDICS group were assessed as 'related' to the study medication by the investigator.

More patients discontinued due to AEs in the roflumilast + LDICS group (45 [11.6%] patients) than in the placebo + LDICS group (23 [6.0%] or in the placebo + HDICS group (17 [4.3%] patients). Of these, eight patients in the roflumilast + LDICS group, six patients in the placebo + LDICS group, and three patients in the placebo + HDICS group discontinued due to SAEs.

Clinical laboratory assessments

Overall, no clinically relevant changes in hematology, biochemistry and urine cortisol values were observed in any of the three treatment groups during the course of the study. During the double-blind treatment period, 12 patients in the roflumilast + LDICS group, 17 patients in the placebo + LDICS group, and 12 patients in the placebo + HDICS group experienced AEs associated with abnormal laboratory values. Most laboratory AEs assessed by the investigator as 'related' to study medication occurred in the placebo + LDICS group (five incidents), with one 'related' laboratory AE in the roflumilast + LDICS group.

Vital signs

BP and HR measured during the study period did not reveal any influence of the two different treatments. ECG findings were similar for all treatment groups.

In conclusion, the observed safety data for roflumilast in this study were generally in line with the known safety profile of this drug.

Conclusions:

In conclusion, following roflumilast + LDICS treatment for 24 weeks, the improvement in the primary efficacy parameter of FEV_1 was statistically superior to placebo + LDICS. For the comparison of roflumilast + LDICS with placebo + HDICS, the improvement in FEV_1 for roflumilast + LDICS was statistically non-inferior to the improvement following placebo + HDICS. Superiority of roflumilast + LDICS over placebo + HDICS was not shown for FEV_1. There were clear trends towards improvement in the roflumilast + LDICS treatment group for a variety of key secondary and secondary variables compared with placebo + LDICS. The improvements in efficacy variables following roflumilast + LDICS compared with placebo + LDICS (and non-inferiority of roflumilast + LDICS compared with placebo + HDICS for FEV_1) were countered by a higher incidence of AEs in the roflumilast + LDICS treated group.

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