



Clinical trial results:

A Phase II, Randomised, Double-Blind, Placebo-Controlled, Parallel Group Study to Assess the Efficacy of 28 Day Oral Administration of AZD9668 in Patients with Cystic Fibrosis

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2008-001530-27 |
| Trial protocol | GB DE SE DK |
| Global end of trial date | 20 January 2010 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 24 February 2016 |
| First version publication date | 24 February 2016 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D0520C00009 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | AstraZeneca R&D Charnwood |
| Sponsor organisation address | Bakewell Road, Loughborough,, United Kingdom, |
| Public contact | Kulasiri Gunawardena MD, AstraZeneca R&D Charnwood, LE11 5RH. +44 1509 647103, |
| Scientific contact | Professor Stuart Elborn MD, Belfast City Hospital, BT9 7AB. +44 289 0329241, |

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 | 20 January 2010 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 January 2010 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 January 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to investigate whether AZD9668 showed evidence of efficacy in CF patients by investigation of:

- Absolute and differential neutrophil count in induced sputum.
- Signs and symptoms of CF (including effects on Quality of Life [QoL])

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 30 October 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Poland: 6 |
| Country: Number of subjects enrolled | Russian Federation: 14 |
| Country: Number of subjects enrolled | Sweden: 13 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Worldwide total number of subjects | 55 |
| EEA total number of subjects | 41 |

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) | 55 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 30 October 2008 . Last patient last visit: 04 August 2009. Fifteen centres across 6 countries participated in this study: Denmark (4), Germany (13), Poland (6), Russia (14), Sweden(13)and United Kingdom (5)

Pre-assignment

Screening details:

506 patients enrolled were not randomized due to eligibility not fulfilled (10 patients), voluntary discontinuation (1 patient) and Adverse event (2)

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 |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description: -

| | |
|--|----------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Tablet to AZD9668

| | |
|------------------|---------|
| Arm title | AZD9668 |
|------------------|---------|

Arm description:

60 mg bd [twice daily]

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | AZD9668 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

30mg ,twice a day

| Number of subjects in period 1 | Placebo | AZD9668 |
|---------------------------------------|---------|---------|
| Started | 29 | 26 |
| Completed | 27 | 24 |
| Not completed | 2 | 2 |
| Voluntary Discontinuation by Subject | - | 1 |
| Adverse event, non-fatal | 2 | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | AZD9668 |
| Reporting group description: | |
| 60 mg bd [twice daily] | |

| Reporting group values | Placebo | AZD9668 | Total |
|------------------------|---------|---------|-------|
| Number of subjects | 29 | 26 | 55 |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|-------|------|----|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 27 | 29 | |
| standard deviation | ± 8.5 | ± 10 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 0 | 1 | 1 |
| Male | 29 | 25 | 54 |

Subject analysis sets

| | |
|----------------------------|-----------------------|
| Subject analysis set title | Efficacy Analysis Set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

This set comprised all patients randomised into the study, who received at least one dose of study medication and had at least one piece of evaluable data.

| Reporting group values | Efficacy Analysis Set | | |
|------------------------|-----------------------|--|--|
| Number of subjects | 54 | | |
| Age Categorical | | | |
| Units: Subjects | | | |

| | | | |
|--------------------|-------|--|--|
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 28 | | |
| standard deviation | ± 9.2 | | |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 1 | | |
| Male | 53 | | |

End points

End points reporting groups

| | |
|-----------------------------------|---|
| Reporting group title | Placebo |
| Reporting group description: | - |
| Reporting group title | AZD9668 |
| Reporting group description: | 60 mg bd [twice daily] |
| Subject analysis set title | Efficacy Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | This set comprised all patients randomised into the study, who received at least one dose of study medication and had at least one piece of evaluable data. |

Primary: Absolute neutrophil counts in sputum

| | |
|------------------------|--|
| End point title | Absolute neutrophil counts in sputum |
| End point description: | The end point was the arithmetic mean of the counts in the end of the treatment samples (Visit 3a and 4) |
| End point type | Primary |
| End point timeframe: | Baseline and End of treatment |

| End point values | Placebo | AZD9668 | | |
|---|-----------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 24 | | |
| Units: 10 ⁶ /g | | | | |
| geometric mean (geometric coefficient of variation) | 9 (± 227.728) | 13.95 (± 105.813) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | absolute sputum neutrophils |
| Statistical analysis description: | Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale. |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.891 |
| Method | ANCOVA |
| Parameter estimate | Ratio of AZD9668 to Placebo |
| Point estimate | 0.97 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.38 |

Primary: percentage neutrophil counts in sputum

| | |
|---|--|
| End point title | percentage neutrophil counts in sputum |
| End point description: | |
| The endpoint was the arithmetic mean of the counts in the end of treatment samples (Visits 3a and 4). | |
| End point type | Primary |
| End point timeframe: | |
| End of treatment | |

| End point values | Placebo | AZD9668 | | |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 28 | 24 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 90.19 (± 16.628) | 96.48 (± 3.931) | | |

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | % sputum neutrophils |
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.581 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1.25 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -2.53 |
| upper limit | 5.04 |

Primary: Peak Expiratory Flow

| | |
|---|----------------------|
| End point title | Peak Expiratory Flow |
| End point description: | |
| The endpoint was the difference between the mean of the assessment for the last 7 days of the treatment period and the mean of the last 7 days before the first day of dosing (baseline). | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and post treatment | |

| End point values | Placebo | AZD9668 | | |
|--------------------------------------|-----------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 24 | | |
| Units: L/min | | | | |
| arithmetic mean (standard deviation) | | | | |
| PEF morning | 8.38 (± 34.187) | -4.83 (± 36.81) | | |
| PEF evening | 3.15 (± 28.252) | -2.29 (± 33.586) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | BronkoTest© diary card variables: PEF morning |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.143 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -15.22 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -32.37 |
| upper limit | 1.93 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 10.21 |

| | |
|-----------------------------------|---|
| Statistical analysis title | BronkoTest© diary card variable PEF Evening |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 53 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.516 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -5.72 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -20.39 |
| upper limit | 8.95 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 8.735 |

Primary: Summary of change from baseline in BronkoTest© diary card variables

| | |
|---|---|
| End point title | Summary of change from baseline in BronkoTest© diary card variables |
| End point description: | |
| The endpoint was the difference between the mean of the assessment for the last 7 days of the treatment period and the mean of the last 7 days before the first day of dosing (baseline). | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and End of treatment | |

| End point values | Placebo | AZD9668 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 25 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Night-Time Symptom Score | 0.17 (± 0.668) | 0.11 (± 0.406) | | |
| Describe Your Breathing | 0.04 (± 0.229) | 0.11 (± 0.395) | | |
| Sputum Colour | 0 (± 0.277) | -0.16 (± 1.011) | | |
| Sputum Amount | 0 (± 0.332) | 0.05 (± 0.509) | | |
| Sputum Type | 0.04 (± 0.365) | 0.06 (± 0.341) | | |
| How do you feel | 0.02 (± 0.38) | 0.11 (± 0.417) | | |
| How often do you cough | 0.01 (± 0.377) | 0.11 (± 0.297) | | |
| Reliever Medication Taken Today | -0.19 (± 0.78) | 0.04 (± 0.175) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | change from baseline in Night-Time Symptom Score |
| Comparison groups | Placebo v AZD9668 |

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|---|--------------------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.373 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | 0.12 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.154 |

| | |
|---|---|
| Statistical analysis title | Change from Baseline in Describe Your Breathing |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.33 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0.25 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.093 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Change from Baseline in Sputum Colour |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.612 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.11 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.48 |
| upper limit | 0.26 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.22 |

| | |
|---|---------------------------------------|
| Statistical analysis title | Change from Baseline in Sputum Amount |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.234 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.15 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.06 |
| upper limit | 0.36 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.125 |

| | |
|---|-------------------------------------|
| Statistical analysis title | Change from Baseline in Sputum Type |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.581 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.11 |
| upper limit | 0.22 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.096 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from baseline in How do you feel |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.413 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.09 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.09 |
| upper limit | 0.27 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.106 |

| | |
|---|--|
| Statistical analysis title | Change from Baseline in How often do you cough |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.195 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.13 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.04 |
| upper limit | 0.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.101 |

| | |
|---|---------------------------------|
| Statistical analysis title | Reliever Medication Taken Today |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.887 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.01 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.15 |
| upper limit | 0.13 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.083 |

Primary: Change from Baseline for the Cystic Fibrosis Questionnaire data

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|------------------------|---|
| End point title | Change from Baseline for the Cystic Fibrosis Questionnaire data |
| End point description: | The endpoint is change from baseline (Visit 2) at Visit 4. |
| End point type | Primary |
| End point timeframe: | Baseline and Visit 4 |

| End point values | Placebo | AZD9668 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 25 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Overall Score | 1 (± 56.65) | -8.7 (± 86.78) | | |
| Physical | -1.3 (± 7.27) | -3.6 (± 13.63) | | |
| Vitality | -0.9 (± 13.67) | 1.9 (± 12.32) | | |
| Emotion | 3 (± 11.23) | 1.2 (± 10.26) | | |
| Eat | 2.8 (± 7.17) | -1 (± 10.23) | | |
| Treatment Burden | 4 (± 13.93) | 1.5 (± 12.5) | | |
| Health Perceptions | -2.8 (± 14.06) | -1.5 (± 12.5) | | |
| Social | -4.8 (± 11.29) | -3.5 (± 11.18) | | |
| Body | 0.8 (± 17.87) | -0.5 (± 12.11) | | |
| Role | -0.3 (± 8.17) | 1.6 (± 11.37) | | |
| Weight | -2.5 (± 26.03) | -7.9 (± 34.81) | | |
| Respiratory | 1 (± 8.99) | 0 (± 13.17) | | |
| Digestion | 4.1 (± 11.99) | 2 (± 11.7) | | |

Statistical analyses

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|---|---------------------------------------|
| Statistical analysis title | Change from Baseline in Overall Score |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.293 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -24.4 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -62.9 |
| upper limit | 14.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 22.87 |

| | |
|---|---------------------------------|
| Statistical analysis title | Change from baselin in Physical |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.344 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -9 |
| upper limit | 2.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.4 |

| | |
|---|---------------------------------|
| Statistical analysis title | Change from Baseline in Emotion |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.02 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -6.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | -1.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.52 |

| | |
|-----------------------------------|-----------------------------|
| Statistical analysis title | Change from Baseline in Eat |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.081 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7.8 |
| upper limit | -0.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.24 |

| | |
|---|--|
| Statistical analysis title | Change from Baseline in Treatment Burden |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.368 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -10.8 |
| upper limit | 3.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.16 |

| | |
|---|--|
| Statistical analysis title | Change from Baseline in Health Perceptions |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.869 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 6.2 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.08 |

| | |
|---|--------------------------------|
| Statistical analysis title | Change from Baseline in Social |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.938 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 6.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.61 |

| | |
|---|--------------------------------|
| Statistical analysis title | Change from Baseline in Body |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -4.6 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -11.9 |
| upper limit | 2.6 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.33 |

| | |
|-----------------------------------|------------------------------|
| Statistical analysis title | Change from Baseline in Role |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.775 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -6.1 |
| upper limit | 4.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.09 |

| | |
|---|--------------------------------|
| Statistical analysis title | Change from Baseline in Weight |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.331 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -7.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -19.8 |
| upper limit | 5.2 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 7.44 |

| | |
|---|-------------------------------------|
| Statistical analysis title | Change from Baseline in Respiratory |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.611 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -7.5 |
| upper limit | 4 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.43 |

| | |
|---|-----------------------------------|
| Statistical analysis title | Change from Baseline in Digestion |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.676 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.3 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -6.5 |
| upper limit | 3.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.08 |

Primary: Change from Baseline in 24-hour sputum weight

| | |
|--|---|
| End point title | Change from Baseline in 24-hour sputum weight |
| End point description: | |
| Patients were asked to collect sputum for a 24 hour period before Visit 1a and Visit 4. The endpoint was change from baseline (Visit 1a) at Visit 4. | |
| End point type | Primary |
| End point timeframe: | |
| visit 1a and visit 4 | |

| | | | | |
|--------------------------------------|------------------|------------------|--|--|
| End point values | Placebo | AZD9668 | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 24 | | |
| Units: gram | | | | |
| arithmetic mean (standard deviation) | -4.34 (± 12.206) | -5.19 (± 11.922) | | |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | Change from Baseline in 24-hour Sputum Weight |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 51 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.341 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2.83 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -2.11 |
| upper limit | 7.78 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.94 |

Primary: Change from Baseline in Lung Function test

| | |
|------------------------|--|
| End point title | Change from Baseline in Lung Function test |
| End point description: | Change from baseline (Visit 2) at the end of treatment (Visit 4) was the endpoint. |
| End point type | Primary |
| End point timeframe: | visit 2 and visit4 |

| End point values | Placebo | AZD9668 | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 25 | | |
| Units: Liter L/s % | | | | |
| arithmetic mean (standard deviation) | | | | |
| FEV1(L) | -0.01 (± 0.212) | 0 (± 0.199) | | |
| SVC(L) | -0.12 (± 0.32) | 0.04 (± 0.468) | | |
| FVC(L) | -0.01 (± 0.265) | 0 (± 0.361) | | |
| FEF25-75 (L/s) | 0.08 (± 0.46) | -0.04 (± 0.255) | | |
| % Predicted FEV1 (%) | -0.15 (± 4.872) | -0.26 (± 5.089) | | |

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Change from Baseline in FEV1 |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|--------------------------------|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.651 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.03 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.13 |
| upper limit | 0.08 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.062 |

| | |
|---|--------------------------------|
| Statistical analysis title | Chnage from Baseline in SVC |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.364 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.11 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.32 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.125 |

| | |
|---|----------------------------------|
| Statistical analysis title | Change from Baseline in FEF25-75 |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.231 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.14 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.34 |
| upper limit | 0.05 |

| | |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.118 |

| | |
|---|--------------------------------|
| Statistical analysis title | Change from Baseline in FVC |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.412 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.07 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -0.21 |
| upper limit | 0.07 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.085 |

| | |
|---|--|
| Statistical analysis title | Change from Baseline in % Predicted FEV1 |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.451 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.1 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -3.53 |
| upper limit | 1.33 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.445 |

Secondary: sputum neutrophil elastase activity

| | |
|--|-------------------------------------|
| End point title | sputum neutrophil elastase activity |
| End point description: | |
| Assay of NE activity in induced sputum collections at Visits 1a,2, 3a and 4. The endpoint was end of treatment data (mean of Visits 3a and 4). | |
| End point type | Secondary |

End point timeframe:
end of treatment

| End point values | Placebo | AZD9668 | | |
|---|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 17 | | |
| Units: $\mu\text{mol/L AMC/hr}$ | | | | |
| geometric mean (geometric coefficient of variation) | 106.67 (\pm 746) | 148.4 (\pm 375) | | |

Statistical analyses

| Statistical analysis title | Ratio of AZD9668 over Placebo |
|---|-------------------------------|
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on logtransformed data. The table presents the results back-transformed after the analysis on the original scale. If ratio CI contains 1, there is no evidence of a difference between AZD9668 and Placebo. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.292 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.3 |
| upper limit | 1.31 |

Secondary: Inflammatory markers in sputum

| End point title | Inflammatory markers in sputum |
|---|--------------------------------|
| End point description: | |
| Assay of induced sputum collections at Visits 1a, 2, 3a and 4 for the following markers: (including, but not limited to) TNF α , IL-6, IL-1 β , RANTES, MCP-1 (exploratory non-GLP assays) LTB4 and IL-8 (validated assays). The endpoint was end of treatment data (mean of Visits 3a and 4). | |
| End point type | Secondary |
| End point timeframe: | |
| End of treatment | |

| End point values | Placebo | AZD9668 | | |
|---|---------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 26 | | |
| Units: pg/ml | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| TNF α | 30.75 (\pm 162.984) | 28.48 (\pm 129.895) | | |
| IL-6 | 36.7 (\pm 153.923) | 20.26 (\pm 119.341) | | |
| IL-8 | 16215.69 (\pm 122.519) | 14310.01 (\pm 58.854) | | |
| IL-1 β | 732.62 (\pm 179.177) | 1037.34 (\pm 95.671) | | |
| LTB4 | 951.76 (\pm 93.26) | 808.64 (\pm 91.431) | | |
| RANTES | 6.26 (\pm 74.072) | 4.41 (\pm 69.745) | | |
| MCP-1 | 131.16 (\pm 98.78) | 88.5 (\pm 65.083) | | |

Statistical analyses

| Statistical analysis title | Ratio of AZD9668 over placebo in TNF α |
|--|---|
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log transformed data. The table presents the results back transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.139 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.04 |

| Statistical analysis title | Ratio of AZD9668 over placebo in IL-6 |
|--|---------------------------------------|
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log transformed data. The table presents the results back-transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |

| | |
|---|---------------|
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.006 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.59 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.44 |
| upper limit | 0.8 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Ratio of AZD9668 over placebo in IL-8 |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log transformed data. The table presents the results back transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.238 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.83 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.08 |

| | |
|-----------------------------------|---|
| Statistical analysis title | Ratio of AZD9668 to placebo in IL-1 β |
|-----------------------------------|---|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.481 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.87 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.2 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Ratio of AZD9668 over placebo in LTB4 |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.901 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 1.02 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.24 |

| | |
|-----------------------------------|---------------------------------------|
| Statistical analysis title | Ratio of AZD9668 to placebo in RANTES |
|-----------------------------------|---------------------------------------|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Ratio of AZD9668 over placebo in MCP-1 |
|-----------------------------------|--|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.129 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.63 |
| upper limit | 1.02 |

Secondary: Inflammatory markers in blood

| | |
|---|-------------------------------|
| End point title | Inflammatory markers in blood |
| End point description: | |
| Assay of blood samples taken at Visits 2 and 4 for the following markers: (including, but not limited to) absolute and differential neutrophil cell count, serum amyloid-A and CRP (validated assays) and plasma TNF α , IL-6, IL-8 and IL-1 β (exploratory non-GLP assays). The endpoint was end of treatment data (Visit 4). | |
| End point type | Secondary |
| End point timeframe: | |
| End of treatment | |

| End point values | Placebo | AZD9668 | | |
|---|--------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 26 | | |
| Units: pg/ml mg/L ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| TNF α (pg/mL) | 7.92 (\pm 43.019) | 7.34 (\pm 38.85) | | |
| IL-6 (pg/mL) | 3.83 (\pm 79.305) | 5.02 (\pm 68.793) | | |
| IL-8 (pg/mL) | 6.84 (\pm 54.726) | 7.83 (\pm 54.68) | | |
| IL-1 β (pg/mL) | 1.35 (\pm 27.045) | 1.32 (\pm 24.822) | | |
| CRP (mg/L) | 2.31 (\pm 200.436) | 5.73 (\pm 156.44) | | |
| Amyloid A (ng/mL) | 6565.98 (\pm 356.623) | 22609.16 (\pm 399.631) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Ratio of AZD9668 to placebo in TNF α |
| Statistical analysis description: Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.223 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.02 |

| | |
|---|-------------------------------------|
| Statistical analysis title | Ratio of AZD9668 to placebo in IL-6 |
| Statistical analysis description: Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.797 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.83 |
| upper limit | 1.28 |

| | |
|-----------------------------------|-------------------------------------|
| Statistical analysis title | Ratio of AZD9668 to placebo in IL-8 |
|-----------------------------------|-------------------------------------|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.833 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.3 |

Statistical analysis titleRatio of AZD9668 to placebo in IL-1 β **Statistical analysis description:**

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.083 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.95 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1 |

Statistical analysis title

Ratio of AZD9668 to placebo in CRP

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale.

| | |
|-------------------|-------------------|
| Comparison groups | Placebo v AZD9668 |
|-------------------|-------------------|

| | |
|---|---------------|
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.245 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 1.35 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 2.06 |

| | |
|-----------------------------------|--|
| Statistical analysis title | Ratio of AZD9668 to placebo in Amyloid A |
|-----------------------------------|--|

Statistical analysis description:

Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale

| | |
|---|-------------------|
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.278 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 1.31 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.87 |
| upper limit | 1.98 |

Secondary: plasma concentration data for AZD9668

| | |
|-----------------|--|
| End point title | plasma concentration data for AZD9668 ^[1] |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day1 and Day28

Notes:

[1] - 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: Concentration of AZD9668 was not measured in the placebo group.

| | | | | |
|---|-------------------|--|--|--|
| End point values | AZD9668 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: nM | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 1 3-4 h | 500 (\pm 43.8) | | | |
| Day 28 pre-dose | 189 (\pm 61.5) | | | |
| Day28 3-4h | 723 (\pm 38.2) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: AZD9668 Concentration in induced sputum supernatant

End point title AZD9668 Concentration in induced sputum supernatant^[2]

End point description:

End point type Secondary

End point timeframe:

Day 21-26 and Day28

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: Concentration of AZD9668 was not measured in the placebo group.

| | | | | |
|---|--------------------|--|--|--|
| End point values | AZD9668 | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: nM | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Day 21-26 | 72.8 (\pm 106) | | | |
| Day 28 Pre-dose | 63.4 (\pm 92.6) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Markers of tissue degradation in urine

End point title Markers of tissue degradation in urine

End point description:

End of treatment is the data at Visit 4

End point type Secondary

End point timeframe:

end of treatment

| End point values | Placebo | AZD9668 | | |
|---|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 26 | | |
| Units: nmol/mmol | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Desmosine (Free) Normalised by Creatinine | 2.22 (\pm 51.232) | 1.4 (\pm 35.679) | | |
| Desmosine (Total) Normalised by Creatinine | 2.67 (\pm 104.344) | 1.87 (\pm 44.619) | | |

Statistical analyses

| Statistical analysis title | Ratio of AZD9668 over Placebo in Desmosine (Total) |
|--|--|
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.044 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 0.93 |

| Statistical analysis title | Ratio of AZD9668 over Placebo in Desmosine (free) |
|--|---|
| Statistical analysis description: | |
| Analysis of covariance includes treatment, country and baseline as covariates. The analysis is done on log-transformed data. The table presents the results back-transformed after the analysis on the original scale. | |
| Comparison groups | Placebo v AZD9668 |
| Number of subjects included in analysis | 55 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | ANCOVA |
| Parameter estimate | ratio |
| Point estimate | 0.7 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.58 |
| upper limit | 0.83 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From enrolment to 7 days after the end of treatment (visit 4).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | AZD9668 |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | AZD9668 | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 2 / 29 (6.90%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| pulmonary exacerbation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| pneumonia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 29 (3.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | AZD9668 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 26 (46.15%) | 12 / 29 (41.38%) | |
| Investigations | | | |

| | | | |
|--|---|---|--|
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 | 1 / 29 (3.45%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 7 / 26 (26.92%) 10 | 5 / 29 (17.24%) 10 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Non cardiac chest pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 1 / 26 (3.85%) 1 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 | 1 / 29 (3.45%) 1 2 / 29 (6.90%) 4 2 / 29 (6.90%) 2 | |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) | 0 / 26 (0.00%) 0 0 / 26 (0.00%) 0 | 2 / 29 (6.90%) 2 2 / 29 (6.90%) 2 | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 1 / 26 (3.85%) 1 | 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 1 / 29 (3.45%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| Back pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 2 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 29 (3.45%) | |
| occurrences (all) | 1 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 3 / 29 (10.34%) | |
| occurrences (all) | 2 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported