

TITLE:

Efficacy and Safety of Masitinib in Severe Asthma: Eosinophilic Subgroup Analysis from Study AB07015

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BACKGROUND:

Study AB07015 (NCT01449162) evaluated oral masitinib (6 mg/kg/day) treatment of severe persistent asthma remaining uncontrolled by high-dose ICS/LABA and oral corticosteroids (>5 mg/day), irrespective of baseline blood eosinophil levels. Masitinib (MAS) is a first in class drug in the treatment of asthma, selectively inhibiting tyrosine kinases (KIT, LYN, FYN, PDGFR) and targeting principally mast cell activity.

METHODS:

Randomized (2:1) controlled phase 3 trial. Following a 2-week single-blind, placebo (PBO) run-in period, eligible adult patients (pts) were treated for 36 weeks (with possible blinded extension until at least week-96). Primary endpoint was reduction of annualized severe asthma exacerbation rate (SAER) for overall exposure (including extension period [W0–W96]), 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 pts with initial eosinophil count of ≥ 150 cells/ μ L.

RESULTS:

Baseline characteristics and average exposure times (approx 60 weeks) were well-balanced across treatment-arms. For the primary analysis, MAS (n=240) showed a significant 35% reduction in SAER (p=0.0103) compared with PBO (n=115) in severe asthma pts. This treatment-effect was corroborated by sensitivity analyses and secondary endpoints (see Table). For analysis of the eosinophil ≥ 150 cells/ μ L subgroup, MAS (n=181) showed a significant 38% reduction in SAER with respect to PBO (n=87) (SAER 0.34 vs 0.51, respectively, RR of 0.62 [95%CI 0.42–0.91;p=0.0156]). Secondary endpoints for this subgroup were also significant in favor of MAS, including pulmonary function according to FEV1 (p<0.001) and FVC (p=0.032); and reduction in moderate/severe asthma exacerbation rate (p=0.0249) (see Table). Safety for the overall population (n=404) was consistent with the known profile for MAS, with no new safety signals observed. The rate of pts presenting at least one adverse event was 83.4% for MAS vs 82.0% for PBO.

CONCLUSION:

The primary analysis of study AB07015 was positive, with an acceptable safety profile, for uncontrolled severe asthma irrespective of eosinophil levels. Masitinib also shows significant improvement in severe eosinophilic (≥ 150 cells/ μ L) asthma and may therefore provide a new treatment option for biologic-ineligible pts (e.g. eosinophil count of ≤ 300 cells/ μ L) or pts in failure to biologics.

TABLE: Summary of efficacy results for primary and subgroup analyses of study AB07015

Primary Analysis Population: (Irrespective of baseline eosinophil level)					Predefined Subgroup Analysis: (Baseline eosinophil level ≥ 150 cells/ μ L)				
	N	Exposure (months)				N	Exposure (months)		
Masitinib (MAS)	240	13.7			Masitinib (MAS)	181	13.2		
Placebo (PBO)	115	13.8			Placebo (PBO)	87	13.4		
Primary Analysis									
Annualized severe asthma exacerbation rate (SAER)									
	Rate	RR (95%CI)	Reduction	P-value		Rate	RR (95%CI)	Reduction	P-value
MAS	0.34	0.65	35%	0.0103	MAS	0.34	0.62	38%	0.0156
PBO	0.48	(0.47, 0.90)			PBO	0.51	(0.42, 0.91)		
Sensitivity analysis on primary: FAS Population SAER									
	Rate	RR (95%CI)	Reduction	P-value		Rate	RR (95%CI)	Reduction	P-value
MAS (269)	0.34	0.67	33%	0.0145	MAS (206)	0.32	0.62	38%	0.0138
PBO (133)	0.45	(0.49, 0.92)			PBO (102)	0.49	(0.42, 0.91)		
Secondary Analyses									
Moderate*/severe asthma exacerbation rate									
	Rate	RR (95%CI)	Reduction	P-value		Rate	RR (95%CI)	Reduction	P-value
MAS	0.48	0.64	36%	0.0014	MAS	0.47	0.69	31%	0.0249
PBO	0.69	(0.48, 0.84)			PBO	0.69	(0.49, 0.95)		
FEV1 least-squares mean change from baseline at W96									
	Δ LSM	Δ FEV1 (95% CI)	P-value		Δ LSM	Δ FEV1 (95% CI)	P-value		
MAS	0.0989	0.0675	0.016	MAS	0.1622	0.1125	<0.001		
PBO	0.0314	(0.0125, 0.1225)		PBO	0.0497	(0.0514, 0.1736)			
FEV1/FVC least-squares mean change from baseline W96									
	Δ LSM	Δ FEV1/FVC (95%CI)	P-value		Δ LSM	Δ FEV1/FVC (95%CI)	P-value		
MAS	1.9230	1.5740	0.049	MAS	2.9043	1.6446	0.071		
PBO	0.3490	(0.0081, 3.1399)		PBO	1.2597	(-0.1453, 3.4344)			
FVC least-squares mean change from baseline at W96									
	Δ LSM	Δ FVC (95% CI)	P-value		Δ LSM	Δ FVC (95% CI)	P-value		
MAS	0.0099	0.0362	0.386	MAS	0.0801	0.1024	0.032		
PBO	-0.0262	(-0.0458, 0.1181)		PBO	-0.0223	(0.0086, 0.1961)			
ACQ least-squares mean change from baseline at W96									
	Δ LSM	Δ ACQ (95% CI)	P-value		Δ LSM	Δ ACQ (95% CI)	P-value		
MAS	-0.5369	-0.2128	0.050	MAS	-0.5036	-0.1699	0.160		
PBO	-0.3241	(-0.4259, 0.0004)		PBO	-0.3337	(-0.4076, 0.0678)			
AQLQ least-squares mean change from baseline at W96									
	Δ LSM	Δ AQLQ (95% CI)	P-value		Δ LSM	Δ AQLQ (95% CI)	P-value		
MAS	0.5582	-0.0318	0.850	MAS	0.4549	-0.1175	0.492		
PBO	0.5900	(-0.3625, 0.2990)		PBO	0.5724	(-0.4541, 0.2191)			

SAER: Annualized severe asthma exacerbation rate. FAS: Full Analysis Set population (n=402) is all randomized patients (including non-severe pts receiving low-dose ≤ 5 mg/day OCS who were excluded from the primary analysis following a protocol amendment) with exclusion also of pts having major GCP violations, no intake of product, randomization errors, no reference OCS. *Moderate exacerbation event defined as worsening asthma leading to an increase in rescue medication use for ≥ 2 days or change in asthma treatment (other than an increase in systemic corticosteroids dose or hospitalization). LSM: Least-squares mean. ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; FEV1: forced exhalation volume in 1 second. FVC: forced vital capacity. A positive difference in Δ FEV1, Δ FEV1/FVC, FVC and Δ AQLQ favors masitinib, while a negative difference in Δ ACQ favors masitinib.