



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, 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 (\pm 0.107) | -0.08 (\pm 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) | 1.7 (± 14.6) | | | |
| Week 53 (n=120) | 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 | 4 / 160 (2.50%) | 3 / 164 (1.83%) | |
| occurrences (all) | 4 | 3 | |
| Dyslipidaemia | | | |
| subjects affected / exposed | 3 / 160 (1.88%) | 4 / 164 (2.44%) | |
| occurrences (all) | 3 | 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 \times 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