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/µL.

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/µL 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/µL) asthma and may therefore provide a new treatment option for biologic-ineligible pts (e.g. eosinophil count of ≤300 cells/µL) 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/µL)	
	N	*Exposure (months)*	*N*	*Exposure (months)*
Masitinib (MAS)	*240*	*13.7*	*181*	*13.2*
Placebo (PBO)	*115*	*13.8*	*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

	ΔLSM	*ΔFEV1 (95% CI)*	*P-value*		*ΔLSM*	*ΔFEV1 (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

	ΔLSM	*ΔFEV1/FVC (95%CI)*	*P-value*		*ΔLSM*	*ΔFEV1/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

	ΔLSM	*ΔFVC (95% CI)*	*P-value*		*ΔLSM*	*ΔFVC (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

	ΔLSM	*ΔACQ (95% CI)*	*P-value*		*ΔLSM*	*ΔACQ (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

	ΔLSM	*ΔAQLQ (95% CI)*	*P-value*		*ΔLSM*	*ΔAQLQ (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 ΔFEV1, ΔFEV1/FVC, FVC and ΔAQLQ favors masitinib, while a negative difference in ΔACQ favors masitinib.