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 in Chronic Obstructive Pulmonary Disease (COPD) Patients Treated With Tiotropium: The HELIOS Study (BY217/M2-128) (HELIOS)

This study has been completed.

Sponsor:
Takeda

Information provided by:
Takeda

ClinicalTrials.gov Identifier:
NCT00424268

First received: January 18, 2007
Last updated: May 4, 2012
Last verified: August 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
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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Participant Flow: Overall Study

	Roflumilast	Placebo
STARTED	371 [1]	372 [1]
COMPLETED	309	333

NOT COMPLETED	62	39

[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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled
Total	Total of all reporting groups

Baseline Measures

	Roflumilast	Placebo	Total
Number of Participants [units: participants]	371	372	743
Age [units: years] Mean (Standard Deviation)	64.2 (9.1)	64.0 (9.3)	64.1 (9.2)
Gender [units: participants]			
Female	109	105	214
Male	262	267	529

Outcome Measures

Hide All Outcome Measures

1. Primary: Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) [Time Frame: Change from baseline over 24 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 24 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**365**	**364**
Pre-bronchodilator Forced Expiratory Volume in First Second (FEV1) [units: mL] Least Squares Mean (Standard Error)	**65 (12)**	**-16 (12)**

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]	80
Standard Error of the mean	(15)
95% Confidence Interval	51 to 110

[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 24 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 (0.05) was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

2. Secondary: Post-bronchodilator FEV1 [Time Frame: Change from baseline over 24 weeks of treatment]

Measure Type	Secondary
Measure Title	Post-bronchodilator FEV1
Measure Description	Mean change from baseline during the treatment period in post-bronchodilator FEV1 [L]
Time Frame	Change from baseline over 24 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**364**	**363**
Post-bronchodilator FEV1 [units: mL] Least Squares Mean (Standard Error)	**74 (12)**	**-7 (11)**

Statistical Analysis 1 for Post-bronchodilator FEV1

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	<0.0001
Mean Difference (Net) [4]	81
Standard Error of the mean	(15)
95% Confidence Interval	51 to 110

[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 24 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 (0.05) was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

3. Secondary: COPD Exacerbation Rate (Moderate or Severe) [Time Frame: 24 weeks treatment period]

Measure Type	Secondary
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	24 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Measured Values

	Roflumilast	Placebo
Number of Participants Analyzed [units: participants]	**371**	**372**
COPD Exacerbation Rate (Moderate or Severe) [units: exacerbations per patient per year] Mean (95% Confidence Interval)	**0.262 (0.184 to 0.375)**	**0.342 (0.248 to 0.472)**

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

Groups [1]	All groups
Method [2]	Poisson regression
P Value [3]	0.1957
Rate ratio [4]	0.768
Standard Error of the mean	(0.157)
95% Confidence Interval	0.515 to 1.146

[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 (0.05) was done as a hierarchical approach for hypotheses testing was used.
[4]	Other relevant estimation information:
	No text entered.

4. Secondary: Transition Dyspnea Index (TDI) Focal Score [Time Frame: Change from baseline over 24 weeks of treatment]

Measure Type	Secondary
Measure Title	Transition Dyspnea Index (TDI) Focal Score
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 24 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Measured Values

	Roflumilast	**Placebo**
Number of Participants Analyzed [units: participants]	**364**	**364**
Transition Dyspnea Index (TDI) Focal Score [units: scores on a scale] Least Squares Mean (Standard Error)	**1.4 (0.1)**	**0.9 (0.1)**

Statistical Analysis 1 for Transition Dyspnea Index (TDI) Focal Score

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.0032
Mean Difference (Final Values) [4]	0.4
Standard Error of the mean	(0.1)
95% Confidence Interval	0.1 to 0.7

[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 24 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:
	This secondary endpoint was analyzed in an exploratory manner.
[4]	Other relevant estimation information:

No text entered.

5. Secondary: Shortness of Breath Questionnaire (SOBQ) Total Score [Time Frame: Change from baseline over 24 weeks of treatment]

Measure Type	Secondary
Measure Title	Shortness of Breath Questionnaire (SOBQ) Total Score
Measure Description	Mean change from baseline during the treatment period in SOBQ. This is a 24-item measure that assesses self-reported shortness of breath while performing a variety of activities of daily living. The questions were administered at visits V0, V2, V3, V4, V5, V6 and Vend to assess the perceived shortness of breath of the patient. For each activity listed in the questionnaire the patient should rate his/her breathlessness on a scale between zero and five, where zero is "not at all breathless" and five is "maximally breathless or too breathless to do the activity".
Time Frame	Change from baseline over 24 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Measured Values

	Roflumilast	**Placebo**
Number of Participants Analyzed [units: participants]	**359**	**359**
Shortness of Breath Questionnaire (SOBQ) Total Score [units: scores on a scale] Least Squares Mean (Standard Error)	**-3.4 (0.7)**	**-0.7 (0.7)**

Statistical Analysis 1 for Shortness of Breath Questionnaire (SOBQ) Total Score

Groups [1]	All groups
Method [2]	ANCOVA
P Value [3]	0.0051
Mean Difference (Net) [4]	-2.6
Standard Error of the mean	(0.9)
95% Confidence Interval	-4.5 to -0.8

[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 24 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:
	This secondary endpoint was analyzed in an exploratory manner.
[4]	Other relevant estimation information:
	No text entered.

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	24 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. Three patients randomized to placebo received roflumilast instead and were included in the roflumilast group for safety analyses.

Reporting Groups

	Description
Roflumilast	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Serious Adverse Events

	Roflumilast	Placebo
Total, serious adverse events		
# participants affected / at risk	**22/374 (5.88%)**	**21/369 (5.69%)**
Blood and lymphatic system disorders		
Anaemia † 1		
# participants affected / at risk	**1/374 (0.27%)**	**1/369 (0.27%)**
# events	**1**	**1**
Lymphoid tissue hyperplasia † 1		
# participants affected / at risk	**1/374 (0.27%)**	**0/369 (0.00%)**
# events	**1**	**0**
Cardiac disorders		
Angina pectoris † 1		
# participants affected / at risk	**0/374 (0.00%)**	**1/369 (0.27%)**
# events	**0**	**1**
Atrioventricular block complete † 1		
# participants affected / at risk	**0/374 (0.00%)**	**1/369 (0.27%)**
# events	**0**	**1**
Cardiac failure † 1		
# participants affected / at risk	**0/374 (0.00%)**	**1/369 (0.27%)**
# events	**0**	**1**
Myocardial infarction † 1		
# participants affected / at risk	**0/374 (0.00%)**	**1/369 (0.27%)**
# events	**0**	**1**

Ventricular tachycardia [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Eye disorders		
Retinal artery embolism [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Gastrointestinal disorders		
Haematochezia [†1]		
# participants affected / at risk	2/374 (0.53%)	0/369 (0.00%)
# events	2	0
Colitis [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Colonic polyp [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Duodenal ulcer [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Gastric ulcer [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Inguinal hernia [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
General disorders		
Chest pain [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Hepatobiliary disorders		
Bile duct stone [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Infections and infestations		
Appendicitis [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Perianal abscess [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Pneumonia [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Injury, poisoning and procedural complications		
Contusion [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1

Post procedural myocardial infarction [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Spinal compression fracture [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Investigations		
Weight decreased [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Musculoskeletal and connective tissue disorders		
Metatarsalgia [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
B-cell lymphoma [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Bladder cancer [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Meningioma [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Metastatic neoplasm [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Non-small cell lung cancer [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Pancreatic neoplasm [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Nervous system disorders		
Cerebral ischaemia [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Cerebrovascular accident [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Guillain-Barre syndrome [†1]		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Psychiatric disorders		
Confusional state [†1]		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Renal and urinary disorders		

Renal failure chronic † 1		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease † 1		
# participants affected / at risk	4/374 (1.07%)	5/369 (1.36%)
# events	4	5
Pneumothorax † 1		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Pulmonary fibrosis † 1		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Sleep apnoea syndrome † 1		
# participants affected / at risk	0/374 (0.00%)	1/369 (0.27%)
# events	0	1
Surgical and medical procedures		
Vascular operation † 1		
# participants affected / at risk	1/374 (0.27%)	0/369 (0.00%)
# events	1	0
Vascular disorders		
Aortic aneurysm † 1		
# participants affected / at risk	1/374 (0.27%)	0/369 (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	24 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. Three 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	Roflumilast 500 µg, once daily, oral and tiotropium 18 µg, once daily, inhaled
Placebo	Placebo, once daily, oral and tiotropium 18 µg, once daily, inhaled

Other Adverse Events

	Roflumilast	Placebo
Total, other (not including serious) adverse events		

# participants affected / at risk	106/374 (28.34%)	76/369 (20.60%)
Gastrointestinal disorders		
Diarrhoea † 1		
# participants affected / at risk	33/374 (8.82%)	2/369 (0.54%)
# events	38	2
Infections and infestations		
Nasopharyngitis † 1		
# participants affected / at risk	21/374 (5.61%)	20/369 (5.42%)
# events	24	23
Investigations		
Weight decreased † 1 [3]		
# participants affected / at risk	20/374 (5.35%)	2/369 (0.54%)
# events	20	2
Respiratory, thoracic and mediastinal disorders		
Chronic obstructive pulmonary disease † 1 [3]		
# participants affected / at risk	54/374 (14.44%)	63/369 (17.07%)
# events	64	80

† 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:

Fabbri LM, Calverley PM, Izquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, Rabe KF; M2-127 and M2-128 study groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet. 2009 Aug 29;374(9691):695-703. doi: 10.1016/S0140-6736(09)61252-6.

Responsible Party:	Nycomed
ClinicalTrials.gov Identifier:	NCT00424268 History of Changes
Other Study ID Numbers:	**BY217/M2-128** 2006-004508-37 (EudraCT Number)
Study First Received:	January 18, 2007
Results First Received:	March 17, 2011
Last Updated:	May 4, 2012
Health Authority:	Austria: Federal Office for Safety in Health Care France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Germany: Federal Institute for Drugs and Medical Devices Hungary: National Institute of Pharmacy Italy: The Italian Medicines Agency Spain: Spanish Agency of Medicines United Kingdom: Medicines and Healthcare Products Regulatory Agency