Clinical trial results:
A Phase 2 Placebo-Controlled, Randomized, Double-Blind, Adaptive Dose Trial of the Safety and Efficacy of Inhaled AZD1419 in Adults With Eosinophilic, Moderate to Severe Asthma

Summary

EudraCT number	2016-000977-19
Trial protocol	DK SE HU PL
Global end of trial date	25 September 2018

Results information

Result version number	v1 (current)
This version publication date	11 October 2019
First version publication date	11 October 2019

Trial information

Trial identification

Sponsor protocol code	D2500C00003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02898662
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Research and Development, Södertälje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	Global Clinical Lead, 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	25 September 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that inhaled AZD1419 provided sustained asthma control in eosinophilic asthma participants after removal of inhaled corticosteroids (ICS) + long-acting β2 agonist (LABA) medication.

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 Council for Harmonisation / Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Poland: 21
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Sweden: 5
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	54
From 65 to 84 years	27

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 16 centers in 4 countries (Hungary, Poland, Denmark and Sweden) between 12 October 2016 and 25 September 2018. Participants with eosinophilic moderate to severe asthma on a maintenance treatment of controller ICS + LABA and no other controller medication were recruited.

Pre-assignment

Screening details:

The study had a screening period (2-4 weeks), a 12-week dosing period and an observation period (up to 40 weeks). 81 participants were randomized. Treatment was started at 4 milligram (mg)/week AZD1419 or matching placebo and based on occurrence of flu-like symptoms in the individual participant, the dose was maintained or adapted up or down.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD1419

Arm description:

Participants received AZD1419 for inhalation via nebuliser solution (up to 13 doses). All participants received 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of AZD1419 on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving AZD1419 dose 10.

Arm type	Experimental
Investigational medicinal product name	AZD1419
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

Inhaled AZD1419 once weekly for a 12-week dosing period.

Arm title	Placebo

Arm description:

Participants received placebo for inhalation via nebuliser solution (up to 13 doses). All participants received placebo to match 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of placebo on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving placebo dose 10.

Arm type	Placebo

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

Dosage and administration details:

Inhaled placebo once weekly for a 12-week dosing period.

Number of subjects in period 1	AZD1419	Placebo
Started	40	41
Completed Treatment	25	29
Completed	11	13
Not completed	29	28
Randomized in error	-	1
Consent withdrawn by subject	4	1
Technical issue	-	1
Adverse event, non-fatal	1	-
Subject decision	1	-
Loss of asthma control	23	24
Unspecified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	AZD1419

Reporting group description:

Participants received AZD1419 for inhalation via nebuliser solution (up to 13 doses). All participants received 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of AZD1419 on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving AZD1419 dose 10.

Reporting group title	Placebo

Reporting group description:

Participants received placebo for inhalation via nebuliser solution (up to 13 doses). All participants received placebo to match 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of placebo on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving placebo dose 10.

Reporting group values	AZD1419	Placebo	Total
Number of subjects	40	41	81
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)	25	29	54
From 65-84 years	15	12	27
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	57.4	53.3	
standard deviation	± 13.3	± 15.4	-
Sex: Female, Male Units: Subjects			
Female	22	24	46
Male	18	17	35
Race/Ethnicity, Customized Units: Subjects			
White	40	40	80
Other	0	1	1
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	0	1	1
Not Hispanic or Latino	40	40	80
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	AZD1419

Reporting group description:

Participants received AZD1419 for inhalation via nebuliser solution (up to 13 doses). All participants received 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of AZD1419 on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving AZD1419 dose 10.

Reporting group title	Placebo

Reporting group description:

Participants received placebo for inhalation via nebuliser solution (up to 13 doses). All participants received placebo to match 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of placebo on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving placebo dose 10.

Primary: Number of Participants With Events for Time to Loss of Asthma Control (LOAC) up to Week 52 - Cox Regression Analysis

End point title	Number of Participants With Events for Time to Loss of Asthma Control (LOAC) up to Week 52 - Cox Regression Analysis

End point description:

LOAC was defined as any of the following:
• Increase of asthma control questionnaire-5 (ACQ-5) to ≥ 1.5.
• ≥ 30% reduction in morning peak expiratory flow (PEF) from baseline on 2 consecutive days.
• ≥ 6 additional reliever inhalations of short-acting β agonist (SABA) in a 24-hour period relative to baseline on 2 consecutive days.
• Exacerbation requiring systemic corticosteroids as decided by Investigator.
Time to LOAC was calculated as start date of first LOAC – date of randomization + 1. Start date of LOAC was latest date that 1 of the 4 criteria were satisfied immediately prior to exacerbation start date, provided no more than 7 days between LOAC and exacerbation start date. Time to LOAC was displayed using a Kaplan-Meier plot and endpoint is presented as number of participants with events, analyzed using the full analysis set (FAS) which included all randomized participants who received any investigational product (IP). Cox regression analysis used to compare treatments.

End point type	Primary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: participants	24	24		

Statistical analyses

Statistical analysis title	Time to LOAC

Statistical analysis description:

Comparison between groups. Cox regression model analysis with age and gender included as covariates.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.5722 [2]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.87

Notes:

[1] - The null hypothesis was that during the 52-week double-blind treatment period, the time to LOAC in the AZD1419 arm was equal to the corresponding time to LOAC in the placebo arm.
Hazard ratio < 1 favours AZD1419 over placebo.
[2] - 1-sided p-value

Secondary: Number of Participants Experiencing LOAC up to Week 52 - Generalized Estimating Equation Analysis

End point title	Number of Participants Experiencing LOAC up to Week 52 - Generalized Estimating Equation Analysis

End point description:

LOAC was defined as any of the following:
• An increase of ACQ-5 to ≥ 1.5.
• A ≥ 30% reduction in morning PEF from baseline on 2 consecutive days.
• At least 6 additional reliever inhalations of SABA in a 24-hour period relative to baseline on 2 consecutive days.
• An exacerbation requiring systemic corticosteroids.
Number of participants experiencing LOAC up to Week 52 is presented for the FAS which included all randomized participants who received any IP. A generalized linear model based on a generalized estimating equation was used to compare treatments.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: participants	24	24		

Statistical analyses

Statistical analysis title	Participants with LOAC

Statistical analysis description:

Comparison between groups. Odds ratio was estimated using a generalized linear model based on a generalized estimating equation approach fitting treatment, visit and age and gender as covariates.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2006 [3]
Method	Generalized estimating equation analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	4.79

Notes:

[3] - 2-sided p-value

Secondary: Least Squares (LS) Mean ACQ-5 Score Over 52 Weeks

End point title	Least Squares (LS) Mean ACQ-5 Score Over 52 Weeks

End point description:

ACQ-5 questionnaire: participants were asked to recall status of their asthma during the previous week with regards to symptoms for the items:
• Awoken at night by asthma symptoms.
• Severity of asthma symptoms in the morning.
• Limitation of daily activities due to asthma.
• Shortness of breath.
• Wheeze.
ACQ-5 score was computed as unweighted mean of responses to the 5 items, measured on a 7-point scale from 0 (totally controlled) to 6 (severely uncontrolled). A lower score indicated a better outcome. If ACQ-5 reached ≥ 1.5, the participant was reported as having LOAC. Estimates of the LS mean over 52 weeks were analyzed using a repeated measures analysis with treatment, baseline ACQ-5, week and treatment-by-week with participant as random effects, and age and gender as covariates. Baseline was average of non-missing daily measures/scores over last 5 days prior to and including the morning of randomization. The FAS included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	41		
Units: scores on a scale				
least squares mean (standard error)	0.56 (± 0.07)	0.59 (± 0.07)		

Statistical analyses

Statistical analysis title	ACQ-5 score

Statistical analysis description:

Comparison between groups. Repeated measures analysis.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8166 [4]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.17

Notes:

[4] - 2-sided p-value

Secondary: LS Mean Asthma Daily Diary Score (Weekly Total) Over 52 Weeks

End point title	LS Mean Asthma Daily Diary Score (Weekly Total) Over 52 Weeks

End point description:

Asthma symptoms during night-time and daytime were recorded by the participant each morning and evening in the Asthma Daily Diary using a 4-point scale, ranging from 0 to 3, where 0 indicated no asthma symptoms. Asthma symptom daytime score (recorded in evening), night-time score (recorded in morning), and total score were calculated separately. Daily asthma symptom total score was calculated by taking sum of the night-time and daytime asthma symptom scores recorded each day, ranging from 0 to 6. A lower symptom score indicated a better outcome. Estimates of the LS mean over 52 weeks were analyzed using a repeated measures analysis with treatment, baseline asthma daily diary weekly average, week and treatment-by-week with participant as random effects, and age and gender as covariates. Baseline was the average of non-missing daily measures/scores over the last 5 days prior to and including the morning of randomization. The FAS included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	41		
Units: scores on a scale				
least squares mean (standard error)	0.79 (± 0.10)	0.82 (± 0.10)		

Statistical analyses

Statistical analysis title	Asthma daily diary score

Statistical analysis description:	
Comparison between groups. Repeated measures analysis.	
Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8412 [5]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.26

Notes:

[5] - 2-sided p-value

Secondary: Number of Participants With Events for Time to Moderate Or Severe Exacerbation up to Week 52

End point title	Number of Participants With Events for Time to Moderate Or Severe Exacerbation up to Week 52

End point description:

Moderate exacerbation was defined as a temporary increase in maintenance therapy to prevent a severe event supported by sustained (≥ 2 day) worsening in at least 1 key control metric ie, asthma score, reliever medication use, night time awakening or morning PEF.
Severe exacerbation was defined as a worsening in asthma symptoms and:
• Use of systemic corticosteroids for at least 3 days and/or
• An unscheduled or emergency room visit due to asthma symptoms requiring systemic corticosteroids and/or
• An in-patient hospitalization due to asthma requiring systemic corticosteroids.
Time to moderate or severe asthma exacerbation was calculated as start date of first moderate or severe exacerbation – date of randomization + 1. Time to moderate or severe asthma exacerbation was displayed using a Kaplan-Meier plot and the endpoint is presented as number of participants with events, analysed using the FAS which included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: participants	13	16		

Statistical analyses

Statistical analysis title	Time to moderate or severe exacerbation

Statistical analysis description:

Comparison between groups. Cox regression model analysis with age and gender included as covariates.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.5477 [7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.67

Notes:

[6] - The null hypothesis was that the time to moderate or severe exacerbation was not different between AZD1419 and placebo.
Hazard ratio < 1 favours AZD1419 over placebo.
[7] - 2-sided p-value

Statistical analysis title	Participants with moderate or severe exacerbation

Statistical analysis description:

Comparison between groups. Odds ratio was estimated using a generalized linear model based on a generalized estimating equation approach fitting treatment and visit as covariates.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7294 [8]
Method	Generalized estimating equation analysis
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.86

Notes:

[8] - 2-sided p-value

Secondary: Percentage of Participants Using Reliever Medication up to Week 52

End point title	Percentage of Participants Using Reliever Medication up to Week 52

End point description:

The use of SABAs was allowed as rescue medication (reliever bronchodilator) throughout the study. Reliever medication use was captured in the Asthma Daily Diary twice daily (morning and evening), recorded as the number of inhaler puffs. The number of inhalations (puffs) per day was calculated as: number of night inhaler puffs + number of day inhaler puffs. Percentage of participants using reliever medication (SABA) up to Week 52 is presented for the FAS which included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	41		
Units: percentage of participants	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: LS Mean Pre- and Post-Bronchodilator (BD) Forced Expiratory Volume in 1 Second (FEV1) Over 52 Weeks

End point title	LS Mean Pre- and Post-Bronchodilator (BD) Forced Expiratory Volume in 1 Second (FEV1) Over 52 Weeks

End point description:

Lung function was assessed by pre- and post-BD FEV1 which was measured by spirometry. To ensure quality control, all spirometry measurements were reviewed to ensure that they met American Thoracic Society / European Respiratory Society criteria for acceptability. Estimates of the LS mean over 52 weeks were analyzed using a repeated measures analysis with treatment, baseline FEV1 (pre- or post-BD, as applicable), visit and treatment-by-visit with participant as random effects, and age and gender as covariates. Baseline was the last non-missing measurement recorded prior to randomization. The FAS included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	39		
Units: Liters				
least squares mean (standard error)				
pre-BD FEV1	2.24 (± 0.05)	2.18 (± 0.05)		
post-BD FEV1	2.36 (± 0.05)	2.39 (± 0.05)		

Statistical analyses

Statistical analysis title	Post-BD FEV1

Statistical analysis description:

Comparison between groups. Repeated measures analysis.

Comparison groups	AZD1419 v Placebo

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7013 [9]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	0.11

Notes:

[9] - 2-sided p-value

Statistical analysis title	Pre-BD FEV1

Statistical analysis description:

Comparison between groups. Repeated measures analysis.

Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3764 [10]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.2

Notes:

[10] - 2-sided p-value

Secondary: LS Mean Total PEF (Weekly) Over 52 Weeks

End point title	LS Mean Total PEF (Weekly) Over 52 Weeks

End point description:

Morning and evening PEF measurements were recorded by the participant on a daily basis and then averaged over the week. The weekly average total PEF was calculated by taking the sum of the average of the weekly morning mean and weekly evening mean. Estimates of the LS mean over 52 weeks were analyzed using a repeated measures analysis with treatment, baseline PEF, week and treatment-by-week with participant as random effects, and age and gender as covariates. Baseline was the average of non-missing daily measures/scores over the last 5 days prior to and including the morning of randomization. The FAS included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	41		
Units: Liters/minute				
least squares mean (standard error)	325.33 (± 5.77)	325.65 (± 5.79)		

Statistical analyses

Statistical analysis title	Total PEF
Statistical analysis description:	
Comparison between groups. Repeated measures analysis.	
Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9686 [11]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.54
upper limit	15.9

Notes:

[11] - 2-sided p-value

Secondary: LS Mean Fractional Exhaled Nitric Oxide (FeNO) (Weekly) Over 52 Weeks

End point title	LS Mean Fractional Exhaled Nitric Oxide (FeNO) (Weekly) Over 52 Weeks

End point description:

FeNO measurements were taken at home by participants every second day. The weekly average FeNO was based on the average of measurements taken at home for a specific week. Estimates of the LS mean over 52 weeks were analyzed using a repeated measures analysis with treatment, baseline FeNO, week and treatment-by-week with participant as random effects, and age and gender as covariates. Baseline was the average of non-missing daily measures/scores over the last 5 days prior to and including the morning of randomization. The FAS included all randomized participants who received any IP.

End point type	Secondary

End point timeframe:

Baseline (Week 0) up to Week 52

End point values	AZD1419	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	38		
Units: parts per billion				
least squares mean (standard error)	33.26 (± 2.33)	35.28 (± 2.33)		

Statistical analyses

Statistical analysis title	FeNO
Statistical analysis description: Comparison between groups. Repeated measures analysis.	
Comparison groups	AZD1419 v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5403 [12]
Method	Repeated measures analysis
Parameter estimate	LS Mean difference
Point estimate	-2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.55
upper limit	4.52

Notes:

[12] - 2-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of IP (Week 0) up to Week 52.

Adverse event reporting additional description:

The safety analysis set included all participants who received any IP.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo for inhalation via nebuliser solution (up to 13 doses). All participants received placebo to match 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of placebo on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving placebo dose 10.

Reporting group title	AZD1419

Reporting group description:

Participants received AZD1419 for inhalation via nebuliser solution (up to 13 doses). All participants received 4 mg AZD1419 once weekly for 4 doses. The following 9 doses were adapted based on tolerability (severity of flu-like symptoms). Participants were prescribed their usual controller medication (ICS + LABA) in separate inhalers. During the dosing period, controller medications were gradually reduced and discontinued. Treatment was initiated with 6 doses of AZD1419 on top of the participant's controller medication, LABA was then stopped on the evening prior to receiving dose 7, and ICS was gradually tapered down and discontinued during the next 3 weeks before being discontinued in the evening prior to receiving AZD1419 dose 10.

Serious adverse events	Placebo	AZD1419	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 41 (2.44%)	3 / 40 (7.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Pulmonary eosinophilia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus urinary			

subjects affected / exposed	1 / 41 (2.44%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 41 (0.00%)	1 / 40 (2.50%)	
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: 5 %

Non-serious adverse events	Placebo	AZD1419	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 41 (26.83%)	22 / 40 (55.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 41 (9.76%)	6 / 40 (15.00%)	
occurrences (all)	10	9	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 41 (2.44%)	6 / 40 (15.00%)	
occurrences (all)	1	13	
Pyrexia			
subjects affected / exposed	1 / 41 (2.44%)	10 / 40 (25.00%)	
occurrences (all)	1	22	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 41 (7.32%)	0 / 40 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	0 / 41 (0.00%) 0	5 / 40 (12.50%) 9	
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all)	1 / 41 (2.44%) 2	6 / 40 (15.00%) 13	
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 8	5 / 40 (12.50%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2016	Reasons for amendment: • To include additional study background information in the section for benefit/risk analysis. • To modify visit windows within the study design figure. • Inclusion criterion 3: controller medication clarified. • Exclusion criterion 2: clarification of the timing of the last dose of immunotherapy. • ICS, LABA and SABA restrictions were added to list of restrictions. • Clarification of timing of FEV1 measurement to schedule of events table. • Clarification regarding the timing of influenza vaccination for the dose adaption procedure. • Clarification to the timing of FEV1 measurements for the composite endpoint for exacerbations. • Clarification of urinalysis parameters to be measured for laboratory safety variables.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported