Disclaimer: This study was originally sponsored by Takeda 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.

Effect of Roflumilast on Exacerbation Rate in Patients With Chronic Obstructive Pulmonary Disease (COPD): The AURA Study (BY217/M2-124)

This study has been completed.

Sponsor:
Takeda

Information provided by:
Takeda

ClinicalTrials.gov Identifier:
NCT00297102

First received: February 27, 2006
Last updated: May 4, 2012
Last verified: June 2011
History of Changes

Results First Received: March 17, 2011

Study Type:	Interventional
Study Design:	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Double Blind (Subject, Investigator); Primary Purpose: Treatment
Condition:	Chronic Obstructive Pulmonary Disease (COPD)
Interventions:	Drug: Roflumilast Drug: Placebo

Participant Flow

Hide Participant Flow

Recruitment Details

Key information relevant to the recruitment process for the overall study, such as dates of the recruitment period and locations
No text entered.

Pre-Assignment Details

Significant events and approaches for the overall study following participant enrollment, but prior to group assignment
No text entered.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Participant Flow: Overall Study

	Roflumilast	Placebo
STARTED	765 [1]	758 [1]
COMPLETED	502	525

NOT COMPLETED	263	233

[1] Includes all randomized patients who took at least one dose of the investigational drug.

Baseline Characteristics

Hide Baseline Characteristics

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
No text entered.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily
Total	Total of all reporting groups

Baseline Measures

	Roflumilast	Placebo	Total
Number of Participants [units: participants]	765	758	1523
Age [units: years] Mean (Standard Deviation)	63.53 (9.5)	63.36 (9.2)	63.45 (9.4)
Gender [units: participants]			
Female	225	220	445
Male	540	538	1078

Outcome Measures

Hide All Outcome Measures

1. Primary: Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) [Time Frame: Change from baseline over 52 weeks of treatment]

Measure Type	Primary
Measure Title	Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1)
Measure Description	Mean change from baseline during the treatment period in pre-bronchodilator FEV1 [L]
Time Frame	Change from baseline over 52 weeks of treatment
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT (Intention to Treat) analysis. Number of participants analyzed = number of participants with data available.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**745**	**745**
Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) [units: mL] Least Squares Mean (Standard Error)	**46 (8)**	**8 (8)**

Statistical Analysis 1 for Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.0003
Mean Difference (Net) [4]	39
Standard Error of the mean	(11)
95% Confidence Interval	18 to 60

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Repeated measurements analysis (change from baseline over 52 weeks of treatment taking all post-randomization measurements into account).
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

2. Primary: COPD Exacerbation Rate (Moderate or Severe) [Time Frame: 52 weeks treatment period]

Measure Type	Primary
Measure Title	COPD Exacerbation Rate (Moderate or Severe)
Measure Description	Mean rate of COPD exacerbations requiring oral or parenteral glucocorticosteroids (=moderate COPD exacerbations), or requiring hospitalization, or leading to death (=severe COPD exacerbations), per patient per year. A COPD exacerbation is an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management [American Thoracic Society (ATS) / European Respiratory Society (ERS) 2005].
Time Frame	52 weeks treatment period
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT analysis.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**765**	**758**
COPD Exacerbation Rate (Moderate or Severe) [units: exacerbations per patient per year] Mean (95% Confidence Interval)	**1.077 (0.960 to 1.207)**	**1.266 (1.141 to 1.404)**

Statistical Analysis 1 for COPD Exacerbation Rate (Moderate or Severe)

Groups [1]	All groups
Method [2]	Poisson regression
P Value [3]	0.0278
Rate ratio [4]	0.851
Standard Error of the mean	(0.062)
95% Confidence Interval	0.737 to 0.982

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

3. Secondary: Post-bronchodilator FEV1 [L] [Time Frame: Change from baseline over 52 weeks of treatment]

Measure Type	Secondary
Measure Title	Post-bronchodilator FEV1 [L]
Measure Description	Mean change from baseline during the treatment period in post-bronchodilator FEV1 [L]
Time Frame	Change from baseline over 52 weeks of treatment
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT analysis. Number of participants analyzed = number of participants with data available.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**729**	**736**
Post-bronchodilator FEV1 [L] [units: mL] Least Squares Mean (Standard Error)	**57 (9)**	**8 (8)**

Statistical Analysis 1 for Post-bronchodilator FEV1 [L]

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.0001
Mean Difference (Net) [4]	49
Standard Error of the mean	(11)
95% Confidence Interval	26 to 71

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Repeated measurements analysis (change from baseline over 52 weeks of treatment taking all post-randomization measurements into account).
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: Time to Mortality Due to Any Reason [Time Frame: 52 weeks treatment period]

Measure Type	Secondary
Measure Title	Time to Mortality Due to Any Reason
Measure Description	No text entered.
Time Frame	52 weeks treatment period
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT analysis. Number of participants analyzed = number of participants who died.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**17**	**17**
Time to Mortality Due to Any Reason [units: days] Mean (Standard Deviation)	**213.8 (118.9)**	**207.5 (108.5)**

Statistical Analysis 1 for Time to Mortality Due to Any Reason

Groups [1]	All groups
Method [2]	Cox proportional hazards regression
P Value [3]	0.9212
Hazard Ratio (HR) [4]	1.035
Standard Error of the mean	(0.357)
95% Confidence Interval	0.526 to 2.034

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	No text entered.
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	The statistical analysis is based on the ITT Analysis Set (n= 765 in the roflumilast group, n= 758 in the placebo group).

5. Secondary: Natural Log-transformed C-reactive Protein (CRP) [Time Frame: Change from baseline to last post randomization measurement (52 weeks)]

Measure Type	Secondary
Measure Title	Natural Log-transformed C-reactive Protein (CRP)
Measure Description	Mean change from baseline to the last post randomization measurement in natural log-transformed CRP
Time Frame	Change from baseline to last post randomization measurement (52 weeks)

Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT analysis. Number of participants analyzed = number of participants with data available.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**691**	**694**
Natural Log-transformed C-reactive Protein (CRP) [units: mg/L] Least Squares Mean (95% Confidence Interval)	**1.0475 (0.9584 to 1.1450)**	**1.1003 (1.0071 to 1.2021)**

Statistical Analysis 1 for Natural Log-transformed C-reactive Protein (CRP)

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.4089
Mean Difference calculated as ratio [4]	0.9521
95% Confidence Interval	0.8472 to 1.0699

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	ANCOVA model including last observation carried forward (LOCF) method
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

6. Secondary: Mean Transition Dyspnea Index (TDI) Focal Score During the Treatment Period [Time Frame: Change from baseline over 52 weeks of treatment]

Measure Type	Secondary
Measure Title	Mean Transition Dyspnea Index (TDI) Focal Score During the Treatment Period
Measure Description	The TDI is a recognized questionnaire to measure dyspnea in an out patient COPD population. At baseline, 3 components of dyspnea, each graded with 4 questions, were asked: • Functional Impairment

	• Magnitude of Task • Magnitude of Effort At each of the post-randomization visits questions from the TDI were asked related to 3 components: Change in • Functional Impairment • Magnitude of Task • Magnitude of Effort Each question in the TDI is graded from –3 (major deterioration) to +3 (major improvement). This results in a TDI Focal Score ranging from –9 to +9.
Time Frame	Change from baseline over 52 weeks of treatment
Safety Issue	No

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.
ITT analysis. Number of participants analyzed = number of participants with data available.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Measured Values

	Roflumilast	**Placebo**
Number of Participants Analyzed [units: participants]	**741**	**745**
Mean Transition Dyspnea Index (TDI) Focal Score During the Treatment Period [units: scores on a scale] Least Squares Mean (Standard Error)	**0.658 (0.084)**	**0.426 (0.082)**

Statistical Analysis 1 for Mean Transition Dyspnea Index (TDI) Focal Score During the Treatment Period

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.0356
Mean Difference (Final Values) [4]	0.233
Standard Error of the mean	(0.111)
95% Confidence Interval	0.016 to 0.449

[1]	Additional details about the analysis, such as null hypothesis and power calculation:
	No text entered.
[2]	Other relevant method information, such as adjustments or degrees of freedom:
	Repeated measurements analysis (change from baseline over 52 weeks of treatment taking all post-randomization measurements into account).
[3]	Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:
	No adjustment of the significance level was done as a hierarchical approach for hypotheses testing was used.

[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	52 weeks treatment period
Additional Description	The Safety Set was based on all randomized patients who took at least one dose of the investigational drug after randomization. 4 patients randomized to placebo received roflumilast instead and were included in the roflumilast group for safety analyses. 1 patient was randomized twice. The second randomization is only included in the Safety Set.

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Serious Adverse Events

	Roflumilast	Placebo
Total, serious adverse events		
# participants affected / at risk	**144/769 (18.73%)**	**153/755 (20.26%)**
Cardiac disorders		
Atrial fibrillation † 1		
# participants affected / at risk	**7/769 (0.91%)**	**0/755 (0.00%)**
# events	**7**	**0**
Cardiac failure † 1		
# participants affected / at risk	**1/769 (0.13%)**	**4/755 (0.53%)**
# events	**1**	**4**
Angina pectoris † 1		
# participants affected / at risk	**2/769 (0.26%)**	**2/755 (0.26%)**
# events	**2**	**2**
Cardiac failure acute † 1		
# participants affected / at risk	**2/769 (0.26%)**	**2/755 (0.26%)**
# events	**2**	**2**
Cardiac failure congestive † 1		
# participants affected / at risk	**1/769 (0.13%)**	**3/755 (0.40%)**
# events	**1**	**3**
Acute myocardial infarction † 1		
# participants affected / at risk	**0/769 (0.00%)**	**3/755 (0.40%)**
# events	**0**	**3**
Angina unstable † 1		
# participants affected / at risk	**2/769 (0.26%)**	**0/755 (0.00%)**
# events	**2**	**0**
Cardiopulmonary failure † 1		
# participants affected / at risk	**0/769 (0.00%)**	**2/755 (0.26%)**
# events	**0**	**2**

Myocardial infarction [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**1/755 (0.13%)**
# events	**1**	**1**
Acute coronary syndrome [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Atrial tachycardia [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Cardiac arrest [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Left ventricular failure [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Palpitations [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Ventricular tachycardia [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Congenital, familial and genetic disorders		
Adenomatous polyposis coli [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Endocrine disorders		
Hyperthyroidism [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Eye disorders		
Blepharochalasis [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Glaucoma [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Retinal detachment [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Gastrointestinal disorders		
Abdominal pain [†1]		
# participants affected / at risk	**2/769 (0.26%)**	**1/755 (0.13%)**
# events	**3**	**1**
Colonic polyp [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**2/755 (0.26%)**
# events	**0**	**2**
Haematochezia [†1]		
# participants affected / at risk	**2/769 (0.26%)**	**0/755 (0.00%)**
# events	**2**	**0**

Inguinal hernia [†1]		
# participants affected / at risk	**2/769 (0.26%)**	**0/755 (0.00%)**
# events	**2**	**0**
Pancreatitis acute [†1]		
# participants affected / at risk	**2/769 (0.26%)**	**0/755 (0.00%)**
# events	**2**	**0**
Abdominal hernia [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Abdominal pain lower [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Colitis ulcerative [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Colonic pseudo-obstruction [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Constipation [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Diarrhoea [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Diverticulum [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Diverticulum intestinal [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Epigastric discomfort [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Flatulence [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Gastrointestinal haemorrhage [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Hiatus hernia [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Ileus [†1]		
# participants affected / at risk	**1/769 (0.13%)**	**0/755 (0.00%)**
# events	**1**	**0**
Mesenteric artery thrombosis [†1]		
# participants affected / at risk	**0/769 (0.00%)**	**1/755 (0.13%)**
# events	**0**	**1**
Nausea [†1]		

# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Oesophageal spasm [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Oesophageal ulcer [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Oesophageal varices haemorrhage [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Rectal haemorrhage [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Small intestinal obstruction [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Upper gastrointestinal haemorrhage [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Volvulus [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Vomiting [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
General disorders		
Chest pain [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Sudden death [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Asthenia [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Chest discomfort [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Death [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Injection site inflammation [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Malaise [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Non-cardiac chest pain [†1]		

# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Hepatobiliary disorders		
Hepatitis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Hepatitis toxic [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Immune system disorders		
Drug hypersensitivity [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Infections and infestations		
Pneumonia [†1]		
# participants affected / at risk	8/769 (1.04%)	11/755 (1.46%)
# events	8	13
Bronchitis [†1]		
# participants affected / at risk	2/769 (0.26%)	2/755 (0.26%)
# events	2	2
Cellulitis [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Lower respiratory tract infection [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Bacteraemia [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Bronchopulmonary aspergillosis allergic [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Chronic sinusitis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Clostridial infection [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Diverticulitis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Gastroenteritis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Lobar pneumonia [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Septic shock [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)

# events	0	1
Staphylococcal bacteraemia [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Wound sepsis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Ankle fracture [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Chemical eye injury [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Meniscus lesion [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Rib fracture [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Road traffic accident [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Subdural haematoma [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Vascular graft complication [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Investigations		
Anticoagulation drug level above therapeutic [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Bronchoscopy [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Computerised tomogram thorax abnormal [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	2
Metabolism and nutrition disorders		
Dehydration [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Malnutrition [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Musculoskeletal and connective tissue disorders		
Back pain [†1]		

# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Bursitis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Gouty arthritis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Intervertebral disc degeneration [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Muscoloskeletal pain [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	2
Neck mass [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Polyarthritis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Colon cancer [†1]		
# participants affected / at risk	2/769 (0.26%)	0/755 (0.00%)
# events	2	0
Lung squamous cell carcinoma stage unspecified [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Prostate cancer [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Adenoma benign [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Bladder cancer [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Bladder neoplasm [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Breast cancer [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Bronchial carcinoma [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Cervix neoplasm [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Colon adenoma [†1]		

# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Hepatic cancer metastatic [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Lung adenocarcinoma [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Lung cancer metastatic [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Lung neoplasm malignant [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Metastases to bone [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Metastases to liver [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Metastatic bronchial carcinoma [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Small cell lung cancer metastatic [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Squamous cell carcinoma [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Uterine leiomyoma [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Nervous system disorders		
Syncope [†1]		
# participants affected / at risk	3/769 (0.39%)	2/755 (0.26%)
# events	3	4
Transient ischaemic attack [†1]		
# participants affected / at risk	2/769 (0.26%)	2/755 (0.26%)
# events	2	2
Carotid artery stenosis [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Cerebrovascular accident [†1]		
# participants affected / at risk	0/769 (0.00%)	2/755 (0.26%)
# events	0	2
Carotid artery disease [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Cerebral haemorrhage [†1]		

# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Cerebral ischaemia [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Convulsion [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Dizziness [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Hypoaesthesia [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Ischaemic stroke [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Loss of consciousness [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Parkinson's disease [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Partial seizures [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Sciatica [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Psychiatric disorders		
Depression [†1]		
# participants affected / at risk	1/769 (0.13%)	2/755 (0.26%)
# events	1	2
Acute psychosis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Confusional state [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Panic attack [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Suicide attempt [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Renal and urinary disorders		
Calculus urinary [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0

Haematuria [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Nephrolithiasis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Renal artery stenosis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Renal colic [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Renal failure acute [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Reproductive system and breast disorders		
Metrorrhagia [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Uterine haemorrhage [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease [†1]		
# participants affected / at risk	70/769 (9.10%)	82/755 (10.86%)
# events	95	108
Respiratory failure [†1]		
# participants affected / at risk	3/769 (0.39%)	3/755 (0.40%)
# events	5	3
Pneumothorax [†1]		
# participants affected / at risk	2/769 (0.26%)	2/755 (0.26%)
# events	3	2
Pulmonary embolism [†1]		
# participants affected / at risk	2/769 (0.26%)	2/755 (0.26%)
# events	2	2
Acute respiratory failure [†1]		
# participants affected / at risk	1/769 (0.13%)	2/755 (0.26%)
# events	1	3
Bronchospasm [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Dyspnoea [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Emphysema [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Lung disorder [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)

# events	0	1
Pleural effusion [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Pleurisy [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Pneumonitis [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Skin and subcutaneous tissue disorders		
Angioedema [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Eczema [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Skin ulcer [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Social circumstances		
Physical assault [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Surgical and medical procedures		
Hip arthroplasty [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	1
Cataract operation [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Vascular disorders		
Hypertensive crisis [†1]		
# participants affected / at risk	1/769 (0.13%)	1/755 (0.13%)
# events	1	2
Aortic aneurysm [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Arterial disorder [†1]		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Arterial restenosis [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Arterial thrombosis limb [†1]		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Deep vein thrombosis [†1]		

# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Femoral arterial stenosis † 1		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Haematoma † 1		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Hypertension † 1		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1
Peripheral arterial occlusive disease † 1		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Peripheral ischaemia † 1		
# participants affected / at risk	1/769 (0.13%)	0/755 (0.00%)
# events	1	0
Venous thrombosis † 1		
# participants affected / at risk	0/769 (0.00%)	1/755 (0.13%)
# events	0	1

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA (11.0)

Other Adverse Events

Hide Other Adverse Events

Time Frame	52 weeks treatment period
Additional Description	The Safety Set was based on all randomized patients who took at least one dose of the investigational drug after randomization. 4 patients randomized to placebo received roflumilast instead and were included in the roflumilast group for safety analyses. 1 patient was randomized twice. The second randomization is only included in the Safety Set.

Frequency Threshold

Threshold above which other adverse events are reported	5

Reporting Groups

	Description
Roflumilast	500 mcg, once daily, oral administration in the morning
Placebo	once daily

Other Adverse Events

	Roflumilast	Placebo
Total, other (not including serious) adverse events		
# participants affected / at risk	232/769 (30.17%)	136/755 (18.01%)
Gastrointestinal disorders		
Diarrhoea † 1 [3]		
# participants affected / at risk	62/769 (8.06%)	26/755 (3.44%)

# events	72	30
Nausea † 1 [3]		
# participants affected / at risk	40/769 (5.20%)	15/755 (1.99%)
# events	44	15
Infections and infestations		
Nasopharyngitis † 1		
# participants affected / at risk	57/769 (7.41%)	50/755 (6.62%)
# events	76	65
Bronchitis † 1 [3]		
# participants affected / at risk	33/769 (4.29%)	39/755 (5.17%)
# events	41	49
Investigations		
Weight decreased † 1		
# participants affected / at risk	92/769 (11.96%)	24/755 (3.18%)
# events	94	24

† Events were collected by systematic assessment
1 Term from vocabulary, MedDRA (11.0)
[3] non-serious

Limitations and Caveats

Hide Limitations and Caveats

Limitations of the study, such as early termination leading to small numbers of participants analyzed and technical problems with measurement leading to unreliable or uninterpretable data

No text entered.

More Information

Hide More Information

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☐ The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

☑ Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

Restriction Description: The study results may be published and/or presented at scientific meetings. Prior to any submission, all manuscripts/abstracts must be presented to the sponsor for possible comments.

Results Point of Contact:

Name/Title: Respiratory Medical Advisor
Organization: Nycomed GmbH
phone: 0049-7531-840
e-mail: clinicaltrials@nycomed.com

Publications of Results:

Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet. 2009 Aug 29;374(9691):685-94. doi: 10.1016/S0140-6736(09)61255-1. Erratum in: Lancet. 2010 Oct 2;376(9747):1146.

Publications automatically indexed to this study by ClinicalTrials.gov Identifier (NCT Number):

Hanania NA, Calverley PM, Dransfield MT, Karpel JP, Brose M, Zhu H, Goehring UM, Rowe P. Pooled subpopulation analyses of the effects of roflumilast on exacerbations and lung function in COPD. Respir Med. 2014 Feb;108(2):366-75. doi: 10.1016/j.rmed.2013.09.018. Epub 2013 Sep 30.

Wedzicha JA, Rabe KF, Martinez FJ, Bredenbröker D, Brose M, Goehring UM, Calverley PM. Efficacy of roflumilast in the COPD frequent exacerbator phenotype. Chest. 2013 May;143(5):1302-11. doi: 10.1378/chest.12-1489.

Responsible Party:	Nycomed
ClinicalTrials.gov Identifier:	NCT00297102 History of Changes
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Study First Received:	February 27, 2006
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