Safety and efficacy results from the phase 3, multicenter, 18-month STEADFAST trial of azeliragon in participants with mild Alzheimer's disease

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STEADFAST Safety and Efficacy Results: Disclosures

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- Intellectual property rights (Royalties or patent sales) Harper Collins
- Ownership interest (stock, stock options) in Versanum Inc., Brain Health Inc, Optimal Cognitive Health Company, uMethod Health, Neurotrope
- Consultant for Allergan, Biogen, Bracket, Grifols, vTv Therapeutics, Sanofi, Neurotrope, Cortexyme, Roche-Genentech

Imogene Dunn, Ann Gooch, Carmen Valcarce and Aaron Burstein

- Full time employees of vTv Therapeutics LLC

Larry Altstiel

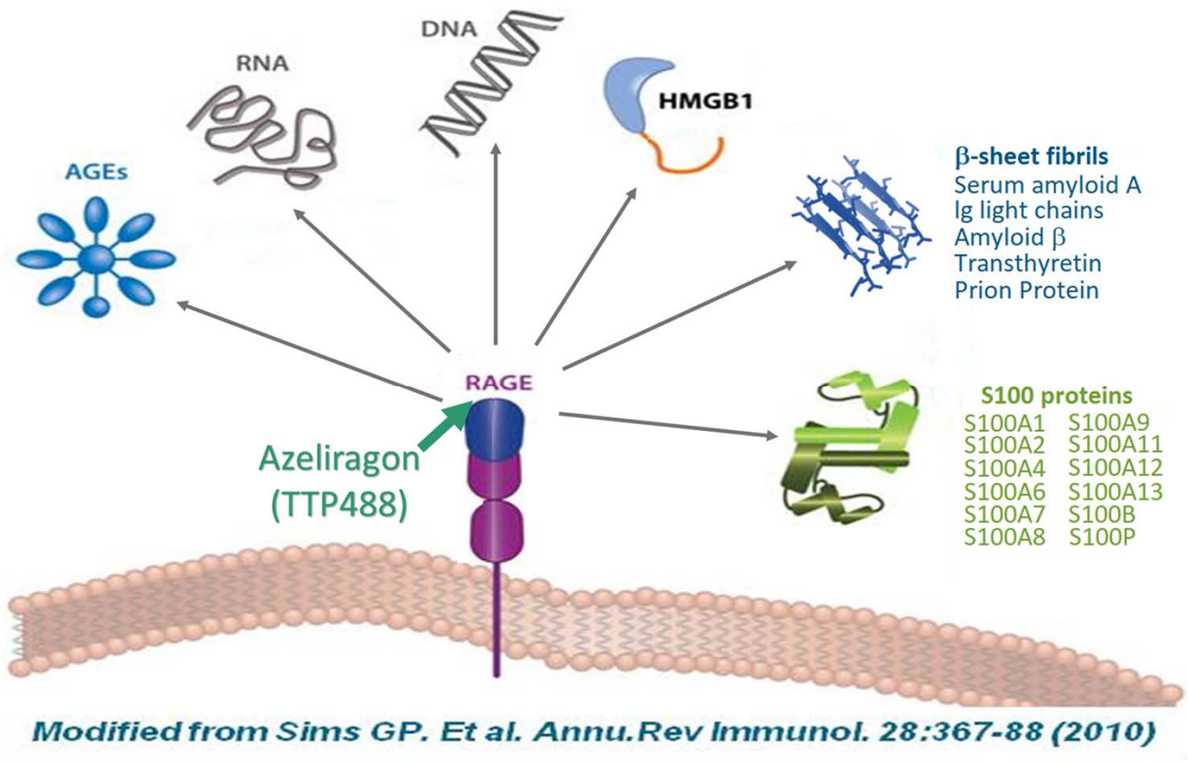
- Former employee of vTv Therapeutics LLC; employed at time of study conduct and A-Study readout

Karl Kieburtz and Tom Soeder

- Paid consultants for vTv Therapeutics LLC

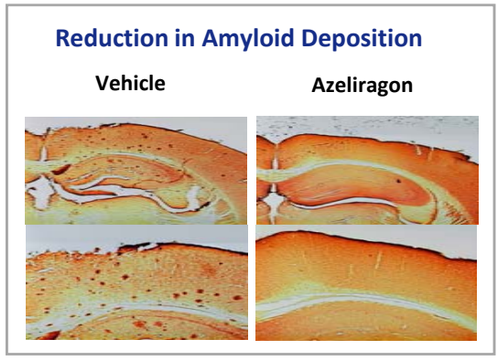
RAGE as a Target in Humans

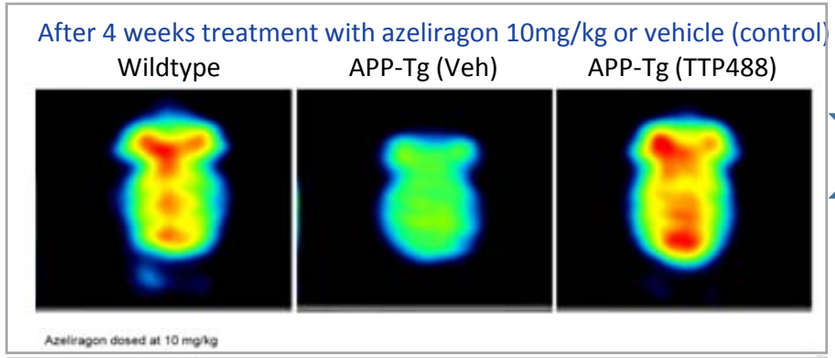
- RAGE is a 35kDa membrane protein member of the Ig supergene family that is a receptor for pro-inflammatory ligands including AGEs, Aβ peptides, S100 proteins, HMGB1 (amphoterin), and oxLDL
- Analysis of RAGE expression in AD brains indicated that increases in RAGE protein and percentage of RAGE-expressing microglia paralleled the severity of disease[(1)]
- Patients who suffered AD and diabetes simultaneously exhibited an increased immunostaining for RAGE protein in hippocampal regions[(2)]
- Strong positive microvascular RAGE immunoreactivity has been observed in AD hippocampi [(3)]

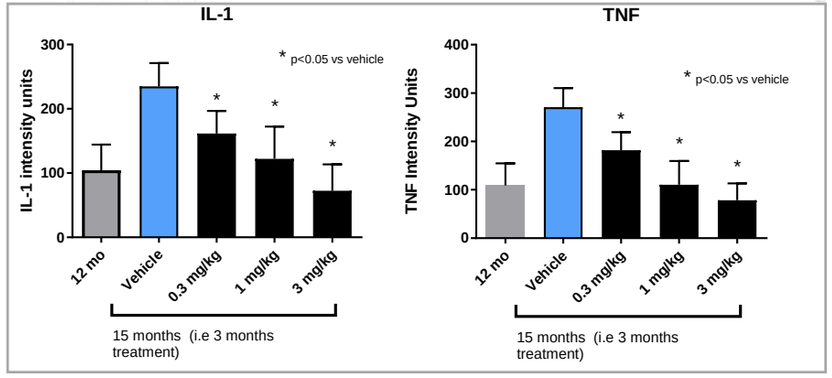


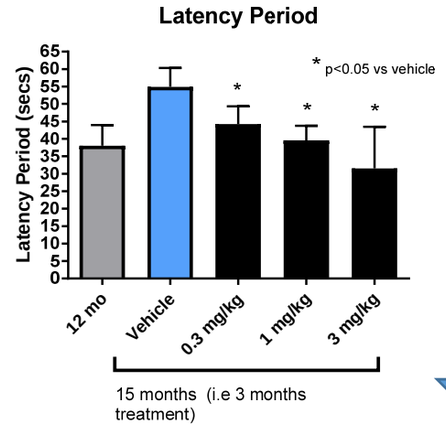
[(1)] Curr.Drug Targets CNS Neurol.Disord. 2005 Jun;4(3):249-66
[(2)] Neurobiology of Disease 37 (2010) 67–76
[(3)] Curr. Alzheimer Res.2008 Oct;5(5):432-7.

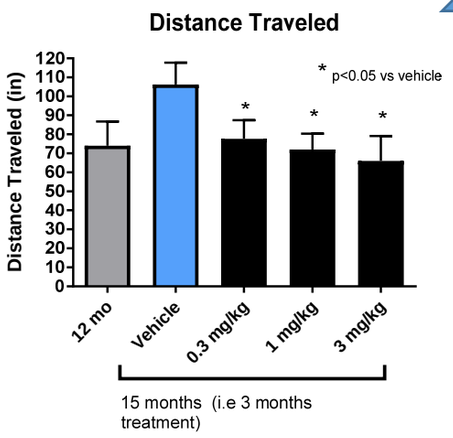
Azeliragon effects in APP-Tg mice and in Phase 2b mild subgroup as basis for advancing to Phase 3



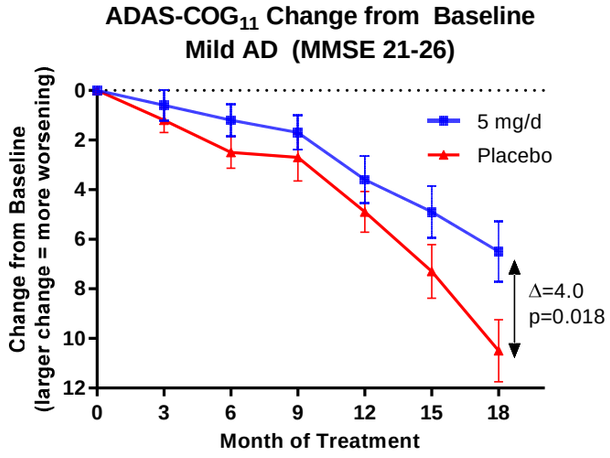


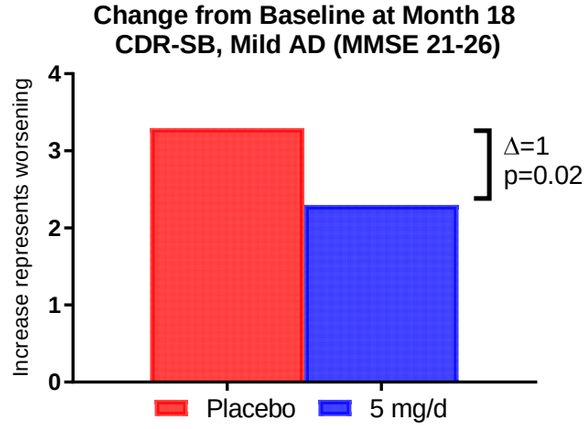






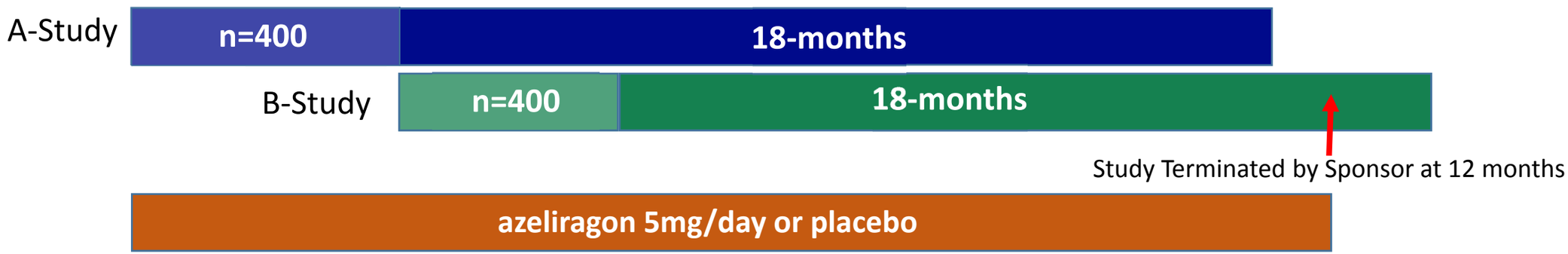
Phase 2b results in subgroup with mild AD





Azeliragon STEADFAST Study Design

- Randomized, double-blind, placebo-controlled, parallel group, 18-month trial
- Two identical, independently powered studies operationally conducted under a single protocol
- Subjects with probable mild AD: 2011 NIA-AA criteria, Screening MMSE 21-26, CDR-global 0.5-1
- Subjects on stable acetylcholinesterase inhibitor and/or memantine for at least 3 months
- A-Study and B-study enrolled sequentially and randomized independently (site based randomization)



Co-Primary Endpoints

- ADAS-cog11: every 3 months
- CDR-sb: M3, M6, M12, M18

Key-Secondary Endpoints

MRI volumetric measures:
Baseline, M18

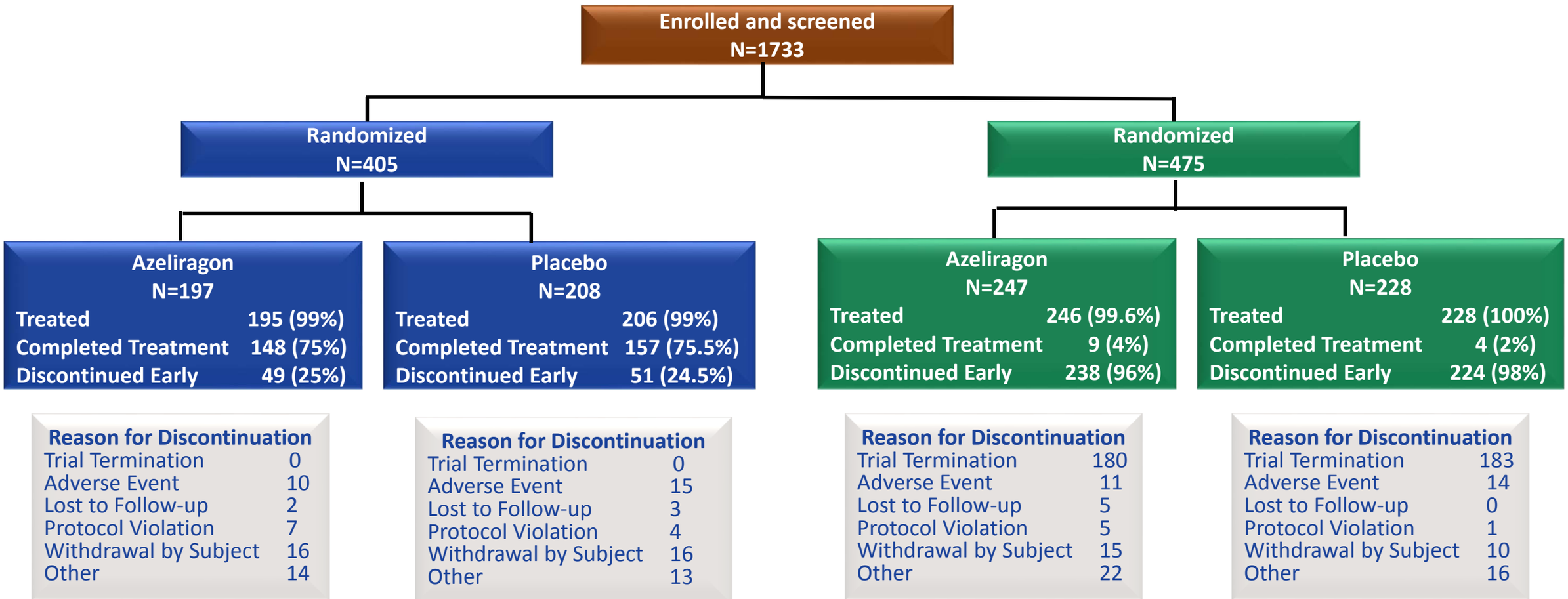
Secondary Endpoints

ADCS-ADL, NPI, MMSE, COWAT, CFT, Trails A and B, RUD-lite, DEMQOL, FDG-PET sub-study
Biomarkers: Plasma $A\beta_{1-40}$, $A\beta_{1-42}$

Analyses

- Co-Primary Endpoints: A-Study and B-Study analyzed independently
- Secondary Endpoints: A- and B-Studies combined for analysis

Subject Disposition



Demographics and Baseline Characteristics (full analysis set)

Characteristic	A-Study Azeliragon n=179	A-Study Placebo n=196	B-Study Azeliragon n=238	B-Study Placebo n=216
Age, years	74 ± 9.1	75 ± 7.9	75 ± 8.6	74 ± 8.5
Female sex – n (%)	92 (51%)	85 (43%)	102 (43%)	101 (47%)
Race, White, n (%)	163 (91%)	184 (94%)	223 (94%)	208 (96%)
Ethnicity, Non-Hispanic or Latino, n (%)	154 (86%)	174 (89%)	230 (97%)	202 (94%)
Years since diagnosis	2.4 ± 2.4	2.3 ± 2.4	2.1 ± 1.9	1.9 ± 1.9
Apo ε4 allele (%)	50%	52%	61%	57%
Acetylcolinesterase Inhibitor, n(%) Memantine, n (%) Both, n (%)	167 (93%) 69 (39%) 58 (32%)	181 (92%) 78 (40%) 63 (32%)	221 (93%) 87 (37%) 70 (29%)	193 (89%) 79 (37%) 57 (26%)
MMSE	23.5 ± 2.6	23.2 ± 2.5	23.3 ± 2.5	23.4 ± 2.7
ADAS-cog11	15.3 ± 5.5	15.6 ± 5.2	17.0 ± 5.6	16.1 ± 5.4
CDR-sb	4.1 ± 1.8	4.1 ± 1.6	4.62 ± 1.6	4.54 ± 1.6
ADCS-ADL	67.8 ± 7.3	67.5 ± 8.4	66.4 ± 8.2	67.2 ± 7.6

- A-Study
  - Treatment groups well matched
  - % Apo ε4 carriers overall lower than expected based on historical norm
- B-Study
  - 4% more Apo ε4 carriers and 1 point higher baseline ADAS-cog in azeliragon vs. placebo
  - B-study participants slightly less mild (higher CDR-global, CDR-SB and ADAS-cog) than A-study

Values reports as mean (SD) or n (%) where noted

No identified tolerability concerns with azeliragon 5 mg/day: A and B-Studies Combined

- **No differences between azeliragon and placebo in TEAE, Treatment-related TEAE, SAE, Deaths**

Overview of Treatment-Emergent Adverse Events (TEAE) Safety Analysis Set		
	Azeliragon N=441 n (%)	Placebo N=434 n (%)
Number of TEAEs	1304	1351
Subjects with at least one TEAE	320 (72.6%)	324 (74.7%)
Subjects with at least on Treatment-related TEAE	41 (9.3%)	32 (7.4%)
Subjects with at least one SAE	70 (15.9%)	67 (15.4%)
Subjects with at least one AE leading to Discontinuation	22 (5%)	31 (7.1%)
Subjects with at least one TEAE leading to Death	4 (0.9%)	5 (1.2%)

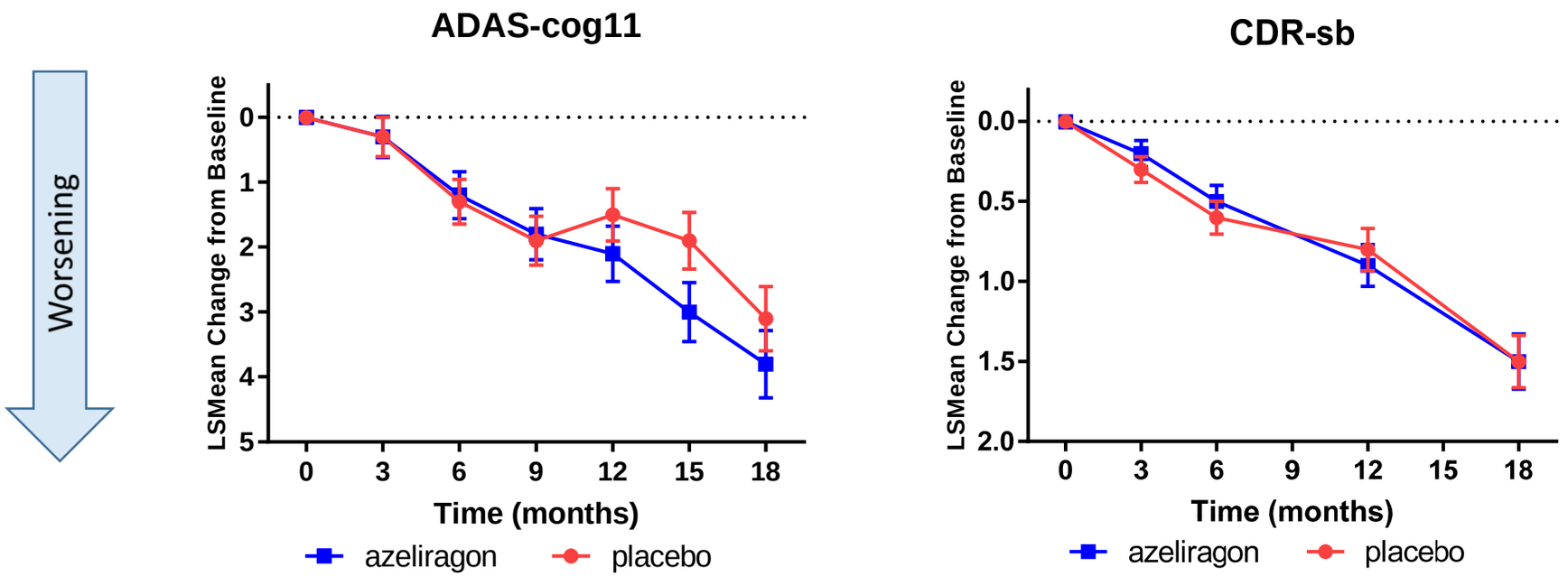
TEAEs occurring in >2% of azeliragon treated subjects and more frequent than placebo		
Preferred Term	Azeliragon N=441 n (%)	Placebo N=434 n (%)
Urinary tract infection	45 (10.2%)	35 (8.1%)
Depression	21 (4.8%)	20 (4.6%)
Upper respiratory tract infection	20 (4.5%)	16 (3.7%)
Dizziness	18 (4.1%)	15 (3.5%)
Weight decreased	17 (3.9%)	13 (3.0%)
Nausea	14 (3.2%)	10 (2.3%)
Cough	13 (2.9%)	9 (2.1%)
Insomnia	11 (2.5%)	7 (1.6%)
Syncope	11 (2.5%)	9 (2.1%)
Constipation	10 (2.3%)	8 (1.8%)
Musculoskeletal pain	10 (2.3%)	5 (1.2%)

A-Study failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints of ADAS-cog and CDR-sb

A-Study Final Analysis: Full Analysis Set*, MMRM

***FAS: subjects who received ≥1 dose and had at least one post baseline efficacy assessment**

Data reported as LSMean (SE)



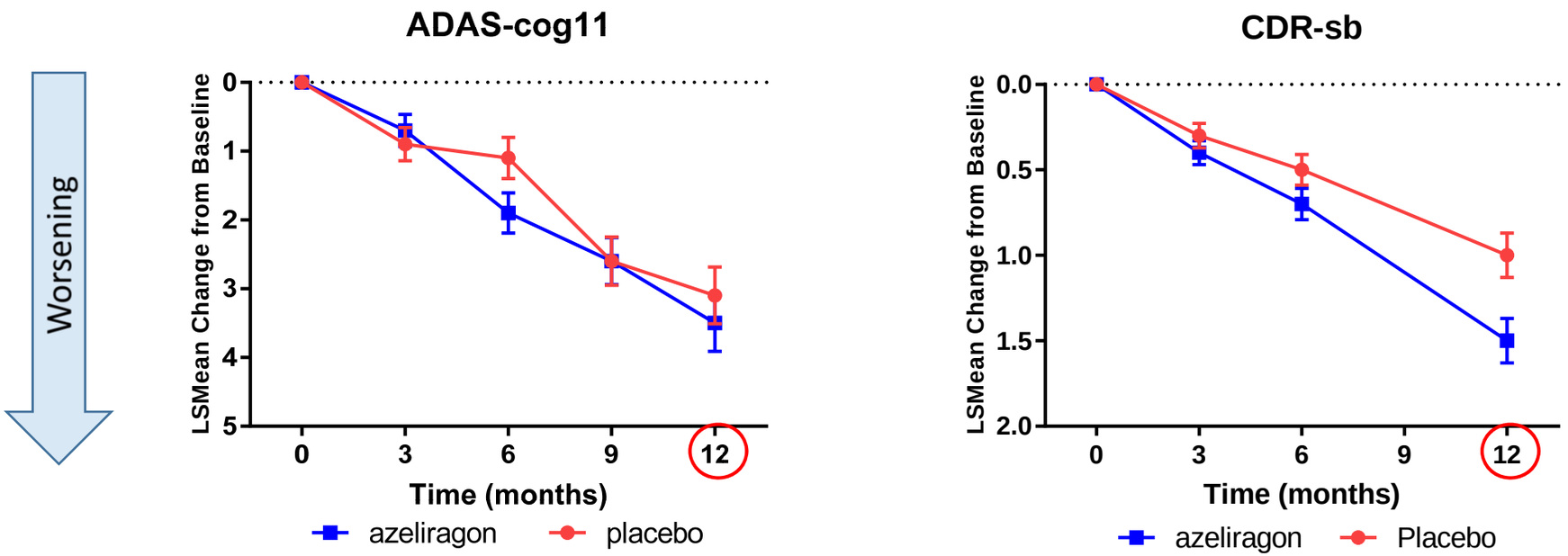
- Part B and OLE studies stopped at time of Part A Top Line Results
  - Subjects instructed to stop study medication and return for Early Termination and Follow-up visits for efficacy and safety assessments

B-Study failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints of ADAS-cog and CDR-sb

B-Study Final Analysis: Full Analysis Set*, MMRM

***FAS: subjects who received ≥1 dose and had at least one post baseline efficacy assessment**

Data reported as LSMean (SE)



- B-Study terminated by sponsor at time of M12 visit for majority of subjects (little data beyond M12)
  - 190 placebo and 179 azeliragon subjects with data through M12

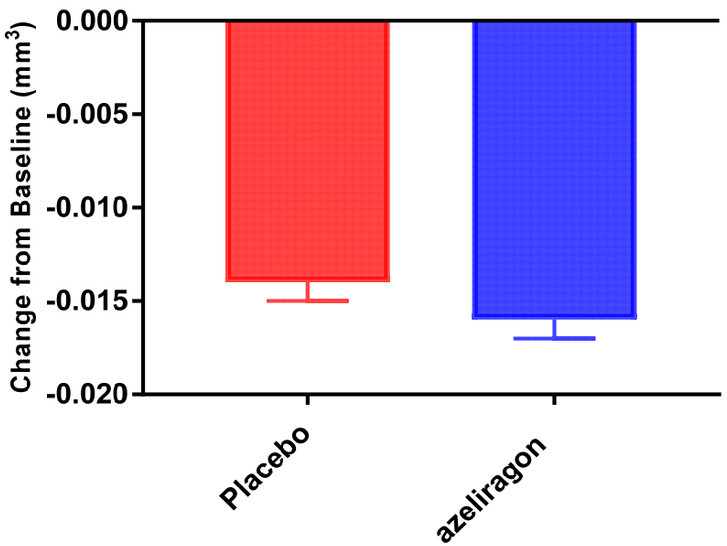
No indication of effect of azeliragon on MRI volumetric measures

A- and B-Study Combined: Full Analysis Set*

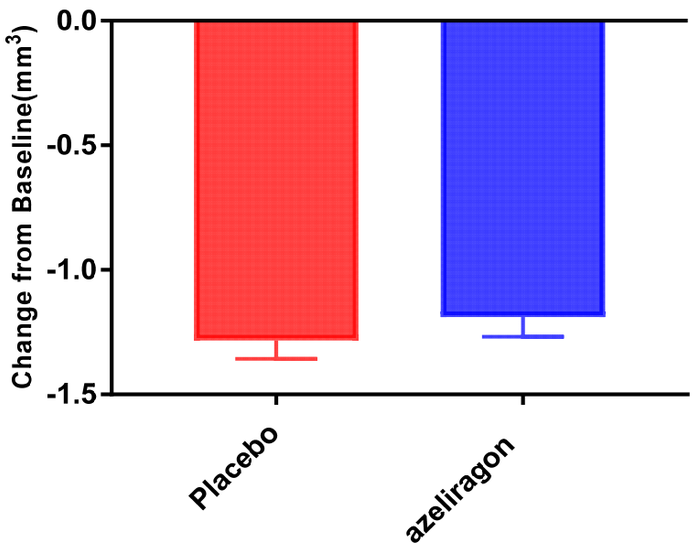
***FAS: subjects who received ≥1 dose and had at least one post baseline efficacy assessment**

Data reported as LSMean (SE)

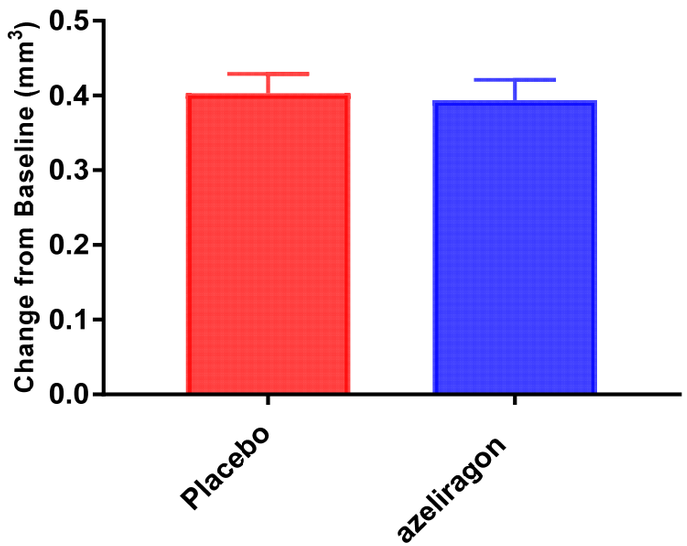
Hippocampal Atrophy* at Month 18



Whole Brain Atrophy* at Month 18



Ventricular Enlargement* at Month 18



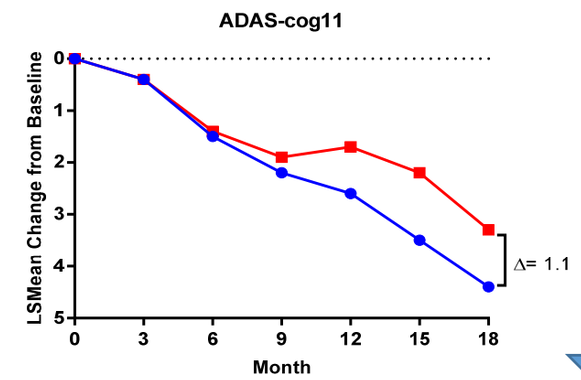
*Volumes normalized to subject's intracranial volume

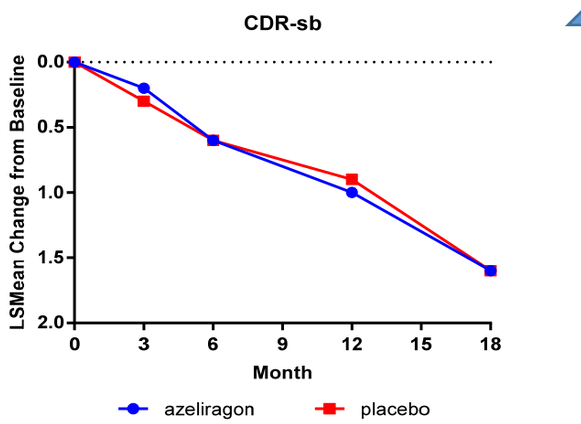
Topline Results Chronology and Summary (April 2018 – June 2018)

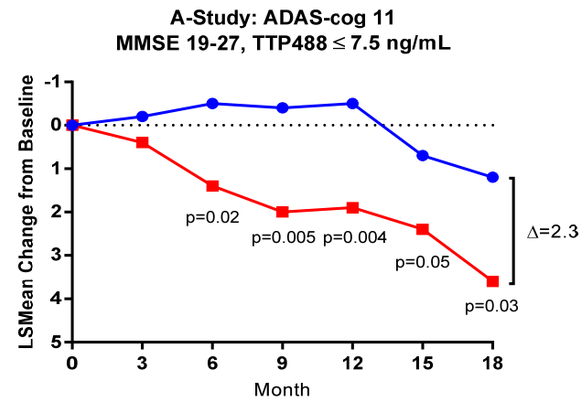
- A-Study failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints
- B-Study stopped, subjects underwent ET and F/U visits

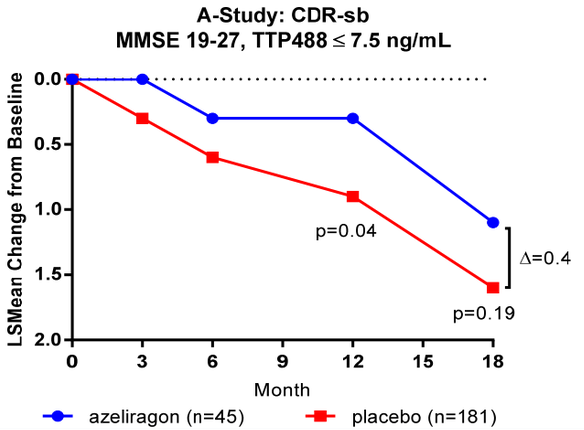
- Post-hoc analysis suggests azeliragon < 7.5 ng/mL subgroup associated with favorable effect vs placebo
- PAS defined for B-Study prior to database lock for top-line result

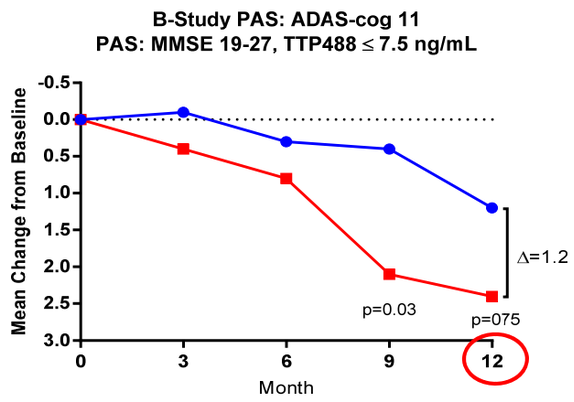
B-Study failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints

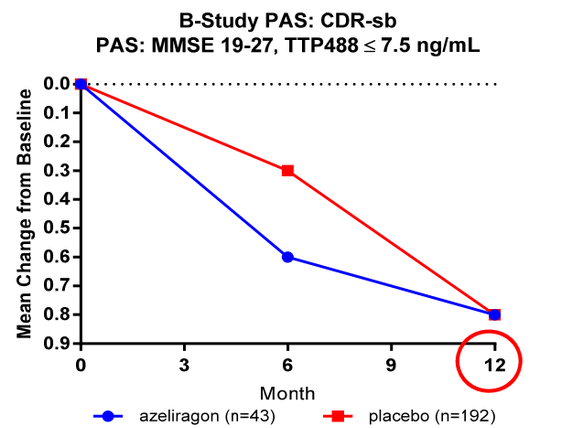






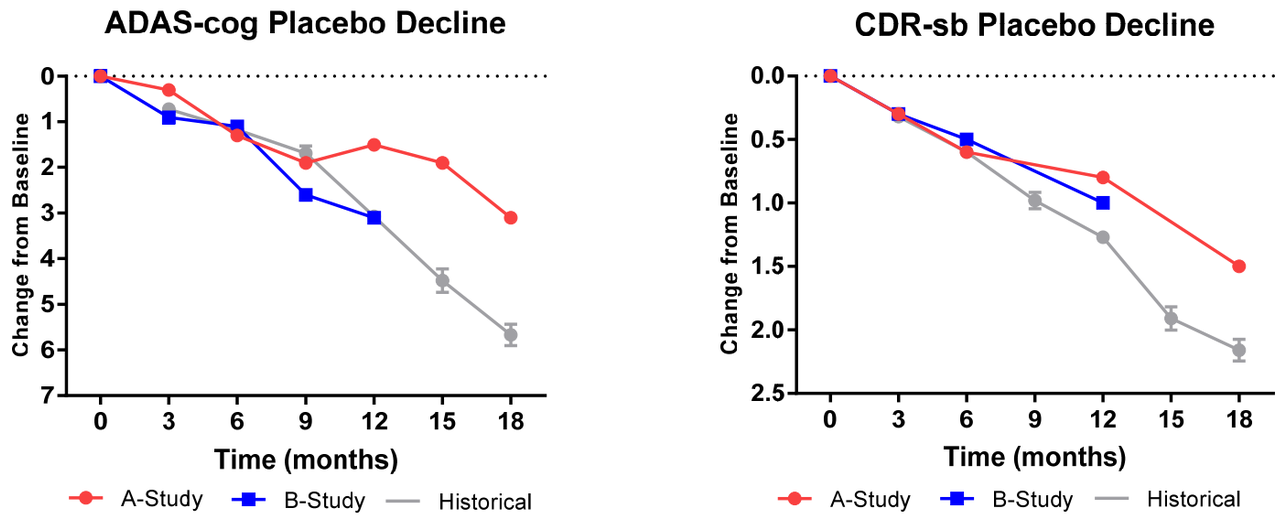






Post-hoc analyses ongoing to evaluate for subgroups with expected placebo decline and/or response to a RAGE antagonist / azeliragon

- Subject with baseline characteristics predicting likely expected to exhibit progressive decline over 12-18 months



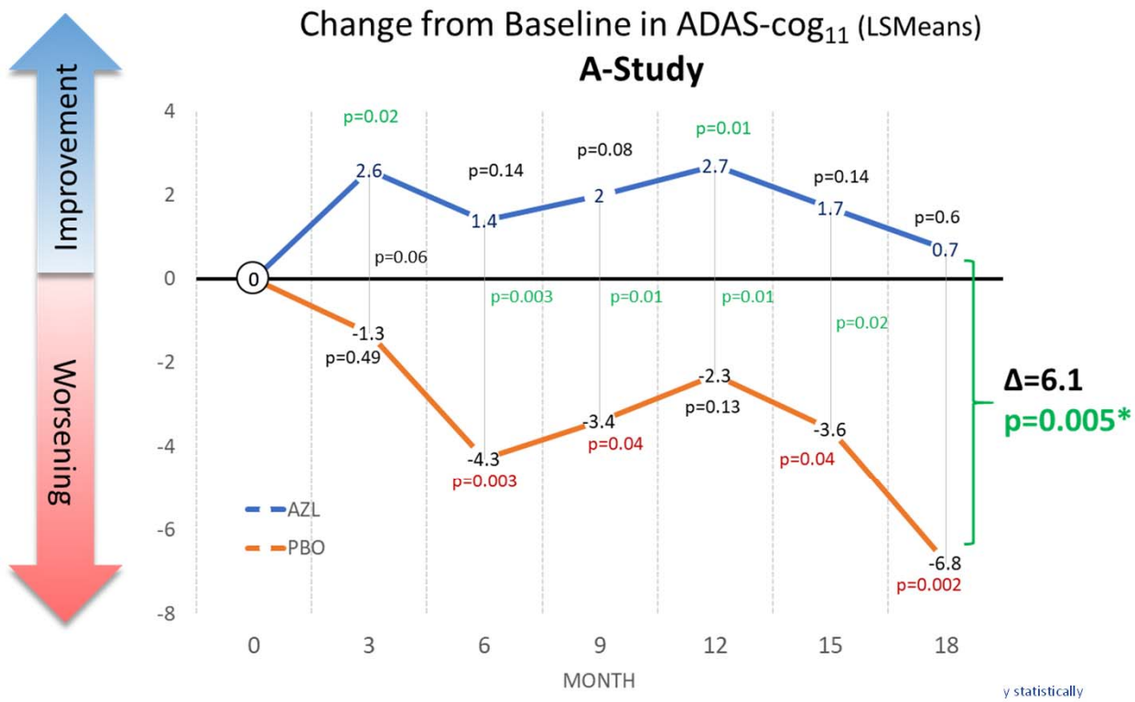
Historical data from Thomas RG et al. Alz Dementia 2016

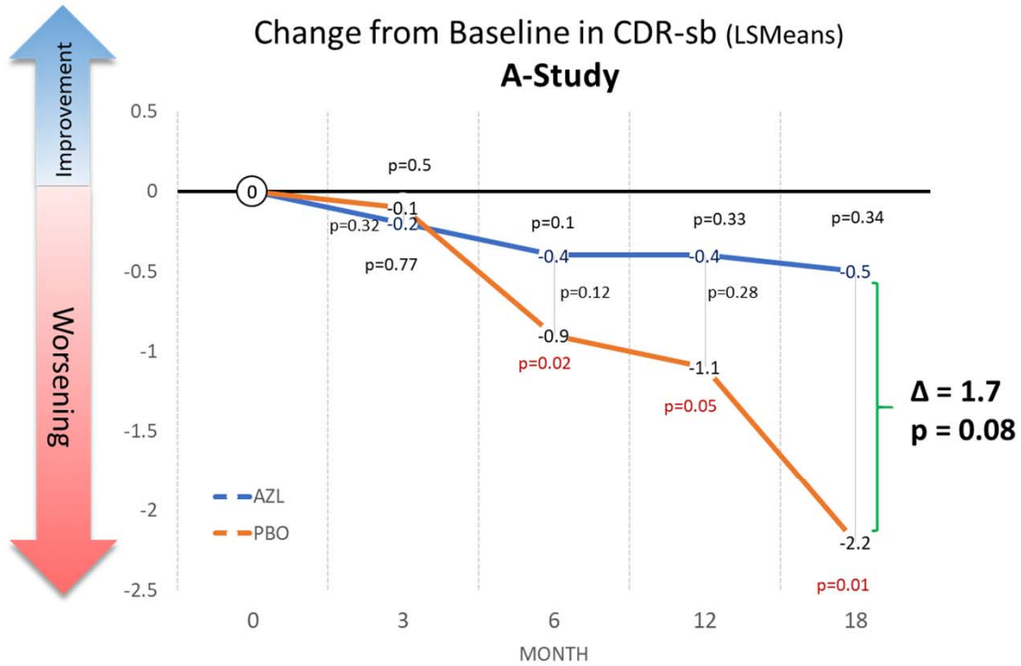
- Robust examination of population PK / exposure relationship
  - Linearity of exposure-response suggested in A-study not supported by B-Study (non-linear u-shaped)

- Subgroups with baseline elevated RAGE expression / ligand concentrations / biomarker signature
  - HbA1c ≥ 6.5%

In subjects with presumed increased RAGE expression (i.e. baseline HbA1c ≥ 6.5%) azeliragon delayed decline in cognition and function

- RAGE-ligands upregulate the receptor's expression establishing a forward feedback cycle perpetuating inflammation, inducing vascular damage, and preventing tissue repair
- HbA1c is a marker of increased RAGE expression. Subjects with elevated circulating levels of HbA1c experienced cognitive and functional benefit of azeliragon
- Poster LBP18, *"Is RAGE the missing link between diabetes and dementia? Results from a subgroup analysis of the STEADFAST trial"*





Azeliragon STEADFAST study summary

- Study failed to demonstrate a statistically significant benefit of azeliragon on co-primary endpoints of ADAS-cog and CDR-sb
  - Placebo decline less than anticipated thereby confounding the ability to demonstrate a treatment effect
    - Post-hoc subgroup analysis ongoing to identify subgroups anticipated to experience progressive decline in whom treatment benefit may be detected.
  - Concentration-effect relationship seen in A-Study suggests azeliragon's potential for beneficial effects
    - Further analysis necessary to fully understand the PopPK and exposure-response relationship
- Azeliragon 5 mg/day was well tolerated in this study
- Post-hoc subgroup analysis indicates a potential benefit in patients with diabetes (HbA1c 6.5%), hypothesized to have increased RAGE substrate concentrations / increased RAGE expression
  - Poster LBP18: *"Is RAGE the missing link between diabetes and dementia? Results from a subgroup analysis of the STEADFAST trial"*

Thank you

We greatly appreciate all the patients, families, investigators and staff for their participation in STEADFAST