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BOOK OF ABSTRACTS

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**C36 Sensitivity analyses from the first phase 3 clinical study of masitinib (AB10015) in ALS demonstrate robustness of the positive primary analysis**

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Masitinib (MAS) has previously reported positive phase 3 (AB10015) findings in ALS, signaling that it could provide an important new treatment option. Here we present results from various sensitivity analyses on the primary endpoint. The primary efficacy population of study AB10015 was predefined as patients (pts) receiving MAS 4.5 mg/kg/day with a ALSFRS-R progression rate from disease-onset to baseline ( $\Delta$ FS) of  $<1.1$  points/month. The primary endpoint, decline in ALSFRS-R from baseline to week-48 ( $\Delta$ ALSFRS-R), showed significant benefit for MAS ( $n=99$ ) over placebo ( $n=102$ ) with a between-group least-squares means difference ( $\Delta$ LSM) of 3.39 ( $-9.24$  vs  $-12.63$ ); 95%CI 0.65–6.13,  $P=0.016$ . Missing data were imputed via last observation carried forward (LOCF) methodology for those pts discontinuing because of toxicity or lack of efficacy before week 48. In total, six predefined sensitivity analyses were conducted on the primary analysis, including two full analysis dataset (non-LOCF) imputation methods and four variations on LOCF via censoring on reason for discontinuation. All results from these sensitivity analyses were consistent with the significant outcome of the primary analysis, corroborating the robustness of this finding. Considering the most pessimistic full analysis dataset (imputation with penalty), which estimates progression for similarly clustered pts then imputes missing values using this average trend,  $\Delta$ ALSFRS-R for MAS ( $n=104$ ) was  $-11.4$  versus  $-14.4$  for placebo ( $n=111$ ); corresponding to a  $\Delta$ LSM of 3.0 and significant 26% slowing in rate of decline ( $P=0.018$ ). This result was further verified via tipping point analysis, a form of stress testing that assesses how large departures from the 'Missing at Random' assumption must be to overturn conclusions from the primary analysis. The tipping point was achieved with a penalty of 76% (i.e. as if 76% of discontinued MAS pts were equivalent to placebo). Because this is an improbable scenario, we can say that the analysis is robust. Additionally, a multiple imputation method was performed post-hoc using a monotone regression model (with initial conditioning by MCMC imputation). Results showed a significant slowing in decline of ALSFRS-R for MAS ( $n=105$ ) versus placebo ( $n=113$ ) by 21%, with  $\Delta$ LSM of 2.8 ( $-11$  vs  $-13.8$ ); ( $P=0.0454$ ). Taken together, these positive results from multiple/single imputation sensitivity analyses corroborate the robustness of study AB10015 primary endpoint data.

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# SENSITIVITY ANALYSES FROM THE FIRST PHASE 3 CLINICAL STUDY OF MASITINIB (AB10015) IN ALS DEMONSTRATE ROBUSTNESS OF THE POSITIVE PRIMARY ANALYSIS

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## BACKGROUND ON MASITINIB AND STUDY AB10015

### STUDY AB10015 WAS THE FIRST SUCCESSFULLY COMPLETED PLACEBO CONTROLLED PHASE 3 TRIAL OF MASITINIB IN ALS

- Masitinib is an oral tyrosine kinase inhibitor that exerts a protective effect on both the CNS and PNS [1,2] (also ENCALS Poster C33).
- The positive benefit-risk balance observed for study AB10015 signals that masitinib may provide an important new therapeutic option in ALS.
  - Primary efficacy outcome was decline in ALSFRS-R from baseline to week-48 in ALS patients having a baseline ALSFRS-R progression ( $\Delta$ FS) of <1.1 points/month and treated with masitinib at 4.5 mg/kg/day.
  - The  $\Delta$ FS-stratified design and cut-off used is supported by the literature [Gordon, 2006; Kimura, 2006; Kollawe, 2008; Labra, 2016].
  - Masitinib demonstrated a clinically meaningful and significant benefit with acceptable safety in this prospectively declared population.

	n	LSM	$\Delta$ LSM [95% CI]	Effect	P value
ALSFRS-R					
PBO	102	-12.6	3.4 [0.7 ; 6.1]	27%	0.016
M4.5	99	-9.2			

## SENSITIVITY ANALYSES FOR TESTING ROBUSTNESS OF PRIMARY OUTCOME

### RESULTS FROM PREDEFINED SENSITIVITY ANALYSES WERE CONSISTENT WITH THE SIGNIFICANT OUTCOME OF THE PRIMARY ANALYSIS, CORROBORATING THE ROBUSTNESS OF THIS FINDING

- Interpretation of the primary analysis is complicated by use of last observation carried forward (LOCF) for missing data imputation as this method can generate bias.
- This concern was mitigated through sensitivity analyses, including predefined full analysis dataset (non-LOCF) imputation methods and variants on LOCF via censoring on reason for discontinuation.
- Additional validation was obtained through exploratory analyses based on methods widely recommended by industry guidelines and authorities [3–7].
- Of note also is that the discontinuation rate was similar between treatment-arms (34.2% versus 34.9%).
- Predefined sensitivity analyses
  - Rule 1 (primary analysis): Missing data was imputed via LOCF only when patients discontinued before week-48 for documented reasons of toxicity or lack of efficacy.
  - Rules 2 to 5: As for rule 1 with additional reasons for withdrawal imputed via LOCF.
  - Rule 6: Imputation done by clustering patients on a given prognostic factor, then using the average increment within groups (FDA recommended).
  - Rule 7: As for rule 6 with the penalty of 50% applied for lack of efficacy.
- Exploratory analyses
  - Multiple imputation (MI) is a well-established widely recommended technique [3–7]
    - Fully Conditional Specification Regression Predictive Mean Matching (FCS REGPMM) method (non-monotone regression).
    - Monotone regression model (with initial conditioning by MCMC imputation).
    - Jump to reference (different thresholds). Assumes any patient discontinuing treatment early would behave similarly to placebo patients post discontinuation.
  - Worst observation carried forward (WOCF) is a conservative method compared with LOCF and more appropriate due to the degenerative nature of the disease.
  - Tipping-point analysis assesses how severe departures from the MAR assumption must be in order to overturn conclusions from the primary analysis (serves as form of stress-testing). A high penalty (range 100–0) indicates greater robustness.
    - Tipping-point for the primary endpoint (rule 6) was achieved with a penalty of 76%.

	Primary	Rule 2	Rule 3	Rule 4	Rule 5	Rule 6	Rule 7
Reason of discontinuation							
Lack of Efficacy	LOCF	LOCF	LOCF	LOCF	LOCF	Imput.	Imput. with penalty
Toxicity	LOCF	LOCF	LOCF	LOCF	LOCF	Imput.	Imput.
Procedure	OC	LOCF	OC	LOCF	LOCF	Imput.	Imput.
Travel	OC	OC	LOCF	LOCF	LOCF	Imput.	Imput.
Lost to follow up	OC	OC	OC	OC	LOCF	Imput.	Imput.
Protocol deviation	OC	OC	OC	OC	OC	Imput.	Imput.
Other	OC	OC	OC	OC	LOCF	Imput.	Imput.
Non-compliance	OC	OC	OC	OC	LOCF	Imput.	Imput.

Patients analyzed in primary endpoint							
PBO	102/113	103/113	107/113	108/113	111/113	111/113	111/113*
M4.5	99/105	99/105	102/105	102/105	104/105	104/105	104/105*

	n	LSM (ALSFRS-R)	$\Delta$ LSM [95%CI]	P value
Rule 2: (LOCF)				
PBO	103	-12.5	3.3 [0.6;6.0]	0.019
M4.5	99	-9.3		
Rule 3: (LOCF)				
PBO	107	-12.1	3.1 [0.4;5.7]	0.025
M4.5	102	-9.0		
Rule 4: (LOCF)				
PBO	108	-12.0	3.0 [0.3;5.6]	0.029
M4.5	102	-9.0		
Rule 5: (LOCF)				
PBO	111	-11.8	2.9 [0.3;5.4]	0.029
M4.5	104	-9.0		
Rule 6: Imputation for all patients by clustering (Full analysis dataset)				
PBO	111	-14.0	3.0 [0.5;5.5]	0.018
M4.5	104	-11.0		
Rule 7: Imputation by clustering with 50% penalty for lack of efficacy (Full analysis dataset)				
PBO	111	-14.4	3.0 [0.5;5.5]	0.018
M4.5	104	-11.4		

Method	n	LSM (ALSFRS-R)	$\Delta$ LSM [95%CI]	P value
FCS REGPMM – Full model				
PBO	111	-13.77	2.95 [0.435;5.853]	0.047
M4.5	104	-10.82		
FCS REGPMM – Best model (AICC criteria)				
PBO	111	-14.18	3.34 [0.430;6.238]	0.025
M4.5	104	-10.85		
FCS REGPMM – 2 <sup>nd</sup> best model (AICC criteria)				
PBO	111	-14.06	3.17 [0.278;6.054]	0.032
M4.5	104	-10.89		
MI Jump to reference (100% penalty)				
PBO	111	-12.98	2.64 [0.136;5.136]	0.039
M4.5	104	-10.34		
MI Jump to reference (50% penalty)				
PBO	111	-11.66	4.57 [1.61;7.53]	0.002
M4.5	104	-7.093		
MI Monotone regression				
PBO	111	-13.8	2.84 [0.04;5.61]	0.45
M4.5	104	-11.0		
WOCF (Rule 1)				
PBO	102	-12.62	3.29 [0.558;6.032]	0.0185
M4.5	99	-9.32		
WOCF (Rule 6)				
PBO	111	-14.01	2.98 [0.504;5.464]	0.0186
M4.5	104	-11.03		

The positive primary outcome from study AB10015 has now been corroborated by numerous (>10) industry recognized, health authority recommended, standard statistical techniques

Reassures that the masitinib treatment-effect demonstrated in AB10015 was not due to LOCF bias

References: [1]Trias (2016) J Neuroinflammation; 13(1):177. [2] Trias (2017) JCI Insight; 2(20):e95934. [3] EMA Guideline on Missing Data in Confirmatory Clinical Trials (2010). [4] NRC report (2010): Prevention and Treatment of Missing Data in Clinical Trials. [5] ICH Guideline E9 (1998): Statistical Principles for Clinical Trials. [6] ICH Guideline E9(R1) (2017): Estimands and Sensitivity Analysis in Clinical Trials. [7] Mallinckrodt (2013) Preventing and Treating Missing Data in Longitudinal Clinical Trials.