# Clinical trial results:
# A prospective, multicenter, randomised, double-blind, placebo-controlled, 2-parallel groups, Phase 3 study to compare the efficacy and the safety of masitinib at 6 mg/kg/day versus placebo in the treatment of patients with Severe Persistent Asthma treated with oral corticosteroids

## Summary

| | |
|---|---|
| EudraCT number | 2010-020803-63 |
| Trial protocol | FR CZ BG DE SK ES GR |
| Global end of trial date | 29 May 2018 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 15 December 2022 |
| First version publication date | 15 December 2022 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | AB07015 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01449162 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | AB Science |
| Sponsor organisation address | 3 avenue George V, Paris, France, 75008 |
| Public contact | Clinical Study Coordinator, AB Science, clinical@ab-science.com |
| Scientific contact | Clinical Study Coordinator, AB Science, clinical@ab-science.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 | 23 October 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 May 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of the study was to compare the efficacy and the safety of masitinib at 6.0 mg/kg/day versus placebo in the treatment of patients with severe uncontrolled asthma treated with oral corticosteroids at ≥7.5 mg/day without and with an elevated eosinophil count (≥150 cells/µL).

Results showed that orally administered masitinib reduces the risk of asthma exacerbations in severe asthma patients, with an acceptable safety profile. Overall, these positive findings provide further clinical evidence implicating mast cells and/or PDFGR signaling to the pathophysiology of severe asthma, which could influence the future direction of drug development. In conclusion, orally administered masitinib, as used in the present randomized control study, may potentially provide a treatment option for oral corticosteroid-dependent severe asthma, including severe asthmatics that are either ineligible to receive or in failure to registered biologics.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All participants were required to read and sign an informed consent form prior to participation in the study. Only investigators qualified by training and/or experience were selected as appropriate experts to investigate the study drug.

Background therapy:

A growing body of research implicates mast cells as being a crucial factor for initiating, promoting and sustaining pathophysiological processes that drive asthma exacerbations and structural changes of the airway in severe asthmatics. This occurs directly via intercellular cross-talk and indirectly through mediator release; moreover, increased mast cell activity is associated with both Type-2-high and Type-2-low asthma, suggesting it represents a steroid insensitive pathway. Hence, there is a strong rationale to target mast cells in severe asthma.

Masitinib is an oral tyrosine kinase inhibitor that selectively targets mast cell activity via its action on the c-Kit (stem cell factor receptor), Lyn, and Fyn protein kinases. Masitinib is also a potent inhibitor of platelet-derived growth factor receptor (PDGFR) signaling, which is associated with pathologic airway smooth muscle cell proliferation and airway remodeling. In preclinical models of asthma, masitinib significantly improved airway inflammation and lung mechanics in cats. Proof-of-concept that masitinib may improve the control of severe corticosteroid-dependent asthma with respect to placebo was previously demonstrated in a small (n = 44) placebo-controlled study.

Our hypothesis was that masitinib as an add-on to standard maintenance therapy would significantly reduce asthma related symptoms (eg, rate of exacerbations and pulmonary function) as compared with placebo in the treatment of oral corticosteroid-dependent severe asthma.

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 February 2011 |
| 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 | Argentina: 20 |
| Country: Number of subjects enrolled | Bulgaria: 13 |
| Country: Number of subjects enrolled | Czechia: 20 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Algeria: 2 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | France: 25 |
| Country: Number of subjects enrolled | Greece: 12 |
| Country: Number of subjects enrolled | Hungary: 8 |
| Country: Number of subjects enrolled | India: 73 |
| Country: Number of subjects enrolled | Poland: 15 |
| Country: Number of subjects enrolled | Romania: 41 |
| Country: Number of subjects enrolled | Slovakia: 6 |
| Country: Number of subjects enrolled | Thailand: 2 |
| Country: Number of subjects enrolled | Tunisia: 20 |
| Country: Number of subjects enrolled | Taiwan: 1 |
| Country: Number of subjects enrolled | Ukraine: 133 |
| Country: Number of subjects enrolled | South Africa: 18 |
| Worldwide total number of subjects | 419 |
| EEA total number of subjects | 150 |

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) | 341 |
| From 65 to 84 years | 78 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

First patient randomized (09 February 2011) Last patient, last visit (29 May 2018).

### Pre-assignment

Screening details:

Patients aged from 18 to 75, with severe asthma and already treated with oral corticosteroids at a minimal daily dose of 7.5 mg prednisone or equivalent or history of asthma ≥1 year, patients treated during at least one period of 21 days with oral corticosteroids, non smokers for at least a year and normal organ function

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Investigators were provided with technical options and password information to selectively break the code for an individual patient, if necessary. The premature breaking of the code was to be done only in emergency cases in which knowledge of the administered drug was necessary to provide adequate treatment. Whenever possible, the sponsor was contacted before the blinding was broken.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Masitinib 6.0 mg/kg/day |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Masitinib mesylate |
| Investigational medicinal product code | AB1010 |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Masitinib was supplied as 100 mg and 200 mg tablets of AB1010 base (respectively corresponding to 119.3 mg and 238.5 mg of the mesylate salt AB1010) packaged in polyethylene bottles.

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

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

Dosage and administration details:

Patients randomized to the placebo group received matching placebo at 6.0 mg/kg/day

| **Number of subjects in period 1** | Masitinib 6.0 mg/kg/day | Placebo |
|---|---|---|
| Started | 279 | 140 |
| Completed | 86 | 43 |
| Not completed | 193 | 97 |
| Adverse event, serious fatal | 3 | 1 |
| Consent withdrawn by subject | 78 | 40 |
| Physician decision | 10 | 5 |
| Adverse event, non-fatal | 30 | 7 |
| Other | 6 | 3 |
| Lost to follow-up | 16 | 9 |
| Exited study at week 36 | 24 | 14 |
| GCP violation | 8 | 7 |
| Lack of efficacy | 14 | 8 |
| Protocol deviation | 4 | 3 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Masitinib 6.0 mg/kg/day |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Masitinib 6.0 mg/kg/day | Placebo | Total |
|---|---|---|---|
| Number of subjects | 279 | 140 | 419 |
| Age categorical<br>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) | 219 | 122 | 341 |
| From 65-84 years | 60 | 18 | 78 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| median | 55.0 | 51.0 | |
| full range (min-max) | 18 to 79 | 21 to 75 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 179 | 90 | 269 |
| Male | 100 | 50 | 150 |
| Eosinophil level | | | |
| Patients with eosinophil count ≥0.15 K/µL (150 cells/µL), n % | | | |
| Units: Subjects | | | |
| >= 0.15 | 213 | 107 | 320 |
| <0.15 | 66 | 33 | 99 |
| Long acting Beta-agonist | | | |
| Long-acting beta-agonists (LABAs) are taken on a daily basis to relax the muscles lining the airways that carry air to the lungs. This allows the tubes to remain open, making breathing easier. LABAs should be taken only in combination with a corticosteroid to treat asthma. | | | |
| Units: Subjects | | | |
| Yes | 222 | 107 | 329 |
| No | 57 | 33 | 90 |
| Former smoker<br>Units: Subjects | | | |
| Yes | 45 | 18 | 63 |
| No | 234 | 122 | 356 |

| | | | |
|---|---|---|---|
| History of asthma exacerbations (previous year) | | | |
| Inclusion criterion that patients had experienced a minimum of two exacerbations in the previous year (including one severe asthma exacerbation as per protocol definition). | | | |
| Units: events per year | | | |
| arithmetic mean | 2.3 | 2.1 | |
| standard deviation | ± 0.9 | ± 0.7 | - |
| Stable dose of oral corticosteroid, mg/day | | | |
| Units: mg/day | | | |
| arithmetic mean | 12.2 | 12.0 | |
| standard deviation | ± 8.8 | ± 7.6 | - |
| AQLQ | | | |
| Asthma Quality of Life Questionnaire.<br>A disease-specific health-related quality of life instrument that taps both physical and emotional impact of disease | | | |
| Units: Points | | | |
| median | 3.84 | 4.03 | |
| full range (min-max) | 1.17 to 6.97 | 1.63 to 6.53 | - |
| ACQ | | | |
| Asthma Control Questionnaire (ACQ)<br>A simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment. | | | |
| Units: Points | | | |
| median | 3.00 | 3.00 | |
| full range (min-max) | 0.00 to 5.17 | 0.00 to 5.86 | - |
| FEV1 | | | |
| Forced expiratory volume in 1 second (FEV1) is the maximum amount of air that the subject can forcibly expel during the first second following maximal inhalation. | | | |
| Units: litre(s) | | | |
| median | 1.45 | 1.59 | |
| full range (min-max) | 0.43 to 3.30 | 0.71 to 3.55 | - |
| FVC | | | |
| Forced vital capacity; the total volume of air that can be exhaled during a maximal forced expiration effort. | | | |
| Units: litre(s) | | | |
| median | 2.33 | 2.42 | |
| full range (min-max) | 0.86 to 5.83 | 1.03 to 4.95 | - |
| FEV1/FVC % | | | |
| The FEV1/FVC ratio is the amount of air exhaled in the first second divided by all of the air exhaled during a maximal exhalation. | | | |
| Units: percent | | | |
| median | 62.67 | 66.67 | |
| full range (min-max) | 0.38 to 111.0 | 0.61 to 104.0 | - |
| Eosinophil level | | | |
| Blood test | | | |
| Units: cells/µL | | | |
| arithmetic mean | 290 | 310 | |
| standard deviation | ± 300 | ± 300 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Masitinib 6.0 mg/kg/day |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |
| Subject analysis set title | Masitinib 6.0 mg/kg/d (Primary Analysis Population) |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Primary analysis was performed on patients with severe asthma in a cohort referred to as the "primary population". These patients had confirmed severe asthma with an oral corticosteroids (OCS) intake of ≥7.5 mg/d (no minimum baseline blood eosinophil count was specified). A total of 355 patients (240 masitinib and 115 placebo) were included in the primary population.

| | |
|---|---|
| Subject analysis set title | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

A predefined subgroup analysis was performed based on patients with a baseline blood eosinophil count of ≥150 cell/µL. The primary endpoint analysis was performed sequentially, first on the primary population and then on the eosinophil (≥150 cell/µL) subgroup, using a hierarchical alpha-spending procedure with alpha set to 5% at each step. A total of 268 patients (181 masitinib and 87 placebo) were included in the eosinophil (≥150 cell/µL) subgroup.

| | |
|---|---|
| Subject analysis set title | Placebo (Primary Analysis Population) |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

Primary analysis was performed on patients with severe asthma in a cohort referred to as the "primary population". These patients had confirmed severe asthma with an oral corticosteroids (OCS) intake of ≥7.5 mg/d (no minimum baseline blood eosinophil count was specified). A total of 355 patients (240 masitinib and 115 placebo) were included in the primary population.

| | |
|---|---|
| Subject analysis set title | Placebo (Eosinophil Subgroup) |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

A predefined subgroup analysis was performed based on patients with a baseline blood eosinophil count of ≥150 cell/µL. The primary endpoint analysis was performed sequentially, first on the primary population and then on the eosinophil (≥150 cell/µL) subgroup, using a hierarchical alpha-spending procedure with alpha set to 5% at each step. A total of 268 patients (181 masitinib and 87 placebo) were included in the eosinophil (≥150 cell/µL) subgroup.

### Primary: Severe asthma exacerbation rate

| | |
|---|---|
| End point title | Severe asthma exacerbation rate |

End point description:

The primary endpoint was the annualized severe asthma exacerbation rate (SAER) in each treatment group adjusted for the overall time on treatment. A severe asthma exacerbation was defined as a worsening in asthma symptoms that required an increase in the stable maintenance dose of systemic corticosteroids for at least 3 days, with or without hospital admission.
The primary endpoint analysis was performed sequentially, first on the primary population and then on the eosinophil (≥150 cell/µL) subgroup, using a hierarchical alpha-spending procedure with alpha set to 5% at each step.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Overall duration of patient exposure

| End point values | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: events per year | | | | |
| number (not applicable) | 0.34 | 0.34 | 0.48 | 0.51 |

**Statistical analyses**

| Statistical analysis title | Ratio Rate (Primary Analysis Population) |
|---|---|
| Comparison groups | Masitinib 6.0 mg/kg/d (Primary Analysis Population) v Placebo (Primary Analysis Population) |
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 [1] |
| Method | Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 0.9 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.17 |

Notes:

[1] - Poisson regression is a generalized linear model used for counting data

| Statistical analysis title | Ratio Rate (Eosinophil Subgroup) |
|---|---|
| Comparison groups | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) v Placebo (Eosinophil Subgroup) |
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.016 [2] |
| Method | Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.62 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.91 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.2 |

Notes:

[2] - Poisson regression is a generalized linear model used for counting data

## Secondary: Moderate/Severe exacerbation rate

| End point title | Moderate/Severe exacerbation rate |
|---|---|

End point description:

A key secondary endpoint was the overall (moderate/severe) annualized rate of asthma exacerbations (adjusted for the overall time on treatment). This endpoint included both moderate and severe asthma exacerbations; a moderate asthma exacerbation being defined as a worsening in asthma symptoms and/or an increase in rescue medication use that lasted for 2 or more days and required a change in asthma treatment without hospitalization. Secondary endpoints were tested at the 0.05 significance level.

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

End point timeframe:

Overall duration of patient exposure

| **End point values** | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: events per year | | | | |
| number (not applicable) | 0.48 | 0.48 | 0.69 | 0.71 |

## Statistical analyses

| **Statistical analysis title** | Rate Ratio (Primary Analysis Population) |
|---|---|

Statistical analysis description:

Measure of reduction in the moderate/severe asthma exacerbation rate for the masitinib treatment-arm relative to placebo

| Comparison groups | Masitinib 6.0 mg/kg/d (Primary Analysis Population) v Placebo (Primary Analysis Population) |
|---|---|
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 [3] |
| Method | Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.64 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.48 |
| upper limit | 0.84 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.14 |

Notes:

[3] - Poisson regression is a generalized linear model used for counting data

| **Statistical analysis title** | Rate Ratio (Eosinophil Subgroup) |
|---|---|

Statistical analysis description:

Measure of reduction in the moderate/severe asthma exacerbation rate for the masitinib treatment-arm relative to placebo

| Comparison groups | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) v Placebo (Eosinophil Subgroup) |
|---|---|
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.025 [4] |
| Method | Poisson regression |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.69 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.95 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.17 |

Notes:

[4] - Poisson regression is a generalized linear model used for counting data

## Secondary: ΔFEV1

| End point title | ΔFEV1 |
|---|---|

End point description:

Assessment of pulmonary function was performed according to change from baseline in prebronchodilator forced expiratory volume in 1 s (FEV1) .
For the analysis of secondary endpoints, changes from baseline over 96 weeks were estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI). Secondary endpoints were tested at the 0.05 significance level.
For FEV1, a positive between-group difference favors masitinib. Precision/Dispersion type = Standard Error.

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

End point timeframe:

96 weeks

| **End point values** | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: litre(s) | | | | |
| least squares mean (standard deviation) | 0.0989 (± 0.02298) | 0.1599 (± 0.0265) | 0.0314 (± 0.02751) | 0.0470 (± 0.0305) |

## Statistical analyses

| **Statistical analysis title** | ΔFEV1 (Primary Analysis Population) |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in FEV1, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| Comparison groups | Placebo (Primary Analysis Population) v Masitinib 6.0 mg/kg/d (Primary Analysis Population) |
|---|---|
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.016 [5] |
| Method | Mixed models analysis |
| Parameter estimate | difference in least-squares mean change |
| Point estimate | 0.0675 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0125 |
| upper limit | 0.1225 |

Notes:

[5] - multivariate mixed model of repeated measures (MMRM)

| **Statistical analysis title** | ΔFEV1 (Eosinophil Subgroup) |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in FEV1, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| Comparison groups | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) v Placebo (Eosinophil Subgroup) |
|---|---|
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.1129 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0523 |
| upper limit | 0.1734 |

## Secondary: ΔFVC

| End point title | ΔFVC |
|---|---|

End point description:

Assessment of pulmonary function was performed according to change from baseline in forced vital capacity (FVC).
For the analysis of secondary endpoints, changes from baseline over 96 weeks were estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).
Secondary endpoints were tested at the 0.05 significance level.
For FVC, a positive between-group difference favors masitinib.

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

End point timeframe:

96 weeks

| **End point values** | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: litre(s) | | | | |
| least squares mean (standard error) | 0.009926 (± 0.03337) | 0.0801 (± 0.03984) | -0.02625 (± 0.04020) | -0.0223 (± 0.04594) |

### Statistical analyses

| **Statistical analysis title** | FVC (Primary Analysis Population) |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in FVC, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| Comparison groups | Masitinib 6.0 mg/kg/d (Primary Analysis Population) v Placebo (Primary Analysis Population) |
|---|---|
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.386 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.03617 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.04576 |
| upper limit | 0.1181 |

| | FVC (Eosinophil Subgroup) |
|---|---|

| Statistical analysis title | |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in FVC, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| | |
|---|---|
| Comparison groups | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) v Placebo (Eosinophil Subgroup) |
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.032 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | 0.1024 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.0086 |
| upper limit | 0.1961 |

## Secondary: ΔACQ-7

| | |
|---|---|
| End point title | ΔACQ-7 |

End point description:

Evaluation of asthma disease control was according to change from baseline in the 7-question version of the Asthma Control Questionnaire (ACQ-7) score (with a change of 0.5 points considered the minimum clinically significant difference).
For the analysis of secondary endpoints, changes from baseline over 96 weeks were estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).
Secondary endpoints were tested at the 0.05 significance level.
For ACQ-7, a negative between-group difference favors masitinib.

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

End point timeframe:

96 weeks

| End point values | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: Points | | | | |
| least squares mean (standard error) | -0.5369 (± 0.08198) | -0.5036 (± 0.09785) | -0.3241 (± 0.09851) | -0.3337 (± 0.1073) |

## Statistical analyses

| **Statistical analysis title** | ACQ-7 (Primary Analysis Population) |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in ACQ-7, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| | |
|---|---|
| Comparison groups | Masitinib 6.0 mg/kg/d (Primary Analysis Population) v Placebo (Primary Analysis Population) |
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.05 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | -0.2128 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4259 |
| upper limit | 0.0004 |

| **Statistical analysis title** | ACQ-7 (Eosinophil Subgroup) |
|---|---|

Statistical analysis description:

Change from baseline over 96 weeks in ACQ-7, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

| | |
|---|---|
| Comparison groups | Placebo (Eosinophil Subgroup) v Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) |
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.16 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | -0.1699 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4076 |
| upper limit | 0.0678 |

## Secondary: ΔAQLQ

| End point title | ΔAQLQ |
|---|---|

End point description:

Evaluation of quality-of-life assessment was according to change from baseline in the Asthma Quality of Life Questionnaire score (AQLQ).
For the analysis of secondary endpoints, changes from baseline over 96 weeks were estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI).

Secondary endpoints were tested at the 0.05 significance level.
For AQLQ, a positive between-group difference favors masitinib.

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| 96 weeks | |

| **End point values** | Masitinib 6.0 mg/kg/d (Primary Analysis Population) | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) | Placebo (Primary Analysis Population) | Placebo (Eosinophil Subgroup) |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 240 | 181 | 115 | 87 |
| Units: Points | | | | |
| least squares mean (standard error) | 0.5582 (± 0.1250) | 0.4549 (± 0.1346) | 0.5900 (± 0.1369) | 0.5724 (± 0.1415) |

**Statistical analyses**

| **Statistical analysis title** | AQLQ (Primary Analysis Population) |
|---|---|
| Statistical analysis description: | |
| Change from baseline over 96 weeks in AQLQ, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI). | |
| Comparison groups | Masitinib 6.0 mg/kg/d (Primary Analysis Population) v Placebo (Primary Analysis Population) |
| Number of subjects included in analysis | 355 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.85 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | -0.0318 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.3625 |
| upper limit | 0.299 |

| **Statistical analysis title** | AQLQ (Eosinophil Subgroup) |
|---|---|
| Statistical analysis description: | |
| Change from baseline over 96 weeks in AQLQ, estimated using a multivariate mixed model of repeated measures (MMRM) with treatment effect (masitinib versus placebo) reported as the between-group difference with corresponding 95% confidence intervals (CI). | |
| Comparison groups | Masitinib 6.0 mg/kg/d (Eosinophil Subgroup) v Placebo (Eosinophil Subgroup) |

| | |
|---|---|
| Number of subjects included in analysis | 268 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.492 |
| Method | Mixed models analysis |
| Parameter estimate | Risk ratio (RR) |
| Point estimate | -0.1175 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4541 |
| upper limit | 0.2191 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

96 weeks

Adverse event reporting additional description:

Adverse events (AEs) were collected for all patients from the time of informed consent signature until 28 days after the last dose of study treatment. Treatment-emergent AEs (TEAEs) were defined as those with an onset date on or after the first dose of study treatment and before 28 days after the last dose of study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Masitinib |
| Reporting group description: - | |
| Reporting group title | Placebo |

Reporting group description: -

| Serious adverse events | Masitinib | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 90 / 271 (33.21%) | 31 / 133 (23.31%) | |
| number of deaths (all causes) | 3 | 1 | |
| number of deaths resulting from adverse events | 3 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lipoma | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung Neoplasm Malignant | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic Neoplasm | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myeloproliferative Neoplasm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep Vein Thrombosis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Face Oedema | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal Ulceration | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Cervical Dysplasia | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Postmenopausal Haemorrhage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 20 / 271 (7.38%) | 13 / 133 (9.77%) | |
| occurrences causally related to treatment / all | 1 / 28 | 2 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Failure | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasal Polyps | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Adjustment Disorder | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug Use Disorder | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Foreign Body | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil Count Decreased | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary Failure | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Nervous system disorders | | | |
| Sciatica | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic Stroke | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diabetic Neuropathy | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Mouth Ulceration | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral Mucosa Erosion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal Polyp | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis Acute | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash Maculo-Papular | | | |
| subjects affected / exposed | 3 / 271 (1.11%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug Eruption | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Purpura | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash Macular | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash Morbilliform | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling Face | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Failure | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral Polyp | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|---|---|---|---|
| disorders | | | |
| Lumbar Spinal Stenosis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Pain | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial Cyst | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 4 / 271 (1.48%) | 3 / 133 (2.26%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Bacterial | | | |
| subjects affected / exposed | 3 / 271 (1.11%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 271 (0.74%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis Infected | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 2 / 133 (1.50%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Herpes Virus Infection | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Pseudomonal | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia Viral | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genital Herpes Simplex | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 271 (0.00%) | 1 / 133 (0.75%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lipomatosis | | | |
| subjects affected / exposed | 1 / 271 (0.37%) | 0 / 133 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Masitinib | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 184 / 271 (67.90%) | 92 / 133 (69.17%) | |
| Investigations | | | |
| Gamma-Glutamyltransferase Increased | | | |
| subjects affected / exposed | 32 / 271 (11.81%) | 13 / 133 (9.77%) | |
| occurrences (all) | 42 | 15 | |
| Blood Phosphorus Decreased | | | |
| subjects affected / exposed | 35 / 271 (12.92%) | 9 / 133 (6.77%) | |
| occurrences (all) | 52 | 11 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 33 / 271 (12.18%) | 7 / 133 (5.26%) | |
| occurrences (all) | 43 | 8 | |
| Weight Decreased | | | |
| subjects affected / exposed | 29 / 271 (10.70%) | 8 / 133 (6.02%) | |
| occurrences (all) | 32 | 8 | |
| Blood Triglycerides Increased | | | |
| subjects affected / exposed | 23 / 271 (8.49%) | 11 / 133 (8.27%) | |
| occurrences (all) | 31 | 14 | |

| | | | |
|---|---|---|---|
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 22 / 271 (8.12%) | 7 / 133 (5.26%) | |
| occurrences (all) | 26 | 9 | |
| Blood Lactate Dehydrogenase Increased | | | |
| subjects affected / exposed | 21 / 271 (7.75%) | 7 / 133 (5.26%) | |
| occurrences (all) | 28 | 11 | |
| Lymphocyte Count Decreased | | | |
| subjects affected / exposed | 20 / 271 (7.38%) | 8 / 133 (6.02%) | |
| occurrences (all) | 25 | 9 | |
| Alanine Aminotransferase Decreased | | | |
| subjects affected / exposed | 16 / 271 (5.90%) | 11 / 133 (8.27%) | |
| occurrences (all) | 20 | 15 | |
| Blood Cholesterol Increased | | | |
| subjects affected / exposed | 19 / 271 (7.01%) | 8 / 133 (6.02%) | |
| occurrences (all) | 30 | 9 | |
| Weight Increased | | | |
| subjects affected / exposed | 14 / 271 (5.17%) | 13 / 133 (9.77%) | |
| occurrences (all) | 16 | 17 | |
| Haemoglobin Decreased | | | |
| subjects affected / exposed | 20 / 271 (7.38%) | 4 / 133 (3.01%) | |
| occurrences (all) | 30 | 4 | |
| Haematocrit Increased | | | |
| subjects affected / exposed | 11 / 271 (4.06%) | 12 / 133 (9.02%) | |
| occurrences (all) | 12 | 19 | |
| Blood Creatinine Decreased | | | |
| subjects affected / exposed | 14 / 271 (5.17%) | 8 / 133 (6.02%) | |
| occurrences (all) | 22 | 8 | |
| White Blood Cell Count Increased | | | |
| subjects affected / exposed | 12 / 271 (4.43%) | 10 / 133 (7.52%) | |
| occurrences (all) | 14 | 12 | |
| Protein Total Decreased | | | |
| subjects affected / exposed | 14 / 271 (5.17%) | 7 / 133 (5.26%) | |
| occurrences (all) | 17 | 10 | |
| Neutrophil Count Increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 12 / 271 (4.43%) | 8 / 133 (6.02%) | |
| occurrences (all) | 16 | 12 | |
| Monocyte Count Increased | | | |
| subjects affected / exposed | 11 / 271 (4.06%) | 8 / 133 (6.02%) | |
| occurrences (all) | 17 | 10 | |
| Blood Calcium Decreased | | | |
| subjects affected / exposed | 15 / 271 (5.54%) | 1 / 133 (0.75%) | |
| occurrences (all) | 19 | 1 | |
| Red Blood Cell Count Decreased | | | |
| subjects affected / exposed | 14 / 271 (5.17%) | 0 / 133 (0.00%) | |
| occurrences (all) | 17 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 271 (4.43%) | 10 / 133 (7.52%) | |
| occurrences (all) | 16 | 15 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 9 / 271 (3.32%) | 10 / 133 (7.52%) | |
| occurrences (all) | 11 | 12 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 24 / 271 (8.86%) | 6 / 133 (4.51%) | |
| occurrences (all) | 34 | 6 | |
| Diarrhoea | | | |
| subjects affected / exposed | 25 / 271 (9.23%) | 3 / 133 (2.26%) | |
| occurrences (all) | 31 | 3 | |
| Vomiting | | | |
| subjects affected / exposed | 16 / 271 (5.90%) | 1 / 133 (0.75%) | |
| occurrences (all) | 26 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 70 / 271 (25.83%) | 38 / 133 (28.57%) | |
| occurrences (all) | 147 | 97 | |
| Infections and infestations | | | |
| Viral Upper Respiratory Tract Infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 18 / 271 (6.64%) | 9 / 133 (6.77%) | |
| occurrences (all) | 25 | 13 | |
| Bronchitis | | | |
| subjects affected / exposed | 13 / 271 (4.80%) | 8 / 133 (6.02%) | |
| occurrences (all) | 16 | 12 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 June 2013 | Major protocol amendments were implemented during the study with an aim of improving the study's benefit/risk balance and to enhance the clinical relevance of response. To ensure enrolment was restricted to severe corticosteroid-dependent asthmatics, and consistent with revised GINA guidance,17 the inclusion criterion for stable baseline OCS dose (prednisone-equivalent) was raised from a minimum of 5 mg/day to a prolonged exposure of ≥7.5 mg/day (protocol version 9.0, after about 27% of patients had been randomized). At this time, exposure for the primary endpoint was also changed from assessment of person-time exposure at week 36 to an overall person-time exposure, i.e., the full exposure period incorporating both initial 36-week period plus blinded extension period (protocol version 9). |
| 22 May 2014 | Major amendment concerning the primary endpoint which was changed to assess the rate of severe asthma exacerbations instead of moderate and severe exacerbations. Severe exacerbations are more clinically relevant in patients with severe uncontrolled asthma. In addition, moderate exacerbations are more difficult to assess and may not be clinically informative. |
| 02 September 2015 | Major amendment concerning definition of a targeted subgroup with ≥150/µL eosinophils at screening or baseline, and stratification of these patients. Once activated, mast cells release multiple mediators that produce a localized allergic response, and subsequently, secrete various cytokines, which then participate in the local recruitment and activation of other inflammatory cells including eosinophils. Thus, high levels of eosinophils may be an indication of elevated mast cell activity in asthma. |

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.

One limitation of the current study is that it did not evaluate masitinib's potential OCS-sparing properties, which is also considered an important therapeutic objective.

Notes:

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/35698580

http://www.ncbi.nlm.nih.gov/pubmed/19614621

http://www.ncbi.nlm.nih.gov/pubmed/22487554