Masitinib Significantly Decreases the Rate of Asthma Exacerbations in Patients with Severe Asthma Uncontrolled by Oral Corticosteroids: A Phase 3 Multicenter Study

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Rationale: Masitinib is a small molecule drug targeting KIT, LYN and FYN. These kinases are involved in the function of dendritic, epithelial, and mast cells, which are implicated in various mechanisms of asthma pathogenesis. Proof-of-concept that masitinib may improve control of steroid-dependent asthma was previously demonstrated in a small study. Objectives: Study AB07015 (NCT01449162) evaluated oral masitinib (6 mg/kg/day) treatment of severe persistent asthma remaining uncontrolled by oral corticosteroids (OCS) (>5mg/day) and high-dose ICS/LABA. Methods: Randomized (2:1), double-blinded, placebo-controlled trial. Following a 2-week single-blind, placebo run-in period, eligible adult patients were treated for 36 weeks (with possible blinded extension until at least week-96). Primary endpoint was reduction of annualized severe asthma exacerbation rate for overall exposure (including extension period), with a severe exacerbation event defined as worsening asthma leading to an increase from stable maintenance dose of corticosteroids for ≥3 days or hospitalization. A key predefined subgroup analysis was assessment of patients with initial eosinophil count of ≥150 cells/µL. Secondary endpoints included FEV1, FVC, AQC and AQLQ (see table). Safety was assessed in patients that received at least one dose of study drug, including those receiving low-dose (≤5mg/day) OCS who were excluded from the primary analysis following a protocol amendment. Results:355 patients were included in the primary analysis population (240 masitinib, 115 placebo) and 404 patients in the safety population (271 masitinib, 133 placebo). Baseline characteristics and average exposure times (approximately 60 weeks) were well-balanced across treatment-arms. Masitinib significantly reduced severe asthma exacerbation rate by 35% compared with placebo

(rate ratio 0.64 [95%CI 0.48-0.84; p=0·0014]). This treatment-effect was corroborated by sensitivity analyses, including the Full Analysis Set population (n=402), and the secondary endpoints of reduction in moderate/severe asthma exacerbation rate and change from baseline to week-96 in pulmonary function and asthma control (see table). A significant reduction in severe exacerbations of 38% (rate ratio 0.69 [95%CI 0.49-0.95; p=0·0249]) was seen for the eosinophil ≥150 cells/µL subpopulation (see table). The rate of patients presenting at least one adverse events (AE) was 83.4% (226/271) for masitinib versus 82.0% (109/133) for placebo. Likewise, the rates for serious AE and severe AE were, respectively, 17.7% (48/271) versus 16.5% (22/133), and 48.0% (130/271) versus 45.9% (61/133). Conclusions: Masitinib, a first-in-class tyrosine kinase inhibitor targeting mast cell activity in severe asthma patients, demonstrated a positive benefit/risk ratio over a sustained period and may provide a new treatment option in severe asthma, irrespective of baseline eosinophil level.

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