Efficacy and safety of masitinib in severe asthma: Results from study AB07015

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In relation to this presentation, I declare the following, real or perceived conflicts of interest:

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

Masitinib Simultaneously Targets Independent Mechanisms Of Asthma Pathophysiology

- **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**
  - Release of pro-inflammatory mediators
  - Modulates airway smooth muscle (ASM) cell function
  - Induces airway hyper-responsiveness
- **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**

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

Study design

- Randomized (2:1), double-blinded, placebo-controlled.
- Patient with severe asthma, uncontrolled by OCS, 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

Main inclusion criteria

- Oral corticosteroid (OCS) dose ≥7.5 mg daily for at least 3 months prior to screening visit
- Patient with history of severe asthma ≥1 year:
  - baseline FEV1 ≥35% to <80%
  - ≥2 asthma exacerbations within prior year
  - ≥2 uncontrolled asthma symptoms within prior 2 weeks

Primary analysis

- Endpoint: Reduction of annualized severe asthma exacerbation rate for overall exposure
- Population: Patients with severe asthma (OCS ≥7.5 mg/d)
- If significant, sequential analysis in patients with severe asthma with eosinophil count ≥150 cells/µL (multiplicity addressed using a fixed hierarchical procedure with 5% α for each analysis)

2 Summary of study AB07015 populations

	MASITINIB	PLACEBO	TOTAL
Overall population	**279**	**140**	**419**
Safety Assessment			
SAF	**271**	**133**	**404**
Efficacy Assessment			
Full Analysis Set (FAS)	**269**	**133**	**402**
Severe Asthma (OCS ≥ 7.5 mg/d)	**240**	**115**	**355**
Severe Asthma with High Eosinophil (OCS ≥ 7.5 mg/d and eosinophil count ≥150 cells/µL)	**181**	**87**	**268**

Difference in SAF and FAS due to exclusion of patients with no OCS intake at baseline

3 Masitinib significantly decreases the rate of severe asthma exacerbations in patients with severe asthma uncontrolled by oral corticosteroids, 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) well-balanced across treatment-arms**
- **The analyses in ITT and in FAS were positive (-33%, p-value=0.0156 and -33%, p-value=0.0145, respectively).**
- **Therefore, no impact on study outcome of patients with OCS intake <7.5 mg/d.**

3 Benefit of masitinib was greatest in patients who had higher cumulated use of OCS

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

	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

	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.

- **Higher cumulative prednisone-equivalent OCS dose is indicative of more severe asthma that is harder to control**

3 Safety was consistent with known masitinib profile

Summary of Adverse Events (AE) - Safety Population

	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%**

- **Safety for the overall population (n=404) was consistent with the known profile for masitinib**
- **No new safety signals observed**

4 Study AB07015 demonstrated efficacy in a difficult to treat population

- **Study AB07015 population 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 (severe asthma 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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