

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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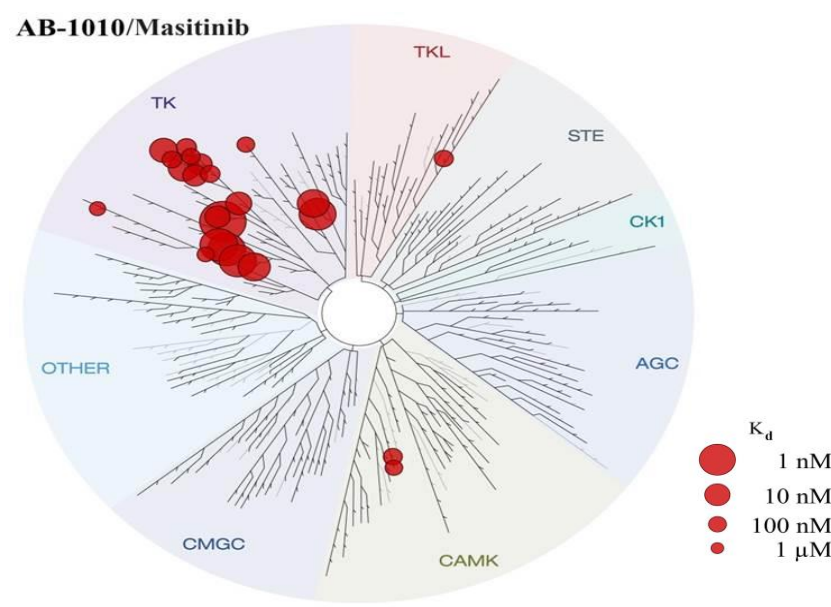
Background, Objectives & Design of Study AB07015

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]	K _d [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

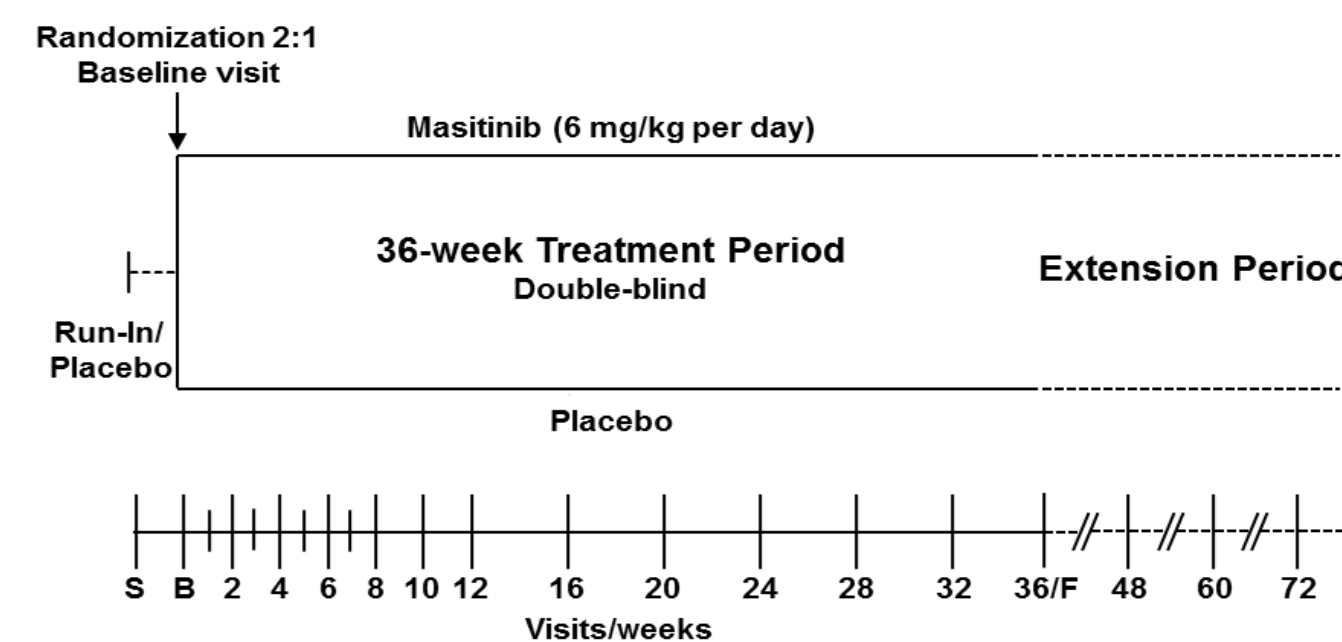
Masitinib activity in mouse models of asthma

- 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/ μ L) and low (< 150 cells/ μ L) eosinophils
- 2-week run-in (blinded placebo) \rightarrow 36-week treatment period [W0–W36] \rightarrow possible blinded extension



- Patient with history of severe asthma ≥ 1 year:
 - Baseline FEV1 $\geq 35\%$ 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)					Sequential Analysis (Severe Asthma with High Eosinophil)					
	Exp	Rate	RR [95%CI]	Reduction	P-value	Exp	Rate	RR [95%CI]	Reduction	P-value	
MAS (240)	1.14	0.34	0.65 [0.47, 0.90]	35%	0.0103	MAS (181)	1.10	0.34	0.62 [0.42, 0.91]	38%	0.0156
PBO (115)	1.15	0.48				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/ μ L) 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)					Sensitivity Analysis (Severe Asthma with High Eosinophil)					
	Exp	Rate	RR [95%CI]	Reduction	P-value	Exp	Rate	RR [95%CI]	Reduction	P-value	
Cumulative OCS >500 mg											
MAS (161)	1.15	0.34	0.59 [0.39, 0.88]	41%	0.0092	MAS (127)	1.12	0.32	0.51 [0.32, 0.82]	49%	0.0049
PBO (82)	1.20	0.55				PBO (60)	1.16	0.60			
Cumulative OCS >1000 mg											
MAS (120)	1.16	0.26	0.49 [0.29, 0.82]	51%	0.0060	MAS (92)	1.11	0.22	0.29 [0.15, 0.57]	71%	0.0003
PBO (66)	1.27	0.53				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

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/ μ L) or those in failure to biologics

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