INFLAMMATORY BIOMARKERS, BRAIN VOLUMETRIC MRI, FDG-PET RESULTS IN PATIENTS WITH TYPE 2 DIABETES IN AZELIRAGON PHASE 3 TRIAL IN MILD ALZHEIMER'S DISEASE (AD)

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Disclosure

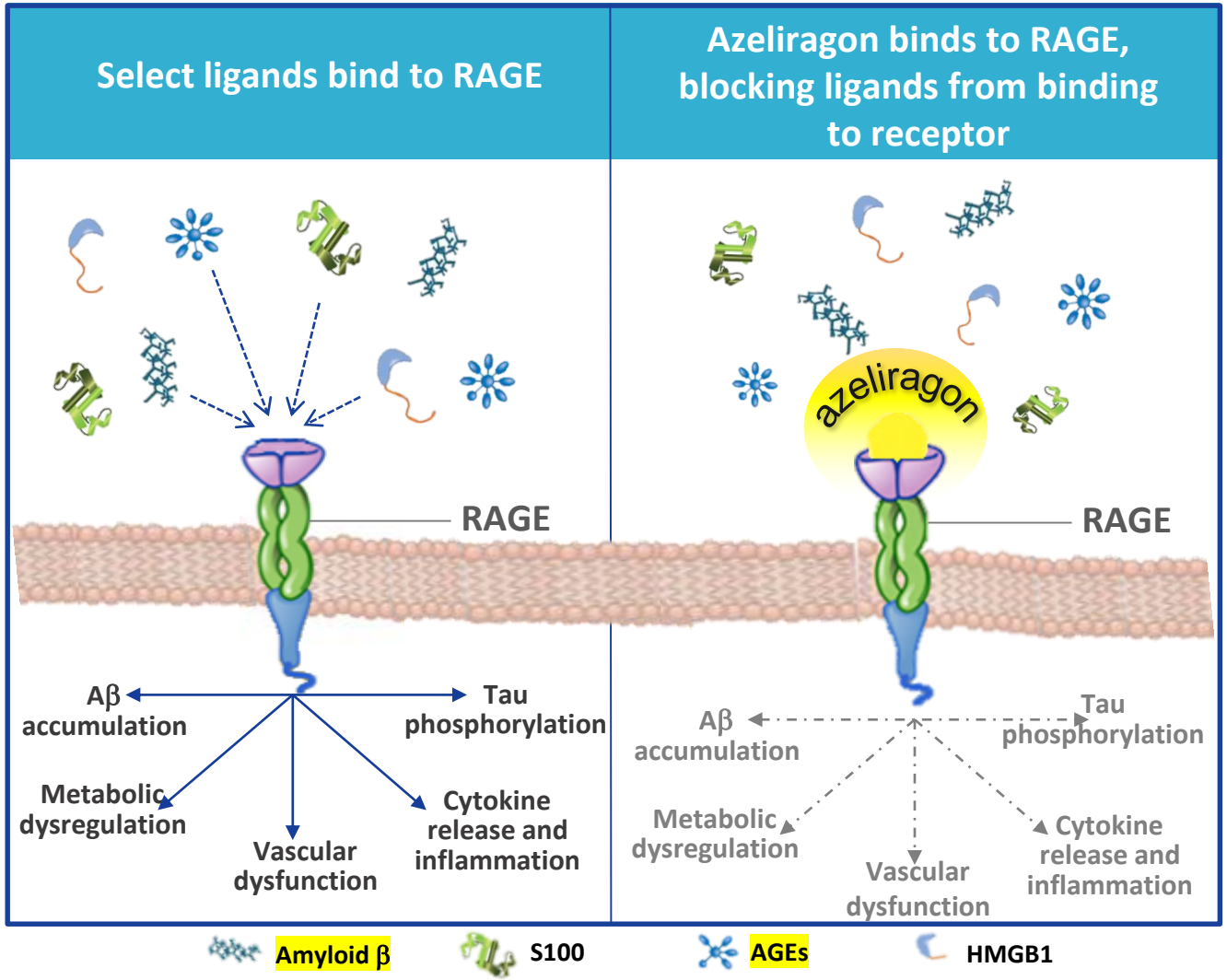
Carmen Valcarce

Full time employees of vTv Therapeutics LLC

Targeting RAGE with Azeliragon

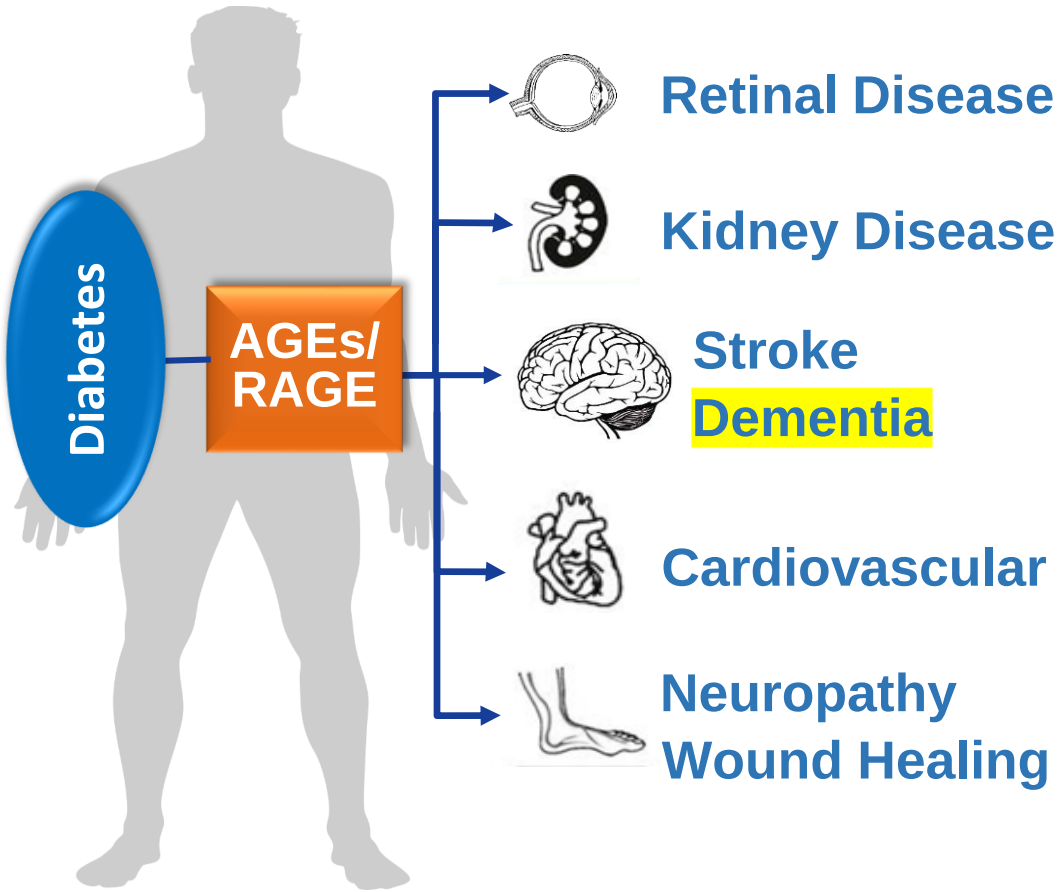
- Azeliragon's **novel MOA**: antagonizing the Receptor for Advanced Glycation Endproducts (RAGE)
  - **RAGE** is expressed at **low levels** in healthy tissues (except skin and mucus membranes)
  - Increases in the concentration of RAGE ligands induce RAGE expression
    - **In AD**, increases in RAGE protein and **percentage of RAGE-expressing microglia parallel the severity of disease**
  - The interaction of **AGEs** (or other RAGE-ligands) with **RAGE** leads to:
    - Sustained **cellular damage** and **inflammation**; and
    - **Insulin resistance**
- Unlike most investigational AD treatments, azeliragon does not rely on just one hypothesis (e.g., amyloid or tau), but it targets **several components** of AD pathology

Azeliragon Mechanism of Action



For review see Dhananjayan et al. (2018) Advance Glycation, Diabetes and Dementia https://doi.org/10.1016/B978-0-12-809454-9.00009-3

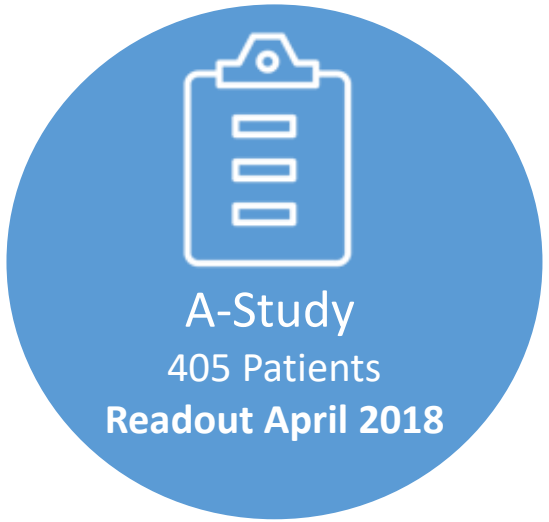
RAGE Involved in Diabetic Complications and AD



Pre-clinical Evidence with Azeliragon Treatment

Animal model	Main Results: Treatment with Azeliragon
Rat Diabetic Retinopathy	Protection Against Vascular and Neuronal Lesions: • Reduces acellular capillaries and improves pericyte/endothelial cell ratio • Reduces activated microglia
Adriamycin Induced Mouse Nephropathy model	Protection from the Development of Massive Albuminuria, Mesangial Expansion and Glomerular Sclerosis
Alzheimer's disease Transgenic Mouse model (human APP Swedish and London mutations)	• Reduces amyloid deposition and inflammation in the brain • Increase Glucose Uptake in the brain • Preserves cognitive/ behavioral function
C57BLKS/J-m+/+Lepr db mice (Lepr db)	Dose related decrease in wound closure time and % closure at all doses

Phase 3 STEADFAST Study Design



Two Pivotal Studies Under One Protocol

5mg/day azeliragon (AZL) or Placebo (PBO) + Standard of Care

Patients with probable mild AD, MMSE 21-26, CDR global 0.5-1

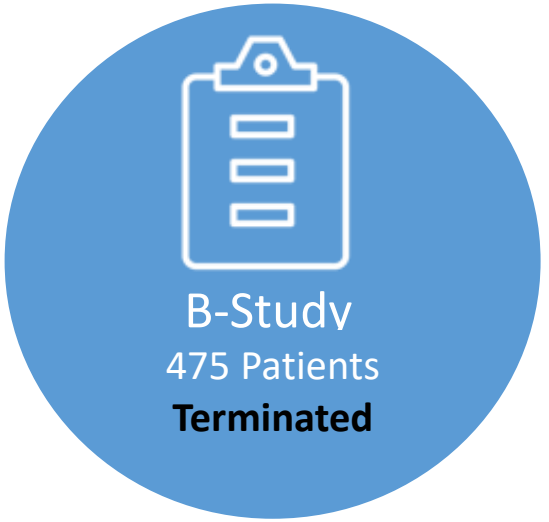
Co-Primary Endpoints: ADAS-cog11 and CDR-SB

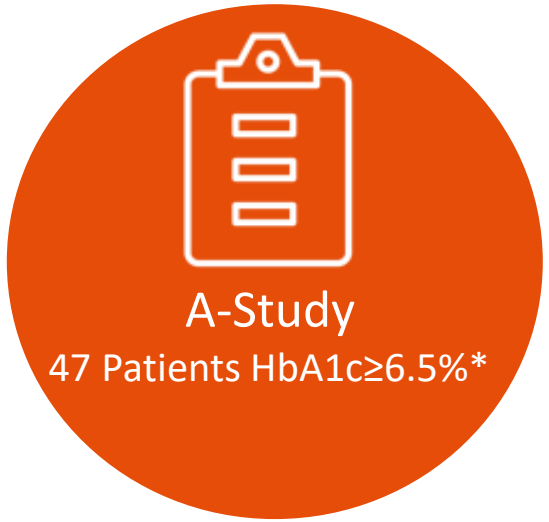
Co-Primary Endpoints to be analyzed as independent studies

Secondary Endpoints: MRI volumetric measures, FDG-PET, functional / behavioral measures, etc

Secondary Endpoints to be analyzed as one study

Patients with diabetes were included in the study (HbA1c ≤7.7%)



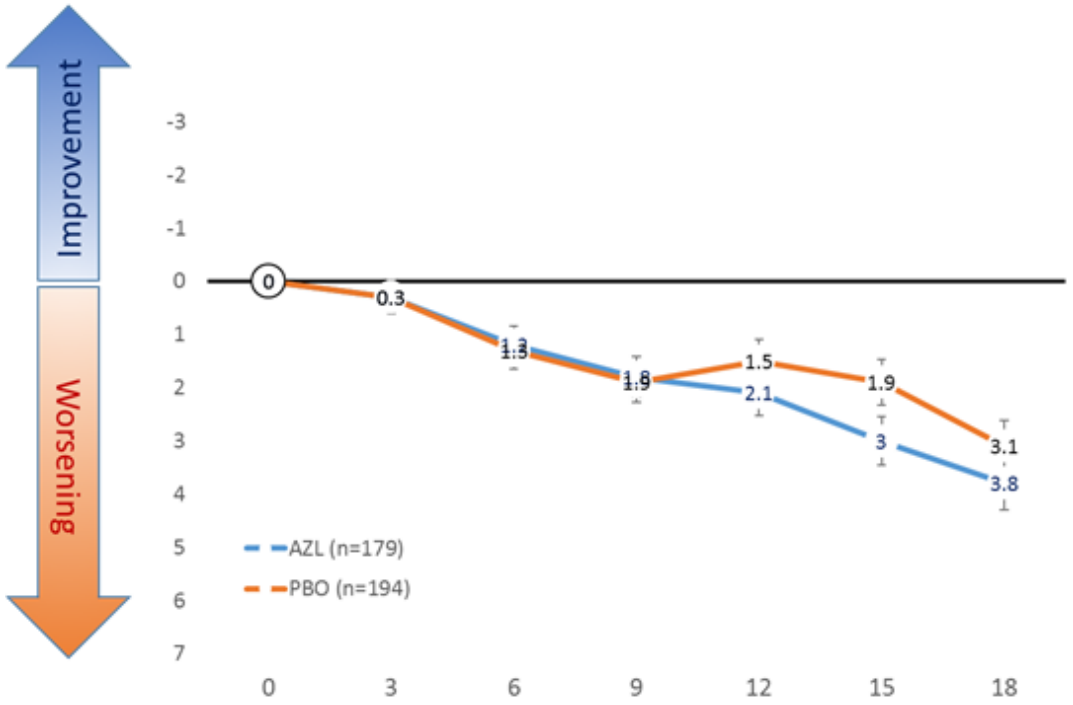


*At any time during the study; referred to as ADA-T2D subgroup throughout the presentation

Potential Beneficial Effect on Cognition in Patients with Elevated HbA1c

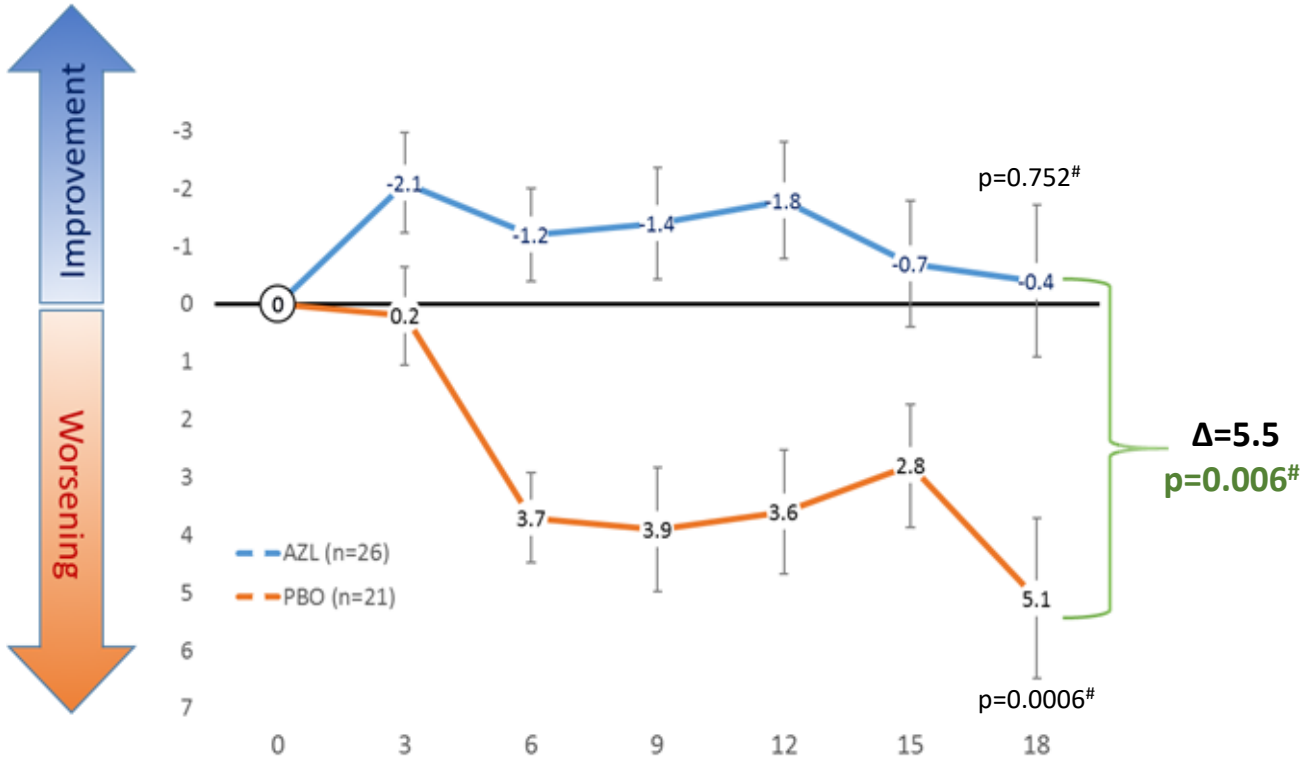
STEADFAST A-Study (FAS)

Change from Baseline in ADAS-cog11 (LSMEANS)



STEADFAST A-Study ADA-T2D Subgroup (FAS)

Change from Baseline in ADAS-cog11 (LSMEANS)

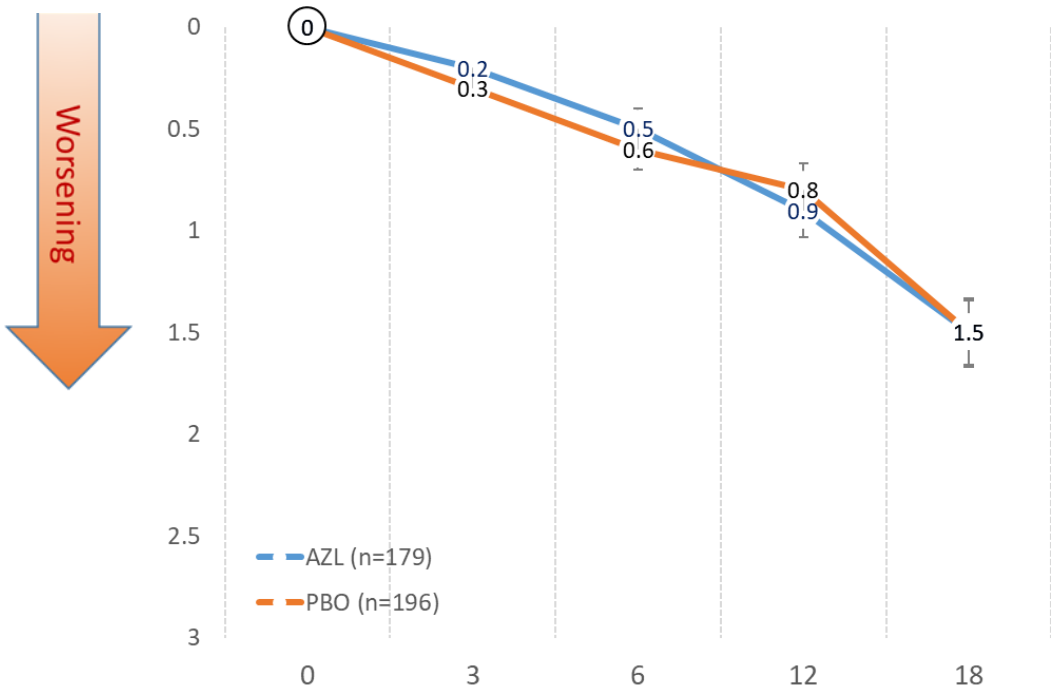


Results are LSMeans ± SE based on MMRM model. AD-T2D=HbA1c ≥6.5% at anytime during the study. #All p values are nominal. FAS =Full Analysis Set

Potential Beneficial Effect on Cognitive Function in Patients with Elevated HbA1c

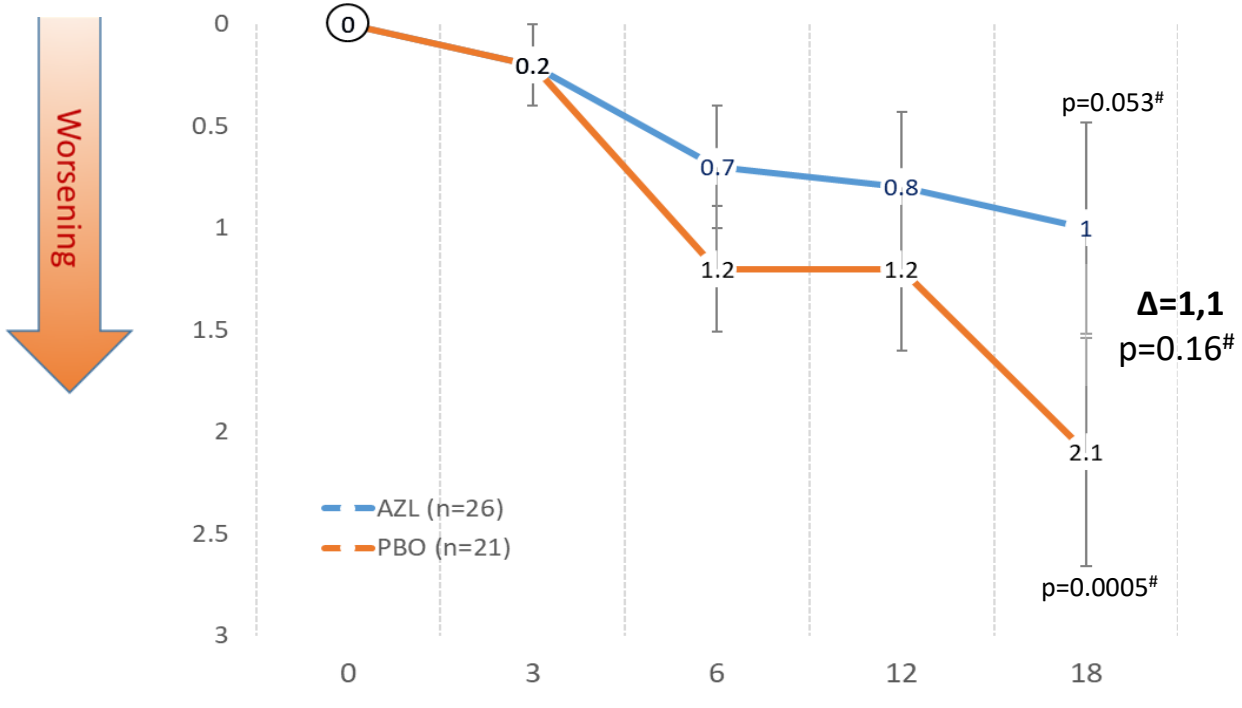
STEADFAST A-Study (FAS)

Change from Baseline in CDR-SB



STEADFAST A-Study ADA-T2D Subgroup (FAS)

Change from Baseline in CDR-SB

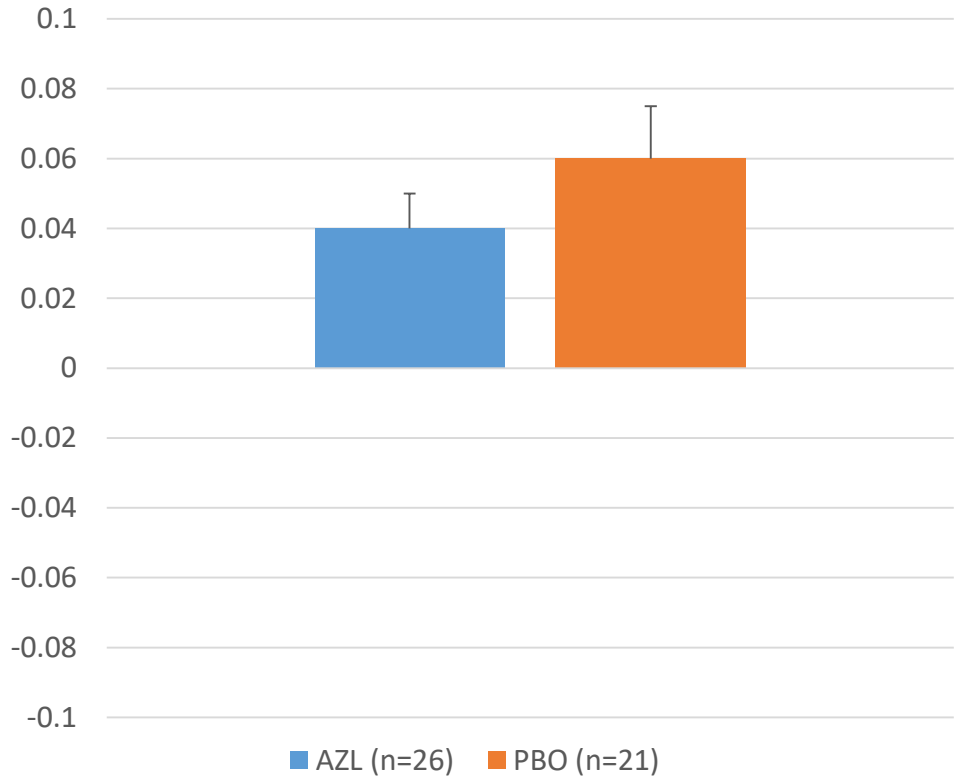


Results are LSMeans ± SE based on MMRM model. AD-T2D=HbA1c ≥6.5% at anytime during the study. #All p values are nominal. FAS =Full Analysis Set

Cognitive Improvement Cannot be Explained by Improvement in Glycemic Control

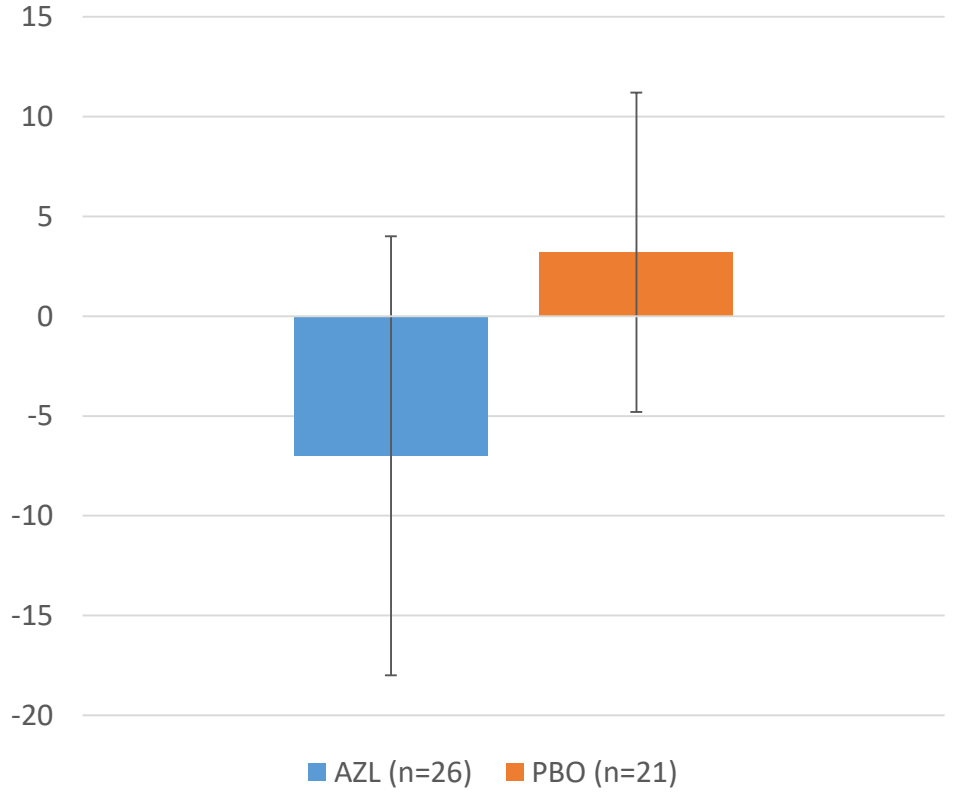
STEADFAST A-Study ADA-T2D Subgroup (FAS)

Change in HbA1c (%) at Month 18



STEADFAST A-Study ADA-T2D Subgroup (FAS)

Change in Non-fasting Glucose (mg/dL) at Month 18



- Stable therapy was required throughout the study
- Insulin was not allowed

AD-T2D=HbA1c ≥6.5% at anytime during the study. Results are Means ± SE ,FAS = Full Analysis Set

Demography and Baseline Characteristics: No Notable Imbalance Between Treatment Arms

STEADFAST Study ADA-T2D Subgroup Demographics (A&B Studies Combined)

Characteristic	Statistic	Placebo (n=43)	Azeliragon (n=51)
Age (years)	Mean (min-max)	78 (58, 91)	76 (58, 92)
Sex (male)	Number (%)	37 (86%)	31 (61%)
Race (white)	Number (%)	39 (91%)	47 (92%)
Ethnicity (not Hispanic or Latino)	Number (%)	36 (84%)	42 (82%)
Weight (kg)	Mean (min-max)	82 (58-110)	78 (52-126)
BMI (kg/m2)	Mean (min-max)	28 (20-38)	27 (19-35)
Years since diagnosis of AD	Mean (min-max)	2.5 (0-13)	2.6 (0-10)
ApoE alleles (at least one copy of E4)	Number (%)	22 (51%)	25 (49%)
Background AD:			
Memantine	Number (%)	12 (28%)	22 (43%)
Acetylcholinesterase inhibitor	Number (%)	40 (93%)	47 (92%)
both	Number (%)	10 (23%)	18 (35%)

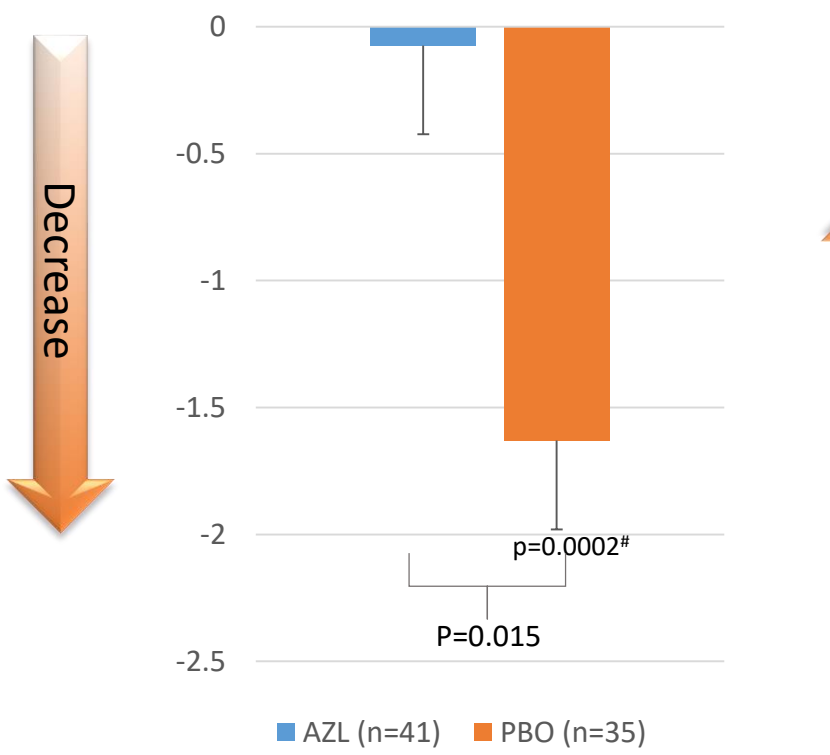
STEADFAST Study ADA-T2D Subgroup Baseline Characteristics (A&B Studies Combined)

Characteristic	Statistic	Placebo (n=43)	Azeliragon (n=51)
Baseline MMSE	Mean (min-max)	23.5 (17-28)	23.4 (19-30)
Baseline ADAS-cog	Mean (min-max)	16.1 (5-27)	16.5 (4-33)
Baseline CDR-sb	Mean (min-max)	4.5 (1.0-8.0)	4.7 (1.5-9.0)
Baseline ADCS-ADL	Mean (min-max)	63 (31-76)	66 (48-78)
Baseline NPI	Mean (min-max)	8.9 (0-50)	10.2 (0-43)
Baseline CDR-global			
CDR-global = 0.5	Number (%)	21 (49%)	21 (41%)
CDR-global = 1	Number (%)	22 (51%)	30 (59%)

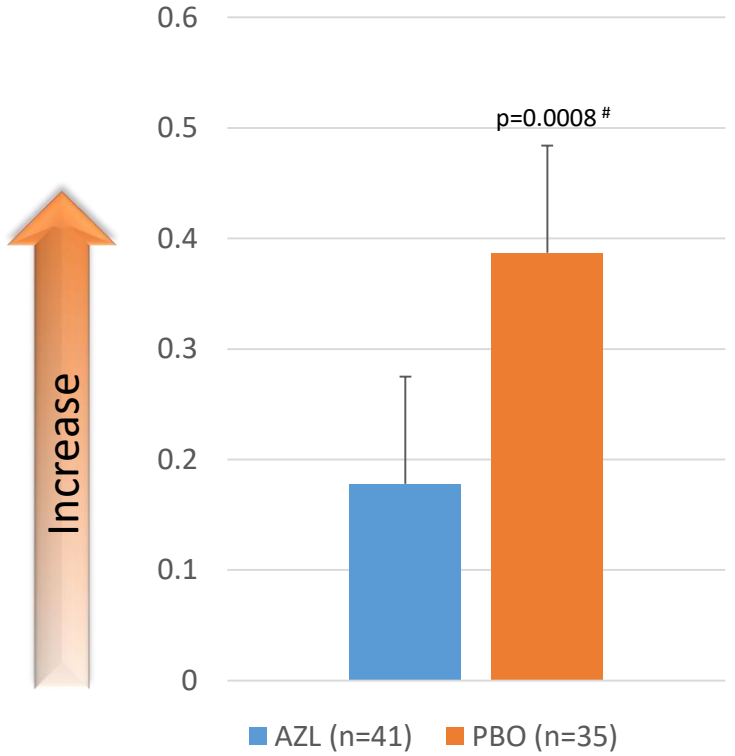
AD-T2D=HbA1c ≥6.5% at anytime during the study

Change in MRI Brain Volume at Month 18 in the ADA-T2D Subgroup: Trend Towards Less Brain Atrophy in the AZL-treated Group

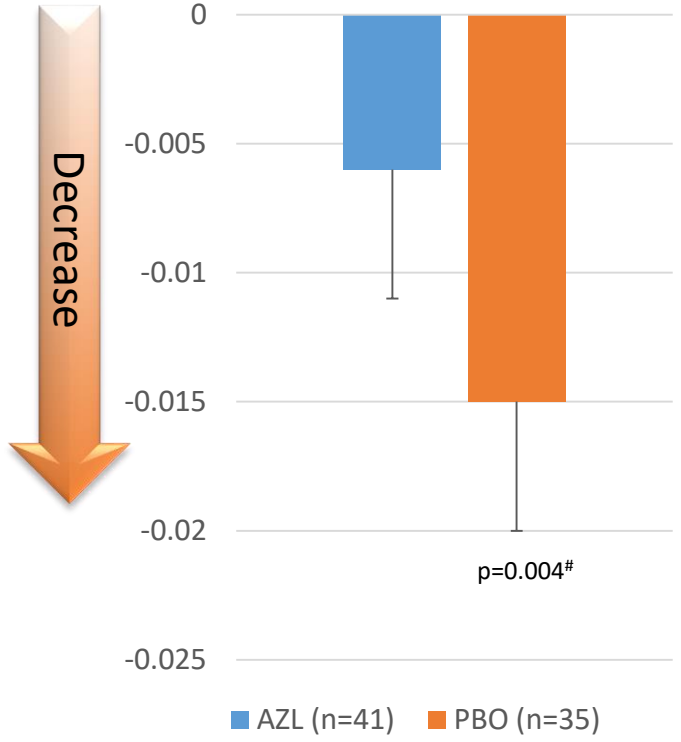
ADA-T2D subgroup
Change in Whole Brain volume (%)



ADA-T2D Subgroup
Ventricular Enlargement (%)

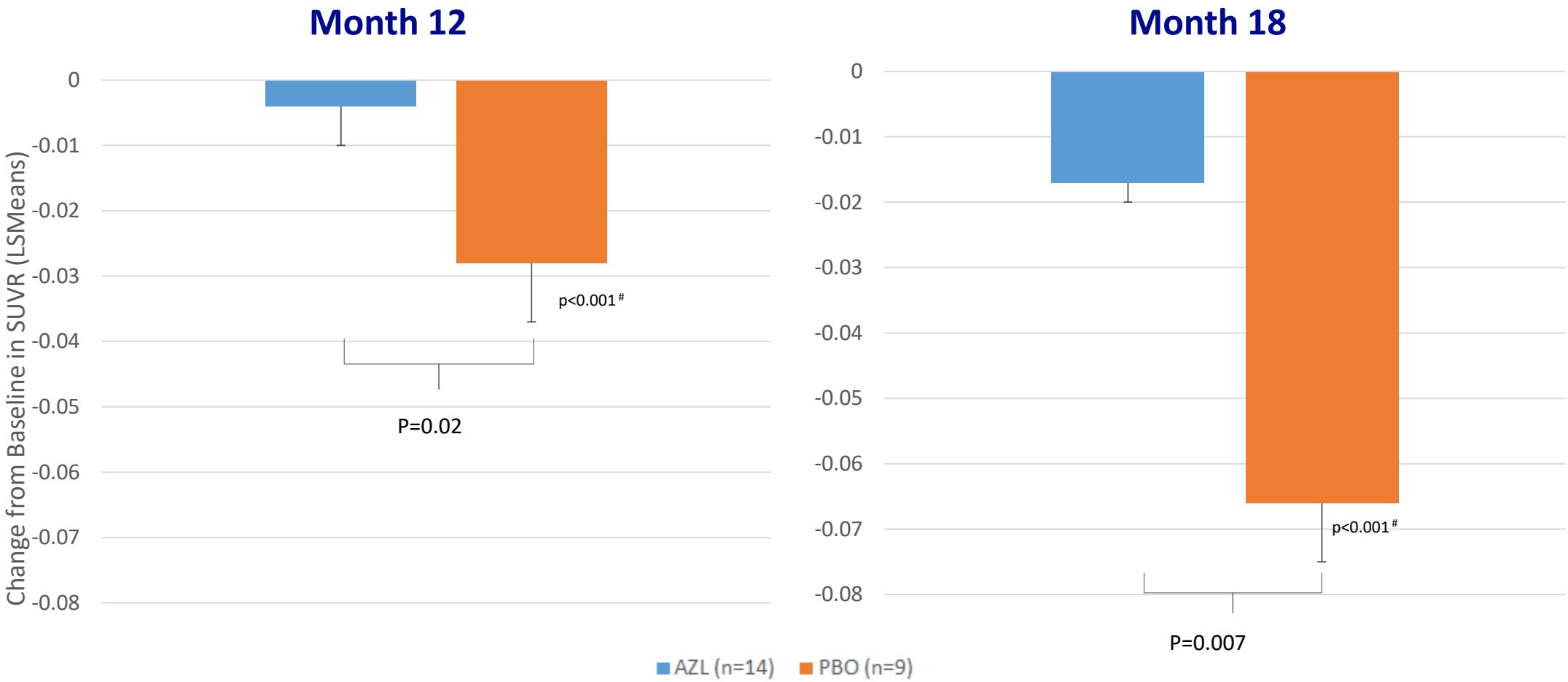


ADA-T2D Subgroup
Change in Total Hippocampus Volume (%)



AD-T2D=HbA1c ≥6.5% at anytime during the study.**Results are change from baseline LSMeans ± SE ANCOVA adjusted for baseline, FAS. # 1-sample test nominal significance indicating worsening. All p values are nominal

Change in FDG-PET SUVR in the ADA-T2D Subgroup: Less Reduction in Glucose Utilization in AZL-treated Group

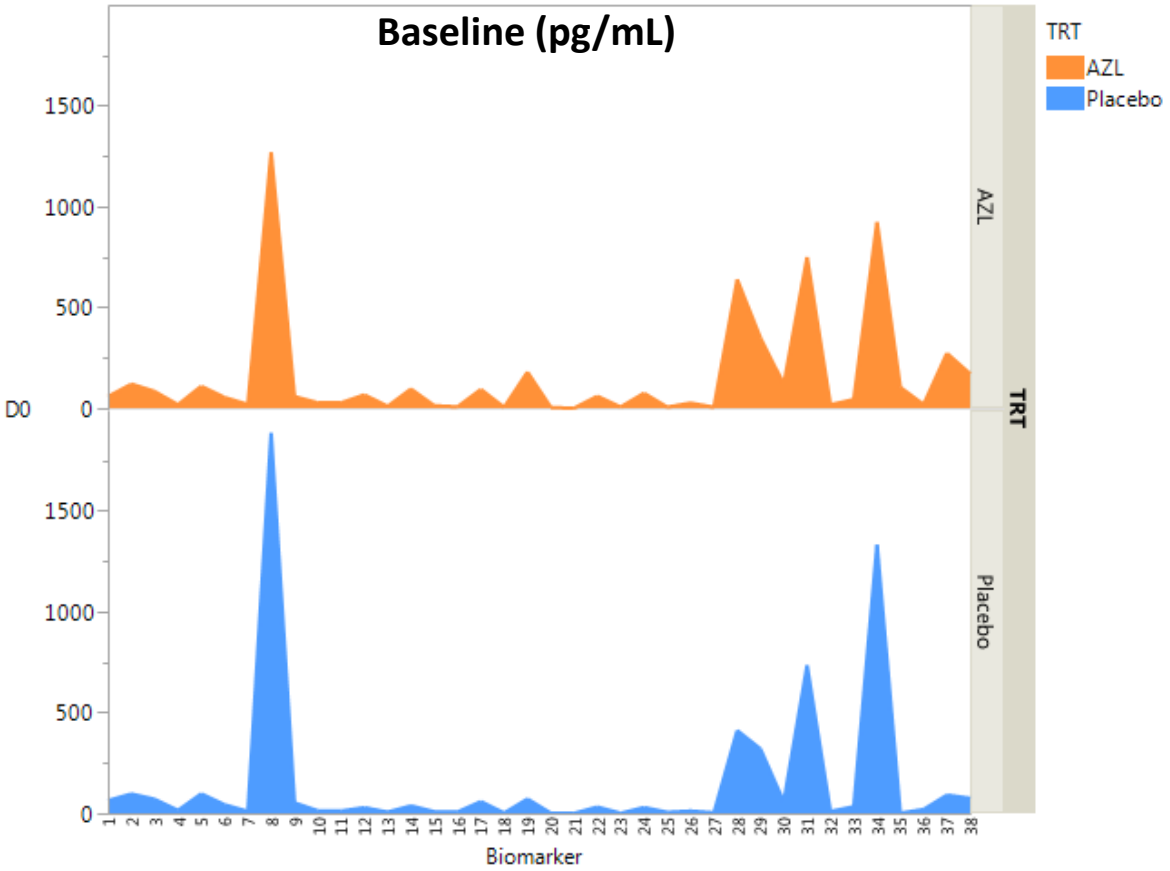


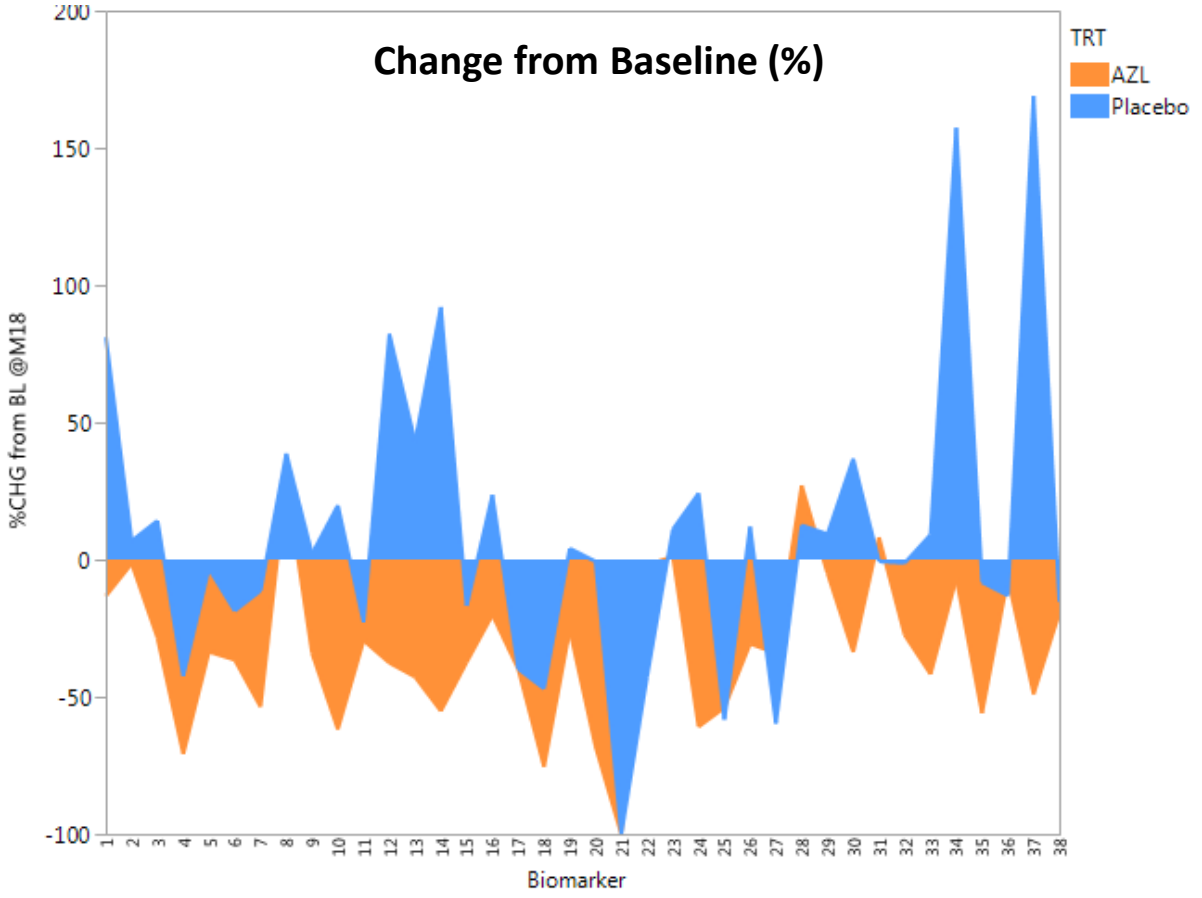
SUVR composite (unweighted combination of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal, and hippocampus)

Results are LSMeans ± SE based on MMRM model, FAS. AD-T2D=HbA1c ≥6.5% at anytime during the study. # 1-sample test nominal significance indicating worsening. All p values are nominal

Inflammatory Marker Panel: Changes at Month 18 of Treatment in ADA-T2D Subgroup

- Inflammatory biomarkers were measured in plasma using LincoPlex system and the human cytokine/chemokine full panel (panel 1, Millipore)
- No notable differences between placebo and azeliragon at baseline
- Statistically meaningful differences between azeliragon and placebo for changes from baseline in select inflammatory markers

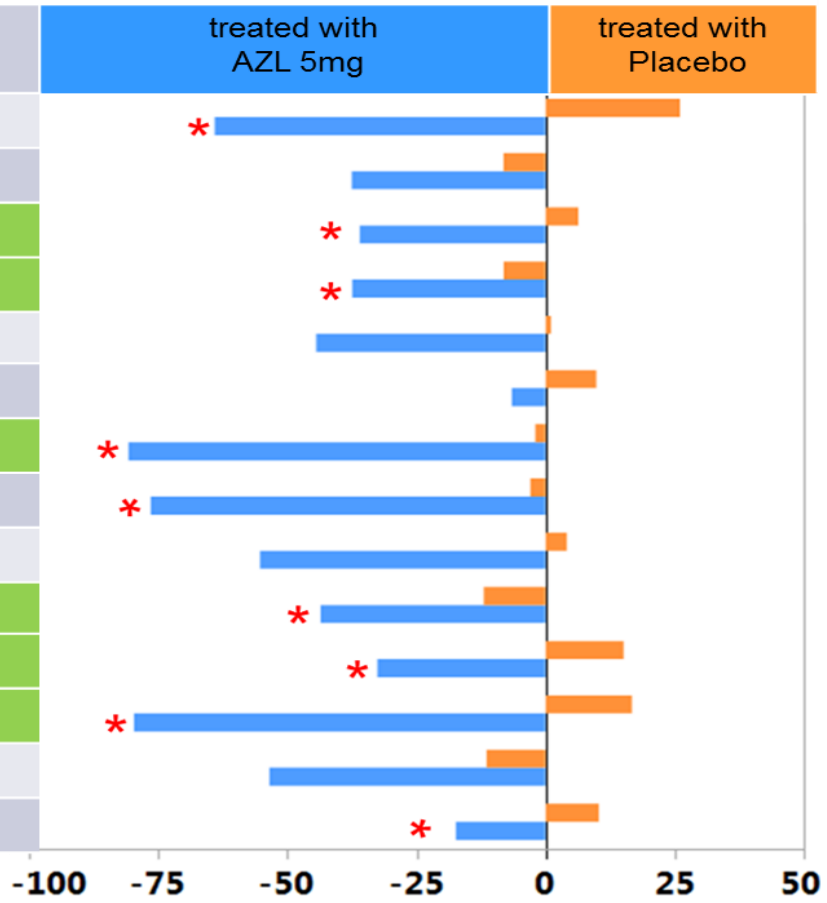




AD-T2D=HbA1c ≥6.5% at pre-dose

Changes in Biomarker Profile Consistent with RAGE Inhibition

Biomarker	Relation to RAGE	Predicted change upon RAGE inhibition
TNFb	Indirect	Decrease
TGF-a	Indirect	Decrease
sCD40L	**Direct**	Decrease
MIP-1b	**Direct**	Decrease
MCP-3	Indirect	Decrease
MCP-1	Indirect	Decrease
IL-6	**Direct**	Decrease
IL-2	Indirect	Decrease
IL-13	Indirect	Decrease
IL-12p70	**Direct**	Decrease
IL-12p40	**Direct**	Decrease
IFNg	**Direct**	Decrease
GM-CSF	Indirect	Decrease
FGF-2	Indirect	Decrease



*nominal p<0.05 Wilcoxon test

Results are Means

Biomarker Profile

Azeliragon treatment significantly decreased the following markers linked to RAGE:

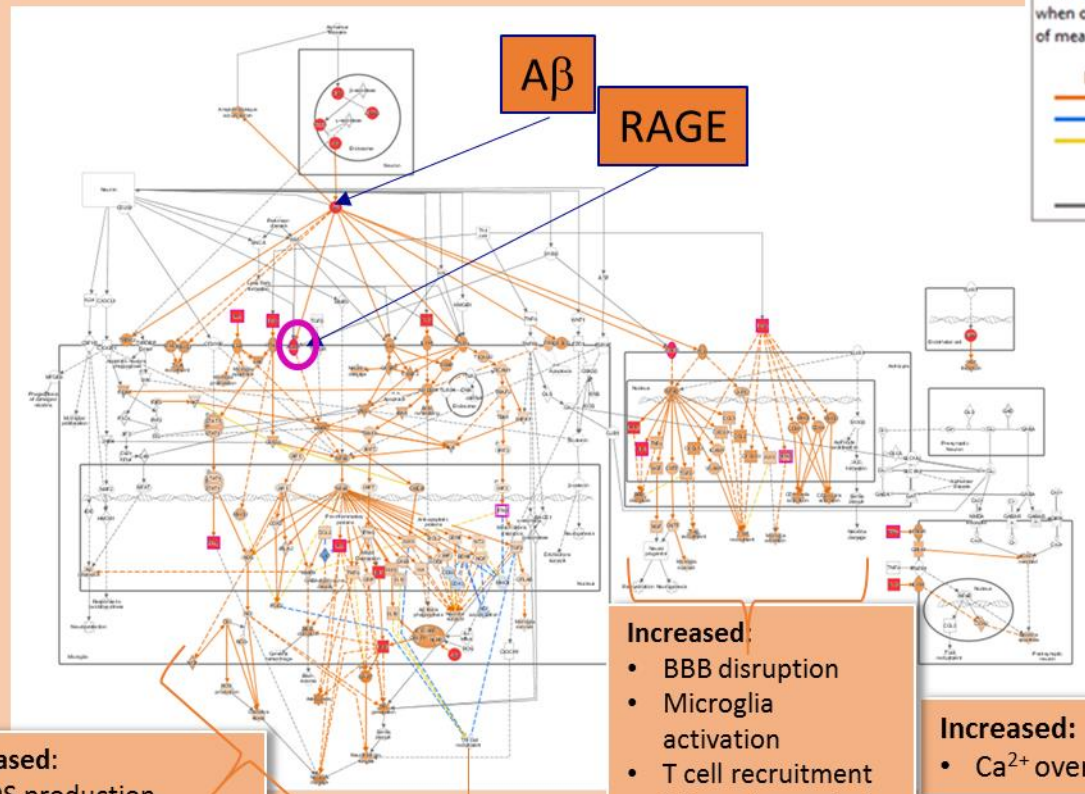
- IL6
- IL12
- INFg
- CD40L
- MIP-1
- IL2
- TNFb

Each of these markers is a major player in the neuroinflammatory pathway[1]

[1]*Based on Ingenuity software predictions*

Data from the ADA-T2D Subgroup and Prediction Using Ingenuity Software Support Hypothesis that Inhibition of RAGE Could Result in Beneficial Effects

AD (Increased Aβ and RAGE Activation)

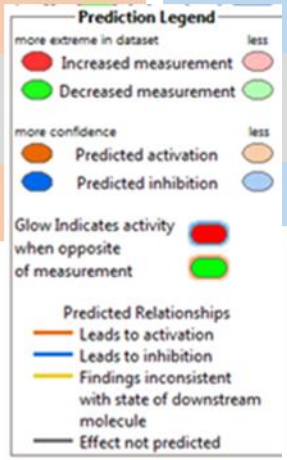


Increased:
- ROS production
- Oxidative stress
- Neuron Damage
- Neurofibrillary tangles
- Aβ generation

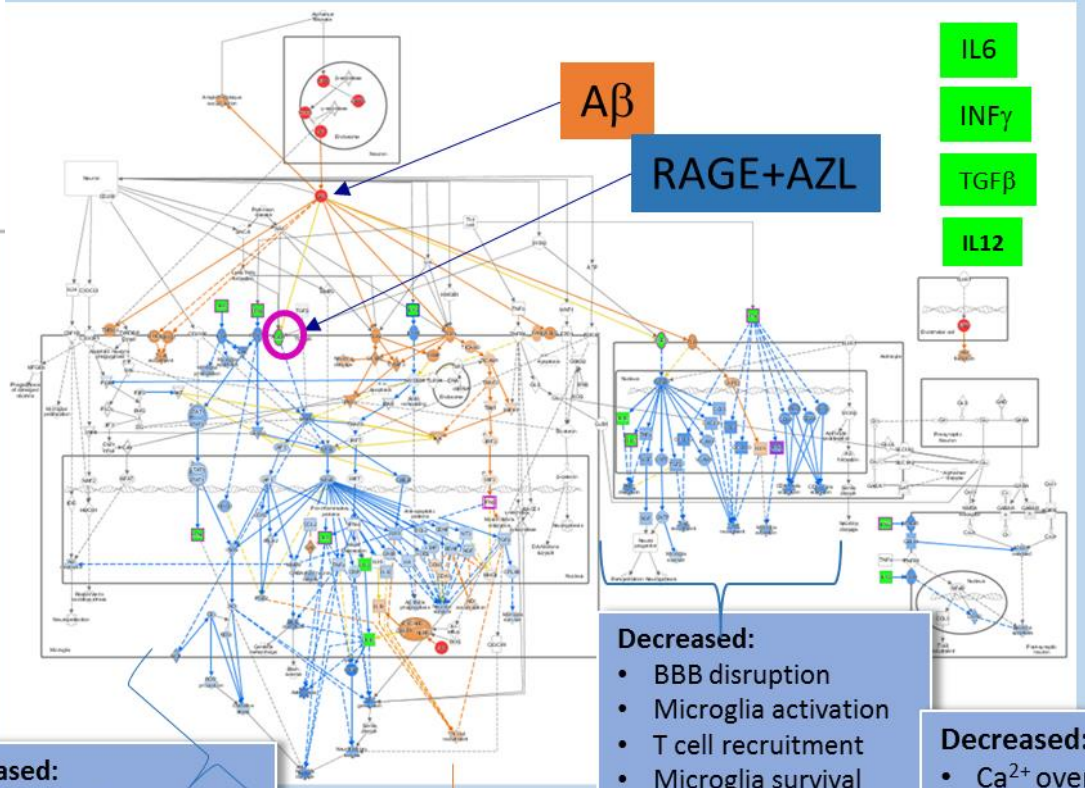
Increased:
- BBB disruption
- Microglia activation
- T cell recruitment
- Microglia survival

Increased:
- Ca^{2+} overload

Decreased:
- Th1 recruitment



AD and RAGE Inhibition



Decreased:
- ROS production
- Oxidative stress
- Neuron Damage
- Neurofibrillary tangles
- Aβ generation

Decreased:
- BBB disruption
- Microglia activation
- T cell recruitment
- Microglia survival

Decreased:
- Ca^{2+} overload

Increased:
- Th1 recruitment

INGENUITY SYSTEMS

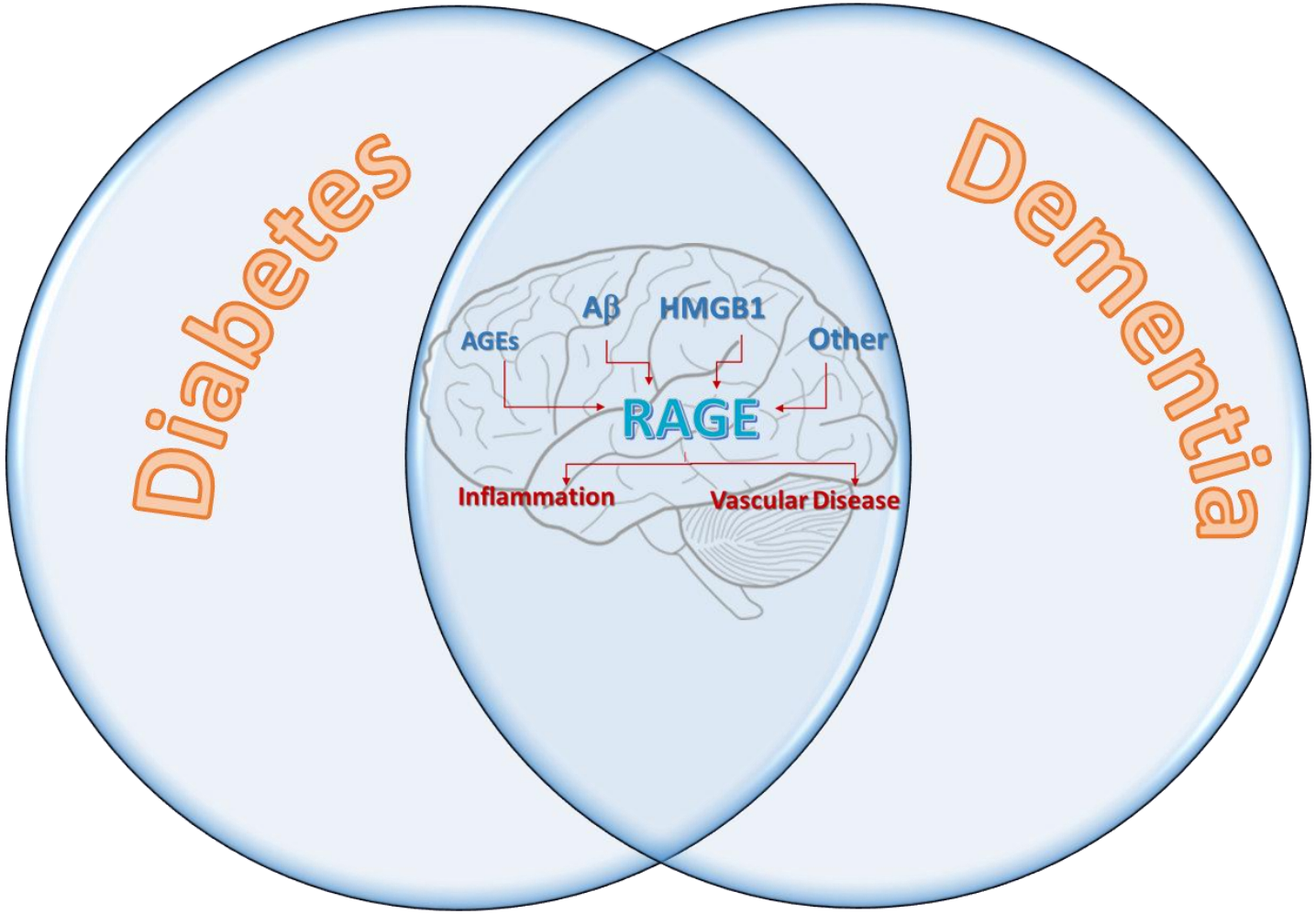
Conclusions

- Results from the post-hoc analysis of a subgroup of patients with HbA1c≥6.5% support the hypothesis that treatment with azeliragon may:
  - Improve/preserve cognition and function
  - Reduce Whole Brain and Hippocampus atrophy and ventricular enlargement
  - Preserve glucose uptake

- The results from the inflammatory marker analyses revealed changes consistent with RAGE inhibition, possibly indicating functional pharmacologic activity of azeliragon in this subgroup of patients

- Further clinical studies are necessary to confirm this hypothesis:
  - **vTv is Initiating start-up activities for a study to evaluate the safety and efficacy of azeliragon in subjects with mild AD and type 2 diabetes (HbA1c ≥6.5%)**
    - Part 1: Objective is to demonstrate efficacy on a cognitive endpoint and establish proof of concept
    - Part 2: To be initiated upon positive results from Part 1. Objective is to demonstrate efficacy on co-primary endpoints of cognition and function

Thank you!



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