Clinical trial results:
A randomised, double-blind, placebo-controlled, parallel group, multi-centre Phase IIa study in asthma patients comparing the efficacy and safety of once daily inhaled Interferon beta-1a to placebo, administered for 14 days after the onset of symptoms of an upper respiratory tract infection for the prevention of severe exacerbations

Summary

EudraCT number	2014-005084-32
Trial protocol	GB ES FR
Global end of trial date	24 November 2016

Results information

Result version number	v1 (current)
This version publication date	23 November 2017
First version publication date	23 November 2017

Trial information

Trial identification

Sponsor protocol code	D6230C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02491684
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Gärturnavägen 1, Södertälje, Sweden, SE-151 85
Public contact	Medical Science Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Medical Science Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2016
Global end of trial reached?	Yes
Global end of trial date	24 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of inhaled interferon beta-1a compared to placebo in preventing severe exacerbations during the 14 days of treatment following onset of an upper respiratory tract infection in asthmatic patients, on top of their regular asthma maintenance treatment.

Protection of trial subjects:

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Council for Harmonisation Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy:

Patients continued to receive their regular asthma maintenance treatment including medium to high dose inhaled corticosteroids (> 250 micrograms fluticasone dry powder formulation equivalents total daily dose), and a second controller medication (long-acting beta2-agonists).

Evidence for comparator: -

Actual start date of recruitment	21 July 2015
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	Argentina: 48
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Colombia: 3
Worldwide total number of subjects	121
EEA total number of subjects	43

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)	107
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 21 July 2015; Last Patient Last Visit: 24 November 2016. The study was performed at 39 sites in 7 countries including Argentina, Australia, Colombia, France, South Korea, Spain and the United Kingdom.

Pre-assignment

Screening details:

349 patients enrolled (signed informed consent) and 228 were not randomised. 121 patients met randomisation criteria and entered the pre-treatment phase. Patients were treated after developing symptoms of an upper respiratory tract infection (URTI) if they met all the inclusion criteria and none of the exclusion criteria for the treatment phase.

Period 1

Period 1 title	Pre-treatment Phase
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD9412

Arm description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Arm type	Experimental
Investigational medicinal product name	AZD9412 nebuliser solution 48 mcg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 6 MIU (24 mcg metered dose) once daily for 14 days.

Arm title	Placebo

Arm description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Arm type	Placebo

Investigational medicinal product name	Placebo nebuliser solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 6 MIU (24 mcg metered dose) once daily for 14 days.

Number of subjects in period 1	AZD9412	Placebo
Started	61	60
Completed	61	60

Period 2

Period 2 title	Treatment Phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD9412

Arm description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Arm type	Experimental
Investigational medicinal product name	AZD9412 nebuliser solution 48 mcg/mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 6 MIU (24 mcg metered dose) once daily for 14 days.

Arm title	Placebo

Arm description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were

evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Arm type	Placebo
Investigational medicinal product name	Placebo nebuliser solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Patients received 6 MIU (24 mcg metered dose) once daily for 14 days.

Number of subjects in period 2	AZD9412	Placebo
Started	61	60
Completed	58	57
Not completed	3	3
Adverse event, non-fatal	2	2
Incorrect randomisation	1	-
Investigator and Sponsor decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AZD9412

Reporting group description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Reporting group values	AZD9412	Placebo	Total
Number of subjects	61	60	121
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	53	54	107
From 65-84 years	8	6	14
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	47.8	47.7	
standard deviation	± 12.95	± 14.10	-
Sex: Female, Male Units: Subjects			
Female	48	43	91
Male	13	17	30

End points

End points reporting groups

Reporting group title	AZD9412

Reporting group description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Reporting group title	AZD9412

Reporting group description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Primary: Proportion of patients with a severe asthma exacerbation during 14 days of treatment

End point title	Proportion of patients with a severe asthma exacerbation during 14 days of treatment

End point description:

Evaluation of the efficacy of inhaled AZD9412 compared to placebo in preventing severe exacerbations during the 14 day treatment phase following the onset of an URTI in asthmatic patients. A severe exacerbation was defined as worsening asthma symptoms and a) use of systemic corticosteroids (or a temporary increase of at least 2-fold in a stable oral corticosteroid background dose) for at least 3 consecutive days and/or b) an unscheduled visit or emergency room visit due to asthma symptoms that required at least 1 dose of systemic corticosteroids and/or c) an in-patient hospitalisation due to asthma requiring at least 1 dose of systemic corticosteroids. The number of patients with severe asthma exacerbations with onset during the treatment phase is presented for each treatment group. The

Intention to treat (ITT) analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available.

End point type	Primary

End point timeframe:

Day 1 - 14 of the treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Number of patients	7	5		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Proportions of patients with exacerbations are compared using a log-binomial regression model with treatment group and region as factors.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.645
Method	log-binomial regression model
Parameter estimate	Ratio of proportions
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	3.85

Secondary: Proportion of patients with severe asthma exacerbations within 7 and 30 days following randomisation

End point title	Proportion of patients with severe asthma exacerbations within 7 and 30 days following randomisation

End point description:

Evaluation of the efficacy of inhaled AZD9412 compared to placebo in preventing severe exacerbations within 7 and 30 days after the start of treatment (Day 1). A severe exacerbation was defined as worsening asthma symptoms and a) use of systemic corticosteroids (or a temporary increase of at least 2-fold in a stable oral corticosteroid background dose) for at least 3 consecutive days and/or b) an unscheduled visit or emergency room visit due to asthma symptoms that required at least 1 dose of systemic corticosteroids and/or c) an in-patient hospitalisation due to asthma requiring at least 1 dose of systemic corticosteroids. The numbers of patients with severe asthma exacerbations with onset during Days 1 - 7 and Days 1 - 30 are presented for each treatment group. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available.

End point type	Secondary

End point timeframe:

Day 1 of treatment phase up to 30 days post-randomisation.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Number of patients				
Days 1 - 7|	4	2		
Days 1 - 30|	8	6		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo for Days 1 - 7

Statistical analysis description:

Proportions of patients with exacerbations are compared using a log-binomial regression model with treatment group and region as factors.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.411
Method	log-binomial regression model
Parameter estimate	Ratio of proportions
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	9.89

Statistical analysis title	AZD9412 versus Placebo for Days 1 - 30

Statistical analysis description:

Proportions of patients with exacerbations are compared using a log-binomial regression model with treatment group and region as factors.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.659
Method	log-binomial regression model
Parameter estimate	Ratio of proportions
Point estimate	1.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	3.41

Secondary: Proportion of patients with moderate asthma exacerbation within 7, 14 and 30 days following randomisation

End point title	Proportion of patients with moderate asthma exacerbation within 7, 14 and 30 days following randomisation

End point description:

Evaluation of the efficacy of inhaled AZD9412 compared to placebo in preventing moderate exacerbations within 7, 14 and 30 days after the start of treatment (Day 1). A moderate exacerbation was defined as a temporary increase in maintenance therapy in order to prevent a severe event supported by a sustained (2 or more days) worsening in at least one key control metric, including asthma score, rescue use, night time awakening or morning peak expiratory flow. The numbers of patients with moderate exacerbations with onset during Days 1 - 7, Days 1 - 14 and Days 1 - 30 are presented for each treatment group. With respect to the Day 1-7 analysis, the model did not converge so the analysis could not be performed. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available.

End point type	Secondary

End point timeframe:

Day 1 of treatment phase up to 30 days post-randomisation.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Number of patients				
Days 1 - 7|	0	1		
Days 1 - 14|	1	1		
Days 1 - 30|	1	1		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo for Days 1 - 14

Statistical analysis description:

Proportions of patients with exacerbations are compared using a log-binomial regression model with treatment group and region as factors.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.944
Method	log-binomial regression model
Parameter estimate	Ratio of proportions
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	15.79

Statistical analysis title	AZD9412 versus Placebo for Days 1 - 30

Statistical analysis description:

Proportions of patients with exacerbations are compared using a log-binomial regression model with treatment group and region as factors.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.944
Method	log-binomial regression model
Parameter estimate	Ratio of proportions
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	15.79

Secondary: Time to first severe asthma exacerbation during 30 days following randomisation

End point title	Time to first severe asthma exacerbation during 30 days following randomisation

End point description:

The time to first event was calculated as start date of events - date of randomisation + 1. Patients with no observed event were censored at the date of their last visit, or for lost-to-follow-up patients, at the last time point after which an event could not be assessed. The median time to first exacerbation was not calculated in either treatment group due to low numbers of events. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available.

End point type	Secondary

End point timeframe:

From Day 1 of treatment phase up to 30 days post-randomisation.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Days				
median (full range (min-max))	99999999 (99999999 to 99999999)	99999999 (99999999 to 99999999)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of time to first severe exacerbation within 30 days of treatment start.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.634
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	3.77

Secondary: Time to first moderate asthma exacerbation during 30 days following randomisation

End point title	Time to first moderate asthma exacerbation during 30 days following randomisation
End point description:	
The time to first event was calculated as start date of events - date of randomisation + 1. Patients with no observed event were censored at the date of their last visit, or for lost-to-follow-up patients, at the last time point after which an event could not be assessed. The median time to first exacerbation was not calculated in either treatment group due to low numbers of events. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available.	
End point type	Secondary
End point timeframe:	
From Day 1 of treatment phase up to 30 days post-randomisation.	

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Days				
median (full range (min-max))	99999999 (99999999 to 99999999)	99999999 (99999999 to 99999999)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of time to first moderate exacerbation within 30 days of treatment start.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.973
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	16.78

Secondary: Duration of moderate or severe exacerbations

End point title	Duration of moderate or severe exacerbations

End point description:

The duration of each individual moderate or severe exacerbation was calculated as: Cessation date of exacerbation - Start date of exacerbation + 1. The start date of a severe exacerbation was defined as the start date of systemic corticosteroids or increase of systemic corticosteroids or emergency room visit or hospital admission, whichever occurred first. The stop date was defined as the last day of systemic corticosteroids/increase of systemic corticosteroids or hospital discharge, whichever occurred last. The start date of a moderate exacerbation was defined as the first day of increase in temporary maintenance therapy. The stop date was defined as the last day of this treatment. The mean duration of moderate or severe exacerbations is presented. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. The number of patients in the analysis are those with at least 1 exacerbation.

End point type	Secondary

End point timeframe:

Day 1 of treatment phase up to 30 days post-randomisation.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	6		
Units: Days				
arithmetic mean (standard deviation)	10 (± 7.7)	8 (± 4.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in asthma control from baseline up to 30 days as measured by the Asthma Control Questionnaire (ACQ-6)

End point title	Change in asthma control from baseline up to 30 days as measured by the Asthma Control Questionnaire (ACQ-6)

End point description:

The ACQ-6 consists of 6 questions to assess asthma control, each question measured on a 7-point scale scored from 0 (totally controlled) to 6 (severely uncontrolled). The ACQ-6 total score is computed as the un-weighted mean of the responses to the 6 questions. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The change from baseline at Visit 4 (Day 7 +/- 1), at Visit 6 (Day 14 +/- 1) and at Visit 8 (Day 30) is presented for the total score and for each of the 6 questions. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Units on a Scale				
least squares mean (standard error)				
ACQ-6 Total Score, Visit 4|	0.02 (± 0.11)	-0.07 (± 0.12)		
ACQ-6 Total Score, Visit 6|	-0.15 (± 0.14)	-0.21 (± 0.14)		
ACQ-6 Total Score, Visit 8|	-0.42 (± 0.15)	-0.35 (± 0.15)		
Q1: Woken by Asthma, Visit 4|	0.09 (± 0.18)	-0.09 (± 0.18)		
Q1: Woken by Asthma, Visit 6|	0.15 (± 0.20)	-0.28 (± 0.21)		
Q1: Woken by Asthma, Visit 8|	-0.50 (± 0.18)	-0.32 (± 0.18)		
Q2: Symptoms at Awakening, Visit 4|	0.06 (± 0.18)	-0.17 (± 0.18)		
Q2: Symptoms at Awakening, Visit 6|	-0.40 (± 0.16)	-0.33 (± 0.17)		
Q2: Symptoms at Awakening, Visit 8|	-0.76 (± 0.19)	-0.47 (± 0.19)		
Q3: Limited in Activities, Visit 4|	0.04 (± 0.15)	0.06 (± 0.15)		
Q3: Limited in Activities, Visit 6|	-0.12 (± 0.17)	0.16 (± 0.18)		
Q3: Limited in Activities, Visit 8|	-0.43 (± 0.18)	-0.33 (± 0.18)		
Q4: Shortness of Breath, Visit 4|	-0.13 (± 0.15)	-0.11 (± 0.16)		
Q4: Shortness of Breath, Visit 6|	-0.34 (± 0.19)	-0.38 (± 0.21)		
Q4: Shortness of Breath, Visit 8|	-0.46 (± 0.18)	-0.37 (± 0.19)		
Q5: Wheeze, Visit 4|	0.13 (± 0.17)	0.08 (± 0.17)		

Q5: Wheeze, Visit 6|	-0.17 (± 0.17)	-0.17 (± 0.18)		
Q5: Wheeze, Visit 8|	-0.33 (± 0.21)	-0.42 (± 0.21)		
Q6: Puffs of Short-Acting Bronchodilator; Visit 4|	0.06 (± 0.13)	0.00 (± 0.14)		
Q6: Puffs of Short-Acting Bronchodilator; Visit 6|	0.07 (± 0.14)	-0.11 (± 0.15)		
Q6: Puffs of Short-Acting Bronchodilator; Visit 8|	0.04 (± 0.14)	-0.03 (± 0.14)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of change from baseline in total score at Visit 4.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.495
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.35

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of change from baseline in total score at Visit 6.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.715
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.38

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of change from baseline in total score at Visit 8.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.687
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.42
upper limit	0.28

Secondary: AUC for change in daytime and night-time asthma symptom score from baseline up to 30 days

End point title	AUC for change in daytime and night-time asthma symptom score from baseline up to 30 days

End point description:

Asthma symptoms during night-time and daytime were recorded by the patient each morning and evening in the Asthma Daily Diary on a daily basis. Symptoms were recorded using a scale of 0 to 3 where 0 indicates no asthma symptoms up to an absolute score of 3. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The total daily asthma symptom score was calculated by taking the sum of the night-time and daytime asthma scores recorded each day. The outcome variable is the area under the curve (AUC) for change from baseline in day-time, night-time and total daily asthma symptom scores over Days 1-14, Days 1-7, Days 8-14 and Days 15-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Units on Scale				
least squares mean (standard error)				
Total asthma score, Days 1-14|	-0.20 (± 0.16)	-0.31 (± 0.16)		
Total asthma score, Days 1-7|	-0.11 (± 0.13)	-0.22 (± 0.13)		
Total asthma score, Days 8-14|	-0.40 (± 0.15)	-0.41 (± 0.16)		
Total asthma score, Days 15-30|	-0.77 (± 0.16)	-0.77 (± 0.16)		
Daytime asthma score, Days 1-14|	-0.22 (± 0.07)	-0.26 (± 0.07)		
Daytime asthma score, Days 1-7|	-0.17 (± 0.06)	-0.17 (± 0.06)		
Daytime asthma score, Days 8-14|	-0.23 (± 0.07)	-0.27 (± 0.07)		
Daytime asthma score, Days 15-30|	-0.44 (± 0.07)	-0.41 (± 0.07)		

Night-time asthma score, Days 1-14|	-0.17 (± 0.07)	-0.16 (± 0.08)		
Night-time asthma score, Days 1-7|	-0.10 (± 0.06)	-0.09 (± 0.07)		
Night-time asthma score, Days 8-14|	-0.20 (± 0.07)	-0.17 (± 0.08)		
Night-time asthma score, Days 15-30|	-0.44 (± 0.09)	-0.39 (± 0.09)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline in total score over Days 1-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.516
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.45

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline in total score over Days 1-7.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.417
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.16
upper limit	0.37

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Analysis of AUC for change from baseline in total score over Days 8-14.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.954
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.36

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline in total score over Days 15-30.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.985
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.35

Secondary: Change in the proportion of night-time awakening using the ePRO questionnaire from baseline up to 30 days

End point title	Change in the proportion of night-time awakening using the ePRO questionnaire from baseline up to 30 days

End point description:

Night-time awakenings due to asthma symptoms were recorded by the patient in the Asthma Daily Diary each morning by answering the question whether he/she woke up during the night due to asthma symptoms with a 'yes' or 'no' response. Biweekly means were calculated as the percentages of times the subject answered 'yes' over a period of 14 sequential days. Biweekly means are presented for the periods over Days 2-15 and Days 16-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Percentage of 'yes' responses				
arithmetic mean (standard deviation)				
Days 2-15|	22.3 (± 30.42)	24.8 (± 29.77)		
Days 16-30|	15.2 (± 26.79)	15.9 (± 26.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in health-related quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ[S]) from baseline up to 30 days

End point title	Change in health-related quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ[S]) from baseline up to 30 days

End point description:

The AQLQ(S) was used to assess health-related quality of life and consisted of 32 questions. Patients were asked to score each of the questions on a 7-point scale ranging from 7 (no impairment) to 1 (severe impairment). The questions were allocated to 4 domains assessing: 1) activity limitation, 2) symptoms, 3) emotional function, and 4) environmental stimuli The overall score was calculated as the mean of the responses to all questions. The mean change in overall score from baseline at Visit 6 (Day 14+/-1) and Visit 8 (Day 30) are presented. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: Units on Scale				
least squares mean (standard error)				
Overall Score Visit 6|	0.28 (± 0.13)	0.35 (± 0.14)		
Overall Score Visit 8|	0.43 (± 0.16)	0.53 (± 0.16)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:	
Analysis of change from baseline in overall score at Visit 6.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.66
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.24

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of change from baseline in overall score at Visit 8.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.624
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0.29

Secondary: AUC for change in daytime and night-time reliever medication use from baseline up to 14 days

End point title	AUC for change in daytime and night-time reliever medication use from baseline up to 14 days

End point description:

Patients recorded the number of reliever medication inhalations taken twice daily in the Asthma Daily Diary. The number of inhalations taken between the morning and evening lung function assessments were recorded in the evening. The number of inhalations taken between the evening and morning lung function assessments were recorded in the morning. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The AUC for change from baseline over Days 1-14 (inclusive of Days 1 and 14) is presented. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to Day 14 of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	48		
Units: Inhalations				
least squares mean (standard error)	-0.12 (± 0.46)	-0.67 (± 0.48)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 1-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.309
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	1.59

Secondary: AUC for change in the morning Peak Expiratory Flow (PEF) from baseline to up to 30 days

End point title	AUC for change in the morning Peak Expiratory Flow (PEF) from baseline to up to 30 days
End point description:	
Patients measured morning PEF at home and recorded the results using the ePRO device. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The mean AUC for change from baseline is presented for the periods Days 1-14, 1-7, 8-14 and 15-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.	
End point type	Secondary
End point timeframe:	
From baseline up to 30 days after start of treatment phase.	

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: litres/minute (l/min)				
least squares mean (standard error)				
Days 1-14|	9.56 (± 14.02)	-7.42 (± 13.91)		
Days 1-7|	19.66 (± 9.66)	0.31 (± 9.11)		
Days 8-14|	7.03 (± 15.90)	-7.35 (± 15.80)		
Days 15-30|	32.75 (± 15.35)	13.49 (± 14.82)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 1-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.059
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	16.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.63
upper limit	34.6

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 1-7.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	19.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.66
upper limit	34.05

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 8-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.153
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	14.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.44
upper limit	34.2

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 15-30.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.096
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	19.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.44
upper limit	41.97

Secondary: AUC for change in the morning Forced Expiratory Volume in 1 second (FEV1) from baseline up to 30 days

End point title	AUC for change in the morning Forced Expiratory Volume in 1 second (FEV1) from baseline up to 30 days

End point description:

Patients measured morning FEV1 at home and recorded the results using the ePRO device. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The mean AUC for change from baseline is presented for the periods Days 1-14, 1-7, 8-14 and 15-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: litres				
least squares mean (standard error)				
Days 1-14|	-0.00 (± 0.08)	-0.08 (± 0.08)		
Days 1-7|	0.10 (± 0.06)	0.02 (± 0.06)		
Days 8-14|	-0.03 (± 0.08)	-0.09 (± 0.08)		
Days 15-30|	0.15 (± 0.09)	0.04 (± 0.08)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Analysis of AUC for change from baseline over Days 1-14.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.161
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.17

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Analysis of AUC for change from baseline over Days 1-7.

Comparison groups	AZD9412 v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.087
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.17

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 8-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.28
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.16

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 15-30.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.086
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.24

Secondary: AUC for change in the evening PEF from baseline to up to 30 days

End point title	AUC for change in the evening PEF from baseline to up to 30 days

End point description:

Patients measured evening PEF at home and recorded the results using the ePRO device. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The mean AUC for change from baseline is presented for the periods Days 1-14, 1-7, 8-14 and 15-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: l/min				
least squares mean (standard error)				
Days 1-14|	10.96 (± 12.58)	-0.73 (± 11.88)		
Days 1-7|	8.78 (± 9.87)	-2.41 (± 9.30)		
Days 8-14|	8.49 (± 13.09)	-2.66 (± 12.55)		
Days 15-30|	11.88 (± 15.70)	-5.25 (± 15.13)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Analysis of AUC for change from baseline over Days 1-14.

Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.211
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	11.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.76
upper limit	30.14

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 1-7.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.125
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	11.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	25.56

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 8-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.277
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	11.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.08
upper limit	31.36

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 15-30.	
Comparison groups	AZD9412 v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.161
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	17.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.92
upper limit	41.18

Secondary: AUC for change in the evening FEV1 from baseline up to 30 days

End point title	AUC for change in the evening FEV1 from baseline up to 30 days

End point description:

Patients measured evening FEV1 at home and recorded the results using the ePRO device. Baseline assessments were taken as the last non-missing assessment prior to randomisation. The mean AUC for change from baseline is presented for the periods Days 1-14, 1-7, 8-14 and 15-30. The ITT analysis set consisted of all randomised patients who received at least 1 dose of investigational product and had some post-dose data available. Patients with non-missing values were included in the analysis.

End point type	Secondary

End point timeframe:

From baseline up to 30 days after start of treatment phase.

End point values	AZD9412	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	60		
Units: litres				
least squares mean (standard error)				
Days 1-14|	-0.01 (± 0.07)	-0.07 (± 0.07)		
Days 1-7|	0.01 (± 0.07)	-0.03 (± 0.07)		
Days 8-14|	-0.02 (± 0.07)	-0.08 (± 0.07)		
Days 15-30|	0.02 (± 0.08)	-0.08 (± 0.08)		

Statistical analyses

Statistical analysis title	AZD9412 versus Placebo

Statistical analysis description:

Analysis of AUC for change from baseline over Days 1-14.

Comparison groups	AZD9412 v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.287
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.16

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 1-7.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.457
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.14

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description:	
Analysis of AUC for change from baseline over Days 8-14.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.315
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.16

Statistical analysis title	AZD9412 versus Placebo
Statistical analysis description: Analysis of AUC for change from baseline over Days 15-30.	
Comparison groups	AZD9412 v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.134
Method	ANCOVA
Parameter estimate	LS Mean difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from the first day of study treatment up to the last date of follow-up (approximately 30 days).

Adverse event reporting additional description:

The safety analysis set consisted of all randomised patients who received at least 1 dose of investigational product and with post-dose data available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients were randomised to receive placebo in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or the flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the placebo group received 6 MIU (24 mcg metered dose) inhaled placebo once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an ePRO device at home.

Reporting group title	AZD9412

Reporting group description:

Patients were randomised to receive investigational product AZD9412 (interferon beta-1a) in the treatment phase. Eligible patients entered the pre-treatment phase until they developed symptoms of a common cold or flu (URTI). Patients were evaluated at a study site for eligibility to enter the treatment phase as soon as possible but no later than 48 hours after the onset of the first symptoms of an URTI. Patients randomised to the AZD9412 group received 6 Million International Units (MIU) (24 micrograms [mcg] metered dose) inhaled AZD9412 once daily for 14 days, delivered by the I-neb® device. Patients continued their regular asthma maintenance treatment, and were assessed for exacerbations, changes in respiratory symptoms and reliever medication use using an electronic Patient Reported Outcome (ePRO) device at home.

Serious adverse events	Placebo	AZD9412	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	3 / 61 (4.92%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 60 (0.00%)	3 / 61 (4.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	AZD9412	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 60 (33.33%)	27 / 61 (44.26%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Injury associated with device			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 60 (6.67%)	1 / 61 (1.64%)	
occurrences (all)	5	1	
Bronchospasm			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	3	
Dysphonia			

subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	2 / 60 (3.33%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Hiccups			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Rhinitis allergic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Sinus pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Throat irritation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	2	1	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Emotional distress			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	

Insomnia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Mood altered			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Blood pressure decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Pulmonary function test decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Mouth injury			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	

Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1	 0 / 61 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	 3 / 60 (5.00%) 3 1 / 60 (1.67%) 1 1 / 60 (1.67%) 1	 2 / 61 (3.28%) 2 0 / 61 (0.00%) 0 0 / 61 (0.00%) 0	
Blood and lymphatic system disorders Eosinophilia subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0 0 / 60 (0.00%) 0	 1 / 61 (1.64%) 1 1 / 61 (1.64%) 1 1 / 61 (1.64%) 1	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 0 / 60 (0.00%) 0	 1 / 61 (1.64%) 3	
Eye disorders Blepharospasm subjects affected / exposed occurrences (all) Periorbital oedema subjects affected / exposed occurrences (all)	 1 / 60 (1.67%) 1 0 / 60 (0.00%) 0	 0 / 61 (0.00%) 0 1 / 61 (1.64%) 1	
Gastrointestinal disorders			

Constipation			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)	2 / 61 (3.28%)	
occurrences (all)	0	2	
Gastritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Odynophagia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Pruritus generalised			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	2	
Musculoskeletal pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Pain in jaw			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)	5 / 61 (8.20%)	
occurrences (all)	1	5	
Conjunctivitis bacterial			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Gastroenteritis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	1 / 60 (1.67%)	2 / 61 (3.28%)	
occurrences (all)	1	2	
Rhinitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 60 (1.67%)	1 / 61 (1.64%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 61 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 61 (1.64%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2016	-To clarify the requirement for stable maintenance treatment during the 12 months prior to inclusion. -To include mannitol challenge as an acceptable challenge method for asthma diagnosis. -Requirement to demonstrate acceptable technique when using ePRO device, home spirometer and I-neb added. -To clarify that patients with a diagnosis of active tuberculosis must not be included and that patients with CT/chest X-ray findings indicating bronchiectasis which in the opinion of the Investigator were not clinically significant could be enrolled at the discretion of the Investigator. -addition of exclusion criterion to ensure long enough washout for drugs with a long half-life. -clarification on systolic blood pressure limits, reliever medication use and pregnancy testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early due to the lower than expected rate of severe exacerbations in the study as a whole, and due to the observed lack of differential effect at interim analysis.

Notes: