



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/ μ L).

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 PDGFR 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			
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			
Units: years			
median	55.0	51.0	
full range (min-max)	18 to 79	21 to 75	-
Gender categorical			
Units: Subjects			
Female	179	90	269
Male	100	50	150
Eosinophil level			
Patients with eosinophil count ≥ 0.15 K/ μ L (150 cells/ μ L), 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			
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. 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) 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/ μ L. The primary endpoint analysis was performed sequentially, first on the primary population and then on the eosinophil (≥ 150 cell/ μ L) 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/ μ L) 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/ μ L. The primary endpoint analysis was performed sequentially, first on the primary population and then on the eosinophil (≥ 150 cell/ μ L) 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/ μ L) 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/ μ L) 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 (\pm 0.1250)	0.4549 (\pm 0.1346)	0.5900 (\pm 0.1369)	0.5724 (\pm 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 occurrences (all)	12 / 271 (4.43%) 16	8 / 133 (6.02%) 12	
Monocyte Count Increased subjects affected / exposed occurrences (all)	11 / 271 (4.06%) 17	8 / 133 (6.02%) 10	
Blood Calcium Decreased subjects affected / exposed occurrences (all)	15 / 271 (5.54%) 19	1 / 133 (0.75%) 1	
Red Blood Cell Count Decreased subjects affected / exposed occurrences (all)	14 / 271 (5.17%) 17	0 / 133 (0.00%) 0	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	12 / 271 (4.43%) 16	10 / 133 (7.52%) 15	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	9 / 271 (3.32%) 11	10 / 133 (7.52%) 12	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	24 / 271 (8.86%) 34	6 / 133 (4.51%) 6	
Diarrhoea subjects affected / exposed occurrences (all)	25 / 271 (9.23%) 31	3 / 133 (2.26%) 3	
Vomiting subjects affected / exposed occurrences (all)	16 / 271 (5.90%) 26	1 / 133 (0.75%) 1	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	70 / 271 (25.83%) 147	38 / 133 (28.57%) 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 $\geq 150/\mu\text{L}$ 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>