MASITINIB AS AN ADD-ON THERAPY TO RILUZOLE IS SAFE AND EFFECTIVE IN THE TREATMENT OF ALS

RESULTS FROM A RANDOMIZED CONTROLLED PHASE 3 TRIAL

AB SCIENCE

FONDATION THIERRY LATRAN

THIERRY LATRAN FOUNDATION LECTURE

Plenary Session

ENCALS Annual Meeting 2017 *Ljubljana, Slovenia (18-20 May 2017)*

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France

ENCALS Annual Meeting 2017 *Ljubljana, Slovenia (18-20 May 2017)*

RATIONALE FOR USE OF MASITINIB IN ALS

STUDY AB10015 DESIGN

BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

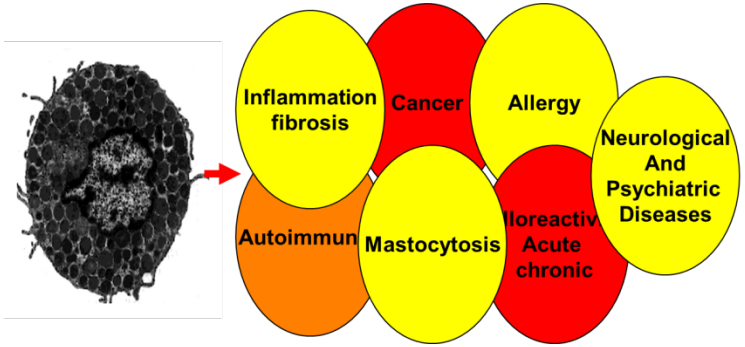
EFFICACY RESULTS

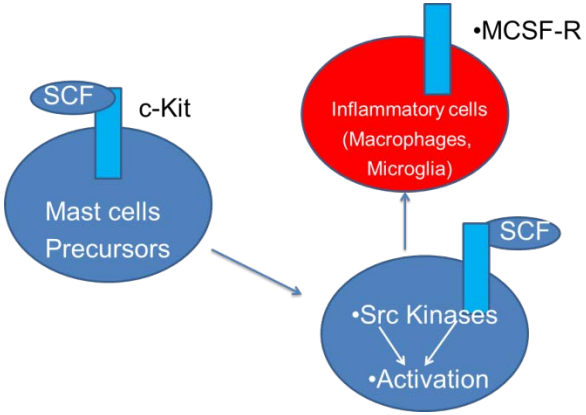
SAFETY RESULTS

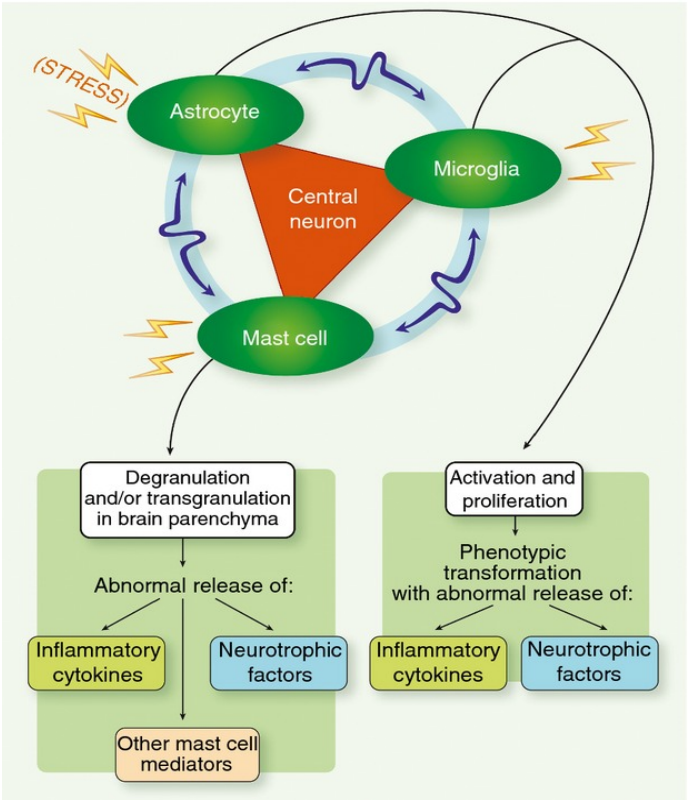
CONCLUDING COMMENTS

Q & A

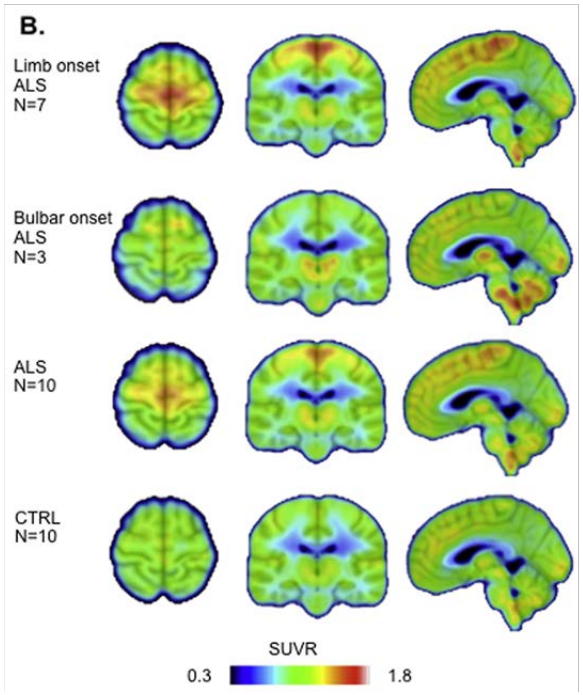
RATIONALE FOR USE OF MASITINIB IN ALS



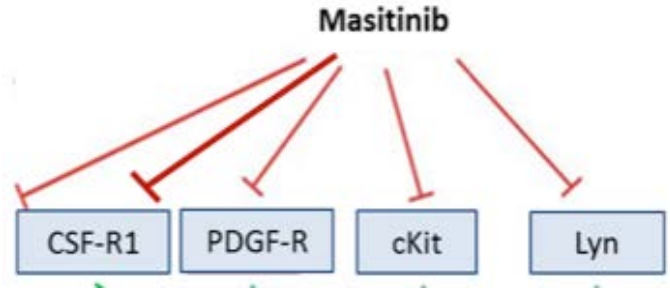




PET Scan of ALS patient's brain versus control, using SUVR as a marker of glial activation

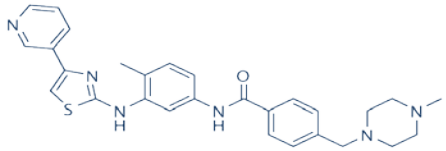


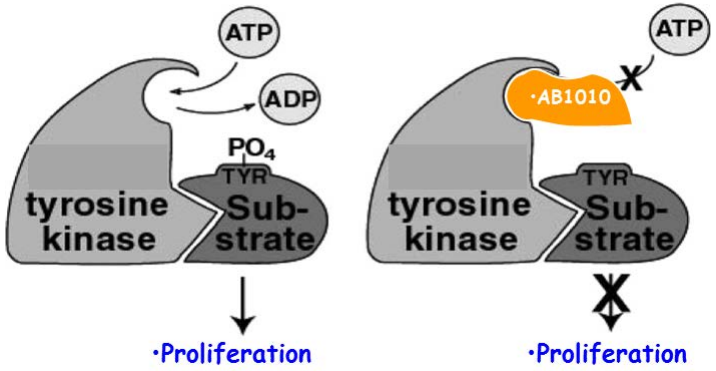
RATIONALE FOR USE OF MASITINIB IN ALS

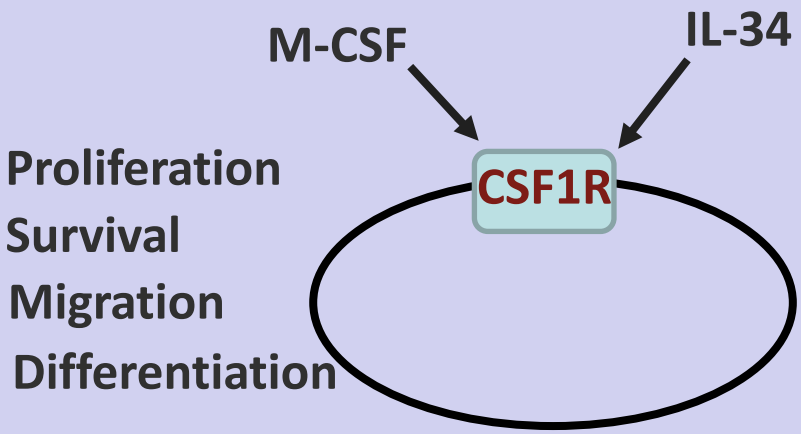


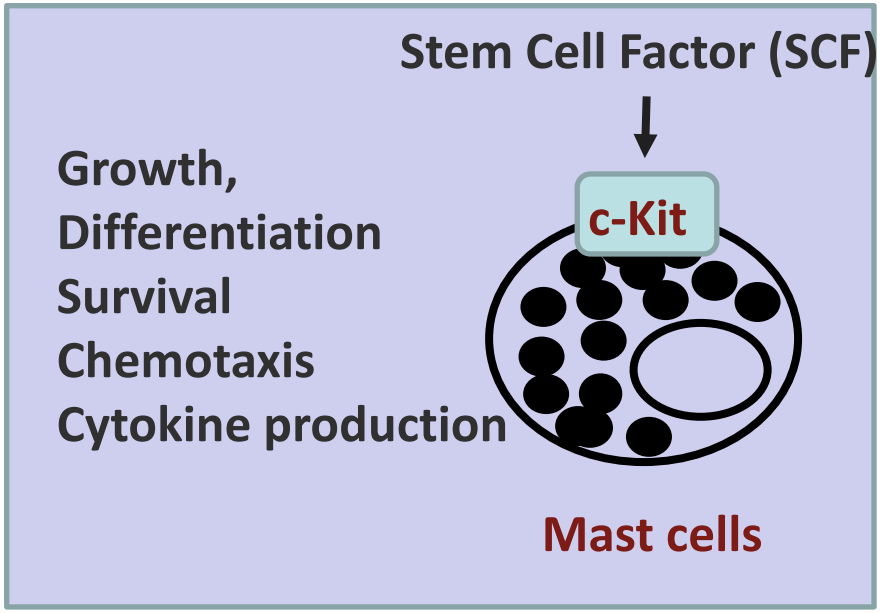
- Anti-neoplastic drug (mast cell tumors & others)
- Currently in phase 3 clinical trials for ALS, Alzheimer's disease and MS

Masitinib (AB1010)



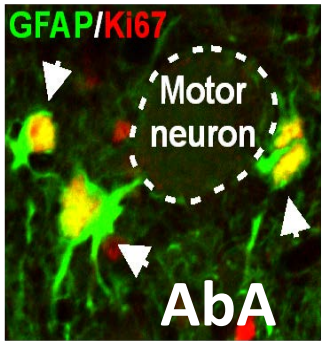


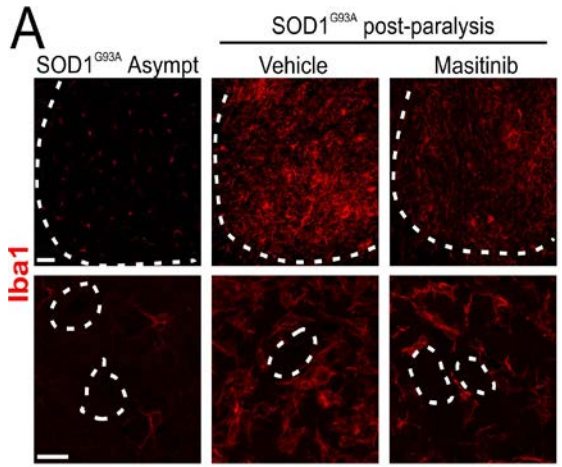


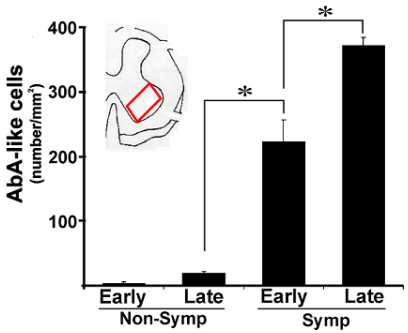


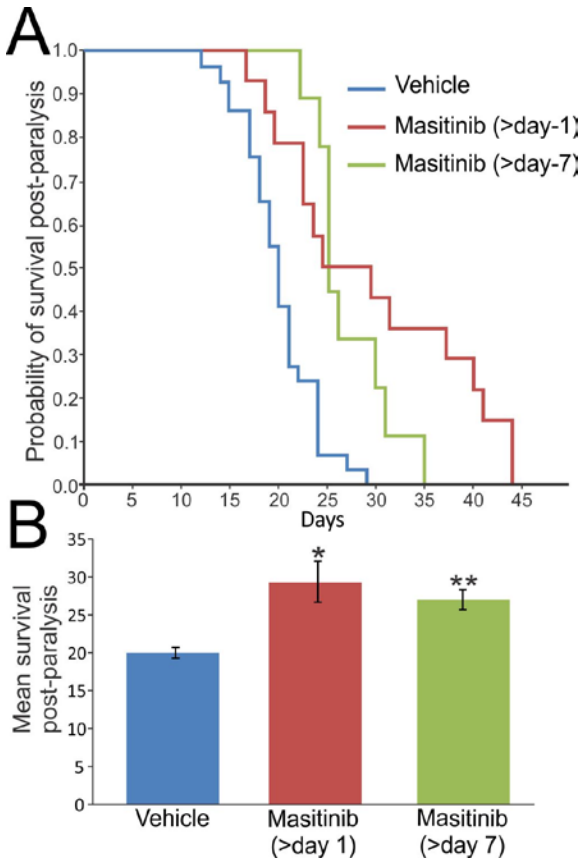
RATIONALE FOR USE OF MASITINIB IN ALS

MoA #1:
Reduction of microgliosis and aberrant glial cells through CSF-1R inhibition









Phenotypically aberrant astrocytes that promote motoneuron damage in a model of inherited amyotrophic lateral sclerosis

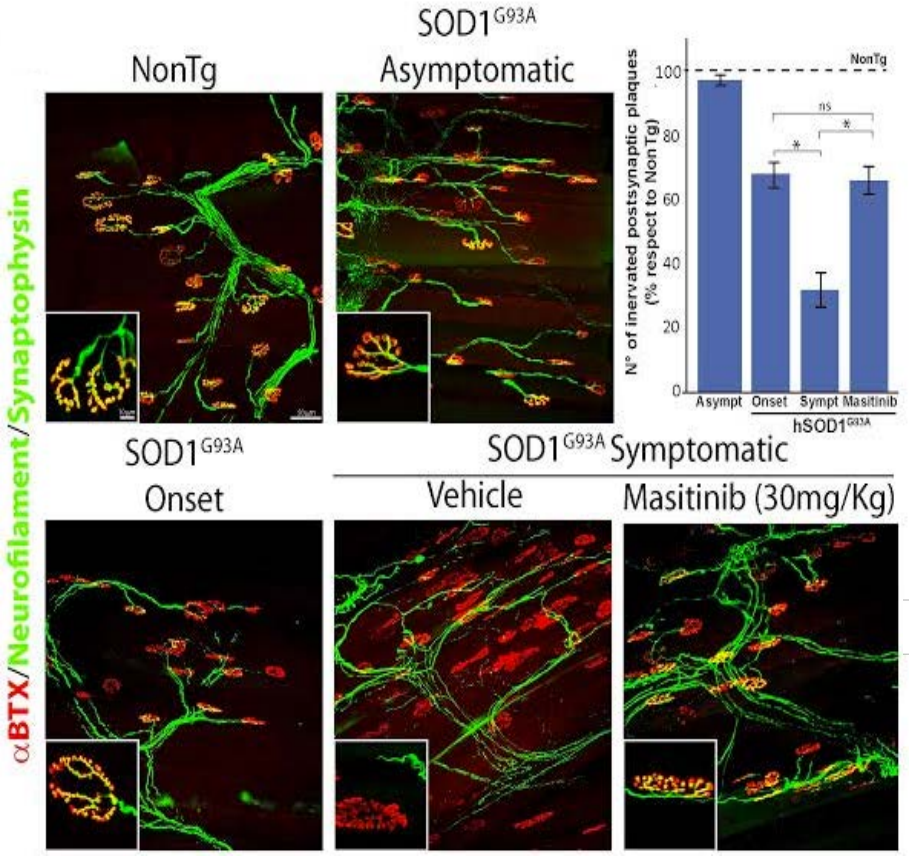
Pablo Diaz-Amarilla[a], Silvia Olivera-Bravo[a], Emiliano Trias[a], Andrea Cragnolini[b], Laura Martínez-Palma[c], Patricia Cassina[c], Joseph Beckman[d,e], and Luis Barbeito[a,b,1]

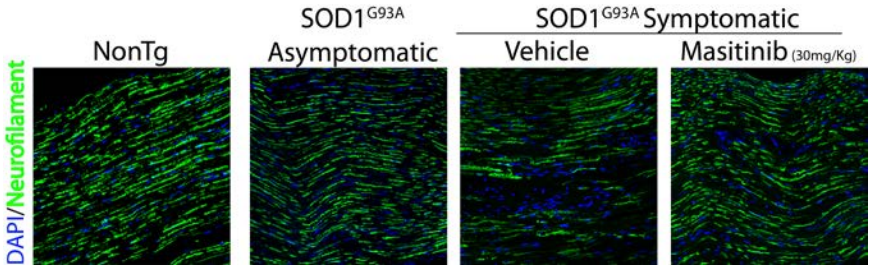
RESEARCH

Post-paralysis tyrosine kinase inhibition with masitinib abrogates neuroinflammation and slows disease progression in inherited amyotrophic lateral sclerosis

RATIONALE FOR USE OF MASITINIB IN ALS

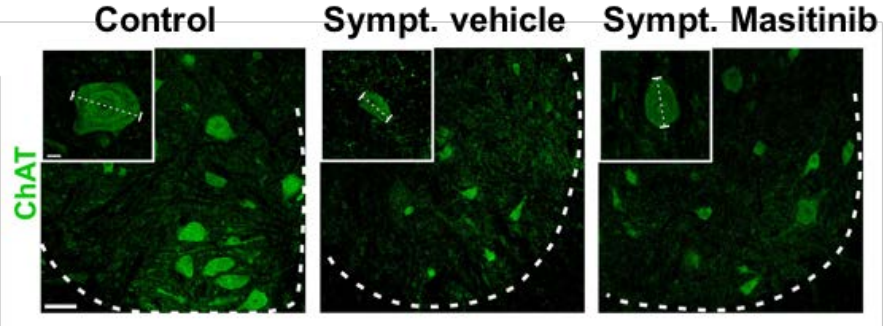
MoA #1:
Masitinib prevents motor neuron degeneration





Sciatic nerve

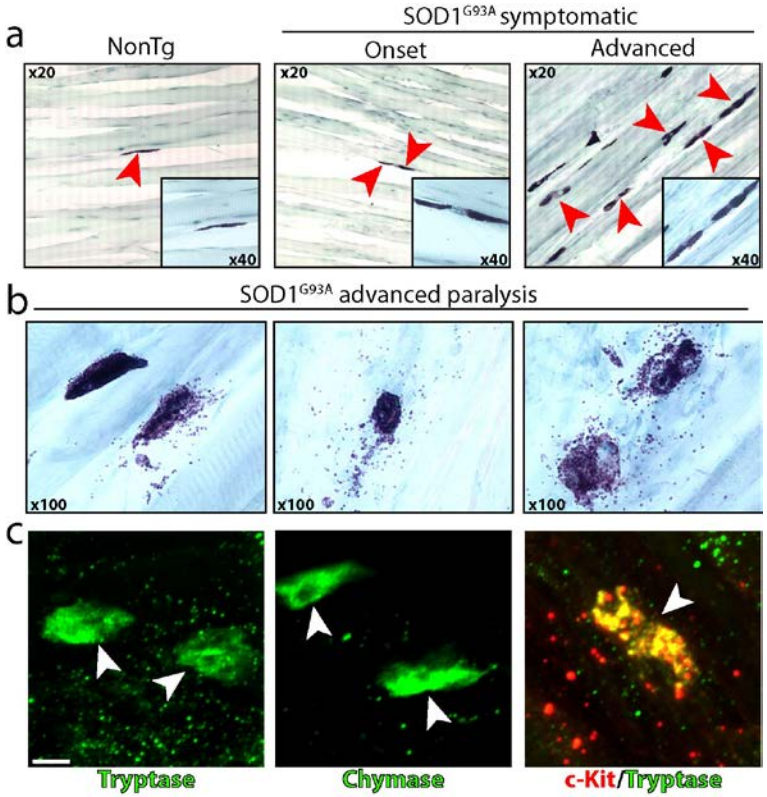
NMJs (EDL muscle)

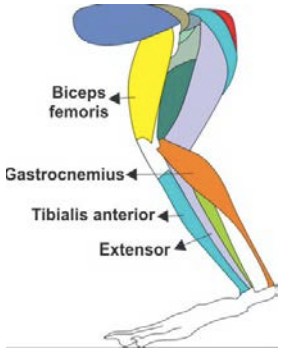


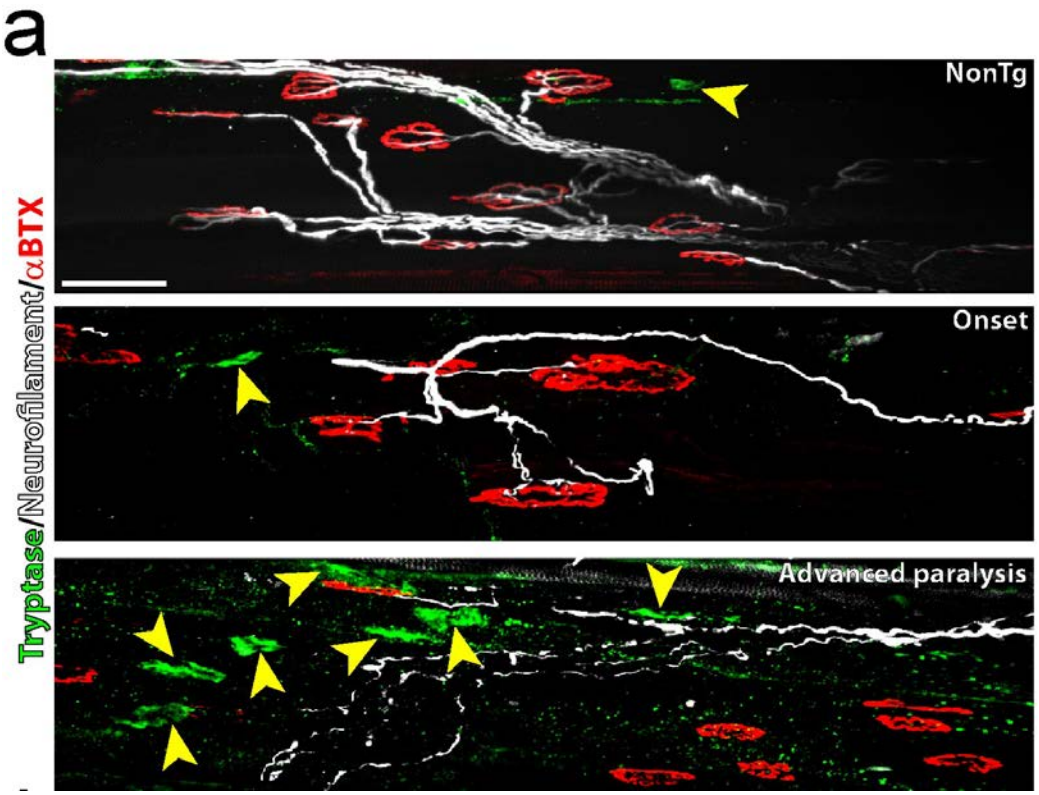
Spinal cord

RATIONALE FOR USE OF MASITINIB IN ALS

MoA #2:
Masitinib prevents mast cell and macrophage infiltration in the PNS







Unpublished data

RATIONALE FOR USE OF MASITINIB IN ALS

- **Masitinib appears unique among other ALS-developmental drugs,** exerting neuroprotection by simultaneously targeting microglia, macrophage and mast cell activity, both in CNS and PNS.

- **Compelling preclinical data strongly support the plausibility of positive phase 3 clinical results.**

- **Full details on masitinib preclinical data in ALS will be presented in a second talk on Friday**

  LINHART HALL

  07:30-08:00 Coffee reception for AB Science satellite meeting

  08:00-09:00 Masitinib for the treatment of amyotrophic lateral sclerosis (ALS): Preclinical overview

MASITINIB AS AN ADD-ON THERAPY TO RILUZOLE IS SAFE AND EFFECTIVE IN THE TREATMENT OF ALS

OVERVIEW OF TRIAL AB10015 RESULTS

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On behalf of the ALS/Masitinib Trial Group

Thierry Latran Foundation Lecture

ENCALS Annual Meeting 2017 *Ljubljana, Slovenia (18-20 May 2017)*

STUDY AB10015 RATIONALE

- Microgliosis, and aberrant glial cells, a major neuropathological feature in ALS animal models
- It is regulated by the CSF1/CSF1R signaling pathway
- Masitinib, a tyrosine kinase inhibitor, targets CSF1R or C-Kit in microglia, macrophages and mastoid cells inhibiting cell proliferation without depletion
- Masitinib prevents microgliosis, migration, and aberrant glial cells formation, and improves motoneuron pathology (Barbeito's group 2016)
- Masitinib slows paralysis progression in post-paralytic $SOD1^{G93A}$ rats (Barbeito's 2016)
- Masitinib prevents mast cells and macrophages migration in the PNS/NMJ (Barbeito's 2017)
- Masitinib 3.0 or 4.5 mg/kg/d provide concentration above its IC_{50}

STUDY DESIGN

BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

STUDY RESULTS

SUMMARY

STUDY AB10015 DESIGN

- **Double blind, placebo controlled, randomized 1:1:1, oral BID**
  - Masitinib 4.5mg/kg/day + riluzole
  - Masitinib 3 mg/kg/day + riluzole,
  - Placebo + riluzole
- **Treatment duration :** 48 weeks
- **Safety Assessments, IDMC**
- **Primary endpoint** : Change in the ALSFRS-R score at 48 weeks
- **Secondary endpoints:** PFS, FVC, ALSAQ-40, CAFS, OS
  - PFS, Progression Free Survival: ALSFRS-R deterioration ≥ 9 points, or death
- **394 patients, 9 countries, 34 sites, Dec 2016**

STUDY DESIGN

❖ Main Inclusion Criteria:

- Patients with the El Escorial DC of lab supported probable, probable, or definite ALS, sporadic or familial ALS
- Patients on stable dose of riluzole for at least 30 days prior to screening
- Patients with disease duration ≤ 36 months and FVC ≥ 60%

❖ Main Exclusion Criteria:

- Patients with gastrostomy
- Patients with dementia or other significant neurological, psychiatric, systemic or organic disease, uncontrolled or that may interfere with the conduct of the trial or its results

STUDY DESIGN

- **Stratification factors at baseline:**
  - **Progression rate of the ALSFRS-R score** from first symptom to baseline, in points/month loss
  - **Site of onset**: Spinal vs Bulbar
  - **ALSFRS-R score**
  - **Age**
  - **Region**: W Europe & N America vs E Europe vs Other Countries

STUDY DESIGN

- **Rate of ALSFRS-R progression from first symptom to randomization (points/month):**

$$\frac{48 \text{ [= score at date of first symptom]} - \text{score at randomization}}{\text{date of randomization} - \text{date of first symptom}}$$

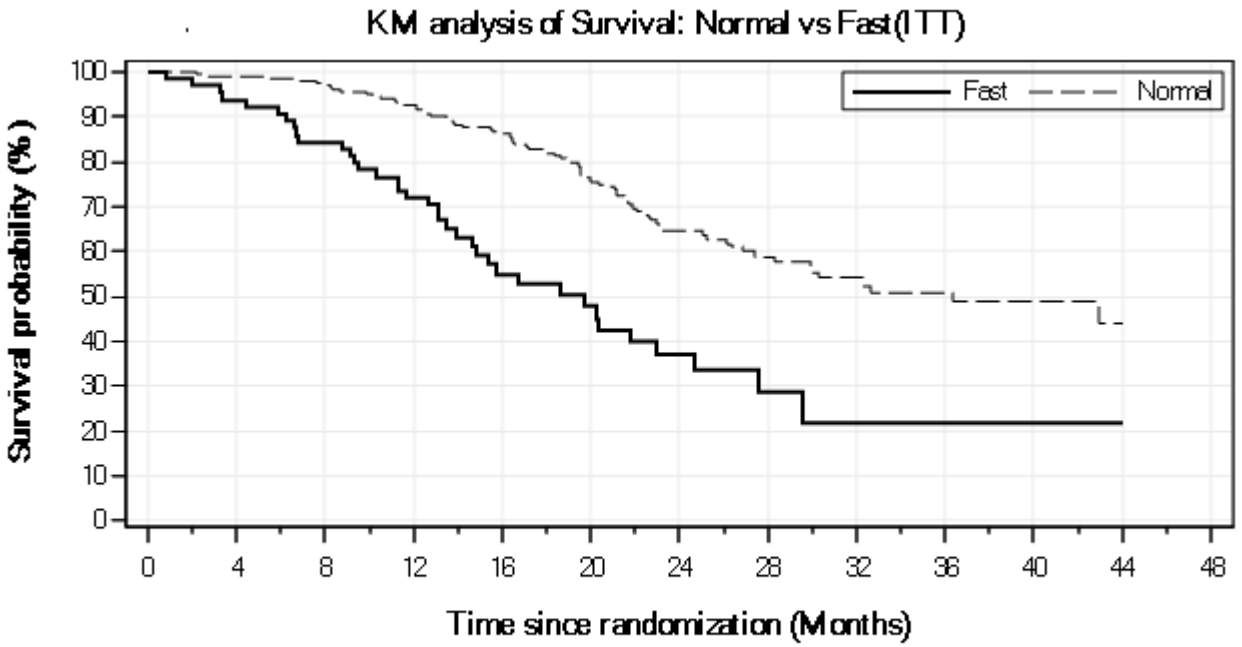
- **Two distinct populations were differentiated:**
  - **'Normal Progressors': rate <1.1 points/month**
  - **'Faster Progressors': rate ≥ 1.1 points/month**
- **Targeted population for primary analysis was Normal Progressors**

Kimura F et al: Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. Neurology 2006;66:265- 267

STUDY DESIGN

Normal Progressors vs **Faster Progressors**

(*pooled patients from the AB10015 trial regardless of treatment administered*)



STUDY DESIGN

- Change in ALSFRS-R score from W0 to W48 was estimated using an ANCOVA model with these hypothesis:
  - Alpha 5% 2-sided test, Power 80%
  - Δ ALSFRS-R between placebo group and masitinib group = 3.3
- Interim analysis with 50% of patients planned using type I error = 0.0311
- 381 patients were calculated, with non evaluable patients

Sample size required for each population of the primary analysis:

Population	Change of ALSFRS from baseline to W48				
	Difference between a Masitinib group and the placebo group	N per arm	N to detect a difference between a Masitinib group to the placebo group	N total	N total taking account non-evaluable patients
Normal progressors	3,3 (+/- 7.5)	93	186	279	300
Normal + Faster progressors	3,3 (+/- 9.0)	118	236	354	381

STUDY DESIGN

- Efficacy analyses were conducted in a stepwise manner, fixed sequence method, to control the global family-wise error rate at the 0.05 level for the primary analysis for each dose

STEP	POPULATION	PRIMARY ANALYSIS	DECISION
1	**Normal** progressors **Masitinib 4.5** mg/kg/day	Absolute change in ALSFRS-R from baseline to week 48, mLOCF method => Rerandomisation test using test associated with the treatment effect estimate in analysis of covariance model	If conclusive at 0.05 signif level : o Claim in NP M4.5 o Analyses continued in Step 2
2	**Normal** progressors **Masitinib 3.0** mg/kg/day	Same as above	If conclusive at 0.05 signif level : o Comparison benefit/risk balance between NP M4.5 and NP M3.0 o Analyses continued in Step 3
3	**Normal+Faster** progressors **Masitinib 4.5** mg/kg/day	Same as above	If conclusive at 0.05 signif level : o Claim in N+FP M4.5 o Analyses continued in Step 4
4	**Normal+Faster** progressors **Masitinib 3.0** mg/kg/day	Same as above	If conclusive at 0.05 signif level : o Comparison benefit/risk balance between N+FP M4.5 and M3.0

STUDY DESIGN

mLOCF Rule 1 used for missing data for the primary analysis:

- **Missing data imputed in patients with premature discontinuation for these documented reasons:**
  - Toxicity
  - Lack of efficacy
- **Missing data not imputed in patients with premature discontinuation for these documented reasons:**
  - Lost to follow up
  - Non-compliance
  - Prohibited concomitant medication
  - Travel, Procedure, Protocol deviation, Cancer not related
- **In case of death, the score was replaced by 0**

Two key sensitivity analyses were provided incorporating all patients (ITT population) based on the imputation model for missing values

STUDY DESIGN

BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

STUDY RESULTS

SUMMARY

BASELINE CHARACTERISTICS

	NORMAL PROGRESSORS			NORMAL + FAST PROGRESSORS		
	Placebo (N=114)	**Masitinib 4.5 (N=106)**	**Masitinib 3.0 (N=110)**	**Placebo (N=133)**	**Masitinib 4.5 (N=130)**	**Masitinib 3.0 (N=131)**
Gender						
Male	69 (60.5%)	69 (65.1%)	70 (63.6%)	80 (60.2%)	83 (63.8%)	81 (61.8%)
Progressors population						
Normal	114 (100.0%)	106 (100.0%)	110 (100.0%)	114 (85.7%)	106 (81.5%)	110 (84.0%)
ALSFRS-R progression before randomization (points/month)						
Mean ± SD	0.49 ± 0.24	0.49 ± 0.25	0.48 ± 0.25	0.71 ± 0.69	0.73 ± 0.63	0.65 ± 0.48
Range	0.05 ; 1.07	0.03 ; 1.08	0.09 ; 1.07	0.05 ; 5.00	0.03 ; 3.69	0.09 ; 2.24
ALSFRS-R score						
Mean ± SD	39.3 ± 4.6	38.3 ± 5.3	38.6 ± 5.1	38.1 ± 5.5	37.5 ± 5.5	37.4 ± 5.7
Range	27.0 ; 47.0	23.0 ; 47.0	23.0 ; 46.0	21.0 ; 47.0	23.0 ; 47.0	21.0 ; 46.0
FVC (in %)						
Mean ± SD	90.3 ± 19.0	89.0 ± 16.5	88.1 ± 18.9	89.2 ± 18.7	87.5 ± 16.9	86.8 ± 18.7
Range	37.0 ; 136.0	60.0 ; 131.0	51.0 ; 149.0	37.0 ; 136.0	45.0 ; 131.0	51.0 ; 149.0
Age (in years)						
Mean ± SD	55.4 ± 10.5	54.8 ± 10.8	54.9 ± 10.3	55.2 ± 10.6	55.5 ± 10.6	55.7 ± 10.2
Range	27.0 ; 75.0	24.0 ; 79.0	33.0 ; 75.0	27.0 ; 75.0	24.0 ; 79.0	33.0 ; 75.0
Site of onset						
Spinal	90 (78.9%)	85 (80.2%)	92 (83.6%)	109 (82.0%)	107 (82.3%)	110 (84.0%)
Bulbar	24 (21.1%)	21 (19.8%)	18 (16.4%)	24 (18.0%)	23 (17.7%)	21 (16.0%)
Region						
West Europe & North America	72 (63.2%)	61 (57.5%)	68 (61.8%)	86 (64.7%)	81 (62.3%)	84 (64.1%)
Eastern Europe	8 (7.0%)	8 (7.5%)	5 (4.5%)	8 (6.0%)	8 (6.2%)	5 (3.8%)
Other Countries	34 (29.8%)	37 (34.9%)	37 (33.6%)	39 (29.3%)	41 (31.5%)	42 (32.1%)

SUMMARY OF THE STUDY POPULATION

POPULATION	NORMAL PROGRESSORS	NORMAL+FASTER PROGRESSORS
ITT population	**330**	**394**
Masitinib 4.5 mg/kg/d	106	130
Masitinib 3 mg/kg/d	110	131
Placebo	114	133
Safety Assessment : SAF population Patients with at least one drug intake	**329**	**393**
Masitinib 4.5 mg/kg/d	105	129
Masitinib 3.0 mg/kg/d	110	131
Placebo	114	133
Efficacy Assessment : mITT population Patients with at least one post baseline value*	**328**	**391**
Masitinib 4.5 mg/kg/d	105	128
Masitinib 3.0 mg/kg/d	110	131
Placebo	113	132

*In line with ICH E9 guidance, subjects having no post randomization data were excluded from the analysis.

BASELINE CHARACTERISTICS

Patients' disposition by treatment arm and status

PATIENTS STATUS	PLACEBO	MASITINIB 4.5	MASITINIB 3.0
Normal Progressors			
N	114	106	110
W48 reached	75 (65.8%)	69 (65.1%)	71 (64.5%)
Normal + Faster Progressors			
N	133	130	131
W48 reached	81 (60.9%)	76 (58.5%)	80 (61.1%)

STUDY DESIGN

BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

STUDY RESULTS

SUMMARY

STEP 1 – MASITINIB 4.5 MG / NORMAL PROGRESSORS

STEP 2 – MASITINIB 3.0 MG / NORMAL PROGRESSORS

STEP 3 – MASITINIB 4.5 MG / NORMAL + FASTER PROGRESSORS

STEP 4 – MASITINIB 3.0 MG / NORMAL + FASTER PROGRESSORS

SAFETY

PRIMARY ANALYSIS

The primary analysis (ΔALSFRS-R on the NP4.5 cohort) demostrated significant benefit

Absolute change in ALSFRS-R score
Normal Progressors, Masitinib 4.5 mg/kg/day

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value	Re-randomization p-value
Placebo + riluzole	102	-12.63	3.3878 [0.6451;6.1305]	0.0157	0.0158
Masitinib 4.5 + riluzole	99	-9.24			

LS Mean = Least Square Mean

PRIMARY ANALYSIS

Sensitivity analyses based on reasons for discontinuation confirmed primary analysis (all statistically significant)

Change in ALSFRS-R score
Normal Progressors, Masitinib 4.5 mg/kg/d

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
mLOCF Rule 2:				
Placebo + riluzole	103	-12.53	3.2753 [0.5454;6.0052]	0.0190
Masitinib + riluzole	99	-9.25		
mLOCF Rule 3:				
Placebo + riluzole	107	-12.09	3.0607 [0.3927;5.7287]	0.0248
Masitinib + riluzole	102	-9.03		
mLOCF Rule 4:				
Placebo + riluzole	108	-12.00	2.9641 [0.3087;5.6195]	0.0289
Masitinib + riluzole	102	-9.04		
mLOCF Rule 5:				
Placebo + riluzole	111	-11.82	2.8619 [0.2944;5.4294]	0.0291
Masitinib + riluzole	104	-8.96		

PRIMARY ANALYSIS

Sensitivity analyses based on reasons for discontinuation confirm primary analysis (all statistically significant)

Change in ALSFRS-R score
Normal Progressors, Masitinib 4.5 mg/kg/d

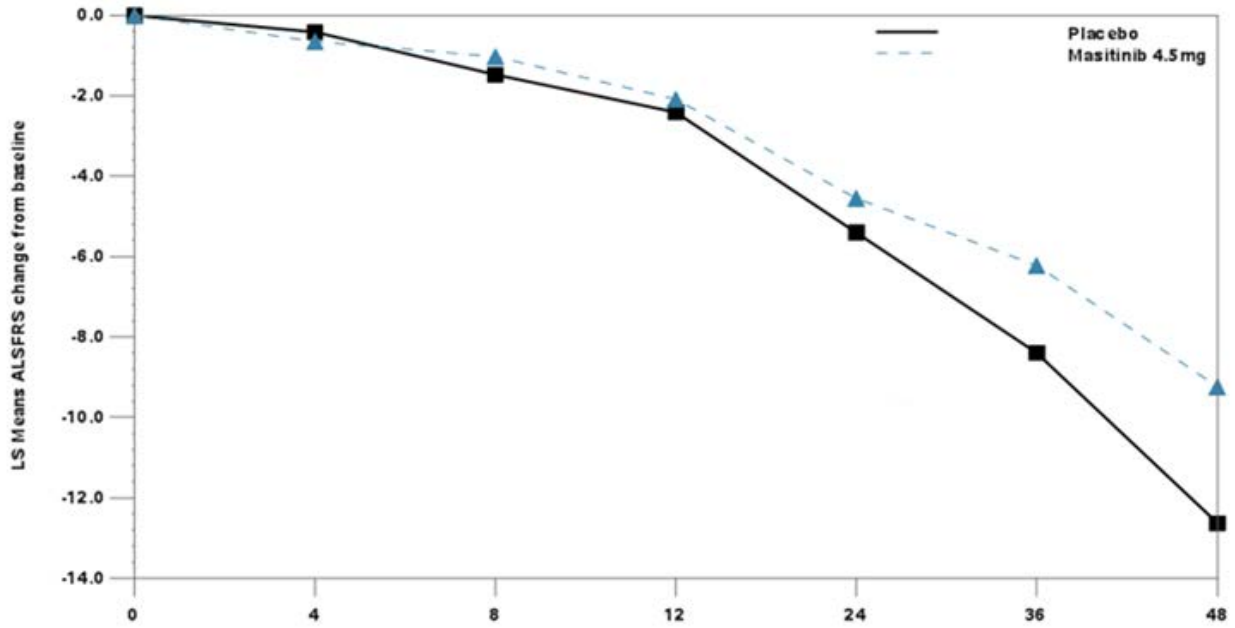
TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) confidence interval]	p-value
Rule 6: Single imputation method copying increment from "similar" patients				
Placebo +riluzole	113	-13.94	2.8873 [0.4392;5.3355]	0.0210
Masitinib +riluzole	105	-11.06		
Rule 7: Single imputation method copying increment from "similar" patients with penalty				
Placebo +riluzole	113	-14.42	2.925 [0.447;5.403]	0.0209
Masitinib +riluzole	105	-11.49		

LS Mean = Least Square Mean

PRIMARY ANALYSIS

On masitinib 4.5, the ALSFRS-R slope slowed down a 27%

ALSFRS-R slope of deterioration
Normal Progressors, Masitinib 4.5 mg/kg/d



Mean change W0-W48:

- **-12.6 in placebo arm => slope: -1.05 per month**
- **-9.2 in masitinib 4.5 arm => slope: -0.77 per month.**

POST HOC ANALYSIS

The benefit increased if shorter disease duration at baseline

Change in ALSFRS-R score - Normal progressor cohort, Masitinib 4.5 mg/kg/day

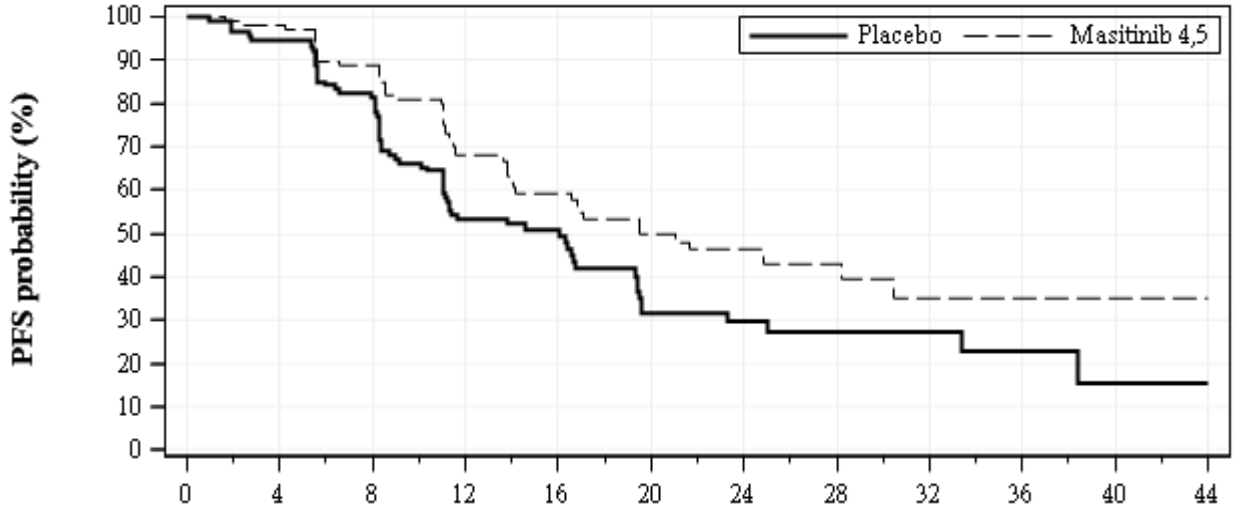
		Rule 1				Rule 6			
	Treatment group	N	LS Mean	Diff. of means [(1-alpha) CI]	p-value	N	LS Mean	Diff. of means [(1-alpha) CI]	p-value
Time to baseline ≤ 36 months (all)	Placebo + riluzole	102	-12.63	3.39 [0.65;6.13]	0.0157	113	-13.94	2.89 [0.44;5.34]	0.0210
	Masitinib + riluzole	99	-9.24			105	-11.06		
Time to baseline ≤ 24 months	Placebo + riluzole	92	-13.46	3.80 [0.93;6.68]	0.0098	106	-14.85	3.31 [0.70;5.93]	0.0131
	Masitinib + riluzole	79	-9.66			91	-11.54		
Time to baseline ≤ 18 months	Placebo + riluzole	85	-13.87	4.40 [1.28;7.53]	0.0061	92	-15.37	4.00 [1.16;6.95]	0.0060
	Masitinib + riluzole	76	-9.46			79	-11.37		

LS Mean= Least Square Mean

SECONDARY ANALYSES

On masitinib 4.5, Progression Free Survival (PFS) was a 25% longer and statistically significant

❖ **Median PFS in NP w/Masitinib 4.5 was 20 months** (95% CI [14; 30]) **vs 16 months in NP w/Placebo** (95% CI [11; 19]), Wilcoxon p = 0.0159



Number of patients at risk

Placebo	113	107	91	49	35	18	14	7	6	3	1	0
Masitinib 4,5	105	103	92	63	41	28	17	12	6	4	1	0

SECONDARY ANALYSES

On masitinib 4.5, the ALSAQ-40 score deteriorated 28.5% less and was statistically significant

Change in ALSAQ-40 score
Normal Progressors, Masitinib 4.5 mg/kg/day

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Rule 1				
Placebo + riluzole	102	27.18	-7.7587 [-13.4543;-2.0631]	0.0078
Masitinib + riluzole	99	19.42		

SECONDARY ANALYSES

On masitinib 4.5 the FVC score deteriorated 22% less and was statistically significant

Change in FVC score
Normal Progressors, Masitinib 4.5 mg/kg/d

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Rule 1				
Placebo + riluzole	102	-33.9	7.5383 [0.7552;14.3214]	0.0296
Masitinib + riluzole	98	-26.45		

SUPPORTIVE ANALYSES

❖ **On masitinib 4.5 the CAFS score improved , but it did not reach significance**

CAFS score
Normal Progressors, Masitinib 4.5 mg(kg/d

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Placebo + riluzole	111	104.73	8.9129 [-6.7297;24.5555]	0.2626
Masitinib + riluzole	104	113.64		

Overall Survival
Normal Progressors, Masitinib 4.5 mg/kg/day

TREATMENT GROUP	N	No. of Events	No. Censored	% Censored	Median [95% CI]	p-value Wilcoxon test
Placebo + riluzole	111	29	84	74.34	NR [25; .]	.
Masitinib + riluzole	104	25	80	76.19	NR [30; .]	0.3727

STEP 1 – MASITINIB 4.5 MG / NORMAL PROGRESSORS

STEP 2 – MASITINIB 3.0 MG / NORMAL PROGRESSORS

STEP 3 – MASITINIB 4.5 MG / NORMAL + FASTER PROGRESSORS

STEP 4 – MASITINIB 3.0 MG / NORMAL + FASTER PROGRESSORS

SAFETY

PRIMARY ANALYSIS

On masitinib 3.0 the ALSFRS-R score deteriorated a 24% less but p= 0.0661

Change in ALSFRS-R score
Normal Progressors, Masitinib 3.0 mg/kg/day

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Rule 1:				
Placebo + riluzole	102	-11.34	2.7317 [-0.1836;5.6469]	0.0661
Masitinib + riluzole	106	-8.61		

- **Progression rate on Placebo: -0.94 points/month**
- **Progression rate on Masitinib 3.0: -0.72 points/month**

SECONDARY ANALYSES

On masitinib 3.0 the ALSAQ-40 score deteriorated 34% less and was statistically significant

Change in ALSAQ-40 score
Normal Progressors, Masitinib 3.0 mg/kg/day

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Rule 1:				
Placebo + riluzole	102	23.65	-8.0446 [-13.7148;-2.3743]	0.0057
Masitinib + riluzole	106	15.60		

SECONDARY ANALYSES

On masitinib 3.0 no significant benefit was observed in FVC, PFS, CAFS and OS

- **Change in FVC was -27.9 with Placebo vs -23.1 with Masitinib 3.0, representing an improvement of 17.3% (p-value = 0.1662)**
- **Median PFS was 16 months (95% CI [11; 19]) with Placebo vs 16 months (95% CI [14; 17]) with Masitinib 3.0 (Wilcoxon p-value = 0.1003)**
- **Change in CAFS score did not show a significant difference**
- **Overall Survival did not show a significant difference**

STEP 1 – MASITINIB 4.5 MG / NORMAL PROGRESSORS

STEP 2 – MASITINIB 3.0 MG / NORMAL PROGRESSORS

STEP 3 – MASITINIB 4.5 MG / NORMAL + FASTER PROGRESSORS

STEP 4 – MASITINIB 3.0 MG / NORMAL + FASTER PROGRESSORS

SAFETY

PRIMARY ANALYSIS

No benefit was observed in Normal+Faster Progressors

Change in ALSFRS-R score
Normal + Faster Progressors, Masitinib 4.5 mg/kg/day

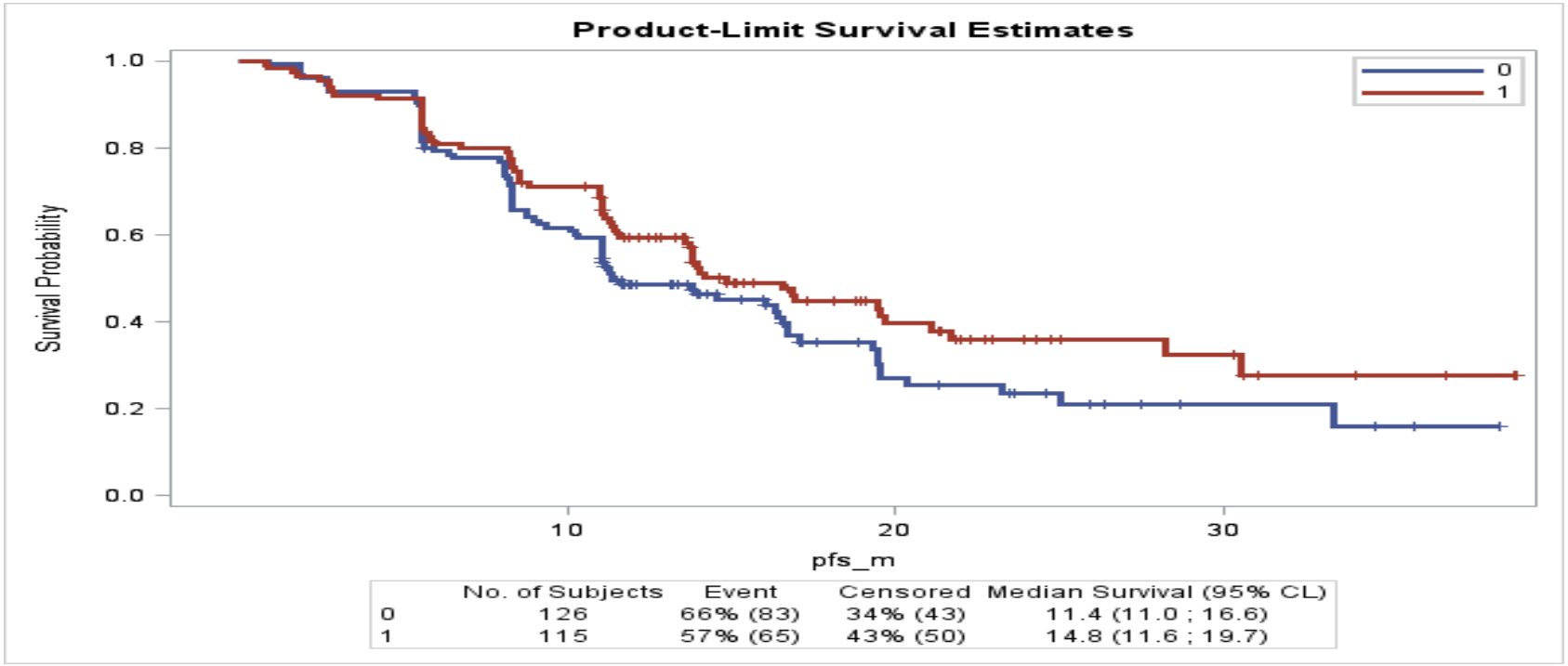
TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Placebo + riluzole	119	-12.97	2.0878 [-0.5498;4.7253]	0.1202
Masitinib + riluzole	120	-10.89		

Change in ALSFRS-R score
Normal + Faster Progressors, Masitinib 3.0 mg/kg/d

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Placebo + riluzole	119	-12.08	1.8002 [-0.9089;4.5093]	0.1918
Masitinib + riluzole	126	-10.27		

POST HOC
PFS on Normal+Fast Progressors: M4.5 vs Placebo, ≤ *24 months*

Treatment group	Total	No. of Events	No. Censored	Median [95% CI]	p-value using Logrank test	Estimate of Hazard Ratio	p-value using Cox-ph model
Placebo	126	83	43	11 [11; 17]	.		.
Masitinib 4.5	115	65	50	15 [12; 20]	0.0809	0.708 [0.508 ; 0.987]	0.0413



STEP 1 – MASITINIB 4.5 MG / NORMAL PROGRESSORS

STEP 2 – MASITINIB 3.0 MG / NORMAL PROGRESSORS

STEP 3 – MASITINIB 4.5 MG / NORMAL + FASTER PROGRESSORS

STEP 4 – MASITINIB 3.0 MG / NORMAL + FASTER PROGRESSORS

SAFETY

SAFETY

Summary of Adverse Events – W0-W48 period (+ 4w)

	Normal Progressors			Normal+Fast Progressors		
	Placebo (N=114)	Masitinib 4.5 (N=105)	Masitinib 3.0 (N=110)	Placebo (N=133)	Masitinib 4,5 (N=129)	Masitinib 3.0 (N=131)
At least one AE	88 (77.2%)	92 (87.6%)	93 (84.5%)	108 (81.2%)	116 (89.9%)	110 (84.0%)
At least one serious AE (non fatal)	19 (16.7%)	30 (28.6%)	21 (19.1%)	28 (21.1%)	39 (30.2%)	25 (19.1%)
AE leading to Death	8 (7.0%)	3 (2.9%)	8 (7.3%)	13 (9.8%)	11 (8.5%)	12 (9.2%)
At least one severe AE	15 (13.2%)	25 (23.8%)	19 (17.3%)	25 (18.8%)	38 (29.5%)	27 (20.6%)
At least one AE leading to study discontinuation (except death)	9 (7.9%)	16 (15.2%)	15 (13.6%)	14 (10.5%)	19 (14.7%)	19 (14.5%)

- Death reported in the above table do not account for all deaths
  - Only those ocurrying while on treatment or within 28 days of discontinuation
- **None of the deaths were related to the study treatment**
- AEs were recorded if onset occurred within 28 days after treatment discontinuation.
  - If it led to death, the AE was reported as an AE leading to death
  - If AE onset occurred after 28 days of treatment discontinuation the AE was not reported

SAFETY

Most frequent (% ≥ 2% in any arm) severe AEs in Normal + Fast Progressors

System Organ Class	Placebo (N=133)	Masitinib 4.5 mg (N=129)	Masitinib 3.0 mg (N=131)	Total (N=393)
At least one severe Adverse Event	20 (15.0%)	37 (28.7%)	28 (21.4%)	85 (21.6%)
Cardiac Disorders	3 (2.3%)	2 (1.6%)	5 (3.8%)	10 (2.5%)
Gastrointestinal Disorders	4 (3.0%)	5 (3.9%)	4 (3.1%)	13 (3.3%)
Lab Safety Investigations	2 (1.5%)	5 (3.9%)	5 (3.6%)	12 (3.1%)
Nervous System Disorders	1 (0.8%)	3 (2.4%)	2 (1.5%)	7 (1.8%)
Respiratory Disorders	7 (5.3%)	13 (10.1%)	13 (9.9%)	33 (8.4%)

STUDY DESIGN

STUDY BASELINE CHARACTERISTICS AND DISPOSITION OF PATIENTS

STUDY RESULTS

SUMMARY

SUMMARY STUDY AB10015

- Oral masitinib at 4.5 mg/kg/day, added to riluzole, demonstrated a significant benefit in ALS patients with baseline ALSFRS-R progression <1.1 points/month:
  - 27% better ΔALSFRS-R score (-9.2 vs -12.6 at 48w). (rate: -0.77 vs -1.05 p/m) (p= 0.0158)
    - Up to 35% in patients with ≤ 18 months of disease
  - 25% better PFS time (20 vs 16 months) (p=0159)
  - 28.5% better ALSAQ-40 score (19.4 vs 27.2) (p= 0.0078)
  - 22% better FVC slope (-26.4 vs -33.9) (p= 0.0296)
  - Benefit seems to be dose and time of disease related
    - Up to 35% better PFS time in N+FP with ≤ 24 months of disease
  - Safety was acceptable, hepatic control recommended

- THE POSITIVE BENEFIT-RISK BALANCE OF THE STUDY SIGNALS THAT MASITINIB PROVIDES A SIGNIFICANT NEW THERAPEUTIC OPTION IN AN ALS POPULATION

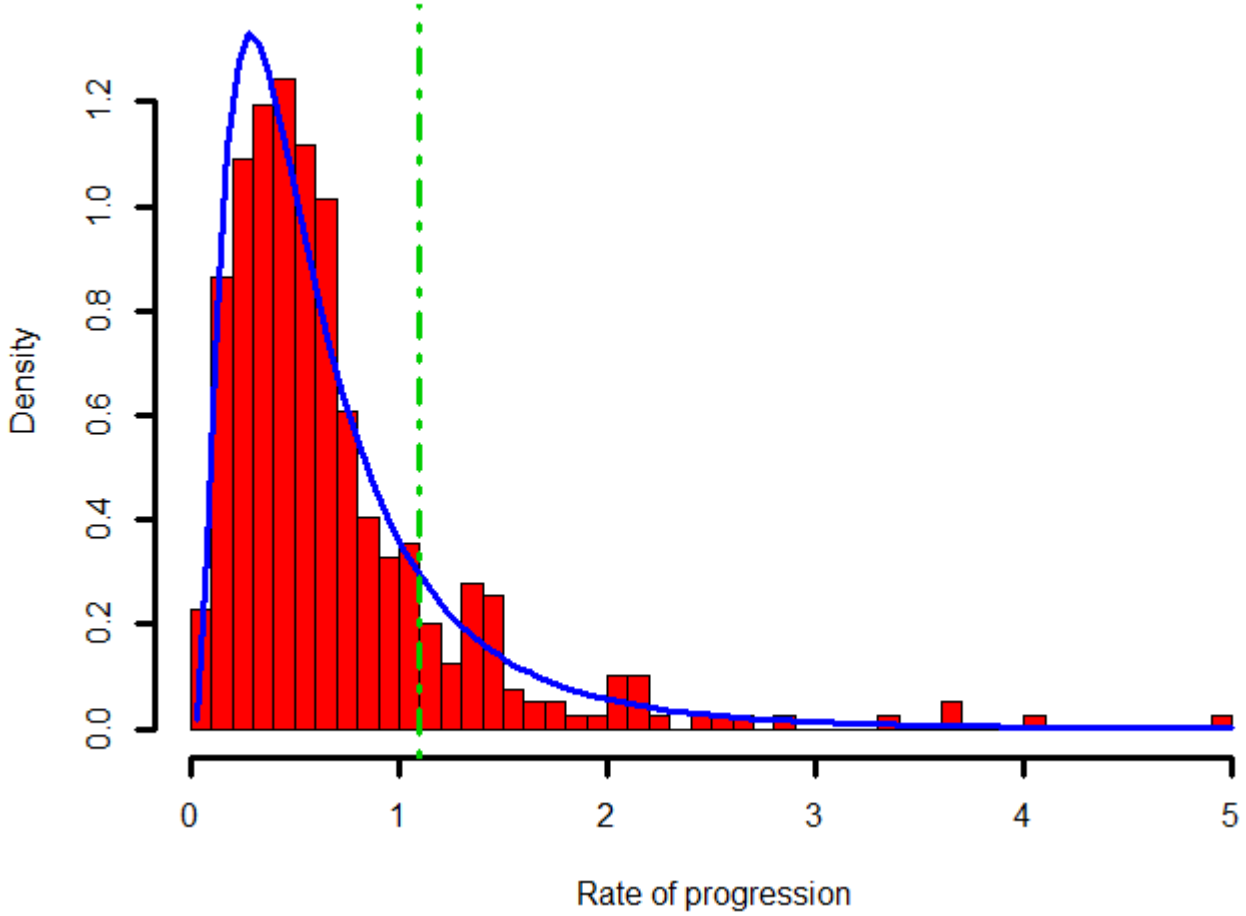
QUESTIONS

Investigators from study AB10015 and AB Science representatives will be available for further discussion after this meeting

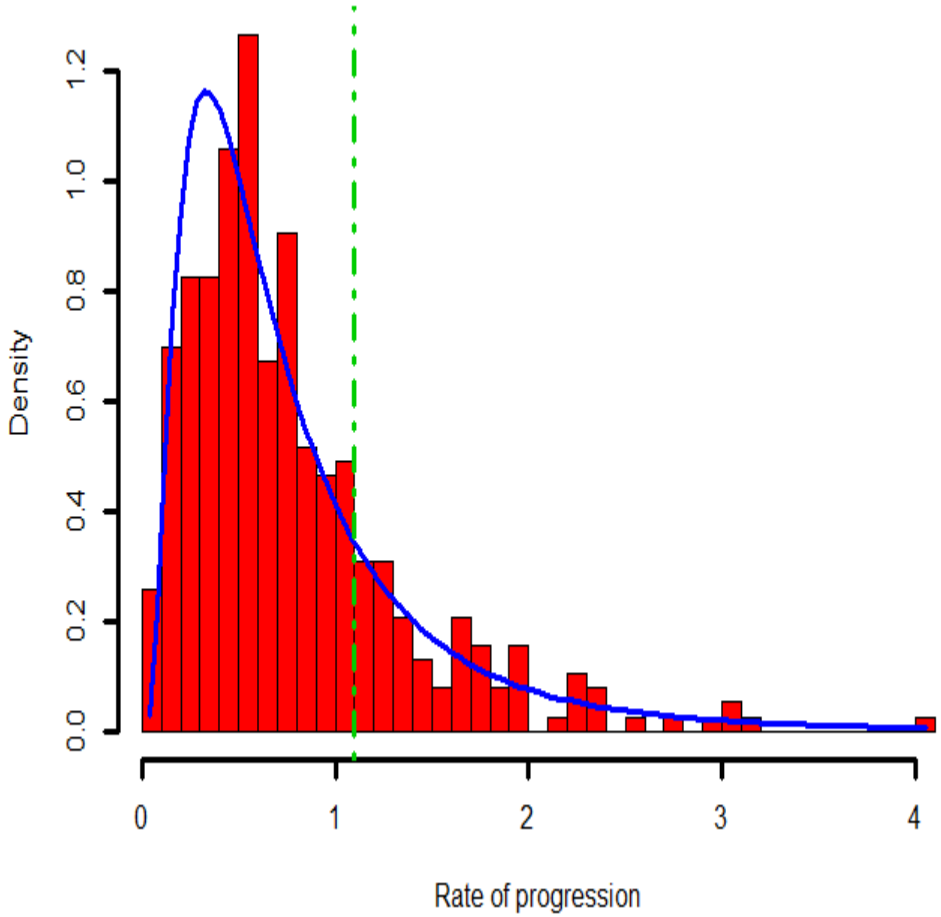
Location: Hall E1.2

Time: 17h30

Histogram with Normal Curve for Baseline Progression Rate



Histogram with Normal Curve for Progression Rate at week 48



Summary of Rate of progression in ALSFRS score by month by treatment arm: at baseline and at end of treatment (mITT)

	Masitinib 4.5		Masitinib 3		Placebo	
	Baseline	End of main part or discontinuation	Baseline	End of main part or discontinuation	Baseline	End of main part or discontinuation
Normal Progressor						
n	105	104	110	110	113	111
Mean (s.d.)	0.49 (0.25)	0.59 (0.33)	0.48 (0.25)	0.56 (0.32)	0.49 (0.25)	0.65 (0.39)
Min, Max	0.03, 1.08	0.06, 1.94	0.09, 1.07	0.04, 1.90	0.05, 1.07	0.07, 2.58
All (Normal + Fast)						
n	128	126	131	131	132	130
Mean (s.d.)	0.72 (0.62)	0.79 (0.57)	0.65 (0.48)	0.75 (0.57)	0.71 (0.69)	0.81 (0.61)
Min, Max	0.03, 3.69	0.06, 3.04	0.09, 2.24	0.04, 3.11	0.05, 5.00	0.07, 4.06

When excluding patients with score for each ALRSRS item <2, as in the Edavarone trial, the masitinib treatment effect increased. Mean change in ALSFRS-R was +4.48 in favor of masitinib (p-value=0.0176) A 35.7% vs 27% improvement

Absolute change from baseline to week 48 in ALSFRS-R score - Rule 1

Treatment group	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Normal progressor cohort, masitinib 4.5 mg/kg/day				
Placebo + riluzole	102	-12.63	3.39 [0.65;6.13]	0.0157
Masitinib + riluzole	99	-9.24		
Normal progressor cohort, masitinib 4.5 mg/kg/day - Score for each ALRSRS item ≥ 2				
Placebo + riluzole	56	-11.03	4.48 [0.84;8.52]	0.0176
Masitinib + riluzole	43	-6.36		

LS Mean= Least Square Mean

Masitinib with 2 key edaravone trial conditions: Patients with ≥ 2 points in each ALSFRS-R item and time of disease ≤ 24 months

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	55	-11.19		.
Masitinib 4,5	40	-6.65	4.54[0.51;8.56]	0.028

Inclusion criteria in the Edavarone pivotal trial restricted the inclusion to one-third of the ALS population enrolled in the masitinib trial:

- **Patients with ≤ 2 years after the onset of ALS**
- **Score for each ALRSRS-R item ≥ 2**
- **Forced Vital Capacity ≥ 80%**

Trial	Masitinib (AB10015)	Patients enrolled in AB10015 study with Edaravone MCI-186-19 trial inclusion criteria
# of patients in ITT	394	117 (30%)
# of patients in Normal Progressors mITT	328	113 (35%)

SAFETY

Drug related Adverse Events Normal Progressors – W0-W48 period (+ 4w)

	Placebo (N=114)	Masitinib 4.5 (N=105)	Masitinib 3.0 (N=110)	Total (N=329)
At least one related AE	30 (26.3%)	67 (63.8%)	50 (45.5%)	147 (44.7%)
At least one serious related AE (non fatal)	1 (0.9%)	8 (7.6%)	4 (3.6%)	13 (4.0%)
Related death	0	0	0	0
At least one related severe AE	1 (0.9%)	5 (4.8%)	2 (1.8%)	8 (2.4%)
At least one related AE leading to study treatment permanent discontinuation*	3 (2.6%)	13 (12.4%)	9 (8.2%)	25 (7.6%)
At least one related AE leading to study treatment temporarily interruption	3 (2.6%)	28 (26.7%)	14 (12.7%)	45 (13.7%)
At least one related AE leading to study treatment dose reduction	0 (0.0%)	12 (11.4%)	1 (0.9%)	13 (4.0%)

Analysis with normal population (Rate of progression<0

New Normal progressors (<0.9)

New normal progressor distribution by Treatment arm				
New Normal Progressor	Armcode			
	Placebo	Masitinib 4.5	Masitinib 3	Total
No	25 (6.39%)	31 (7.93%)	32 (8.18%)	88 (22.51%)
Yes	107 (27.37%)	97 (24.81%)	99 (25.32%)	303 (77.49%)
Total	132 (33.76%)	128 (32.74%)	131 (33.50%)	391 (100.00%)

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (New Normal Progressors < 0.9): Rule 1 - mLOCF method

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	96	-12.7578		.
Masitinib 4,5	91	-9.4223	3.3355[0.5596;6.1114]	0.0188

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (New Normal Progressors < 0.9): Rule 6 - Imputation method

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	105	-14.0139		.
Masitinib 4,5	96	-10.9358	3.0781[0.5532;5.603]	0.0171

Analysis with Modified Normal progressor population (Rate of progression<0.8)

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (Modified Normal Progressors): Rule 1 - mLOCF method

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	90	-12.2914		.
Masitinib 4,5	85	-8.7963	3.4951[0.6217;6.3685]	0.0174

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (Modified Normal Progressors): Rule 6 - Imputation method

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	98	-13.5373		.
Masitinib 4,5	90	-10.2744	3.2629[0.6441;5.8818]	0.0149

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (Modified Normal Progressors): Rule 7 - Imputation method with penalty

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	98	-14.0281		.
Masitinib 4,5	90	-10.6962	3.3319[0.6867;5.9772]	0.0139

Analysis with slow progressor population (Rate of progression<0.5)

Slow progressors (<0.5)

Slow progressor distribution by Treatment arm				
Slow Progressor	Armcode			
	Placebo	Masitinib 4.5	Masitinib 3	Total
No	72 (18.41%)	75 (19.18%)	69 (17.65%)	216 (55.24%)
Yes	60 (15.35%)	53 (13.55%)	62 (15.86%)	175 (44.76%)
Total	132 (33.76%)	128 (32.74%)	131 (33.50%)	391 (100.00%)

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (Slow Progressors): Rule 1 - mLOCF method

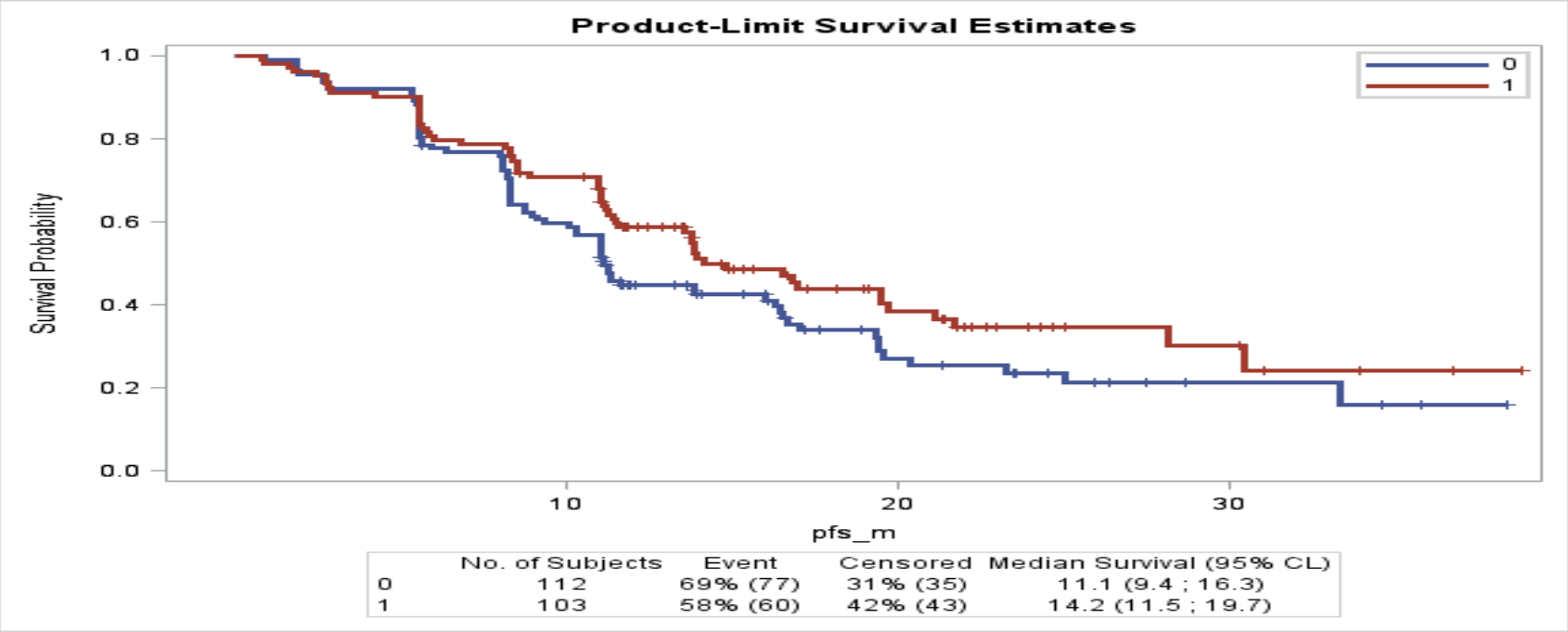
Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	53	-10.6188		.
Masitinib 4,5	50	-7.1229	3.4959[-0.1511;7.1429]	0.0601

Analysis for difference in Mean ALSFRS score: Masitinib 4.5 mg vs Placebo (Slow Progressors < 0.5): Rule 6 - Imputation method

Treatment group	N	LS Mean	Difference of means [95% confidence interval]	p-value (no re-randomisation test)
Placebo	58	-12.0867		.
Masitinib 4,5	52	-9.1444	2.9423[-0.3744;6.259]	0.0815

PFS results on mITT pop (Normal+Fast M4.5 vs Placebo) – *18 months*

Treatment group	Total	No. of Events	No. Censored	Median [95% CI]	p-value using Logrank test	Estimate of Hazard Ratio	p-value using Cox-ph model
Placebo	112	77	35	11 [9.4; 16]	.		.
Masitinib 4.5	103	60	43	14 [11; 20]	0.0766	0.699 [0.495 ; 0.987]	0.0419

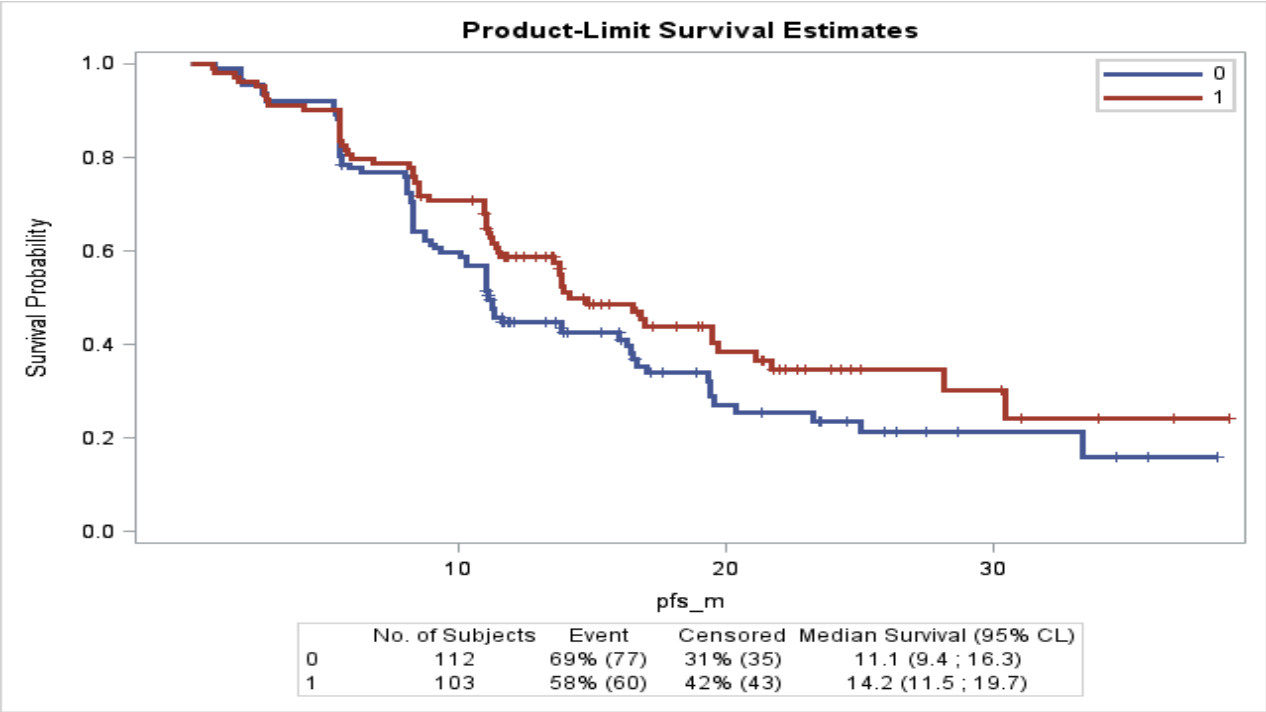


PFS results on mITT pop (Normal+Fast M4.5 vs Placebo) – *18 months*

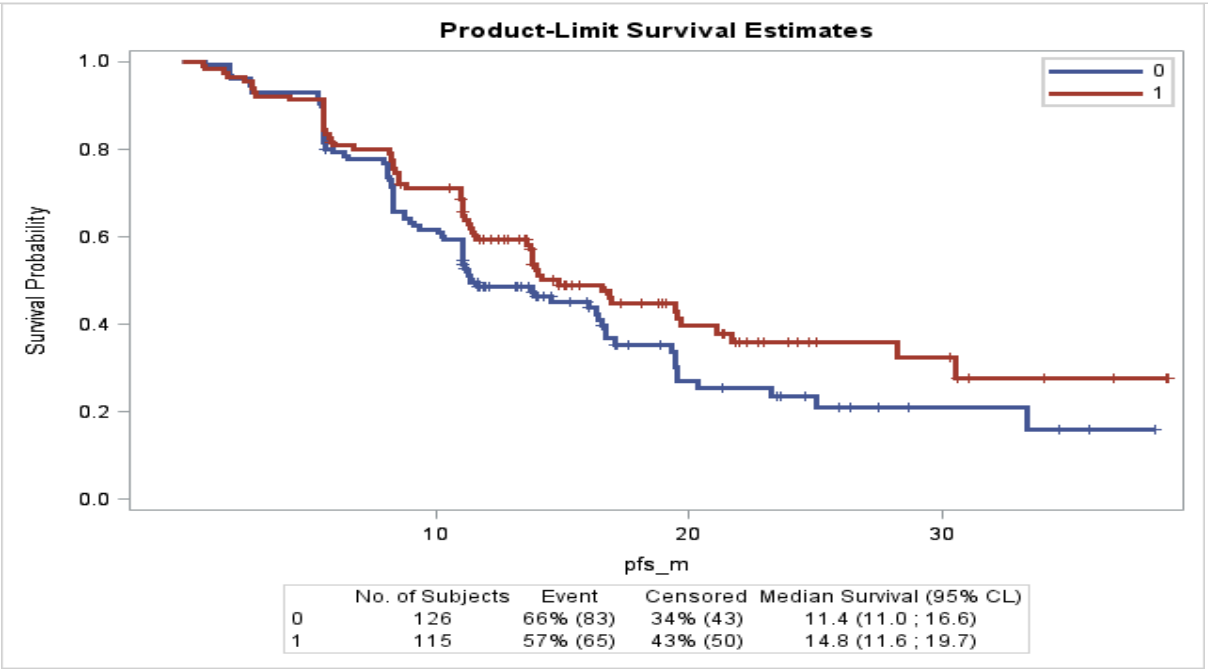
Treatment group	Total	No. of Events	No. Censored	Median [95% CI]	p-value using Logrank test	Estimate of Hazard Ratio	p-value using Cox-ph model
Placebo	112	77	35	11 [9.4; 16]	.		.
Masitinib 4,5	103	60	43	14 [11; 20]	0.0766	0.699 [0.495 ; 0.987]	0.0419

PFS results on mITT pop (Normal+Fast M4.5 vs Placebo) – *24 months*

Treatment group	Total	Treatment group	Total	No. of Events	No. Censored	Median [95% CI]	p-value using Logrank test	Estimate of Hazard Ratio	p-value using Cox-ph model
Placebo	112	Placebo	126	83	43	11 [11; 17]	.		.
Masitinib 4,5	103	Masitinib 4,5	115	65	50	15 [12; 20]	0.0809	0.708 [0.508 ; 0.987]	0.0413



	No. of Subjects	Event	Censored	Median Survival (95% CL)
0	112	69% (77)	31% (35)	11.1 (9.4 ; 16.3)
1	103	58% (60)	42% (43)	14.2 (11.5 ; 19.7)



	No. of Subjects	Event	Censored	Median Survival (95% CL)
0	126	66% (83)	34% (43)	11.4 (11.0 ; 16.6)
1	115	57% (65)	43% (50)	14.8 (11.6 ; 19.7)

The safety of masitinib was acceptable.

Study AB10015 – Summary of AEs – W0-W48 period

	Normal Progressors			Normal+Fast Progressors		
	Placebo (N=114)	Masitinib 4,5 (N=105)	Masitinib 3 (N=110)	Placebo (N=133)	Masitinib 4,5 (N=129)	Masitinib 3 (N=131)
At least one AE	88 (77.2%)	92 (87.6%)	93 (84.5%)	108 (81.2%)	116 (89.9%)	110 (84.0%)
At least one serious AE (non fatal)	19 (16.7%)	30 (28.6%)	21 (19.1%)	28 (21.1%)	39 (30.2%)	25 (19.1%)
AE leading to Death	8 (7.0%)	3 (2.9%)	8 (7.3%)	13 (9.8%)	11 (8.5%)	12 (9.2%)
At least one severe AE	15 (13.2%)	25 (23.8%)	19 (17.3%)	25 (18.8%)	38 (29.5%)	27 (20.6%)
At least one AE leading to study treatment permanent discontinuation (except death)	9 (7.9%)	16 (15.2%)	15 (13.6%)	14 (10.5%)	19 (14.7%)	19 (14.5%)

- **If a patient had an AE onset that occurred within 28 days of treatment discontinuation and that led to death within 48 weeks from randomization, the AE was reported in this table as an AE leading to death.**
- **None of the deaths were related to study treatment.**
- In study AB10015, adverse events were recorded if AE onset occurred within 28 days after treatment discontinuation.
- If a patient had an AE onset that occurred after 28 days of treatment discontinuation and that led to death, the AE was not reported by the investigator as per protocol.

Summary of Adverse Events
Normal+Fast progressor patients (Safety analysis set)

	Placebo (N=133)	Masitinib 4,5 (N=129)	Masitinib 3 (N=131)
At least one AE	108 (81.2%)	116 (89.9%)	110 (84.0%)
At least one serious AE (non fatal)	28 (21.1%)	39 (30.2%)	25 (19.1%)
Death	13 (9.8%)	11 (8.5%)	12 (9.2%)
At least one severe AE	25 (18.8%)	38 (29.5%)	27 (20.6%)
At least one AE leading to study treatment permanent discontinuation (except death)	14 (10.5%)	19 (14.7%)	19 (14.5%)

SAFETY

Most frequent (% ≥ 2% in any arm) severe AEs in Normal Progressors

System Organ Class / Preferred Term	Placebo (N=114)	Masitinib 4.5 mg (N=105)	Masitinib 3.0 mg (N=110)	Total (N=329)
At least one severe Adverse Event	15 (13.2%)	25 (23.8%)	19 (17.3%)	59 (17.9%)
Cardiac Disorders	2 (1.8%)	2 (1.9%)	5 (4.5%)	9 (2.7%)
Gastrointestinal Disorders	4 (3.5%)	5 (4.8%)	3 (2.7%)	12 (3.6%)
Lab Investigations	2 (1.8%)	4 (3.8%)	4 (3.6%)	10 (3.0%)
Nervous System Disorders	0 (0.0%)	3 (2.9%)	2 (1.8%)	5 (1.5%)
Respiratory Disorders	5 (4.4%)	4 (3.8%)	8 (7.3%)	17 (5.2%)

SAFETY

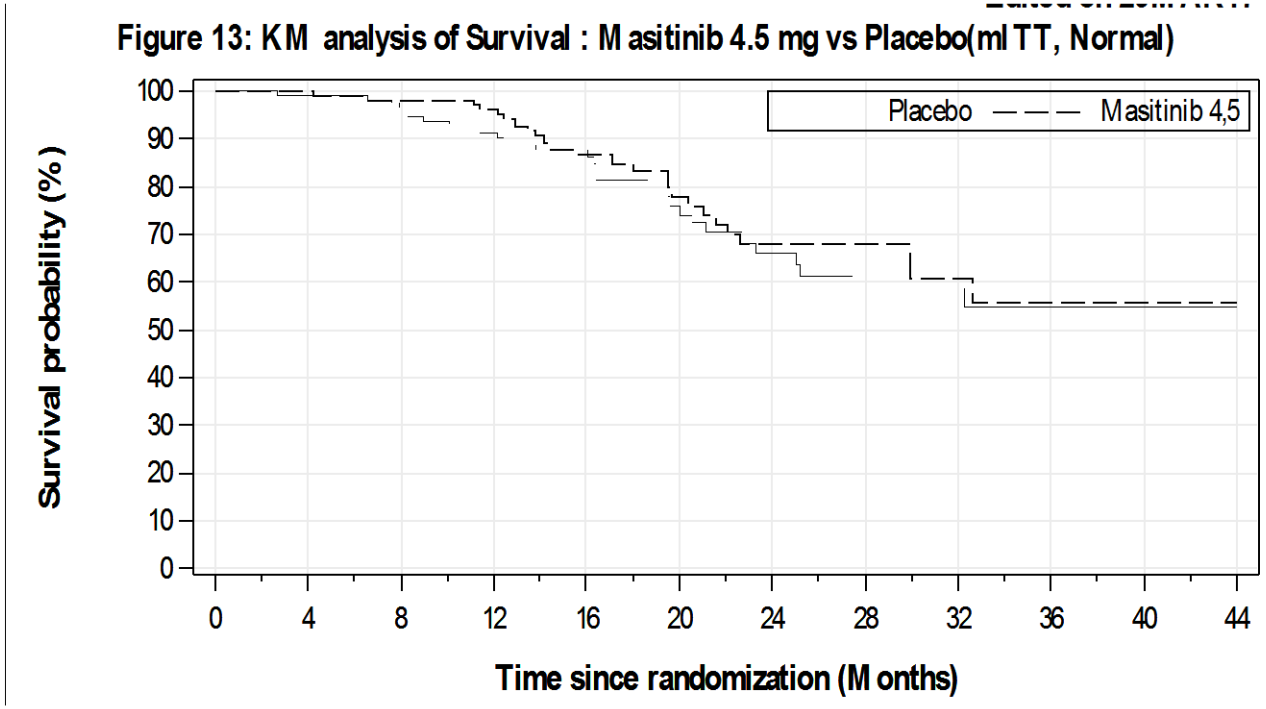
Most frequent (% SOC ≥ 2% in any arm) severe AEs in Normal Progressors

System Organ Class / Preferred Term	Placebo (N=114)	Masitinib 4.5 mg (N=105)	Masitinib 3.0 mg (N=110)	Total (N=329)
At least one severe Adverse Event	15 (13.2%)	25 (23.8%)	19 (17.3%)	59 (17.9%)
Cardiac Disorders	2 (1.8%)	2 (1.9%)	5 (4.5%)	9 (2.7%)
Cardio-Respiratory Arrest*	1 (0.9%)	1 (1.0%)	4 (3.6%)	6 (1.8%)
Gastrointestinal Disorders	4 (3.5%)	5 (4.8%)	3 (2.7%)	12 (3.6%)
Dysphagia*	3 (2.6%)	5 (4.8%)	2 (1.8%)	10 (3.0%)
Lab Investigations	2 (1.8%)	4 (3.8%)	4 (3.6%)	10 (3.0%)
Nervous System Disorders	0 (0.0%)	3 (2.9%)	2 (1.8%)	5 (1.5%)
Respiratory Disorders	5 (4.4%)	4 (3.8%)	8 (7.3%)	17 (5.2%)
Respiratory Failure*	1 (0.9%)	1 (1.0%)	4 (3.6%)	6 (1.8%)
Dyspnoea*	2 (1.8%)	2 (1.9%)	0 (0.0%)	4 (1.2%)

*Only those preferred terms with significant frequencies are shown here

There was a numeral but not significant benefit on overall survival at 4.5 mg/kg/day in the Normal progressors.

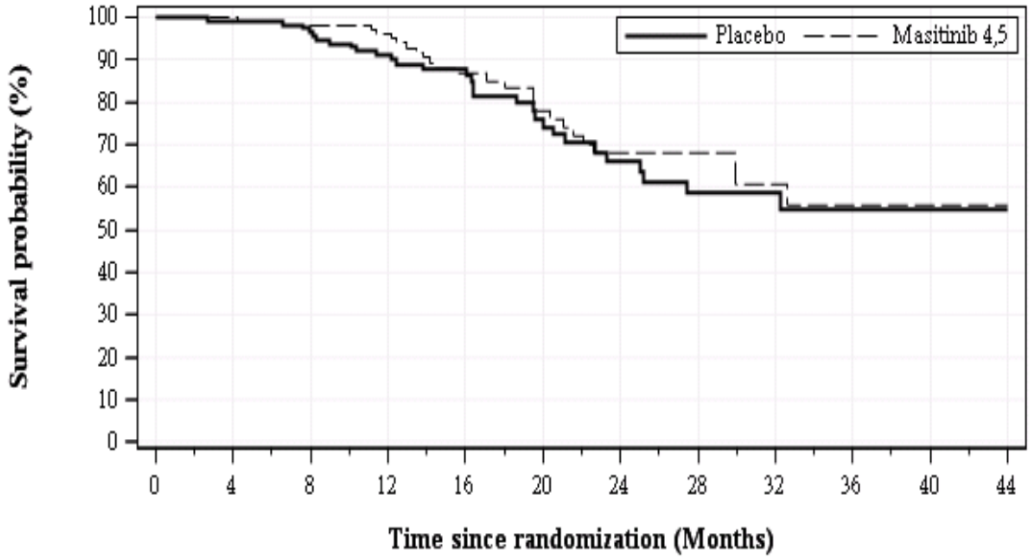
Analysis of Survival, "Normal progressor" cohort, masitinib 4.5 mg/kg/day



Treatment group	N	No. of Events	No. Censored	Percentage censored	Median [95% CI]	p-value using Wilcoxon test
Placebo + riluzole	111	29	84	74.34	NR [25; .]	.
Masitinib + riluzole	104	25	80	76.19	NR [30; .]	0.3727

Survival Probability –ALS final results

Figure 13: KM analysis of Survival : Masitinib 4.5 mg vs Placebo(ITT, Normal)



Time point	Survival Probability	
	Masitinib 4.5	Placebo
Month 12	96.06%	91.00%
Month 18	83.35%	81.52%
Month 24	67.95%	66.08%
Month 28	67.95%	58.44%

e events by SOC/PT till week 48 for Normal + Fast progressor patients (Safety analysis set)

STUDY DESIGN

Interim analysis

- **Type I error of 0.0311 was used to detect treatment effect during the interim analysis and treatment effect was found to be significant**
- **A procedure was documented describing who performed the analysis and who access the interim analysis results**
  - Randomization list remained with an outside independent vendor
  - Statistical analyses were performed by an outside independent vendor
  - AB Science biometry team and clinical study team remained blinded
  - Only a very small regulatory team received the data in order to initiate discussions with regulatory authorities
- Since the interim analysis of the primary endpoint was significant, it was sufficient to do the final efficacy analyses in a descriptive manner. However, if any statistical interpretation had to be made for the final analyses, the interim analysis had to be considered as disregarded and the primary and secondary analyses of the final data had to be performed at a significance level of alpha = 0.05, consequently

STUDY DESIGN

❖ **Rule 2: LOCF-R2**

- Same as mLOCF method for imputation of missing data, as defined in Rule 1
- But imputation was also done in discontinuation due to **study procedure**

❖ **Rule 3: LOCF-R3**

- Same as above, Rule 1
- But imputation was also done in discontinuation due to **travel issue**

❖ **Rule 4: LOCF-R4**

- Same as above, Rule 1
- But imputation was also be done in discontinuation due to **travel issue or study procedure**

❖ **Rule 5: LOCF-Compliant**

- LOCF method for all patients but it excludes data of **non-compliant patients** after the non-compliance. For these patients, imputation uses the last available score before the non-compliance.

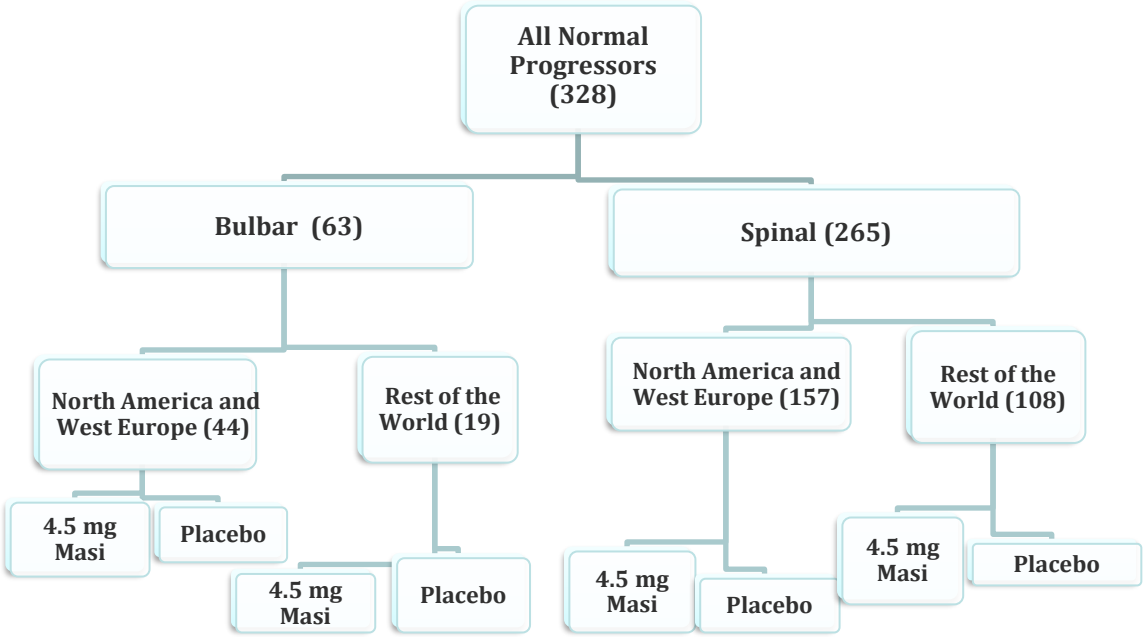
❖ **These analyses follow Guideline EMA/CPMP/EWP/1776/99 Rev. 1:**

- *« An attractive approach for imputing missing data may be to employ a different pre-specified imputation technique for each different reason for withdrawal, rather than the same technique for all patients »*

STUDY DESIGN

❖ **Rule 6: Single imputation method copying increment from "similar" patients**

- Imputation is done by clustering of "similar" patients by site of onset, region and treatment group, and then using the average increment within group.



❖ **This analysis follows Guidance *EMA/CPMP/EWP/1776/99 Rev. 1*:** *« Other simple approaches for single imputation of missing data are to replace the unobserved measurements by values derived from other sources. Possible sources include information from the same subject collected before withdrawal, from other subjects with similar baseline characteristics, a predicted value from an empirically developed model or historical data »*

STUDY DESIGN

❖ **Rule 7: Single imputation method copying increment from "similar" patients with penalty**

- *Imputation is done by clustering of "similar patients" by site of onset, region and treatment group, and then using the mean increment within group + penalty of 50% to those patients who discontinued early due to lack of efficacy.*

❖ **This imputation method is based on Guidance *EMA/CPMP/EWP/1776/99 Rev. 1*: «** *An attractive approach for imputing missing data may be to employ a different pre-specified imputation technique for each different reason for withdrawal, rather than the same technique for all patients »*

- *Permutt T: Sensitivity analysis for missing data in regulatory submissions. Statistics in Medicine 35(17): 2876-2879, 2016*

STUDY DESIGN

Summary of sensitivity analyses for primary analysis

Cause of discontinuation	Primary	Rule 2	Rule 3	Rule 4	Rule 5	Rule 6	Rule 7
Sensitivity analyses							
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	LOCF	Imput.	Imput.
Other	OC	OC	OC	OC	LOCF	Imput.	Imput.
Non compliance	OC	OC	OC	OC	OC	Imput.	Imput.

PRIMARY ANALYSIS

Datasets for the Primary and sensitivity analysis
Normal Progressors cohort, Masitinib 4.5 mg/kg/day

	Patients with LOCF data / mITT population						
	Primary	**Rule 2**	**Rule 3**	**Rule 4**	**Rule 5**	**Rule 6**	**Rule 7**
Placebo + riluzole	102/113	103/113	107/113	108/113	111/113	113/113	113/113
Masitinib 4.5 + riluzole	99/105	99/105	102/105	102/105	104/105	105/105	105/105

There was no benefit on CAFS or overall survival at 3 mg/kg/day in the Normal progressors.

CAFS score, "Normal progressor" cohort, masitinib 3 mg/kg/day

Treatment group	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Placebo + riluzole	111	111.69	6.8446 [-8.894;22.5832]	0.3923
Masitinib + riluzole	110	118.54		

Analysis of Survival, "Normal progressor" cohort, masitinib 3 mg/kg/day– Study AB10015

Treatment group	**N**	**No. of Events**	**No. Censored**	**% Censored**	**Median. [95% CI]**	**p-value Wilcoxon test**
Placebo + riluzole	113	29	84	74.34	NR [25; .]	.
Masitinib + riluzole	110	34	76	69.09	28 [23; 43]	0.7637

STEP 1 – MASITINIB 4.5 MG / NORMAL PROGRESSORS

STEP 2 – MASITINIB 3.0 MG / NORMAL PROGRESSORS

STEP 3 – MASITINIB 4.5 MG / NORMAL + FASTER PROGRESSORS

STEP 4 – MASITINIB 3.0 MG / NORMAL + FASTER PROGRESSORS

SAFETY

PRIMARY ANALYSIS

There was no benefit on ALSFRS-R at 3.0 mg/kg/day in the Normal + Faster Progressors

Change in ALSFRS-R score
Normal + Faster Progressors, Masitinib 3.0 mg/kg/day

TREATMENT GROUP	N	LS Mean	Difference of means [(1-alpha) CI]	p-value
Placebo + riluzole	119	-12.08	1.8002 [-0.9089;4.5093]	0.1918
Masitinib + riluzole	126	-10.27		

STUDY DESIGN

Handling of missing values

- Missing values of ALSFRS-R were replaced based on the Modified Last Observation Carried Forward (mLOCF) method for the primary analysis (Rule 1)

- Four sensitivity analyses were performed based on reasons of discontinuation (Rules 2 to 5)

- Two key sensitivity analyses were provided incorporating all patients (ITT population) based on the imputation model for missing values (Rule 6 & 7).

Masitinib as an add on therapy to riluzol is beneficial in the treatment of ALS, with an acceptable tolerability: FUTURE CLINICAL DEVELOPMENT

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ENCALS Satelite meeting, Ljubljana, 20th May 2017

STUDY AB14008 PRELIMINARY DESIGN I

- Primary Objective: To confirm AB10015 results
- Dosing regime to optimize benefit/risk balance
- Dose scalating scheme: 3.0 to 4.5 to 6.0 mg/kg/d
- Each switch subjected to toxity control
- Exclusion of Fast Progressors (≥1.1 p/m)
- Double blind, placebo controlled
- All on riluzole

STUDY AB14008 PRELIMINARY DESIGN II

- Two treatment arms, randomization 1:1
  - G1: Masitinib 3.0 mg/kg/d 4 wks, then 4.5 mg 4 wks, then 6.0 mg
  - G2: Placebo
- Treatment duration: 48 weeks
- Primary endpoint: ALSFRS-R score
- Secondary assessments: PFS, FVC, ALSAQ-40, CAFS, OS, HHD, CGI
- Ancillary studies: PK, BM, PG

STUDY AB14008 PRELIMINARY DESIGN III

- Planned enrolment: 400 patients
- Estimated schedule:
  - Start date: Q3 2017
  - Recruitment: Q3 2017 – Q3 2018
  - Final data readout: Q3 2019
  - Results: Q4 2019
- No stop for interim analysis unless required by IDMC
- Anticipated strong recruitment rate

Masitinib in ALS
Future Clinical Development

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15th ENCALS meeting, Ljubjiana 18th May 2017