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

P. Chanez[1], E. Israel[2], G. Ursol[3], O. Korzh[4], V. Deshmukh[5], L. Kuryk[6], M. Nortje[7], O. Godlevska[4], G. Devouassoux[8], E. Khodosh[9], O. Hermine[10], L. Davidescu[11] on behalf of the AB07015 Study Group

[1]Aix Marseille Université, Marseille, France. [2]Brigham and Womens Hosp, Boston, MA, United States. [3]Medical and Diagnostic Center "Acinus", Kropyvnytskyi, Ukraine. [4]Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine. [5]Respira Hospital, Nagpur, India. [6]National Academy of Medical Sciences of Ukraine, Kiev, Ukraine. [7]Moriana Clinical Research, Brandfort, South Africa. [8]Hôpital de la Croix Rousse, Lyon, France. [9]City Clinical Hospital #13, Kharkiv, Ukraine. [10]Imagine Institute, INSERM UMR 1163 and CNRS ERL 8254, Hôpital Necker; AB Science, Paris, France. [11]University of Medicine and Pharmacy, Oradea, Romania.

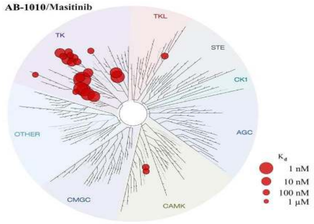
Background, Objectives & Design of Study AB07015

Masitinib Simultaneously Targets Independent Mechanisms Of Severe Asthma Pathophysiology

Masitinib targets mast cell activity (c-Kit, LYN, FYN) and is also a potent inhibitor of PDGFR

Masitinib's high kinase selectivity limits risk of off-target toxicity [1,2] such as infectious complications

Target	IC_{50} [nM]	Kd [µM]
c-Kit	200	0.008
FYN	240	0.14
LYN	225	0.061
PDGFR-α	50	0.025
PDGFR-β	110	0.008



- **Strong scientific rationale to target mast cells**
  - Release of pro-inflammatory mediators
  - Modulates airway smooth muscle cell function
  - Induces airway hyper-responsiveness
- **PDGFR signaling associated with airway remodeling**

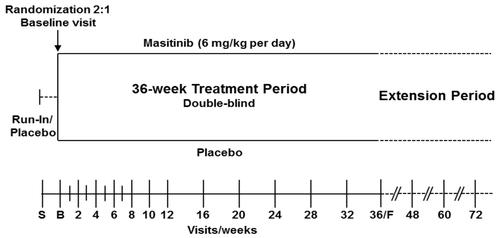
Masitinib activity in mouse models of asthma

- Significant decrease of airway hyper-responsiveness
- Significant decrease of eosinophils recruitment

Clinical proof-of-concept in cat [3] and human [4] studies

Study AB07015 evaluated masitinib 6.0 mg/kg/d in severe asthma uncontrolled by OCS

- **Randomized (2:1), double-blinded, placebo-controlled**
- **Patient with severe asthma, uncontrolled by oral corticosteroid (OCS) dose ≥7.5 mg/d**
- **High (≥150 cells/µl) and low (<150 cells/µl) eosinophils**
- **2-week run-in (blinded placebo) → 36-week treatment period [W0–W36] → possible blinded extension**



- **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 endpoint was reduction of annualized severe asthma exacerbation rate for overall exposure**
  - Severe exacerbation defined as worsening asthma leading to an increase from stable maintenance dose of corticosteroids for ≥3 days or hospitalization.

Results and Conclusion

Masitinib significantly decreases the rate of severe asthma exacerbations (SAER) in patients with severe asthma uncontrolled by OCS, regardless of eosinophil level

- Primary analysis pop. (240 MAS vs 115 PBO)
- Average exposure (approx. 60 weeks)
- Well-balanced across treatment-arms

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.

- **Masitinib significantly reduced SAER by 35% relative to placebo (p=0.0103)**
- **Subgroup analysis (eosinophil ≥150 cells/µL) showed a significant 38% reduction in SAER (p=0.0156)**
  - Corroborated by sensitivity analyses
- **Benefit of masitinib was greatest in pts with higher cumulated use of OCS**
  - Higher cumulative OCS indicates more severe asthma that is harder to control
- **Cumulative OCS intake of >1000 mg, masitinib significantly reduced SAER by 71% in the eosinophil subgroup (p=0·0003)**

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.

- **Safety consistent with known masitinib profile; no new signals**

At least one	Masitinib	Placebo	Diff (M-P)
Adverse Event (AE)	83.4% (226/271)	82.0% (109/133)	+1.4%
Severe AE	48.0% (130/271)	45.9% (61/133)	+2.1%
Serious AE (non-fatal)	17.7% (48/271)	16.5% (22/133)	+1.2%

Masitinib may provide a new treatment option for severe asthma uncontrolled by OCS

- **Positive benefit/risk ratio over a sustained period, irrespective of baseline eosinophil level**
- **Benefits greatest in patients with the highest OCS dose dependency**
- **Potential new treatment for biologic-ineligible patients (eosinophil ≤300 cells/µL) or those in failure to biologics**

References: [1] Dubreuil 2009, PLoSONE;4(9):e7258. [2] Davis 2011, Nat Biotechnol;29(11):1046; [3] Lee-Fowler 2012, Int Arch Allergy Immunol; 158(4):369-74. [4] Humbert 2009, Allergy;Aug;64(8):1194-201.

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