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ORIGINAL RESEARCH

Efficacy and Safety of Masitinib in Corticosteroid-Dependent Severe Asthma: A Randomized Placebo-Controlled Trial

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Background: Masitinib is an oral tyrosine kinase inhibitor that selectively targets mast cell activity and platelet-derived growth factor receptor (PDGFR) signaling, both of which are implicated in various mechanisms of asthma pathogenesis.

Objective: Assessment of masitinib as an add-on to standard maintenance therapy as compared with placebo in the treatment of oral corticosteroid-dependent severe asthma.

Methods: We conducted a randomized (2:1), placebo-controlled study of masitinib (6 mg/kg/d) in adults with severe asthma uncontrolled by high dose inhaled corticosteroids and long-acting beta-adrenoreceptor agonists plus oral corticosteroids (OCS) (≥7.5 mg/d). No minimum baseline blood eosinophil count was specified. Following a protocol amendment, the primary endpoint was reduction of annualized severe asthma exacerbation rate adjusted for the overall time on treatment (SAER). Subgroup analysis according to yearly cumulative OCS intake was also performed, a higher OCS dose indicating more severe asthma that is harder to control.

Results: Following an average exposure of approximately 13 months, masitinib (n = 240) reduced the SAER by 35% relative to placebo (n = 115) (rate ratio (RR) 0.65 (95% CI [0.47–0.90]; P = 0.010)). For patients with eosinophil ≥150 cell/μL, masitinib (n = 181) reduced SAER by 38% relative to placebo (n = 87); RR 0.62 (95% CI [0.42–0.91]; P = 0.016). Benefit of masitinib was shown to increase in the most severely affected patients (OCS intake of >1000 mg/year), with a significant (P < 0.01) reduction in SAER of 50%–70%. Safety was consistent with the known masitinib profile.

Conclusion: Orally administered masitinib reduces the risk of asthma exacerbations in severe asthma patients, with an acceptable safety profile. Masitinib may potentially provide a new treatment option for oral corticosteroid-dependent severe asthma.

Keywords: asthma clinical trials, asthma medication, mast cells, tyrosine kinases, severe asthma

Plain Language Summary

Masitinib is an orally administered, small molecule drug that selectively targets mast cell activity and protein kinase signaling, which are implicated in various mechanisms of asthma pathogenesis. We conducted a randomized controlled trial of masitinib in 419 adults with severe asthma that was uncontrolled by standard treatments, including oral corticosteroids. Results showed that patients treated

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with masitinib had a lower risk of severe asthma exacerbations compared with those in a placebo-control group that did not receive masitinib. Benefit of masitinib was shown to increase in patients that required a higher oral corticosteroid dose, corresponding to the most severely affected patients. Safety results from this study were consistent with the known profile for masitinib, with no new safety concerns. Masitinib may provide a new effective and well-tolerated treatment option for oral corticosteroid-dependent severe asthma, including severe asthmatics that are ineligible to receive or in failure to registered biologics. This represents an entirely different treatment approach to that which is associated with currently registered Type-2 targeted biologics.

Introduction

Corticosteroid-dependent severe asthma, also referred to as severe uncontrolled asthma, is a difficult-to-treat asthma that remains uncontrolled despite adherence to maximal optimized therapy (eg, high dose inhaled corticosteroids with a second controller and/or systemic corticosteroids) or that worsens when high-dose treatment is decreased.[1,2] Patients can be broadly divided into two phenotypes, Type-2-high or Type-2-low, which have distinct inflammatory signatures, clinical characteristics and treatment management strategies. Monoclonal antibodies targeting type-2 cytokines are now an established therapeutic strategy for severe Type-2-high asthma; however, failure to respond or suboptimal response is still a relatively common occurrence and there are currently no targeted therapies available for severe Type-2-low asthmatics.[3] Overall, patients with severe asthma are still recognized as a population having a major unmet medical need with a high burden of costs and reduced quality-of-life.

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.[4–9] 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.[10] 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.[11] 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.[12] In preclinical models of asthma, masitinib significantly improved airway inflammation and lung mechanics in cats.[13] Likewise, imatinib, which is also an inhibitor of c-Kit and PDGFR, has been reported to effect airway smooth muscle thickening in mice, and airway hyperresponsiveness and mast cell counts in patients with severe asthma.[14,15] 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.[16]

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.

Methods

Trial Design and Oversight

Study AB07015 was a randomized, double-blind, placebo-controlled, Phase 3 trial, assessing the efficacy and safety of oral masitinib (6 mg/kg/day) in severe asthma uncontrolled despite the use of high dose inhaled corticosteroids (ICS) and long-acting beta-adrenoreceptor agonists (LABA) plus the need for daily oral corticosteroids (OCS). No minimum baseline blood eosinophil count was specified.

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, ie, the full exposure period incorporating both initial 36-week period plus blinded extension period (protocol version 9). Enhanced clinical relevance was further achieved by modifying the primary endpoint to assess only severe asthma exacerbations, as

opposed to moderate/severe asthma exacerbations, the latter of which being reclassified as a secondary endpoint (protocol version 10, after about 34% of patients had been randomized), and to perform a subgroup analysis based on patients with a baseline blood eosinophil count of ≥150 cell/μL (protocol version 12, after about 52% of patients had been randomized). Adjustments to sample size and statistical analysis were also required to accommodate these changes.

A 2-week, single-blind placebo treatment run-in period served as a reference for evaluating symptoms, rescue medication requirements, OCS dose stability, and study treatment compliance. Upon satisfactory completion of the run-in period, patients were randomly assigned (2:1) to receive masitinib at 6 mg/kg/day (administered orally as two daily intakes) or matching placebo for an initial treatment period of 36 weeks, which was followed by a blinded extension period during which patients continued their assigned treatments. During the initial treatment period, pulmonary function was assessed by spirometry every 4 weeks, while patient-reported outcome questionnaires were assessed at week-12 and every 8 weeks thereafter. During the blinded extension period, assessments were performed every 12 weeks.

Study AB07015 was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and national regulations. An independent data monitoring committee periodically reviewed blinded patient safety and efficacy data. Relevant health authorities and local ethics committees or institutional review boards (including the Comité de Protection des Personnes Ouest VI, Centre Hospitalier Universitaire Morvan, Brest, France) approved the study protocol and amendments. All patients provided written informed consent before trial participation. Data were collected by study investigators and analyzed by the sponsor. This trial was registered to the European Clinical Trials Database (EudraCT #2010-020803-63) prior to enrollment of the first patient on 26 January, 2011. Registration to the ICMJE-compliant ClinicalTrials.gov database (#NCT01449162) occurred about 8 months later, following recruitment of 6% (27/419) of the study population. No protocol amendment occurred during this period and all data remained blinded to patients, physicians, and study staff.

Patients and Study Measurements

Primary analysis was performed on patients with severe asthma in a cohort referred to hereafter as the "primary population". Eligible patients were aged 18–75 years with severe uncontrolled asthma despite being treated with high-dose ICS/LABA plus OCS at ≥7.5 mg/day (prednisone or equivalent) for at least 3 months prior to screening, with no significant change in the regular asthma medication and no severe asthma exacerbation for at least 4 weeks prior to screening. Additionally, patients had experienced a minimum of two exacerbations in the previous year (including one severe asthma exacerbation as per protocol definition), had a prebronchodilator forced expiratory volume in 1 s (FEV_1) of 35%−80% predicted normal value (demonstrated at least 6 hours after short-acting β2-agonist or 12 hours after LABA), were non-smokers for at least 1 year and with a prior tobacco consumption <10 pack-years, and uncontrolled asthma symptoms in the week prior to screening (defined as at least 2 of the following ACQ items: daytime symptoms at least twice/week, need for reliever medication at least twice/week, any nighttime symptoms or any activity limitation). Patients who had continuous exposure to allergens or other asthma trigger factors were excluded, as were patients receiving OCS at <7.5 mg/day. Sensitivity analyses were performed in the intention-to-treat (ITT) population and "full analysis set" (FAS), the latter cohort comprising all patients with documented OCS treatment at baseline, including randomized patients that did not comply with the aforementioned protocol amendment (ie, patients with baseline OCS dose <7.5 mg/day). The safety dataset comprised all patients that received at least one dose of study medication (Figure 1).

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. 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. Assessment of pulmonary function was performed according to change from baseline in prebronchodilator FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio. 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);[18] and quality-of-life assessment was according to change from baseline in the Asthma Quality of Life Questionnaire score (AQLQ).[19]

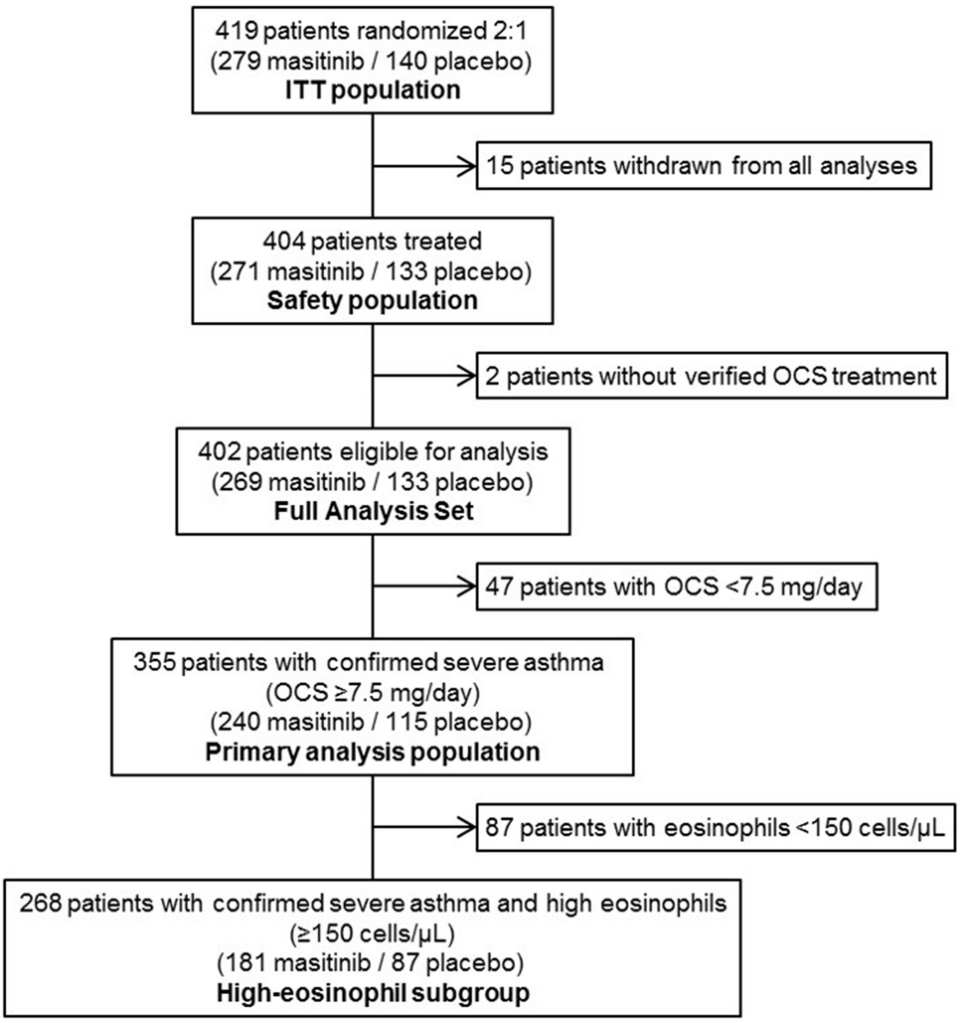

Figure 1 Study populations used for analysis. The intention-to-treat (ITT) population included a total of 419 patients. Following study site audits, 15 patients were excluded from the safety population and efficacy analysis datasets due to critical violations of Good Clinical Practice guidelines.
Abbreviation: OCS, oral corticosteroid.

Patients were monitored for safety from the date of informed consent until 28 days after discontinuing the study drug. Adverse events (AE) were coded according to the MedDRA dictionary (version 20), and severity of AE was graded according to Common Terminology Criteria for Adverse Events (version 4). In the event of severe toxicity related to masitinib, treatment interruption or dose reduction was permitted according to predefined criteria.

Statistical Analysis

We estimated that masitinib would reduce the SAER by 33% relative to placebo (0.08 versus 0.12 severe exacerbations per month, respectively). Detection of this difference, with a two-sided 0.025 significance level and a power of 80% in the primary population, would require a minimum sample size of 339 patients (226 and 113 in the masitinib and placebo arms, respectively).

Patients were centrally randomized using a computerized central randomization system and minimization method according to the covariates of country, OCS dose at baseline (above or below 15 mg/day), concomitant asthma control treatment, and eosinophil count (above or below 150 cells/µL).

Estimation of between-group difference in the SAER (primary endpoint) was calculated using a Poisson regression model (log-link function and Poisson distribution) with factors of age, baseline FEV_1, annual exacerbation rate, and above-mentioned stratification covariates. 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. For the analysis of secondary endpoints, changes from baseline over 96 weeks in ACQ-7, AQLQ, FEV_1, FVC, and FEV_1/FVC ratio 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). For FEV_1, FVC, FEV_1/FVC and AQLQ, a positive between-group difference favors masitinib; whereas for ACQ-7, a negative value favors masitinib. Sensitivity analyses and secondary endpoints were tested at the 0.05 significance level. All analyses and reporting procedures were performed using SAS version 9.4 (SAS Institute. Cary, NC).

Results

Patients

A total of 419 patients (279 and 140 in the masitinib and placebo arms, respectively), from 90 study sites in 18 countries (Supplementary Table 1), were randomized (ITT population) (Figure 1). Of these, 404 patients received at least one dose of study medication (271 masitinib and 133 placebo) and were eligible for safety analysis, and 402 patients (269 masitinib and 133 placebo) were included in the FAS dataset, which comprised all patients with documented OCS treatment at baseline (including 47 patients who were randomized prior to the aforementioned protocol amendment with a baseline OCS dose <7.5 mg/day). A total of 355 patients (240 masitinib and 115 placebo) were included in the primary population, of which 268 patients (181 masitinib and 87 placebo) were included in the eosinophil (≥150 cell/μL) subgroup (Figure 1).

Baseline characteristics were consistent with severe uncontrolled asthma and were balanced between treatment-arms (Table 1). Among patients receiving at least one dose of study medication, 154 (57%) patients from the masitinib arm and 84 (63%) from the placebo arm completed the initial (36-week) treatment period, with 130 (48%) and 70 (53%), respectively, continuing treatment during the blinded extension phase (Supplementary Table 2). Overall duration of exposure was an average of 13.2 ± 12.0 versus 13.1 ± 9.7 months, respectively, with 84 (31%) and 43 (32%) of patients continuing to receive treatment until data cutoff (23 October 2019). Treatment exposure and patient disposition were therefore similar between treatment-arms throughout the study.

Table 1 Baseline Patient Characteristics According to Intention-to-Treat Population, Primary Population, and Eosinophil (≥150 Cell/μL) Subgroup Datasets. Treatment-Arms Were Balanced for All Baseline Parameters

Characteristic (mean ± SD)[a]	ITT Population		Primary Population		Eosinophil Subgroup	
	Masitinib (N=279)	Placebo (N=140)	Masitinib (N=240)	Placebo (N=115)	Masitinib (N=181)	Placebo (N=87)
Age, years	54.3 ± 12.1	51.4 ± 11.2	53.8 ± 12.0	51.5 ± 11.5	53.1 ± 11.9	50.4 ± 11.8
Women, n (%)	179 (64%)	90 (64%)	149 (62.1%)	76 (66.1%)	110 (60.8%)	61 (70.1%)
White or North African, n (%)	181 (65%)	86 (61%)	167 (69.6%)	78 (67.8%)	126 (69.6%)	58 (66.7%)
Incidence of asthma exacerbations (previous year)[b]	2.3 ± 0.9	2.1 ± 0.7	2.2 ± 0.9	2.1 ± 0.7	2.3 ± 0.9	2.1 ± 0.7
Stable dose of oral corticosteroid, mg/day	12.2 ± 8.8	12.0 ± 7.6	13.2 ± 9.0	13.2 ± 7.8	13.1 ± 9.50	13.5 ± 8.24
Long-acting beta-adrenoreceptor agonist therapy, n (%)	222 (80%)	107 (76%)	198 (82.5%)	93 (80.9%)	153 (84.5%)	72 (83.8%)
FEV_1, L	1.5 ± 0.6	1.6 ± 0.5	1.5 ± 0.5	1.6 ± 0.5	1.5 ± 0.6	1.7 ± 0.5
FVC, L	2.4 ± 0.8	2.5 ± 0.8	2.3 ± 0.7	2.4 ± 0.8	2.4 ± 0.8	2.6 ± 0.8
FEV_1/FVC, %	64.1 ± 17.3	66.5 ± 15.8	63.2 ± 16.6	65.1 ± 15.6	64.7 ± 17.0	64.4 ± 15.5
ACQ-7 score	3.0 ± 0.8	2.9 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	2.9 ± 0.9	2.9 ± 1.0
AQLQ score	4.0 ± 1.0	4.0 ± 1.1	3.9 ± 1.0	4.0 ± 1.1	3.9 ± 1.0	4.0 ± 1.1
Former smoker, n (%)	45 (16%)	18 (13%)	42 (18%)	16 (14%)	32 (18%)	11 (13%)
Eosinophils, cells/μL	290 ± 300	310 ± 300	370 ± 376	360 ± 303	460 ± 390	450 ± 301
Patients with eosinophil count ≥150 cells/μL, n %	213 (76%)	107 (76%)	181 (75%)	87 (76%)	181 (100%)	87 (100%)

Notes: [a]Unless otherwise stated. N: Number of patients in population. n: Number of patients with characteristic. [b]Inclusion criterion that patients had experienced a minimum of two exacerbations in the previous year (including one severe asthma exacerbation as per protocol definition).
Abbreviation: SD, standard deviation.

Table 2 Summary of Primary Endpoint (SAER) and Associated Sensitivity Analyses

	Exposure	SAER	Rate Ratio [95% CI]	Reduction[a]	P-value
Primary population (primary analysis)					
Masitinib (240)	13.7 months	0.34	0.65 [0.47, 0.90]	35%	0.010
Placebo (115)	13.8 months	0.48			
Eosinophil (≥150 cell/μL) subgroup (primary analysis)					
Masitinib (181)	13.2 months	0.34	0.62 [0.42, 0.91]	38%	0.016
Placebo (87)	13.4 months	0.51			
Intention-to-treat (sensitivity analysis)					
Masitinib (279)	13.1 months	0.34	0.67 [0.49, 0.93]	33%	0.016
Placebo (140)	12.8 months	0.44			
Full analysis set (sensitivity analysis)					
Masitinib (269)	13.2 months	0.34	0.67 [0.49, 0.92]	33%	0.015
Placebo (133)	13.1 months	0.45			

Notes: n: number of patients in analysis. [a]Reduction in the severe asthma exacerbation rate relative to placebo.
Abbreviations: SAER, severe asthma exacerbation rate (annualized rate adjusted for the overall time on treatment); CI, confidence interval.

Primary Efficacy Analysis

In the primary population, masitinib showed a statistically significant 35% reduction in the SAER relative to placebo, with a rate ratio of 0.65 (95% CI [0.47–0.90]; P = 0.010) (Table 2). This positive treatment effect was corroborated by predefined sensitivity analyses in the ITT and FAS datasets, with a significant 33% reduction in SAER for both (Table 2). For the eosinophil subgroup (sequential second step of the primary analysis), masitinib showed a significant 38% reduction in the SAER relative to placebo with a rate ratio of 0.62 (95% CI [0.42–0.91]; P = 0.016) (Table 2).

Because greater cumulated (long-term) use of OCS is indicative of more severe asthma that is harder to control, a post-hoc sensitivity analysis was performed on the primary endpoint (ie, reduction of annualized severe asthma exacerbation rate adjusted for the overall time on treatment) with cohorts according to cumulative OCS intake (Supplementary Table 3). The magnitude of masitinib treatment effect is correlated with increasing disease severity (ie, higher cumulated use of OCS). For severe asthma patients receiving an annualized cumulative OCS intake of >500, >1000, and >1500 mg/year, masitinib showed a significant reduction in SAER compared with placebo of 41% (P < 0.01), 51% (P < 0.01), and 57% (P = 0.02), respectively. A similar but more pronounced treatment effect was observed in the eosinophil subgroup, with corresponding reductions of 49% (P < 0.01), 71% (P < 0.001), and 72% (P < 0.01), respectively.

An additional post-hoc sensitivity analysis was also performed using the European Respiratory Society and American Thoracic Society (ERS/ATS) task force recommended definition of severe exacerbations for clinical trials;[20,21] ie, an increase in stable maintenance dose of OCS for at least 3 days, wherein said increase was defined for the purpose of this analysis as a dose of at least 40 mg/day (prednisone-equivalent).[22] Masitinib showed a statistically significant reduction compared with placebo in the rate of severe asthma exacerbations according to this definition, across all time points tested (ie, overall time on treatment, weeks 36, 48, 52, 72, and 96) (Supplementary Table 4). In the primary efficacy population, there was a significant 39% to 54% reduction, with respective rate ratios of 0.61 (95% CI [0.38–0.96]; P = 0.033) to 0.46 (95% CI [0.31–0.68]; P = 0.0001). For the eosinophil (≥150 cell/μL) subgroup there was a significant 44% to 53% reduction, with respective rate ratios of 0.56 (95% CI [0.32–0.97]; P = 0.040) to 0.47 (95% CI [0.28–0.79]; P = 0.004), and for the FAS dataset there was a significant 40% to 53% reduction, with respective rate ratios of 0.60 (95% CI [0.38–0.93]; P = 0.023) to 0.47 (95% CI [0.32–0.68]; P < 0.0001).

Secondary Endpoint Analyses

Masitinib showed a statistically significant 36% reduction in the moderate/severe annualized rate of asthma exacerbations relative to placebo for the primary population, with corresponding rate ratio of 0.64 (95% CI [0.48, 0.84]; P = 0.001). Likewise, for the eosinophil (≥150 cell/μL) subgroup, with a significant 31% reduction and rate ratio of 0.69 (95% CI [0.49, 0.95]; P = 0.025) (Supplementary Table 5).

Table 3 Summary of Secondary Efficacy Endpoints (Changes in Asthma Characteristics from Baseline Over 96 Weeks, Mixed Model of Repeated Measures Methodology)

Endpoint	Treatment	LSM	ΔLSM [95% CI]	P-value
Primary population (Masitinib, N=240; Placebo, N=115)				
ΔFEV_1, L	Masitinib Placebo	0.10 0.03	0.07 [0.01, 0.12]	0.016
ΔFVC, L	Masitinib Placebo	0.01 −0.03	0.04 [−0.05, 0.12]	0.386
$\Delta FEV_1/FVC$	Masitinib Placebo	1.9 0.3	1.6 [0.0, 3.1]	0.049
ΔACQ-7	Masitinib Placebo	−0.54 −0.32	−0.21 [−0.43, 0.00]	0.050
ΔAQLQ	Masitinib Placebo	0.56 0.59	0.03 [−0.36, 0.30]	0.850
Eosinophil (≥150 cell/μL) subgroup (Masitinib, N=181; Placebo, N=87)				
ΔFEV_1, L	Masitinib Placebo	0.16 0.05	0.11 [0.05, 0.17]	<0.001
ΔFVC, L	Masitinib Placebo	0.08 −0.02	0.10 [0.01, 0.20]	0.032
$\Delta FEV_1/FVC$	Masitinib Placebo	2.9 1.3	1.6 [−0.1, 3.4]	0.071
ΔACQ-7	Masitinib Placebo	−0.50 −0.33	−0.17 [−0.41, 0.07]	0.160
ΔAQLQ	Masitinib Placebo	0.45 0.57	−0.12 [−0.45, 0.22]	0.492

Note: For ACQ-7, a negative value indicates a favorable effect of masitinib.
Abbreviations: LSM, least-squares mean change from baseline; ΔLSM, difference in least-squares mean change between masitinib and placebo; CI, confidence interval.

Evaluation of pulmonary function (FEV_1, FVC, and FEV_1/FVC ratio) over 96 weeks (MMRM methodology) also corroborated the observed masitinib treatment effect, with statistical significance reached in FEV_1 (0.07 L; P = 0.016) and in FEV_1/FVC ratio (1.6%; P = 0.049) for the primary population (Table 3). This advantage was further improved for the eosinophil subgroup, with significance reached in both FEV_1 (0.11 L; P < 0.001) and FVC (0.1 L; P = 0.032), while the FEV_1/FVC ratio was maintained at 1.6% (P = 0.071).

A statistically significant difference in favor of masitinib was reached in ACQ-7 for the primary population (P = 0.050), with a decrease in score from baseline of 0.54 points and a between-group difference of 0.21 (Table 3).[23] There was no discernable difference between treatment-arms in AQLQ.

Safety

The overall rates of adverse events (AE), severe AE, and serious non-fatal AE (SAE) were similar for both treatment-arms with the exception of patient discontinuation rate due to treatment-related AE, for which masitinib had a greater incidence (relative risk = 3.0) (Table 4). Adverse events (MedDRA preferred terms, regardless of severity) occurring more commonly for masitinib compared with placebo were vomiting, diarrhea, maculopapular rash, upper abdominal pain, nausea, and various asymptomatic abnormal laboratory results (Supplementary Table 6). No new masitinib-related safety signals were detected, and there was no evidence for increased risk of infection relative to placebo. During the

Table 4 Summary of Adverse Events Over the Study Period (Safety Population)

Event	Masitinib (N=271)	Placebo (N=133)	Δ[M/P]
Adverse Event (any grade)	83.4% (226)	82.0% (109)	1.0
Adverse Event leading to death	1.1% (3)	0.8% (1)	1.4
Serious adverse event (non-fatal)	17.7% (48)	16.5% (22)	1.1
Severe adverse event	57.5% (130)	56.0% (61)	1.0
TEAE leading to permanent discontinuation	14.0% (38)	6.8% (9)	2.1
TRAE leading to permanent discontinuation	11.4% (31)	3.8% (5)	3.0
[a]Mild/Moderate	7.0% (19)	3.0% (4)	
[a]Severe	4.4% (12)	0.8% (1)	

Notes: [a]Treatment-related adverse event according to severity.
Abbreviations: Δ[M/P], masitinib to placebo reporting rate ratio; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

study, there were 3 deaths (1.1%) in the masitinib group (pneumonia, ischemic stroke, pulmonary embolism), and 1 death (0.8%) in the placebo group (cardiopulmonary failure), none of which were deemed related to study treatment.

Discussion

Despite numerous drugs now being marketed for the treatment of severe asthma (ie, monoclonal antibody therapies targeting interleukin (IL)-5 and IL-4/IL-13 cytokine pathways), an unmet need persists for many patients. This includes severe Type-2-low asthmatics (estimated to be about 50% of the population), as well as severe Type-2-high asthmatics with sub-optimal response to anti-interleukin therapies (estimated to be as high as 50% for OCS-dependent asthmatics receiving the anti-IL-5 monoclonal antibodies of either mepolizumab or reslizumab).[3,5,24]

Efficacy results from study AB07015 significantly favored oral masitinib over placebo regarding reduced risk of severe asthma exacerbations, improved lung function and improved asthma control. The rate of severe asthma exacerbations was reduced by 35% relative to placebo in the primary population, rising to an improvement of at least 50% in the most severely affected patients (ie, those with a cumulative OCS intake of >1000 mg/year). A positive treatment effect was also evident for masitinib in terms of improved lung function, as measured by FEV_1, with a between-group difference of 0.07 and 0.11 L for the primary population and eosinophil subgroup, respectively. Considering anti-IL-5 therapies for severe asthma, these are collectively associated with reduced clinically significant asthma exacerbation rates of approximately 50%, for example, subcutaneous mepolizumab (55%), intravenous mepolizumab (47%), intravenous reslizumab (58%), and subcutaneous benralizumab (38%).[25] Likewise, in severe eosinophilic asthmatics, intravenous mepolizumab, subcutaneous mepolizumab, intravenous reslizumab, and subcutaneous benralizumab showed a FEV_1 effect size of 0.08, 0.11, 0.12, and 0.13 L, respectively.[25] We note, however, that comparison between masitinib AB07015 results and other treatments for severe asthma is complicated by differences in study design (eg, the use of overall person-time exposure), patient inclusion criteria and pharmacological action.

Masitinib has therefore achieved the main therapeutic objectives for severe asthma and notably does so through an entirely different mechanism to that which is associated with Type-2 targeted biologics. Indeed, masitinib's observed benefit is not associated with a reduction in eosinophil levels, with levels remaining relatively stable throughout 36 weeks of treatment as evidenced from a timeseries of change in blood eosinophil concentration relative to baseline in the eosinophil subgroup (Supplementary Figure 1).

Safety results from this study were consistent with the known profile for masitinib (eg, diarrhea, vomiting, nausea, rash, and dyspepsia), and there were no new safety concerns. Regarding the higher rate of patient discontinuation due to a treatment-related AE in the masitinib arm as compared with placebo, a large proportion (60%) of this was attributable to AEs of mild or moderate severity that can be efficiently managed by dose reduction or temporary interruption.

It is possible that the aforementioned protocol amendments could limit the interpretation of results; however, predefined primary endpoint sensitivity analyses in the ITT and FAS populations (the latter of which included patients

with a baseline OCS dose <7.5 mg/day) were both convergent with data from the primary population. Likewise, for assessment of the moderate/severe asthma exacerbation rate, the implication being that the study's positive outcome cannot therefore be attributed to these changes. 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. However, should masitinib's predominant mechanism of action in severe asthma be via modulation of steroid insensitive pathways, as is suspected, then complete cessation of OCS use is possibly infeasible.

Conclusions

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.

Abbreviations

ACQ-7, 7-question version of the Asthma Control Questionnaire; AE, adverse event; AQLQ, Asthma Quality of Life Questionnaire score; EudraCT, European Clinical Trials Database; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GCP, Good Clinical Practice; ICS, inhaled corticosteroids; IL, interleukin; ITT, intention-to-treat; LABA, long-acting beta-adrenoreceptor agonists; MMRM, multivariate mixed model of repeated measures; OCS, oral corticosteroids; SAE, serious non-fatal adverse event; SAER, severe asthma exacerbation rate (annualized rate adjusted for the overall time on treatment).

Clinical Trial Registration

Study AB07015 was registered to the European Clinical Trials Database (EudraCT #2010-020803-63) prior to enrollment of the first patient on 26 January, 2011. For example, the record for the Bulgarian national competent authority (Bulgarian Drug Agency) was first entered in the EudraCT database on 20th January 2011, and the record for the Hungary national competent authority (National Institute of Pharmacy) was first entered in the EudraCT database on 6th December 2010, at least 2 months before the first participant was randomized to the study (9th February 2011). Registration to the ClinicalTrials.gov database (#NCT01449162) occurred about 8 months later, following recruitment of 6% (27/419) of the study population.

Data Sharing Statement

Masitinib is under clinical investigation and has not yet been approved in any sought-after indication by any health authority worldwide. As such, there is no plan for data-sharing at this point in time.

Ethics Approval and Informed Consent

Study AB07015 was conducted according to the Declaration of Helsinki, Good Clinical Practice (GCP) guidelines, and national regulations. An independent data monitoring committee periodically reviewed blinded patient safety and efficacy data. Trial conduct was overseen by local ethics committees, who approved the study protocol and amendments. All patients provided written informed consent before trial participation.

Consent for Publication

All authors have read and approved the manuscript, which they have collectively written in its entirety.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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