Clinical trial results:
A Phase 2 Double-blind, Placebo-controlled Study to Evaluate the Efficacy of MEDI8968 in Chronic Obstructive Pulmonary Disease

Summary

EudraCT number	2011-002563-23
Trial protocol	GB HU LV CZ LT PL
Global end of trial date	18 February 2014

Results information

Result version number	v1
This version publication date	31 January 2016
First version publication date	31 January 2016

Trial information

Trial identification

Sponsor protocol code	CD-RI-MEDI8968-1103

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01448850
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC.
Sponsor organisation address	Milstein Building, Granta Park, Cambridge, United Kingdom, CB21 6GH
Public contact	Senior Director, Clinical Development, MedImmune, LLC., vandermerwer@medimmune.com
Scientific contact	Senior Director, Clinical Development, MedImmune, LLC., vandermerwer@medimmune.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of MEDI8968 on the rate of moderate or severe acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in adult participants with symptomatic, moderate to very severe COPD (Global Initiative for Chronic Obstructive Lung Disease - GOLD stage II-IV) receiving standard maintenance therapy for their disease.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Participating participant signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

All participants received double or triple background maintenance therapy (tiotropium vs budesonide/formoterol 160/4.5 microgram (mcg) versus budesonide/formoterol 160/4.5 mcg + tiotropium).

Evidence for comparator: -

Actual start date of recruitment	11 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Safety, Safety, Safety, Safety, Safety, Safety, Safety, Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Bulgaria: 41
Country: Number of subjects enrolled	Czech Republic: 30
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	Latvia: 7
Country: Number of subjects enrolled	Lithuania: 24
Country: Number of subjects enrolled	Philippines: 17
Country: Number of subjects enrolled	Ukraine: 46
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 62

Worldwide total number of subjects	324
EEA total number of subjects	199

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	189
From 65 to 84 years	135
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 464 participants were screened and 324 participants were randomized into the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to MEDI8968 as intravenous (IV) infusion on Day 1 followed by subcutaneous (SC) injection every 4 weeks up to Week 53.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

Placebo matched to MEDI8968 as intravenous (IV) infusion on Day 1 followed by subcutaneous (SC) injection every 4 weeks up to Week 53.

Arm title	MEDI8968 600 mg IV on day 1, followed by 300 mg SC

Arm description:

MEDI8968 600 milligram (mg) as IV infusion on Day 1 followed by 300 mg injection SC every 4 weeks up to Week 53.

Arm type	Experimental
Investigational medicinal product name	MEDI8968
Investigational medicinal product code	MEDI8968
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

MEDI8968 600 milligram (mg) as IV infusion on Day 1 followed by 300 mg injection SC every 4 weeks up to Week 53.

Number of subjects in period 1	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC
Started	164	160
Completed	130	120
Not completed	34	40
Adverse event, serious fatal	3	6
Consent withdrawn by subject	13	21
Unspecified	15	12
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to MEDI8968 as intravenous (IV) infusion on Day 1 followed by subcutaneous (SC) injection every 4 weeks up to Week 53.	
Reporting group title	MEDI8968 600 mg IV on day 1, followed by 300 mg SC
Reporting group description:	
MEDI8968 600 milligram (mg) as IV infusion on Day 1 followed by 300 mg injection SC every 4 weeks up to Week 53.	

Reporting group values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC	Total
Number of subjects	164	160	324
Age categorical Units: Subjects			
Adults (18-64 years)	98	91	189
From 65-74 years	64	68	132
>= 75 years	2	1	3
Age Continuous | Units: years			
arithmetic mean	63	62.8	
standard deviation	± 6.8	± 6.7	-
Gender, Male/Female Units: participants			
Female	54	50	104
Male	110	110	220

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matched to MEDI8968 as intravenous (IV) infusion on Day 1 followed by subcutaneous (SC) injection every 4 weeks up to Week 53.	
Reporting group title	MEDI8968 600 mg IV on day 1, followed by 300 mg SC
Reporting group description:	
MEDI8968 600 milligram (mg) as IV infusion on Day 1 followed by 300 mg injection SC every 4 weeks up to Week 53.	

Primary: Incidence Rate of Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Incidence Rate of Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)
End point description:	
An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. The severity of an AECOPD is defined as: Moderate exacerbations require treatment with systemic corticosteroids, and or antibiotics. Severe exacerbations require hospitalization.	
End point type	Primary
End point timeframe:	
Day 1 up to 393	

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: AECOPD events/person-year				
least squares mean (confidence interval)	0.78 (0.63 to 0.96)	0.71 (0.57 to 0.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v MEDI8968 600 mg IV on day 1, followed by 300 mg SC
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.645 [1]
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.92

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.68
upper limit	1.25

Notes:

[1] - Data was analyzed using Poisson regression with Pearson correction, adjusting for treatment, background therapy and history of previous exacerbations.

Secondary: Incidence Rate of Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Incidence Rate of Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

An AECOPD is defined as worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. Severe exacerbations require hospitalization.

End point type	Secondary

End point timeframe:

Day 1 up to 393

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: AECOPD events/person-year				
least squares mean (confidence interval)	0.14 (0.09 to 0.21)	0.1 (0.06 to 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point title	Time to First Moderate or Severe Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

End point description:

Time to first worsening of two or more major symptoms or one major and one minor symptom for two or more consecutive days. The severity of an AECOPD is defined as: Mild exacerbations require treatment with an increase in usual therapy, e.g., increase use of short acting bronchodilators. Moderate exacerbations require treatment with systemic corticosteroids, and or antibiotics. Severe exacerbations require hospitalization. '99999' in the below table indicates median and upper limit of 95% confidence interval (CI). Median and upper limit of 95% CI were not evaluable as less than 50% of the participants had moderate or severe AECOPD, thus not applicable (NA) = '99999'.

End point type	Secondary

End point timeframe:

Day 1 up to 393

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: days				
median (inter-quartile range (Q1-Q3))	99999 (173 to 99999)	99999 (134 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total and Subscales Scores at Week 53

End point title	Change from Baseline in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total and Subscales Scores at Week 53

End point description:

The SGRQ is a health related quality of life questionnaire consisting of 40 items in three domains: symptoms (respiratory symptoms and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). Each question's response has a unique empirically derived weight where lowest possible weight is zero and the highest is 100. The total score and domain score are derived from the relevant items and converted to a score of 0 to 100 with a higher score indicating poorer health status.

End point type	Secondary

End point timeframe:

Baseline and Week 53

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: units on scale				
least squares mean (standard error)				
Change at Week 53: Total Score (n=134, 123)	-2.76 (± 1.069)	-2.22 (± 1.101)		
Change at Week 53: Activity Score (n=134, 123)	-1.15 (± 1.306)	-1.38 (± 1.348)		
Change at Week 53: Impacts Score (n=134, 123)	-2.91 (± 1.326)	-1.08 (± 1.366)		
Change at Week 53: Symptoms Score (n=134, 123)	-5.6 (± 1.279)	-6.81 (± 1.325)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Improvement in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total Score

End point title	Percentage of Participants With Improvement in COPD-Specific Saint George's Respiratory Questionnaire (SGRQ-C) Total Score

End point description:

The SGRQ is a health related quality of life questionnaire consisting of 40 items in three domains: symptoms (respiratory symptoms and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning and psychological disturbances due to airway disease). Each question's response has a unique empirically derived weight where lowest possible weight is zero and the highest is 100. The total score and domain score are derived from the relevant items and converted to a score of 0 to 100 with a higher score indicating poorer health status. A 4-point change in total score demonstrates a clinically meaningful change, while an 8-point change and a 12-point change are interpreted as a moderate and large change in health status, respectively.

End point type	Secondary

End point timeframe:

Week 53

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: percentage of participants				
number (not applicable)				
Week 53: 4-point improvement (n=134,123)	45.5	43.1		
Week 53: 12-point improvement (n=134,123)	17.9	17.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Score at Week 53

End point title	Change from Baseline in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Score at Week 53

End point description:

The BODE index is a multi-dimension COPD grading system that incorporates body-mass index (B), degree of airflow obstruction (O), dyspnea (D), and exercise capacity (E) as measured by the modified medical research council (MMRC) dyspnea scale and the 6-minute walk test. The MMRC dyspnea scale is a 5-point scale that measures the level of dyspnea (trouble breathing) experienced by participants where score range is 0 (none) to 4 (very severe). BODE score is derived into a score range of 0 (healthy) to 10 (severe COPD).

End point type	Secondary

End point timeframe:

Baseline and Week 53

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	116		
Units: units on a scale				
least squares mean (standard error)	-0.27 (± 0.107)	-0.08 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Improvement in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Score

End point title	Percentage of Participants With Improvement in Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Score

End point description:

The BODE index is a multi-dimension COPD grading system that incorporates body-mass index (B), degree of airflow obstruction (O), dyspnea (D), and exercise capacity (E) as measured by the modified medical research council (MMRC) dyspnea scale and the 6-minute walk test. The MMRC dyspnea scale is a 5-point scale that measures the level of dyspnea (trouble breathing) experienced by participants where score range is 0 (none) to 4 (very severe). BODE score is derived into a score range of 0 (healthy) to 10 (severe COPD). Negative change score signifies improvement compared to baseline. Number of participants with improvement in BODE score compared to baseline were reported.

End point type	Secondary

End point timeframe:

Baseline and Week 53

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	116		
Units: percentage of participants				

number (not applicable)	39	33.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants Reporting Treatment-Emergent Adverse Events (TEAEs) and Treatment-Emergent Serious Adverse Events (TESAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between administration of study drug and up to Week 69 that were absent before treatment or that worsened relative to pre-treatment state. TEAEs reported below included both SAEs and non-serious AEs.

End point type	Secondary

End point timeframe:

Day 1 up to Week 69

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	160		
Units: participants				
TEAEs	130	130		
TESAEs	35	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Serum Concentrations of MEDI8968

End point title	Observed Serum Concentrations of MEDI8968[2]

End point description:

End point type	Secondary

End point timeframe:

Pre-dose (Baseline), Post-dose on Week 53

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No formal statistical analyses performed for this End Point

End point values	MEDI8968 600 mg IV on day 1, followed by 300 mg SC			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: nanogram per milliliters (ng/mL)				
arithmetic mean (standard deviation)				
Baseline (n=145) Week 53 (n=120)	1.7 (± 14.6) 28555.7 (± 27545.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Exhibiting Anti-Drug Antibodies for MEDI8968 at any Visit

End point title	Number of Participants Exhibiting Anti-Drug Antibodies for MEDI8968 at any Visit

End point description:

Anti-drug antibodies for MEDI8968 were analyzed for participants who received placebo or MEDI8968 as per planned analysis.

End point type	Secondary

End point timeframe:

Day 1 up to Week 69

End point values	Placebo	MEDI8968 600 mg IV on day 1, followed by 300 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	163	157		
Units: participants	10	19		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 69

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	MEDI8968 300 mg

Reporting group description:

MEDI8968 600 milligram (mg) as IV infusion on Day 1 followed by 300 mg injection SC every 4 weeks up to Week 53.

Reporting group title	PLACEBO

Reporting group description:

Placebo matched to MEDI8968 as intravenous (IV) infusion on Day 1 followed by subcutaneous (SC) injection every 4 weeks up to Week 53.

Serious adverse events	MEDI8968 300 mg	PLACEBO	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 160 (25.63%)	35 / 164 (21.34%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	6	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung cancer metastatic			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 160 (0.63%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			

subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 160 (0.00%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	18 / 160 (11.25%)	17 / 164 (10.37%)	
occurrences causally related to treatment / all	0 / 21	1 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Comminuted fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congenital, familial and genetic disorders			
Ebstein's anomaly			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	6 / 6	3 / 3	
Adams-stokes syndrome			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 160 (0.63%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 160 (0.63%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congestive cardiomyopathy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 160 (1.25%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 160 (1.25%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral artery occlusion			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			

subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 160 (0.63%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			

subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial pneumonia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal oesophagitis			

subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis bacterial			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 160 (4.38%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 160 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	MEDI8968 300 mg	PLACEBO	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 160 (76.25%)	127 / 164 (77.44%)	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 160 (2.50%)	3 / 164 (1.83%)	
occurrences (all)	5	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 160 (3.13%)	7 / 164 (4.27%)	
occurrences (all)	6	10	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 160 (2.50%)	3 / 164 (1.83%)	
occurrences (all)	4	3	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 160 (6.25%)	7 / 164 (4.27%)	
occurrences (all)	10	27	
Dizziness			
subjects affected / exposed	4 / 160 (2.50%)	4 / 164 (2.44%)	
occurrences (all)	4	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 160 (5.00%)	6 / 164 (3.66%)	
occurrences (all)	13	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 160 (3.13%)	3 / 164 (1.83%)	
occurrences (all)	5	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 160 (1.88%)	4 / 164 (2.44%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	64 / 160 (40.00%)	71 / 164 (43.29%)	
occurrences (all)	112	138	
Oropharyngeal pain			
subjects affected / exposed	2 / 160 (1.25%)	5 / 164 (3.05%)	
occurrences (all)	2	5	
Dyspnoea			
subjects affected / exposed	4 / 160 (2.50%)	6 / 164 (3.66%)	
occurrences (all)	5	8	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 160 (1.25%)	5 / 164 (3.05%)	
occurrences (all)	2	5	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 160 (3.13%)	2 / 164 (1.22%)	
occurrences (all)	5	2	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 160 (3.13%)	4 / 164 (2.44%)	
occurrences (all)	7	4	
Nasopharyngitis			
subjects affected / exposed	11 / 160 (6.88%)	11 / 164 (6.71%)	
occurrences (all)	12	13	
Sinusitis			
subjects affected / exposed	3 / 160 (1.88%)	5 / 164 (3.05%)	
occurrences (all)	5	6	
Pneumonia			
subjects affected / exposed	3 / 160 (1.88%)	4 / 164 (2.44%)	
occurrences (all)	3	4	
Urinary tract infection			
subjects affected / exposed	5 / 160 (3.13%)	5 / 164 (3.05%)	
occurrences (all)	8	7	
Upper respiratory tract infection			
subjects affected / exposed	5 / 160 (3.13%)	7 / 164 (4.27%)	
occurrences (all)	5	7	

Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Dyslipidaemia subjects affected / exposed occurrences (all)	 4 / 160 (2.50%) 4 3 / 160 (1.88%) 3	 3 / 164 (1.83%) 3 4 / 164 (2.44%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2011	The blood collection plan for this analysis was modified due to difficulties in the logistics of collecting and processing samples. Including a smaller number of subjects was considered adequate for this as this was an exploratory analysis.
03 October 2011	Added exclusion criterion 27 that subjects with "uncontrolled, clinically significant history of liver disease or elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to (>) 1.5 * upper limit of normal (ULN) at screening" were to be excluded. Added that "Subjects who have AST or ALT > 3 * ULN and evidence of hepatic impairment (total bilirubin > 2 × the ULN or INR > 1.5) confirmed by repeat test within 48 hours" were to be withdrawn. Added text around the administration of an inactivated influenza vaccine, including that subjects may have received an egg-free inactivated influenza vaccination. Added Clinical Global Impression of Exacerbation Severity to assessment of AECOPD.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported