Mitsubishi Tanabe Pharma America

The Influence of Clinical Study Inclusion Criteria on Baseline Characteristics and Disease Progression in Amyotrophic Lateral Sclerosis

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Disclosures

- JK is a consultant for Mitsubishi Tanabe Pharma America, Inc. (MTPA)
- JP, SA, and WA are employees of MTPA
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- This presentation is provided by Mitsubishi Tanabe Pharma America, Inc. for informational and educational purposes only

Background

- The clinical course of amyotrophic lateral sclerosis (ALS) shows a high degree of variability in disease progression[1]
- This heterogeneity creates challenges for conducting clinical studies in ALS[1]
- As a result, a variety of strategies have been employed to help reduce heterogeneity while selecting for patients who are expected to experience adequate disease progression to allow for measurement of intervention effect[2]
- One of the main strategies employed is the use of specific study inclusion criteria[2]
- However, despite the many combinations of inclusion criteria that have been used in clinical studies, little is known regarding their effects on baseline characteristics or on natural disease progression in the selected cohorts of patients

1. Brooks BR, Jorgenson JA, Newhouse BJ, et al. *Am J Manag Care.* 2018;24(9 suppl):S175-S186.
2. Palumbo JM, Hubble J, Apple S, et al. *Amyotroph Lateral Scler Frontotemporal Degener.* 2019;20(5-6):421-431.

Objective

- To assess disease progression rate predictors and correlations among study entry criteria, baseline characteristics, and the outcome of a slope change in scores on the ALS Functional Rating Scale-Revised (ALSFRS-R)

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Methods

- Literature searches identified randomized, controlled clinical studies in ALS published during the past 15 years
- Studies were selected for analysis based on the availability of ALSFRS-R outcomes data
- The following clinical study data were extracted for each study:

Entry Criteria	Baseline Characteristics	Outcomes
• Disease duration • FVC/SVC • El Escorial diagnosis category	• Disease duration • FVC/SVC • Age • Gender • Initial symptom • Riluzole use • ALSFRS-R total score	• ALSFRS-R slope

- The following analyses were conducted:
  - Correlation analysis
  - Linear regression modeling analysis
  - Decision tree analysis

FVC=forced vital capacity; SVC=slow vital capacity.

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Studies Included in the Analyses

			Entry Criteria			Baseline Characteristics							Outcome
First author	Drug	Placebo N	El Escorial	Disease duration	Respiratory function (%p)	Men	Age, yr (mean±SD)	Disease duration (mo)	FVC/SVC (%p)	Initial symptom (% limb)	Riluzole use (%)	ALSFRS-R score	ALSFRS-R slope (units/mo)
Meininger et al[1]	Ozanezumab	151	Def, Prob, Lab, Poss	≤2.5 yr	SVC ≥65%	64%	55.5±11.0	17.9	95.7%	78%	87%	38.4	−0.84
Ludolph et al[2]	Rasagiline	125	Def, Prob, Lab, Poss	≤3 yr	SVC ≥50%	67%	60.4±10.2	17.9	85.4%	78%	100%	38.3	−1.02
Miller et al[3]	NP001	42	Def, Prob	≤3 yr	FVC ≥70%	69%	53.7±9.52	17.2	*92.4%*	83%	69%	38.2	−0.89
Cudkowicz et al (2013)[4]	Dexpramipexole	468	Def, Prob, Lab, Poss	≤2 yr	SVC ≥65%	64%	57.3±11.3	15.5	89.1%	76%	75%	37.9	−1.12
Statland et al[5]	Rasagiline	20	Def, Prob, Lab	≤2 yr	FVC ≥75%	65%	57.5±8.5	16.4	94.4%	85%	80%	35.9	−1.25
Gordon et al[6]	Minocycline	206	Def, Prob, Lab	≤3 yr	FVC ≥75%	64%	57.7±10.9	18.1	93.8%	80%	66%	37.9	−1.04
Cudkowicz et al (2014)[7]	Ceftriaxone	173	Def, Prob, Lab, Poss	≤3 yr	FVC >60%	58%	55±10	18.0	91%	79%	74%	36.9	−1.22
Elia et al[8]	TUDCA	17	Def, Prob	≤1.5 yr	FVC ≥75%	67%	54.0±12.2	13.2	94.9%	*80%*	100%	38.7	−1.69
Writing Group[9]	Edaravone	68	Def, Prob	≤2 yr	FVC ≥80%	59%	60.1±9.6	12.7	97.4%	79%	92%	41.8	−1.358
Amirzagar et al[10]	GCSF	20	Def, Prob	≤2 yr	FVC >50%	60%	52.5±11.6	15.7	*92.4%*	*80%*	70%	36.6	−1.61

Data in italics are imputed as the column average of non-missing data.
GCSF=granulocyte colony-stimulating factor; TUDCA=tauroursodeoxycholic acid.

1. Meininger V, Genge A, van den Berg LH, et al. *Lancet Neurol*. 2017;16(3):208-216.
2. Ludolph AC, Schuster J, Dorst J, et al. *Lancet Neurol*. 2018;17(8):681-688.
3. Miller RG, Block G, Katz JS, et al. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(3):e100.
4. Cudkowicz ME, van den Berg LH, Shefner JM, et al. *Lancet Neurol*. 2013;12(11):1059-1067.
5. Statland JM, Moore D, Wang Y, et al. *Muscle Nerve*. 2019;59(2):201-207.
6. Gordon PH, Moore DH, Miller RG, et al. *Lancet Neurol*. 2007;6(12):1045-1053.
7. Cudkowicz ME, Titus S, Kearney M, et al. *Lancet Neurol*. 2014;13(11):1083-1091.
8. Elia AE, Lalli S, Monsurro MR, et al. *Eur J Neurol*. 2016;23(1):45-52.
9. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. *Lancet Neurol*. 2017;16(7):505-512.
10. Amirzagar N, Nafissi S, Tafakhori A, et al. *J Clin Neurol*. 2015;11(2):164-171.

Correlation Analyses Overview

First analysis

Entry Criteria	Baseline Characteristics	Outcomes
• Disease duration • FVC/SVC • El Escorial diagnosis category	• Disease duration • FVC/SVC • Age • Gender • Initial symptom • Riluzole use • ALSFRS-R total score	• ALSFRS-R slope

Second analysis

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Correlations Among Entry Criteria and Baseline Characteristics

- Analyses of correlations between entry criteria and baseline characteristics were conducted with combined data from the placebo group and the active treatment group
  - Analyses of correlations with the study outcome, ALSFRS-R slope, were conducted only with placebo group data
- Among the entry criteria analyzed, disease duration and FVC entry criteria correlated with baseline ALSFRS-R score
- In addition, El Escorial entry criteria correlated with baseline FVC

Spearman correlation analyses

		Baseline Characteristics						
		Disease duration	FVC/SVC	ALSFRS-R	Age	Gender	Initial symptom	Riluzole use
Entry Criteria	Disease duration	**0.833; *P*<.001**	−0.137; *P*=.543	**−0.453; *P*=.020**	0.038; *P*=.855	0.289; *P*=.152	0.224; *P*=.316	−0.345; *P*=.084
	FVC/SVC	−0.357; *P*=.062	**0.731; *P*<.001**	**0.516; *P*=.005**	0.273; *P*=.160	−0.01; *P*=.962	0.389; *P*=.0734	0.181; *P*=.376
	El Escorial	0.246; *P*=.207	**−0.636; *P*<.001**	−0.194; *P*=.324	0.197; *P*=.314	−0.101; *P*=.608	−0.404; *P*=.0623	−0.129; *P*=.531

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Correlations Among Baseline Characteristics and ALSFRS-R Slope

- Among baseline characteristics, baseline disease duration correlated with ALSFRS-R slope during the study

Pearson correlation analysis of baseline characteristics with ALSFRS-R slope

Baseline Characteristic	Pearson coefficient	*P*-value
Disease duration	**0.72013**	**.0188**
FVC/SVC	−0.31224	.452
ALSFRS-R score	−0.00101	.998
Age	0.29263	.412
Gender	0.34771	.325
Initial symptom	−0.1004	.813
Riluzole use	−0.2239	.534

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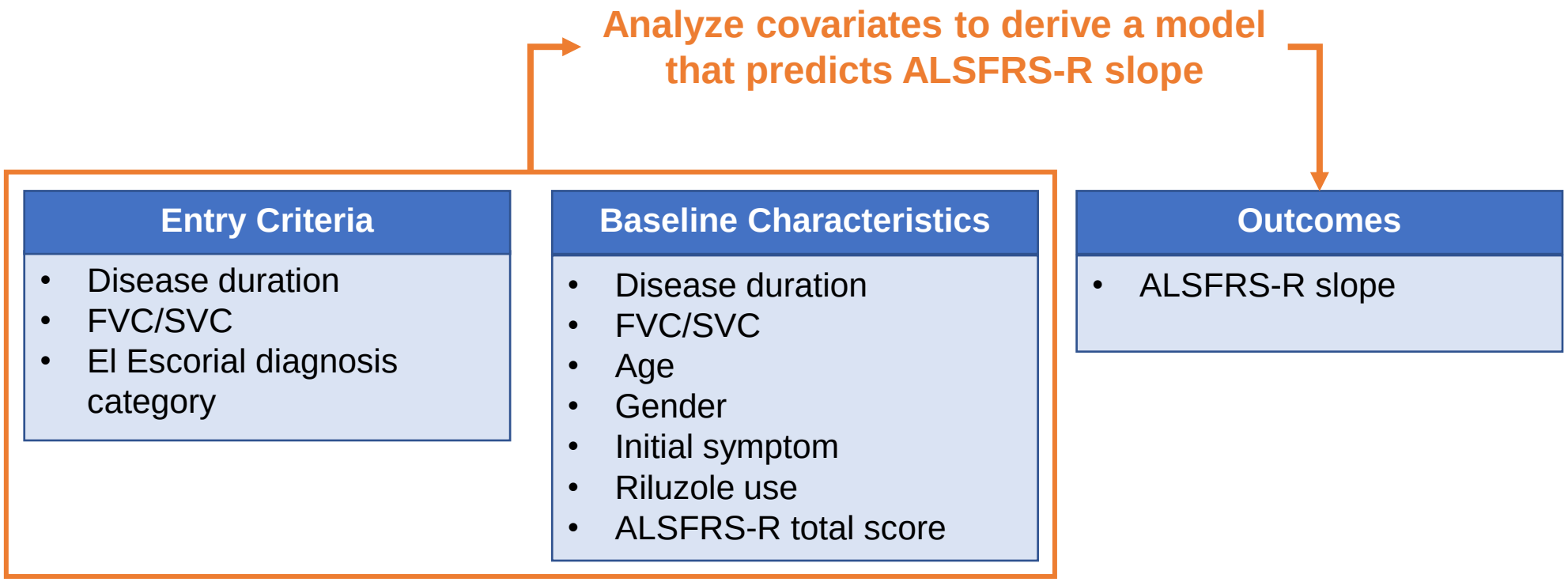
Multiple Linear Regression Modeling Overview

- Multiple linear regression modeling is used to identify which parameters predict the outcomes (ALSFRS-R slope)



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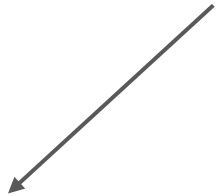
Multiple Linear Regression Modeling

- A total of 8 covariates were considered for the initial model
  - Entry criteria: FVC/SVC and El Escorial
  - Baseline characteristics: Disease duration, ALSFRS-R score; age, gender, initial symptom, and riluzole use
- Baseline disease duration and baseline ALSFRS-R score were the strongest predictors of ALSFRS-R slope
- Final model

Linear regression parameters

Parameter	Estimate	*P*-value	95% CI
beta1	0.149	.0026	(0.0719, 0.226)
beta2	0.103	.0390	(0.00691, 0.199)



ALSFRS-R slope = Intercept + 0.149×baseline disease duration + 0.103×baseline ALSFRS-R

CI=confidence interval.

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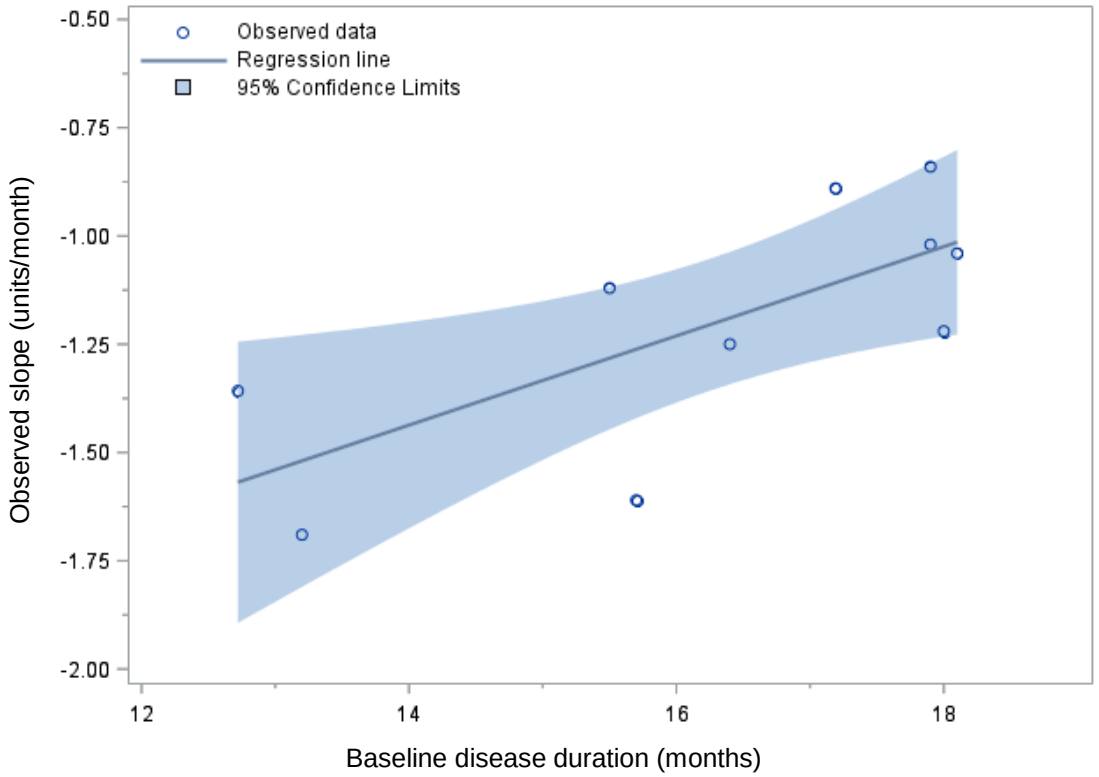
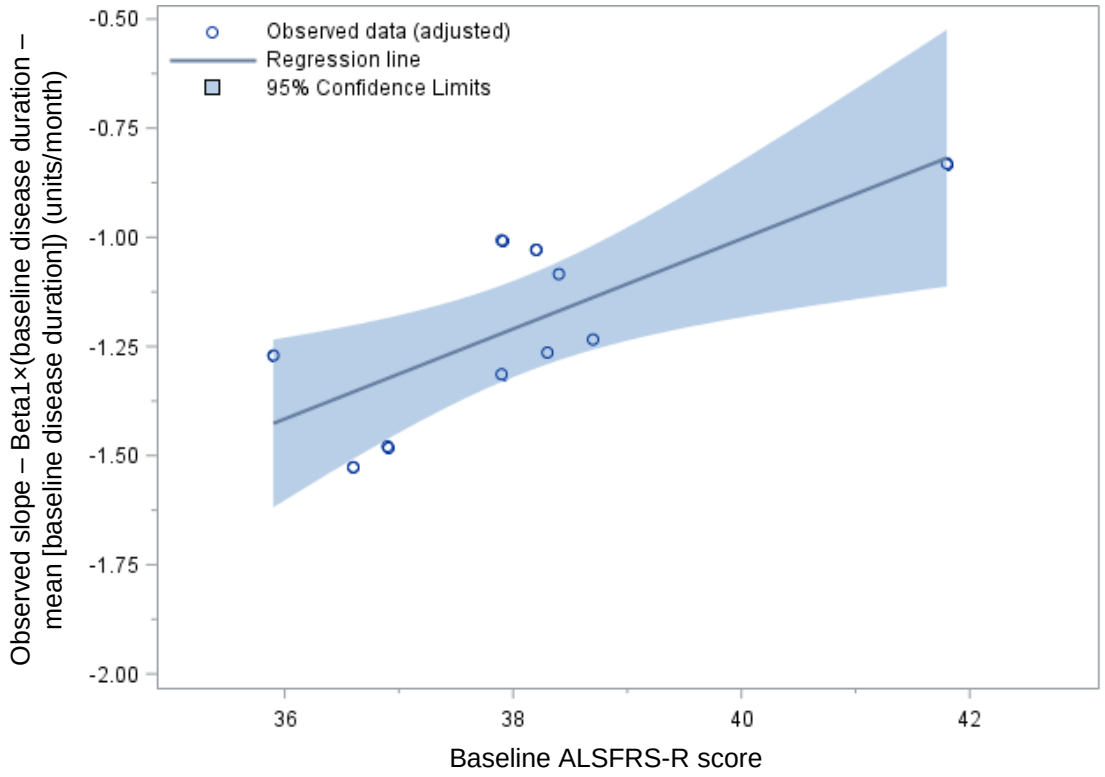
Linear Regression Graphs

Slope of ALSFRS-R vs Baseline Disease Duration



Slope of ALSFRS-R Adjusted by the Regression Model vs the Baseline ALSFRS-R Score



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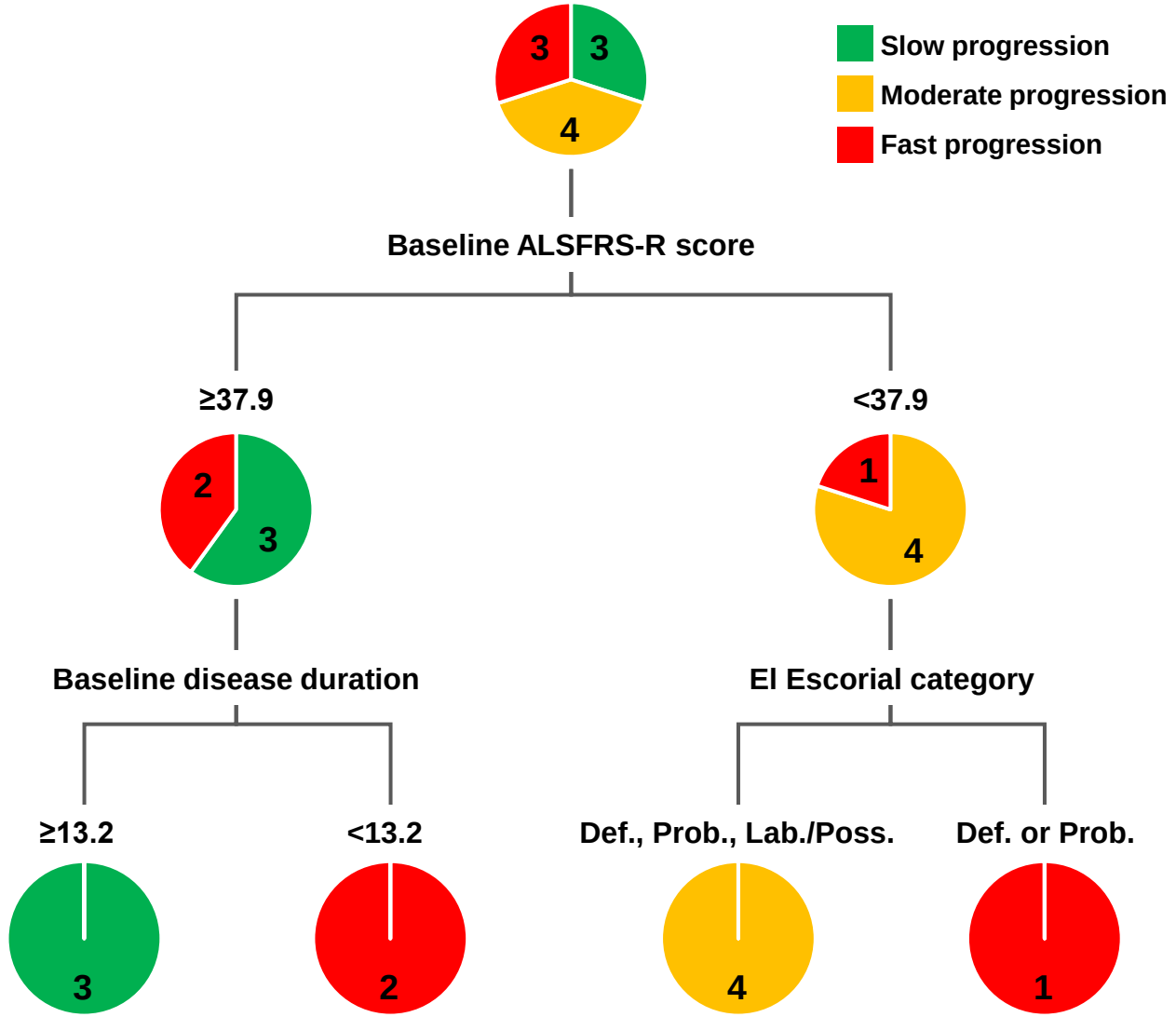
Decision Tree Analysis

- To facilitate the analysis, ALSFRS-R slope was split into 3 groups

Group	ALSFRS-R slope
Slow progression	<1.02 points/month
Moderate progression	≥1.02 and ≤1.33 points/month
Fast progression	>1.33 points/month

- Decision tree analysis indicated that separation of the study populations into fast, medium, and slow progressors was predicted by a combination of baseline ALSFRS-R score, baseline disease duration, and El Escorial entry criteria



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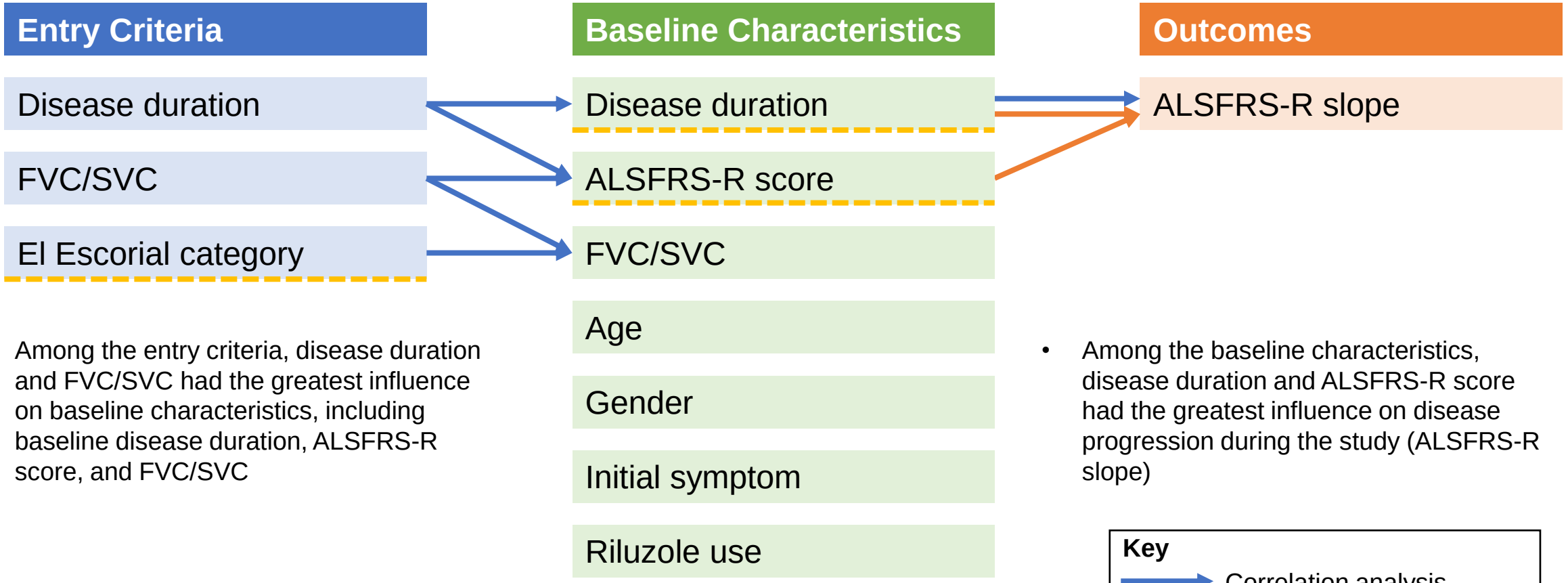
Summary of Analyses



- Among the entry criteria, disease duration and FVC/SVC had the greatest influence on baseline characteristics, including baseline disease duration, ALSFRS-R score, and FVC/SVC

- Among the baseline characteristics, disease duration and ALSFRS-R score had the greatest influence on disease progression during the study (ALSFRS-R slope)

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Conclusions

- Analysis of ALS clinical studies indicated that disease duration and FVC inclusion criteria have effects on baseline characteristics, such as disease duration and ALSFRS-R score
- These 2 baseline characteristics, in turn, affect the ALSFRS-R slope outcome
- Thus, selection of entry criteria (especially disease duration and FVC) have an impact on disease progression during clinical studies in ALS
- These findings show that caution needs to be taken when trying to compare ALSFRS-R slope outcomes from studies that had differences in entry criteria
  - For example, a difference in baseline disease duration of 6 months was associated with a difference in ALSFRS-R slope of approximately 0.5 points/month

Conclusions (cont.)

- Limitations of this study included the number of clinical trials available for the analyses and a lack of access to patient-level data, which would have allowed for more robust analyses
- Additional analyses may include data from more recently published studies and the use of patient-level data, where available