Azeliragon Phase 2b Survival Analysis Supports Beneficial Effects on Delaying Time to Cognitive Deterioration in Patients with Mild Alzheimer's Disease

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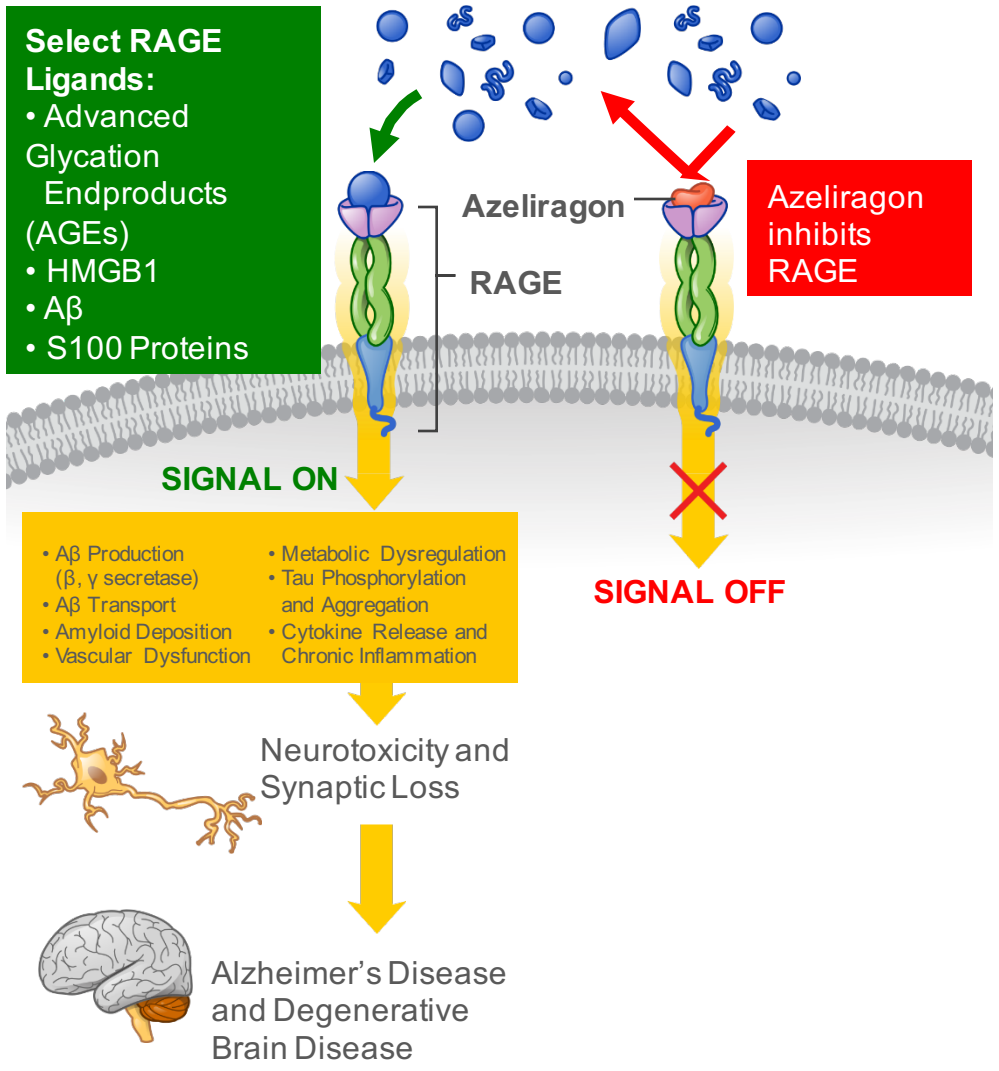
Disclosures

- Dr. Burstein is an employee of vTv Therapeutics LLC
- Dr. Dunn is an employee of vTv Therapeutics LLC
- Dr. Altstiel is an employee of vTv Therapeutics LLC
- Mr. Soeder is a paid consultant for vTv Therapeutics LLC
- Dr. Sabbagh is a clinical trial investigator vTv Therapeutics LLC, Roche, Lilly, Merck, Lundbeck, Avid, Axovant and Biogen; an advisor to vTv Therapeutics, Lilly, Grifols and Biogen; and holds stock in Muses labs and Versanum

RAGE Inhibition
A Novel Mechanism of Action for AD Treatment

AZELIRAGON INHIBITS THE RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS (RAGE)

- Role of RAGE
  - Key component in innate immune system
  - Low expression under normal conditions. Elevated in response to inflammatory stimuli
- RAGE is a key upstream factor that we believe is responsible for progression of AD
  - Increased expression observed in autopsies of human AD brains
  - Higher levels of RAGE expression correlated with disease severity and progression
  - Affects neuronal, microglial and endothelial cells
- RAGE involved in Aβ transport, tau hyperphosphorylation and chronic inflammation
- RAGE knockout mice resist Aβ plaque formation but otherwise normal



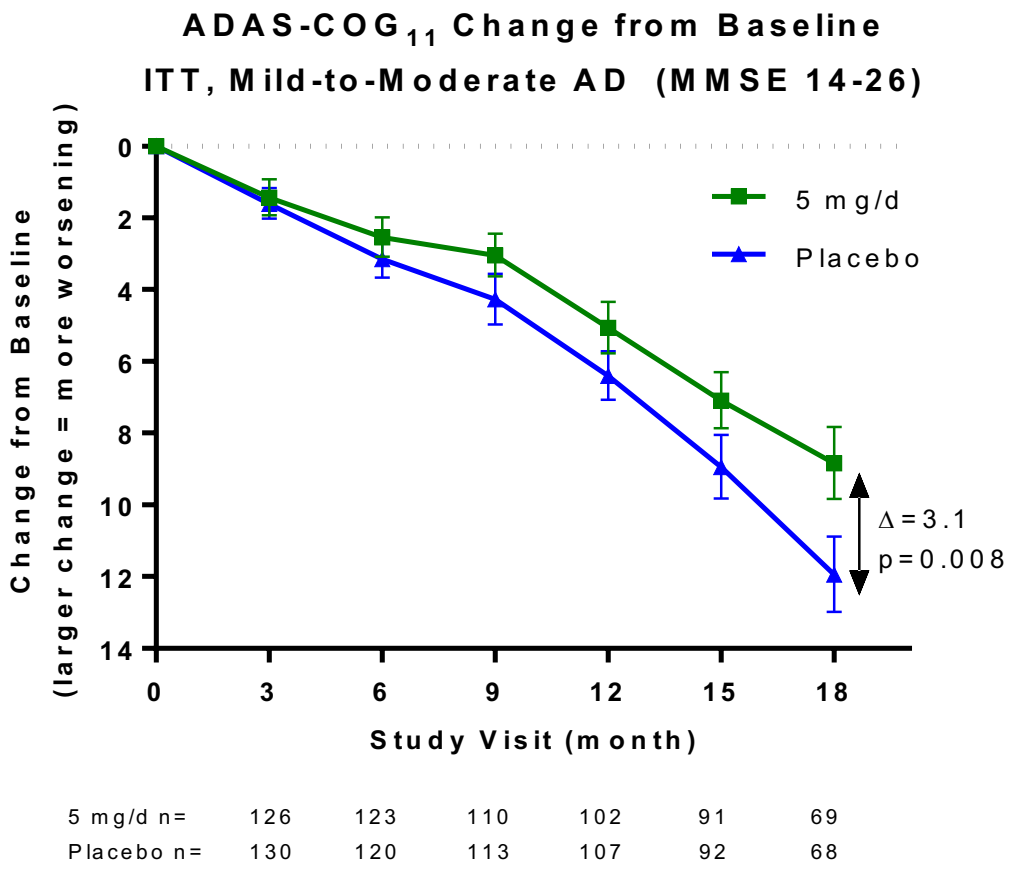
Azeliragon Phase 2b Study Design

- Randomized, double-blind, placebo-controlled trial
- Mild to moderate AD (MMSE 14-26); N=399
  - Power of 80% to detect a treatment benefit of 3 points on the ADAS-cog_{11}
- Stable background therapy with cholinesterase inhibitors and/or memantine
- Three arms (1:1:1)
  - 60mg/d x 6 days, 20 mg/day x 18 months
    - Discontinued due to increased incidence of confusion, falls and greater ADAS-cog_{11} decline not seen with 5 mg/d or placebo
  - 15 mg/d x 6 days, 5 mg/day x 18 months
  - Placebo x 18 months
- Objectives:
  - ADAS-cog_{11} after 18 months of treatment with azeliragon vs placebo
  - Safety/tolerability of treatment with azeliragon vs placebo

Subject Characteristics at Baseline

	azeliragon 20 mg/day (n=135)	azeliragon 5 mg/day (n=131)	Placebo (n=133)
Age (years)	73.0 ± 9.0	73.6 ± 8.8	72.2 ± 9.6
Sex (% women)	61	53	57
Race White	128	120	125
Education (years)	15.0 ± 3.0	14.8 ± 2.8	15.3 ± 2.8
MMSE Mild (MMSE ≥21), n (%) Moderate (MMSE<21), n (%)	19.9 ± 3.6 61 (45%) 74 (55%)	20.8 ± 3.5 73 (56%) 58 (44 %)	20.5 ± 3.4 68 (51%) 65 (49%)
APOE ε4 (%)	62%	65%	74%
ADAS-cog	24.9 ± 9.7	24.4 ± 9.8	24.1 ± 9.6
CDR-sb	5.7 ± 2.9	5.6 ± 2.7	6.0 ± 2.8
ADCS-ADL	61.3 ± 12.9	61.4 ± 12.3	59.9 ± 12.8
NPI	7.9 ± 10.5	7.7 ± 10.3	8.6 ± 10.4
AchEI use, n (%)	134 (99%)	129 (98%)	132 (100%)
Memantine use, n (%)	92 (68%)	87 (66%)	96 (73%)

Final Analysis Demonstrates Azeliragon Meeting Pre-specified ADAS-cog$_{11}$ Primary Endpoint



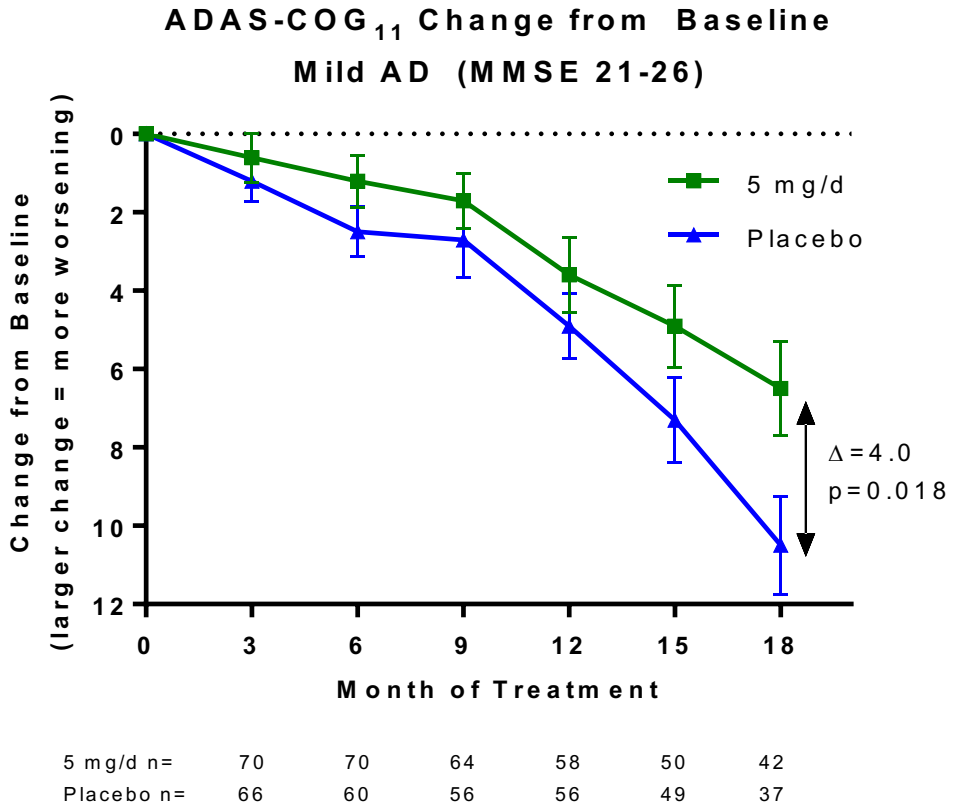
- Protocol-planned analyses, using different methodologies to cope with missing data, all show statistically significant differences in ADAS-cog$_{11}$ favoring 5 mg/d versus placebo

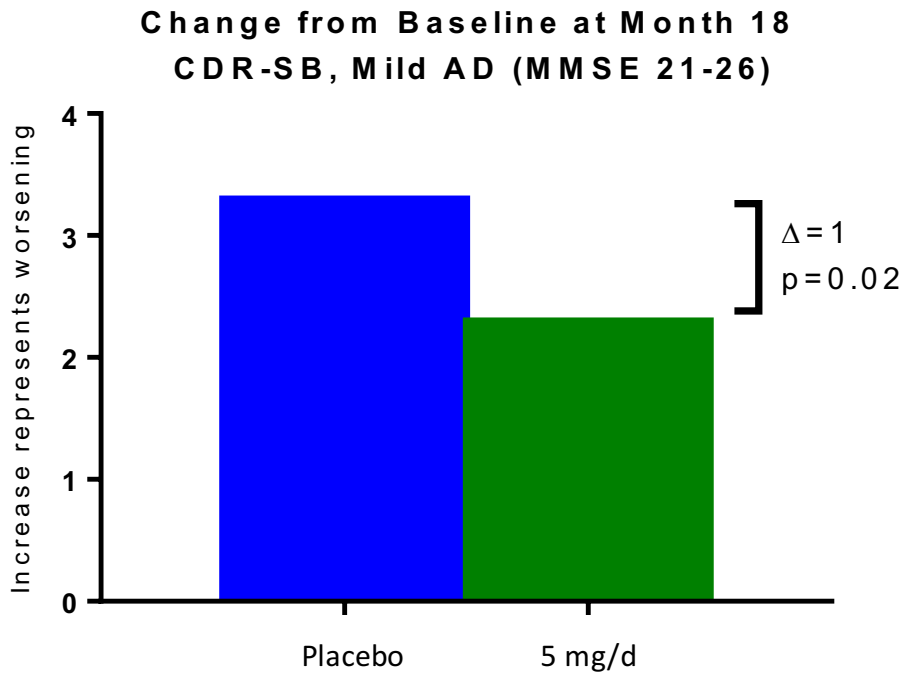
Statistical Methodology	p-value
Primary analysis specified in protocol and SAP ANCOVA with MI imputation	0.008
Supportive Analyses	
Complete Cases ANCOVA	0.02
LOCF ANCOVA	0.03
GEE	0.03
MMRM (random effects)	0.04

Galasko et al. Neurology 2014;82:1536-1542

More Pronounced Efficacy in Mild AD Patients:

Effects on Phase 3 Co-Primary Endpoints Demonstrated in Phase 2b

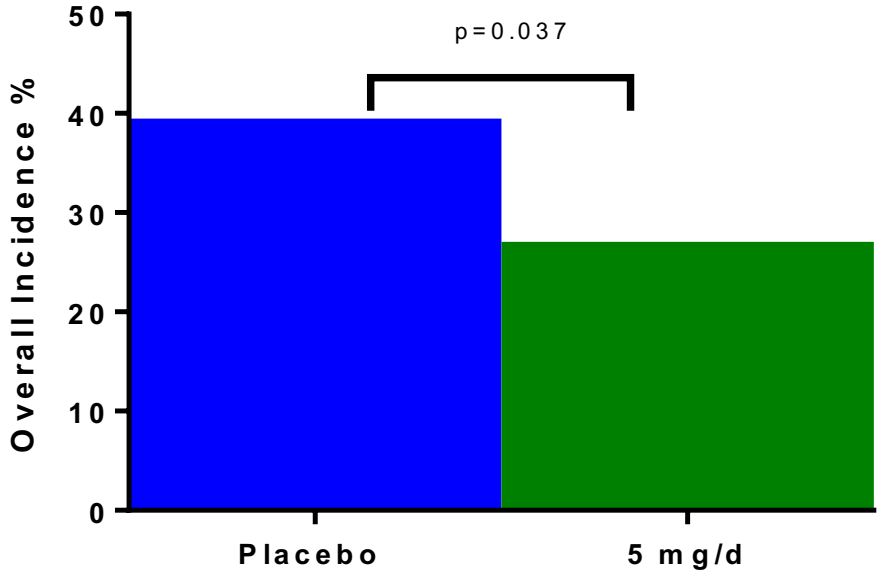




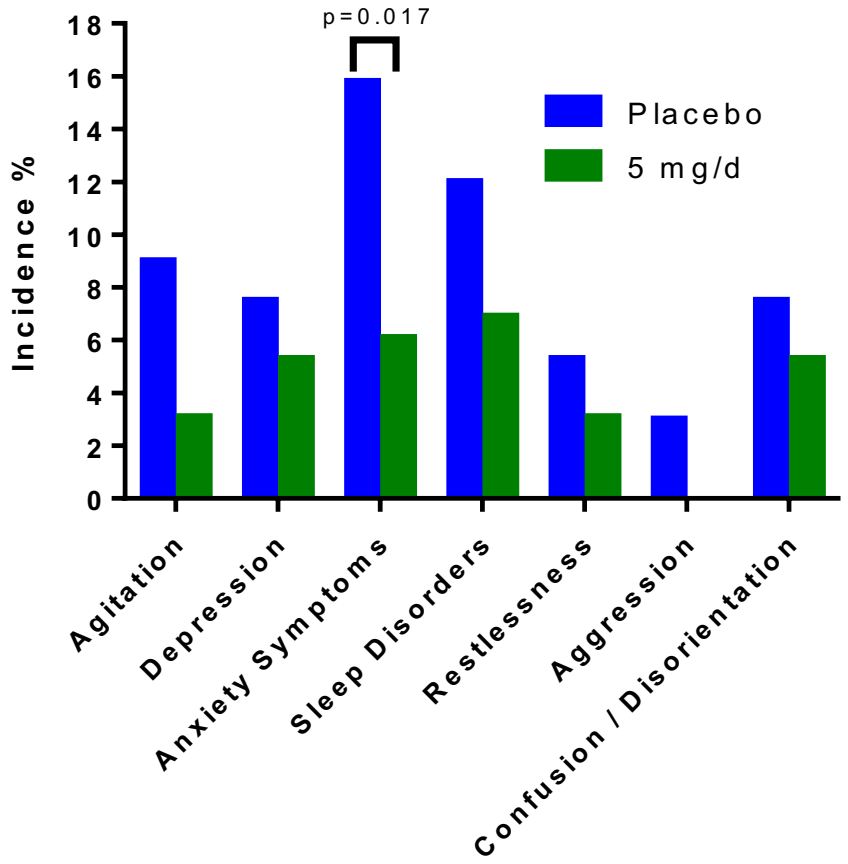
Significant Reduction in Psychiatric Side Effects

Azeliragon 5 mg/day safe and well-tolerated with a statistically significant reduction in psychiatric adverse events in patients with mild-to-moderate AD

Overall Incidence Psychiatric AEs



Incidence Of Specific Psychiatric AEs

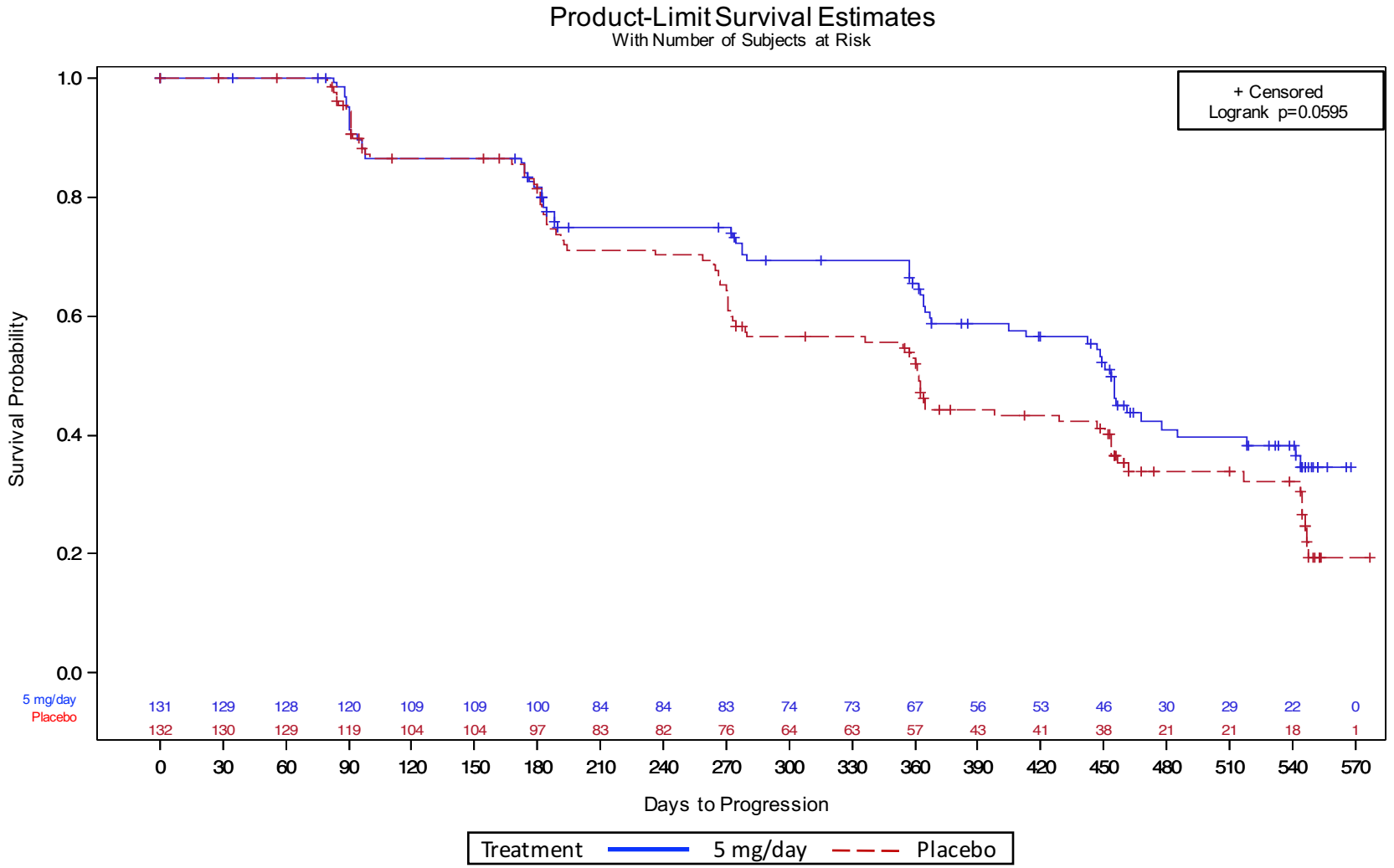


Azeliragon Phase 2b Responder Analysis

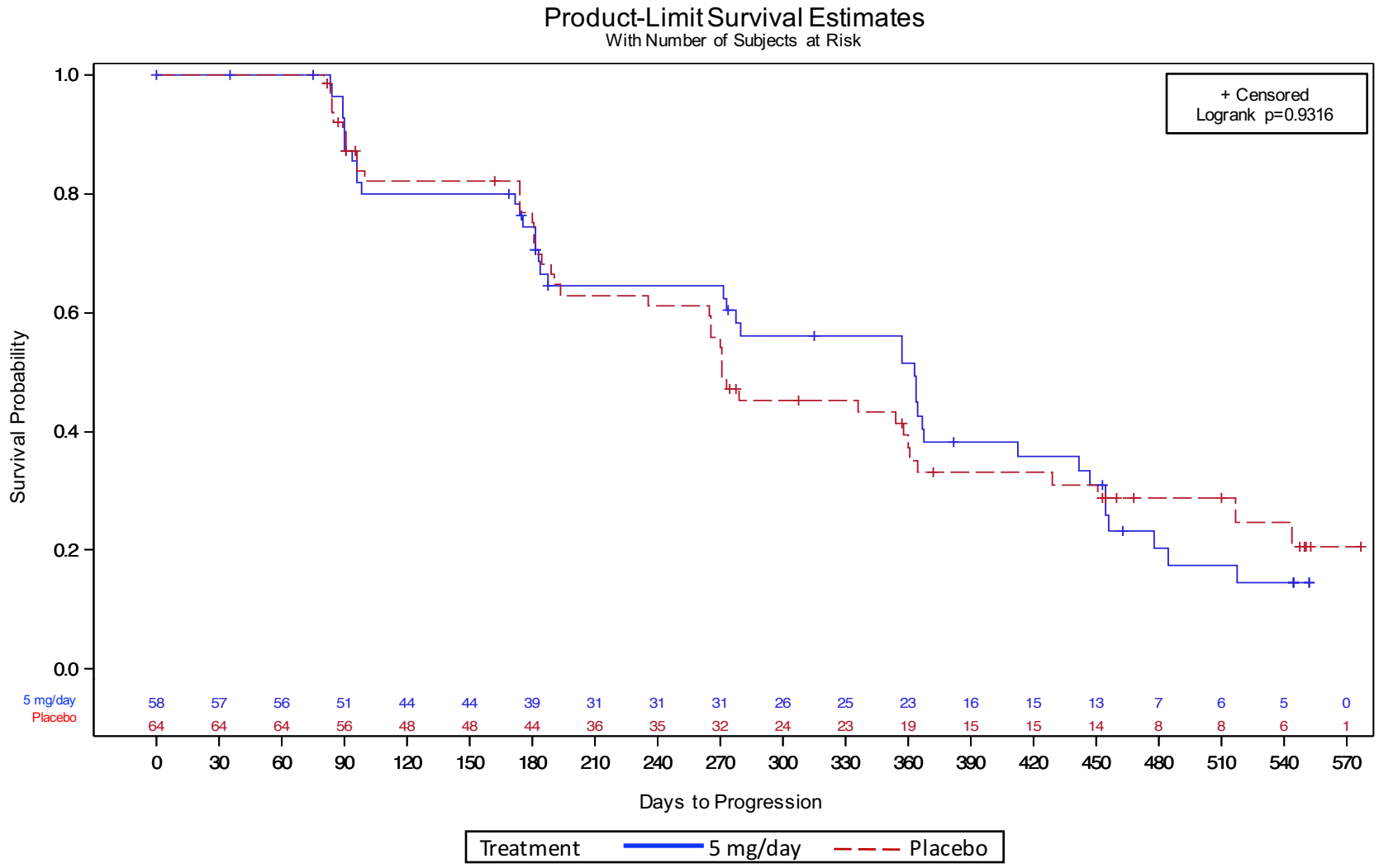
- Data from the overall population of mild–moderate (MMSE 14-26), mild (MMSE ≥21) and moderate (MMSE ≤20) sub-groups evaluated post-hoc using responder criteria for the ADAS-cog_{11}
- Responder analysis using survival analysis methodology was performed using a cut-point of a 7-point* increase in ADAS-cog_{11} over 18 months to define progression
- Sensitivity analyses were performed examining the impact of the selected cut-point evaluating the range of values between 1 and 20

*Vellas et al. J Nutr Health Aging 2007

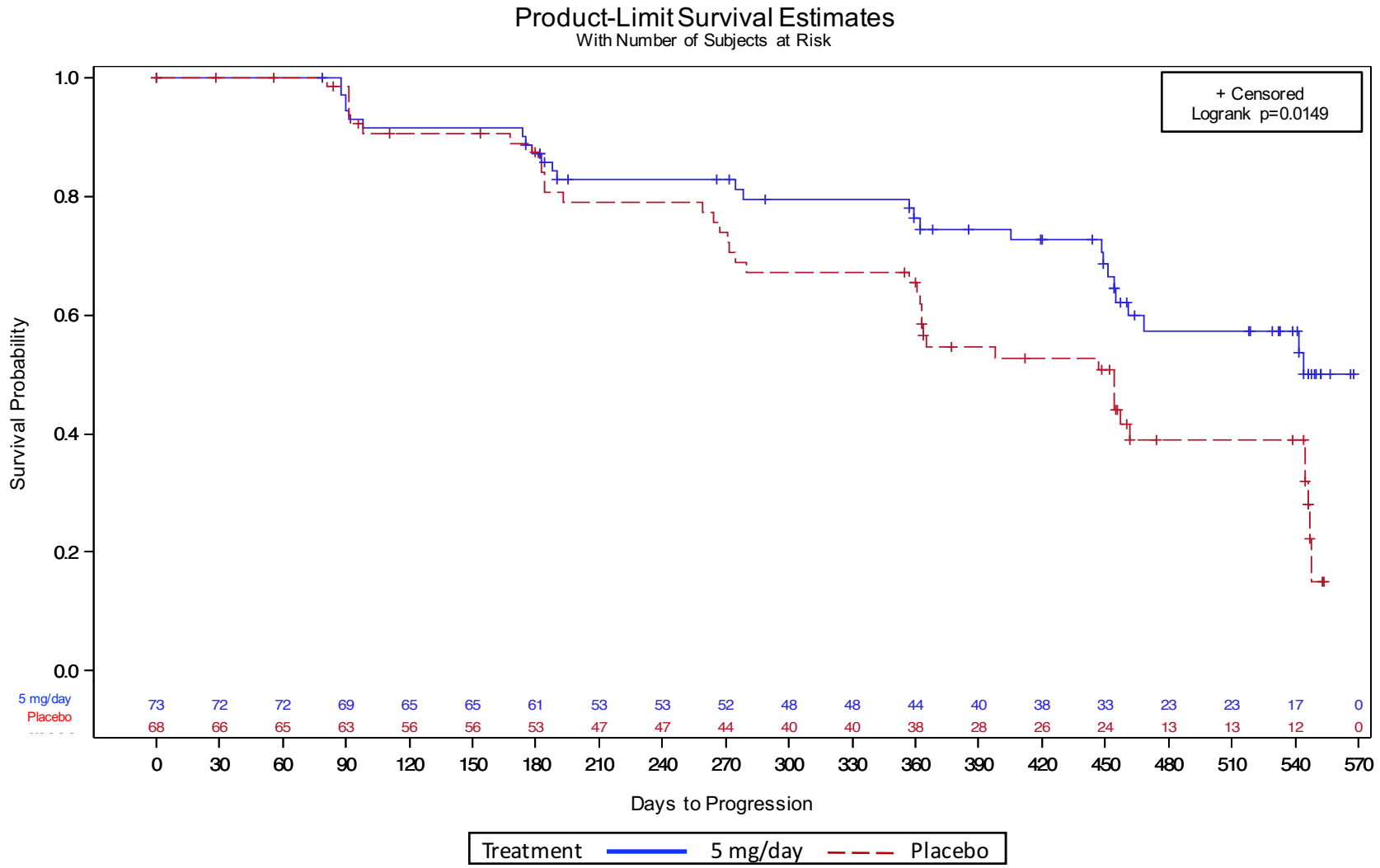
Time to Event Analysis for ADAS-cog$_{11}$ Change from Baseline Progression Defined as ADAS-cog$_{11}$ Increase of 7-points Mild-Moderate AD (MMSE 14-26)



Time to Event Analysis for ADAS-cog$_{11}$ Change from Baseline Progression defined as ADAS-cog$_{11}$ Increase of 7-points Moderate AD (MMSE ≤20)

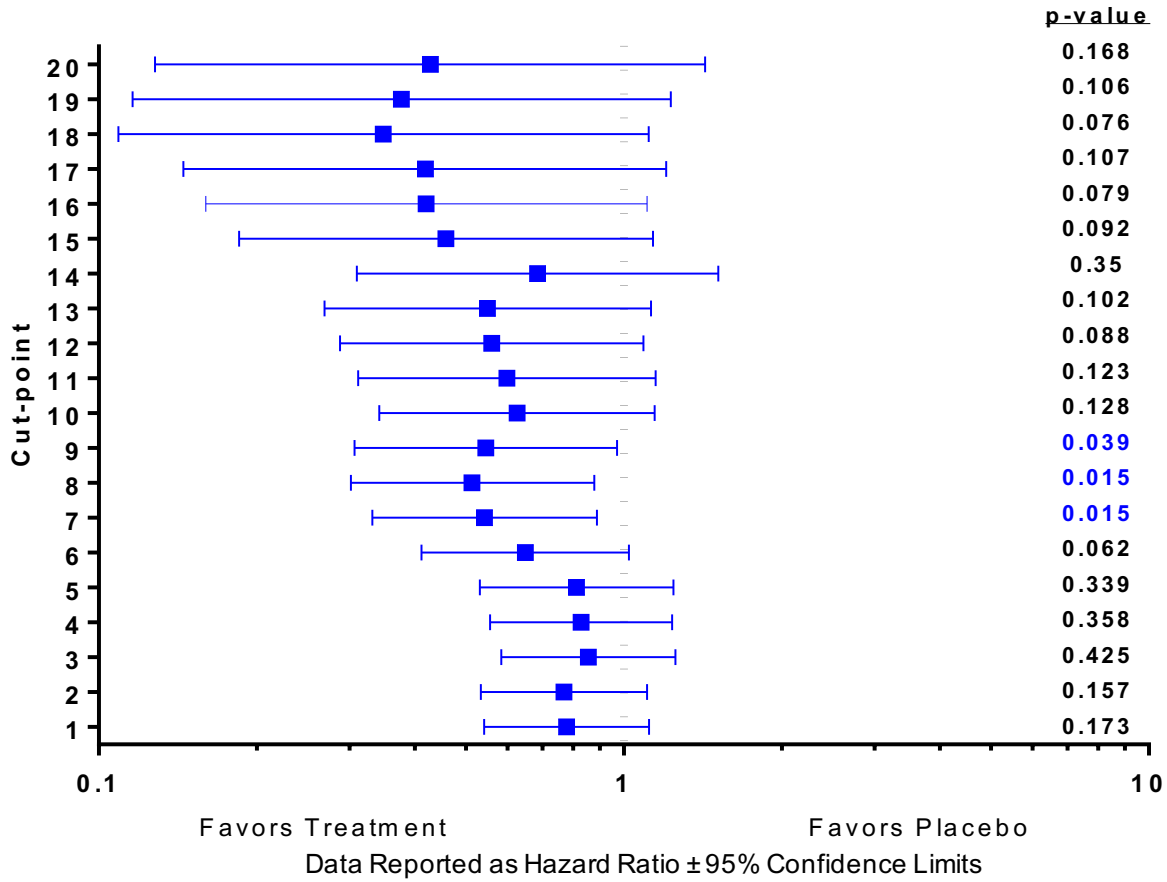


Time to Event Analysis for ADAS-cog$_{11}$ Change from Baseline Progression Defined as ADAS-cog$_{11}$ Increase of 7-points Mild AD (MMSE ≥21)



ADAS-cog$_{11}$ Time To Event Analysis Hazard Ratios Using Multiple Cut-Points Mild AD (MMSE ≥21)

- For all cut-points between a 1 and 20 point worsening in ADAS-cog, the hazard ratio favors azeliragon 5 mg/day
- Effect in overall population primarily driven by the mild sub-group



Conclusions

- Azeliragon 5 mg/day delayed time to cognitive deterioration (i.e. a 7-point worsening in ADAS-cog$_{11}$) relative to placebo in patients with mild AD
- Monotonic increasing difference in ADAS-cog$_{11}$ change from baseline over placebo after month 9
- These results, combined with previously described statistically significant less worsening of ADAS-cog and CDR-sb at 18 months in azeliragon-treated patients, provide further confidence in azeliragon as a disease modifying therapy and support for the design of the ongoing Phase 3 STEADFAST trial in patients with mild AD