



## 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,<br>ClinicalTrialTransparency@astrazeneca.com |
| Scientific contact           | Global Clinical Lead, AstraZeneca,<br>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  $\beta$ 2 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, Data analyst, Carer, Assessor |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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.

| <b>Number of subjects in period 1</b> | 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:   |  |
| <ul style="list-style-type: none"><li>• Increase of asthma control questionnaire-5 (ACQ-5) to <math>\geq 1.5</math>.</li><li>• <math>\geq 30\%</math> reduction in morning peak expiratory flow (PEF) from baseline on 2 consecutive days.</li><li>• <math>\geq 6</math> additional reliever inhalations of short-acting <math>\beta</math> agonist (SABA) in a 24-hour period relative to baseline on 2 consecutive days.</li><li>• Exacerbation requiring systemic corticosteroids as decided by Investigator.</li></ul>  |  |
| 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

|  |                         |
|--|-------------------------|
| <b>Statistical analysis title</b>  | 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 <sup>[1]</sup>    |
| P-value  | = 0.5722 <sup>[2]</sup> |
| 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  $\geq 1.5$ .
- A  $\geq 30\%$  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

|                             |                 |                 |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>     | AZD1419         | Placebo         |  |  |
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 40              | 41              |  |  |
| Units: participants         | 24              | 24              |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | 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 <sup>[3]</sup>                  |
| 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:   |   |  |
| <ul style="list-style-type: none"><li>• Awoken at night by asthma symptoms.</li><li>• Severity of asthma symptoms in the morning.</li><li>• Limitation of daily activities due to asthma.</li><li>• Shortness of breath.</li><li>• Wheeze.</li></ul>   |   |  |
| 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 $\geq 1.5$ , 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 ( $\pm$ 0.07) | 0.59 ( $\pm$ 0.07) |  |  |

### Statistical analyses

|   |                            |
|---|----------------------------|
| <b>Statistical analysis title</b>   | ACQ-5 score                |
| Statistical analysis description:<br>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 <sup>[4]</sup>    |
| 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

|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>             | 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

|                                   |                          |
|-----------------------------------|--------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[5]</sup>    |
| 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 ( $\geq 2$  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 <sup>[6]</sup>    |
| P-value                                 | = 0.5477 <sup>[7]</sup> |
| 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

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[8]</sup>                  |
| 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

|                                   |                 |                 |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>           | 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

|                                     |                 |                 |  |  |
|-------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>             | 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

|                                   |              |
|-----------------------------------|--------------|
| <b>Statistical analysis title</b> | 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 <sup>[9]</sup>    |
| 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

|                                   |             |
|-----------------------------------|-------------|
| <b>Statistical analysis title</b> | 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 <sup>[10]</sup>   |
| 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 ( $\pm$ 5.77) | 325.65 ( $\pm$ 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 <sup>[11]</sup>   |
| 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:  |   |
| <p>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.</p> |   |
| 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 ( $\pm$ 2.33) | 35.28 ( $\pm$ 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 <sup>[12]</sup>   |
| 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          |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |  |
| 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 %

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 17 October 2016 | <p>Reasons for amendment:</p> <ul style="list-style-type: none"><li>• To include additional study background information in the section for benefit/risk analysis.</li><li>• To modify visit windows within the study design figure.</li><li>• Inclusion criterion 3: controller medication clarified.</li><li>• Exclusion criterion 2: clarification of the timing of the last dose of immunotherapy.</li><li>• ICS, LABA and SABA restrictions were added to list of restrictions.</li><li>• Clarification of timing of FEV1 measurement to schedule of events table.</li><li>• Clarification regarding the timing of influenza vaccination for the dose adaption procedure.</li><li>• Clarification to the timing of FEV1 measurements for the composite endpoint for exacerbations.</li><li>• Clarification of urinalysis parameters to be measured for laboratory safety variables.</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported