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 HERMES Study (BY217/M2-125)

This study has been completed.

Sponsor:
Takeda

Information provided by:
Takeda

ClinicalTrials.gov Identifier:
NCT00297115

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	772 [1]	796 [1]
COMPLETED	527	550

NOT COMPLETED	245	246

[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]	772	796	1568
Age [units: years] Mean (Standard Deviation)	63.92 (9.2)	64.31 (9.0)	64.12 (9.1)
Gender [units: participants]			
Female	162	148	310
Male	610	648	1258

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]	730	766
Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) [units: mL] Least Squares Mean (Standard Error)	33 (7)	-25 (7)

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

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.0001
Mean Difference (Net) [4]	58
Standard Error of the mean	(9)
95% Confidence Interval	41 to 75

[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]	**772**	**796**
COPD Exacerbation Rate (Moderate or Severe) [units: exacerbations per patient per year] Mean (95% Confidence Interval)	**1.210 (1.074 to 1.364)**	**1.485 (1.333 to 1.655)**

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

Groups [1]	All groups
Method [2]	Poisson regression
P Value [3]	0.0035
Rate ratio [4]	0.815
Standard Error of the mean	(0.057)
95% Confidence Interval	0.710 to 0.935

[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]	**724**	**764**
Post-bronchodilator FEV1 [L] [units: mL] Least Squares Mean (Standard Error)	**44 (7)**	**-17 (7)**

Statistical Analysis 1 for Post-bronchodilator FEV1 [L]

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.0001
Mean Difference (Net) [4]	61
Standard Error of the mean	(9)
95% Confidence Interval	44 to 79

[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]	**25**	**25**
Time to Mortality Due to Any Reason [units: days] Mean (Standard Deviation)	**201.0 (116.9)**	**214.6 (137.3)**

Statistical Analysis 1 for Time to Mortality Due to Any Reason

Groups [1]	All groups
Method [2]	Cox proportional hazards regression
P Value [3]	0.5028
Hazard Ratio (HR) [4]	1.213
Standard Error of the mean	(0.350)
95% Confidence Interval	0.689 to 2.137

[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= 772 in the roflumilast group, n= 796 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]	**680**	**696**
Natural Log-transformed C-reactive Protein (CRP) [units: mg/L] Least Squares Mean (95% Confidence Interval)	**1.0840 (0.9766 to 1.2033)**	**1.0233 (0.9228 to 1.1348)**

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

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.3627
Mean Difference calculated as ratio [4]	1.0593
95% Confidence Interval	0.9356 to 1.1994

[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]	**729**	**769**
Mean Transition Dyspnea Index (TDI) Focal Score During the Treatment Period [units: scores on a scale] Least Squares Mean (Standard Error)	**0.662 (0.087)**	**0.376 (0.084)**

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]	0.0059
Mean Difference (Final Values) [4]	0.286
Standard Error of the mean	(0.104)
95% Confidence Interval	0.082 to 0.489

[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. Six patients randomized to placebo received roflumilast instead and were included in the roflumilast group for safety analyses.

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	**157/778 (20.18%)**	**183/790 (23.16%)**
Blood and lymphatic system disorders		
Anaemia † 1		
# participants affected / at risk	**1/778 (0.13%)**	**2/790 (0.25%)**
# events	**1**	**2**
Iron deficiency anaemia † 1		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Leukopenia † 1		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Polycythaemia † 1		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Cardiac disorders		
Myocardial infarction † 1		
# participants affected / at risk	**2/778 (0.26%)**	**4/790 (0.51%)**
# events	**2**	**4**
Angina pectoris † 1		
# participants affected / at risk	**2/778 (0.26%)**	**3/790 (0.38%)**
# events	**2**	**3**
Atrial fibrillation † 1		
# participants affected / at risk	**3/778 (0.39%)**	**2/790 (0.25%)**
# events	**3**	**2**
Cardiac failure congestive † 1		
# participants affected / at risk	**2/778 (0.26%)**	**3/790 (0.38%)**

# events	2	3
Acute myocardial infarction [†1]		
# participants affected / at risk	1/778 (0.13%)	2/790 (0.25%)
# events	1	2
Cardiopulmonary failure [†1]		
# participants affected / at risk	3/778 (0.39%)	0/790 (0.00%)
# events	3	0
Coronary artery disease [†1]		
# participants affected / at risk	0/778 (0.00%)	3/790 (0.38%)
# events	0	3
Right ventricular failure [†1]		
# participants affected / at risk	1/778 (0.13%)	2/790 (0.25%)
# events	1	2
Bradycardia [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Cardiac arrest [†1]		
# participants affected / at risk	2/778 (0.26%)	0/790 (0.00%)
# events	2	0
Cardiac failure [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	3
Cardio-respiratory arrest [†1]		
# participants affected / at risk	2/778 (0.26%)	0/790 (0.00%)
# events	2	0
Cor pulmonale [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Left ventricular failure [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Myocardial ischaemia [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Ventricular extrasystoles [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Angina unstable [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Arteriosclerosis coronary artery [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Atrioventricular block [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Ischaemic cardiomyopathy [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1

Mitral valve stenosis [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Supraventricular tachyarrhythmia [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Tachycardia [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Ventricular fibrillation [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Ventricular tachycardia [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Eye disorders		
Cataract [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**1/790 (0.13%)**
# events	**1**	**1**
Gastrointestinal disorders		
Diarrhoea [†1]		
# participants affected / at risk	**4/778 (0.51%)**	**0/790 (0.00%)**
# events	**4**	**0**
Pancreatitis acute [†1]		
# participants affected / at risk	**2/778 (0.26%)**	**1/790 (0.13%)**
# events	**2**	**1**
Abdominal pain upper [†1]		
# participants affected / at risk	**2/778 (0.26%)**	**0/790 (0.00%)**
# events	**2**	**0**
Gastrointestinal haemorrhage [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Haemorrhoids [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**1/790 (0.13%)**
# events	**1**	**1**
Intestinal polyp [†1]		
# participants affected / at risk	**2/778 (0.26%)**	**0/790 (0.00%)**
# events	**2**	**0**
Lower gastrointestinal haemorrhage [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Colitis [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Haemorrhoidal haemorrhage [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Inguinal hernia [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**

# events	0	1
Nausea [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Pancreatic cyst [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Small intestinal obstruction [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Upper gastrointestinal haemorrhage [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Vomiting [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
General disorders		
Sudden death [†1]		
# participants affected / at risk	1/778 (0.13%)	3/790 (0.38%)
# events	1	3
Chest pain [†1]		
# participants affected / at risk	0/778 (0.00%)	3/790 (0.38%)
# events	0	3
Non-cardiac chest pain [†1]		
# participants affected / at risk	1/778 (0.13%)	2/790 (0.25%)
# events	1	2
Death [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Asthenia [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Malaise [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Metaplasia [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Pyrexia [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Ulcer haemorrhage [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Hepatobiliary disorders		
Cholecystitis acute [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Cholelithiasis [†1]		

# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Immune system disorders		
Anti-neutrophil cytoplasmic antibody positive vasculitis [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Infections and infestations		
Pneumonia [†1]		
# participants affected / at risk	18/778 (2.31%)	10/790 (1.27%)
# events	18	10
Bronchopneumonia [†1]		
# participants affected / at risk	1/778 (0.13%)	3/790 (0.38%)
# events	1	3
Lower respiratory tract infection [†1]		
# participants affected / at risk	0/778 (0.00%)	3/790 (0.38%)
# events	0	3
Bronchitis [†1]		
# participants affected / at risk	2/778 (0.26%)	0/790 (0.00%)
# events	2	0
Lobar pneumonia [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Viral infection [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Appendicitis [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Cellulitis [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Clostridium difficile colitis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Localised infection [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Pneumonia primary atypical [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Pulmonary tuberculosis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Septic shock [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Urinary tract infection [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0

Urosepsis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Injury, poisoning and procedural complications		
Ankle fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Cervical vertebral fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Comminuted fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Device dislocation [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Eye penetration [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Femur fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Fibula fracture [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Foot fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Foreign body trauma [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Humerus fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Limb injury [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Procedural pain [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Tibia fracture [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Wound dehiscence [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Investigations		
Blood creatine phosphokinase increased [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)

# events	0	1
Blood creatinine increased [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Blood urea increased [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Metabolism and nutrition disorders		
Hypokalaemia [†1]		
# participants affected / at risk	3/778 (0.39%)	0/790 (0.00%)
# events	3	0
Dehydration [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Diabetes mellitus [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Diabetic ketoacidosis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Hyponatraemia [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	2	0
Malnutrition [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Metabolic acidosis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Musculoskeletal and connective tissue disorders		
Arthralgia [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Intervertebral disc degeneration [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Rotator cuff syndrome [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Prostate cancer [†1]		
# participants affected / at risk	4/778 (0.51%)	1/790 (0.13%)
# events	4	1
Non-small cell lung cancer [†1]		
# participants affected / at risk	2/778 (0.26%)	1/790 (0.13%)
# events	2	1
Bladder cancer [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1

Gastric cancer [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Lung neoplasm [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Plasmacytoma [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Renal cell carcinoma [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**2/790 (0.25%)**
# events	**0**	**2**
Acute myeloid leukaemia [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Adenoma benign [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Bladder neoplasm [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Breast cancer [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Bronchial carcinoma [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Carcinoid tumour of the small bowel [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Chronic lymphocytic leukaemia [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Colon cancer [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Gastric cancer stage II [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Lung adenocarcinoma [†1]		
# participants affected / at risk	**0/778 (0.00%)**	**1/790 (0.13%)**
# events	**0**	**1**
Lung neoplasm malignant [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Metastases to liver [†1]		
# participants affected / at risk	**1/778 (0.13%)**	**0/790 (0.00%)**
# events	**1**	**0**
Metastasis [†1]		

# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Metastatic carcinoma of the bladder [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Neuroendocrine carcinoma [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Non-small cell lung cancer metastatic [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Oesophageal neoplasm [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Small cell lung cancer stage unspecified [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Nervous system disorders		
Cerebrovascular accident [†1]		
# participants affected / at risk	1/778 (0.13%)	3/790 (0.38%)
# events	1	3
Cerebral infarction [†1]		
# participants affected / at risk	2/778 (0.26%)	0/790 (0.00%)
# events	2	0
Syncope [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Anoxic encephalopathy [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Dizziness [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Encephalopathy [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Hypoxic encephalopathy [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Optic neuritis [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Transient ischaemic attack [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Wernicke's encephalopathy [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Psychiatric disorders		

Depression [†1]		
# participants affected / at risk	2/778 (0.26%)	1/790 (0.13%)
# events	2	1
Alcohol withdrawal syndrome [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Completed suicide [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Mental status changes [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Suicidal ideation [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Renal and urinary disorders		
Renal failure acute [†1]		
# participants affected / at risk	3/778 (0.39%)	1/790 (0.13%)
# events	3	1
Micturition disorder [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Renal failure [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Reproductive system and breast disorders		
Benign prostatic hyperplasia [†1]		
# participants affected / at risk	2/778 (0.26%)	0/790 (0.00%)
# events	2	0
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease [†1]		
# participants affected / at risk	87/778 (11.18%)	121/790 (15.32%)
# events	110	160
Respiratory failure [†1]		
# participants affected / at risk	4/778 (0.51%)	5/790 (0.63%)
# events	4	6
Acute respiratory failure [†1]		
# participants affected / at risk	2/778 (0.26%)	4/790 (0.51%)
# events	2	4
Bronchospasm [†1]		
# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Hypoxia [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Pulmonary embolism [†1]		
# participants affected / at risk	0/778 (0.00%)	2/790 (0.25%)
# events	0	2
Respiratory arrest [†1]		

# participants affected / at risk	1/778 (0.13%)	1/790 (0.13%)
# events	1	1
Cough [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Dyspnoea [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Hyperventilation [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	2	0
Hypoventilation [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Pneumonia aspiration [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Pneumothorax [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Pulmonary oedema [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Respiratory acidosis [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Respiratory distress [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Skin and subcutaneous tissue disorders		
Eczema [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Leukocytoclastic vasculitis [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Rash [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Urticaria [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Surgical and medical procedures		
Coronary artery bypass [†1]		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Endarterectomy [†1]		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1

Knee arthroplasty † 1		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	2	0
Vascular disorders		
Arterial stenosis † 1		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Femoral artery occlusion † 1		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Haematoma † 1		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Hypertension † 1		
# participants affected / at risk	0/778 (0.00%)	1/790 (0.13%)
# events	0	1
Hypotension † 1		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Ischaemia † 1		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0
Peripheral artery aneurysm † 1		
# participants affected / at risk	1/778 (0.13%)	0/790 (0.00%)
# events	1	0

† 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. Six patients randomized to placebo received roflumilast instead and were included in the roflumilast group for safety analyses.

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	145/778 (18.64%)	81/790 (10.25%)
Gastrointestinal disorders		
Diarrhoea † 1 [3]		
# participants affected / at risk	64/778 (8.23%)	23/790 (2.91%)
# events	71	25
Infections and infestations		
Nasopharyngitis † 1		
# participants affected / at risk	35/778 (4.50%)	47/790 (5.95%)
# events	43	57
Investigations		
Weight decreased † 1		
# participants affected / at risk	65/778 (8.35%)	20/790 (2.53%)
# events	67	20

† 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
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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.

Responsible Party:	Nycomed
ClinicalTrials.gov Identifier:	NCT00297115 History of Changes
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