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	Overrall 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 theassessment for the last 7 days of the treatment period and themean 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 theassessment for the last 7 days of the treatment period and themean 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: uints 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 Amout	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

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

End point title	Change from Baseline for the Cystic Fibrosis Questionnaire data
End point description: The endpointis 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

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 Respirtory
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 periodbefore Visit 1a and Visit 4. The endpoint was change frombaseline (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 ofVisits 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: µmol/L AMC/hr				
geometric mean (geometric coefficient of variation)	106.67 (± 746)	148.4 (± 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) TNFα, IL-6, IL-1β, 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)				
TNFα	30.75 (± 162.984)	28.48 (± 129.895)		
IL-6	36.7 (± 153.923)	20.26 (± 119.341)		
IL-8	16215.69 (± 122.519)	14310.01 (± 58.854)		
IL-1β	732.62 (± 179.177)	1037.34 (± 95.671)		
LTB4	951.76 (± 93.26)	808.64 (± 91.431)		
RANTES	6.26 (± 74.072)	4.41 (± 69.745)		
MCP-1	131.16 (± 98.78)	88.5 (± 65.083)		

Statistical analyses

Statistical analysis title	Ratio of AZD9668 over placebo in TNFα

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-1β

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 resultsback-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 TNFα, IL-6, IL-8 and IL-1β (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)				
TNFα (pg/mL)	7.92 (± 43.019)	7.34 (± 38.85)		
IL-6 (pg/mL)	3.83 (± 79.305)	5.02 (± 68.793)		
IL-8 (pg/mL)	6.84 (± 54.726)	7.83 (± 54.68)		
IL-1β (pg/mL)	1.35 (± 27.045)	1.32 (± 24.822)		
CRP (mg/L)	2.31 (± 200.436)	5.73 (± 156.44)		
Amyloid A (ng/mL)	6565.98 (± 356.623)	22609.16 (± 399.631)		

Statistical analyses

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

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 resultsback-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 resultsback-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 (± 43.8)			
Day 28 pre-dose	189 (± 61.5)			
Day28 3-4h	723 (± 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 (± 106)			
Day 28 Pre-dose	63.4 (± 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 (± 51.232)	1.4 (± 35.679)		
Desmosine (Total) Normalised by Creatinine	2.67 (± 104.344)	1.87 (± 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	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 26 (26.92%)	5 / 29 (17.24%)	
occurrences (all)	10	10	
General disorders and administration site conditions			
Fatique			
subjects affected / exposed	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Non cardiac chest pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	4	
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 26 (7.69%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 26 (7.69%)	1 / 29 (3.45%)	
occurrences (all)	2	1	
Cough			
subjects affected / exposed	1 / 26 (3.85%)	1 / 29 (3.45%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			

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