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Masitinib in severe asthma: Results from a randomized, phase 3 trial

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On behalf of the AB07015 Study Group

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Introduction

Masitinib is a first-in-class oral tyrosine kinase inhibitor in severe asthma

- Masitinib selectively targets mast cell activity (c-Kit, LYN, FYN) and is also a potent inhibitor of PDGFR
- Strong scientific rationale to target mast cells in severe asthma
- PDGFR signaling associated with airway remodeling in severe asthma
- Masitinib activity demonstrated via preclinical mouse models of asthma
  - Significant decrease of airway hyper-responsiveness
  - Significant decrease of eosinophils recruitment
- Clinical proof-of-concept in cat [Lee-Fowler, 2012] and human [Humbert, 2009] studies

Study AB07015 Design

Study AB07015 evaluated masitinib 6.0 mg/kg/day in severe asthma uncontrolled by OCS with no restriction on baseline eosinophil level

- Randomized (2:1), double-blinded, placebo-controlled.
- Patient with severe asthma, uncontrolled by OCS (≥7.5 mg/d), both high (≥150 cells/µL) and low (<150 cells/µL) eosinophils
- Timing: 2-week run-in (blinded placebo) → 36-week treatment period [W0–W36] → possible blinded extension
- Primary endpoint: Reduction of annualized severe asthma exacerbation rate for overall exposure
- If significant, sequential analysis in pts with severe asthma and eosinophil count ≥150 cells/µL (fixed hierarchical procedure with 5% α for each analysis)

Study AB07015 Primary Endpoint Results

Masitinib significantly decreased the rate of severe asthma exacerbations in patients with severe asthma uncontrolled by OCS, regardless of eosinophil level

Primary Analysis (Severe Asthma)

Annualized severe asthma exacerbation rate

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (240)	1.14	0.34	0.65 [0.47, 0.90]	35%	0.0103
PBO (115)	1.15	0.48			

Sequential Analysis (Severe Asthma with High Eosinophil)

Annualized severe asthma exacerbation rate

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (181)	1.10	0.34	0.62 [0.42, 0.91]	38%	0.0156
PBO (87)	1.12	0.51			

Exp: Exposure in years. RR: rate ratio. MAS: Masitinib 6.0 mg/kg/d. PBO: Placebo.

- Average exposure (approx. 60 weeks) was well-balanced across treatment-arms
- Sensitivity analysis on ITT population was similarly significant (-33%, p-value=0.0156)

Sensitivity Analysis on Primary Endpoint

Benefit of masitinib was greatest in patients who had higher cumulated use of OCS (indicative of more severe asthma that is harder to control)

Sensitivity Analysis (Severe Asthma)

Annualized severe asthma exacerbation rate

Cumulative OCS >500 mg

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (161)	1.15	0.34	0.59 [0.39, 0.88]	**41%**	**0.0092**
PBO (82)	1.20	0.55			

Cumulative OCS >1000 mg

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (120)	1.16	0.26	0.49 [0.29, 0.82]	51%	0.0060
PBO (66)	1.27	0.53			

Sensitivity Analysis (Severe Asthma with High Eosinophil)

Annualized severe asthma exacerbation rate

Cumulative OCS >500 mg

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (127)	1.12	0.32	0.51 [0.32, 0.82]	49%	0.0049
PBO (60)	1.16	0.60			

Cumulative OCS >1000 mg

	Exp	Rate	RR [95%CI]	Reduction	P-value
MAS (92)	1.11	0.22	0.29 [0.15, 0.57]	**71%**	**0.0003**
PBO (46)	1.27	0.55			

Exp: Exposure in years. RR: rate ratio. MAS: Masitinib 6.0 mg/kg/d. PBO: Placebo. OCS oral corticosteroid.

Study AB07015 Safety Results

Safety was consistent with the known profile for masitinib

Summary of Adverse Events (AE) - Safety Population (n = 404)

	Masitinib % (n)	Placebo % (n)	Difference
At least one AE	**83.4%** (226/271)	**82.0%** (109/133)	**+1.4%**
At least one severe AE	**48.0%** (130/271)	**45.9%** (61/133)	**+2.1%**
At least one serious AE (non-fatal)	**17.7%** (48/271)	**16.5%** (22/133)	**+1.2%**

- No new safety signals were observed

Conclusions

Study AB07015 demonstrated efficacy in a difficult to treat population

- **Study AB07015 population is distinct from other asthma trials**
  - Patients dependent on OCS (100% receiving high dose OCS therapy) and no weaning
  - Patients were treated irrespective of baseline eosinophil count
  - Evaluated over a long period of time (approx. 60 weeks)

- **Significant reduction in severe asthma exacerbation rate**
  - -35% reduction in primary analysis population irrespective of baseline eosinophil level
  - -38% reduction in subgroup with baseline eosinophil level ≥150 cells/µL
  - Greatest benefit (-41% to -71%) for patients who had the most severe asthma

- **Masitinib may therefore provide a new treatment option for severe asthma uncontrolled by OCS**
  - Biologic-ineligible patients (e.g. eosinophil count of ≤300 cells/µL)
  - Patients in failure to biologics

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