Linking Diabetes and Alzheimer's Disease through RAGE. A Retrospective Analysis of Azeliragon Phase 2 and Phase 3 Studies

Carmen Valcarce, Imogene Dunn, Aaron Burstein

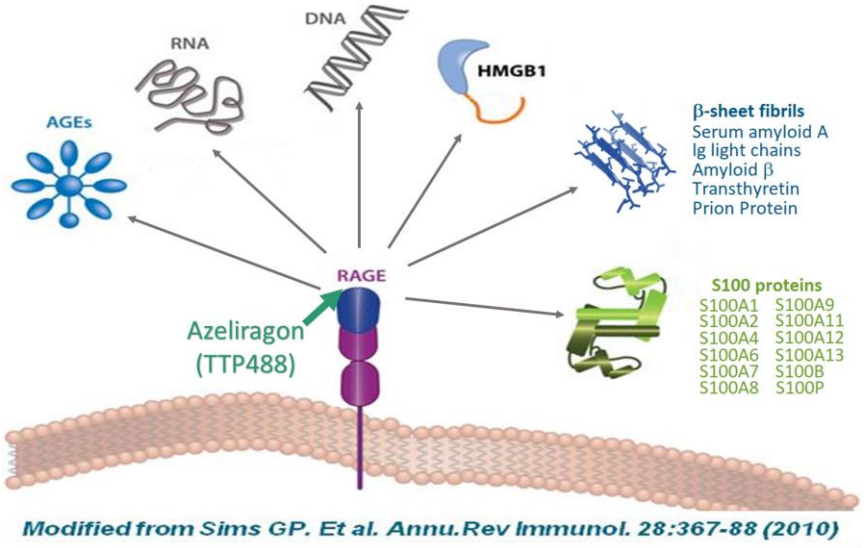
Disclosure

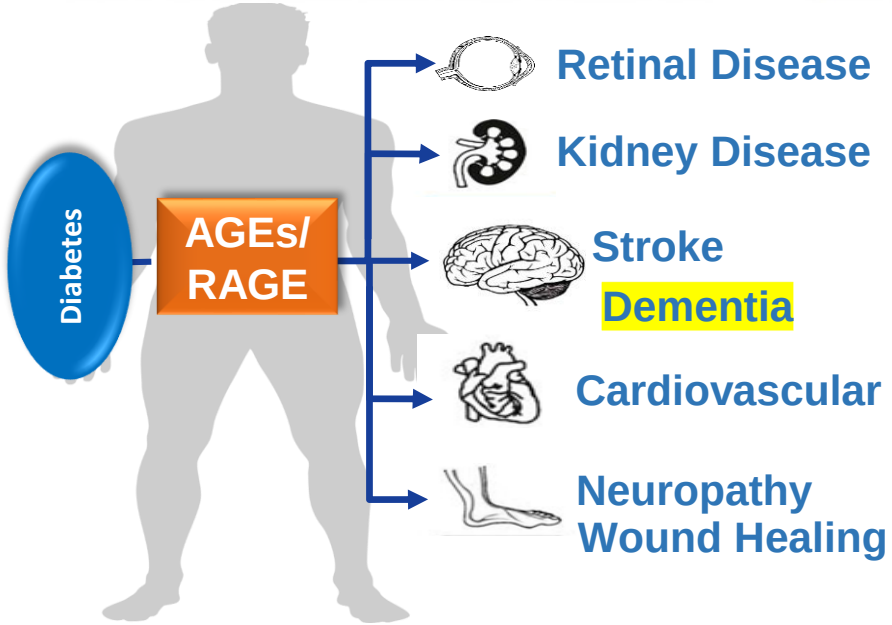
- Dr. Valcarce is an employee of vTv Therapeutics LLC
- Dr. Dunn is an employee of vTv Therapeutics LLC
- Dr. Burstein is an employee of vTv Therapeutics LLC

This presentation is not eligible for CME/CE

RAGE as a Target in Humans

- **RAGE** is a 35kDa membrane protein member of the Ig supergene family
  - Expressed at low levels in healthy tissues (except skin and mucus membranes)
  - Increases in the concentration of RAGE ligands (AGEs, HMGB1, S100 and Aβ) induce RAGE expression
  - Interaction of AGEs (or other ligands) with RAGE leads to sustained cellular damage, inflammation, insulin resistance
- **RAGE in Alzheimer's disease and Diabetes**
  - RAGE / AGEs well established in contributing to diabetic complications
  - Analysis of RAGE expression in postmortem AD brains indicated that increases in RAGE protein and percentage of RAGE-expressing microglia paralleled the severity of disease[(1)]
  - Patients with 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)]

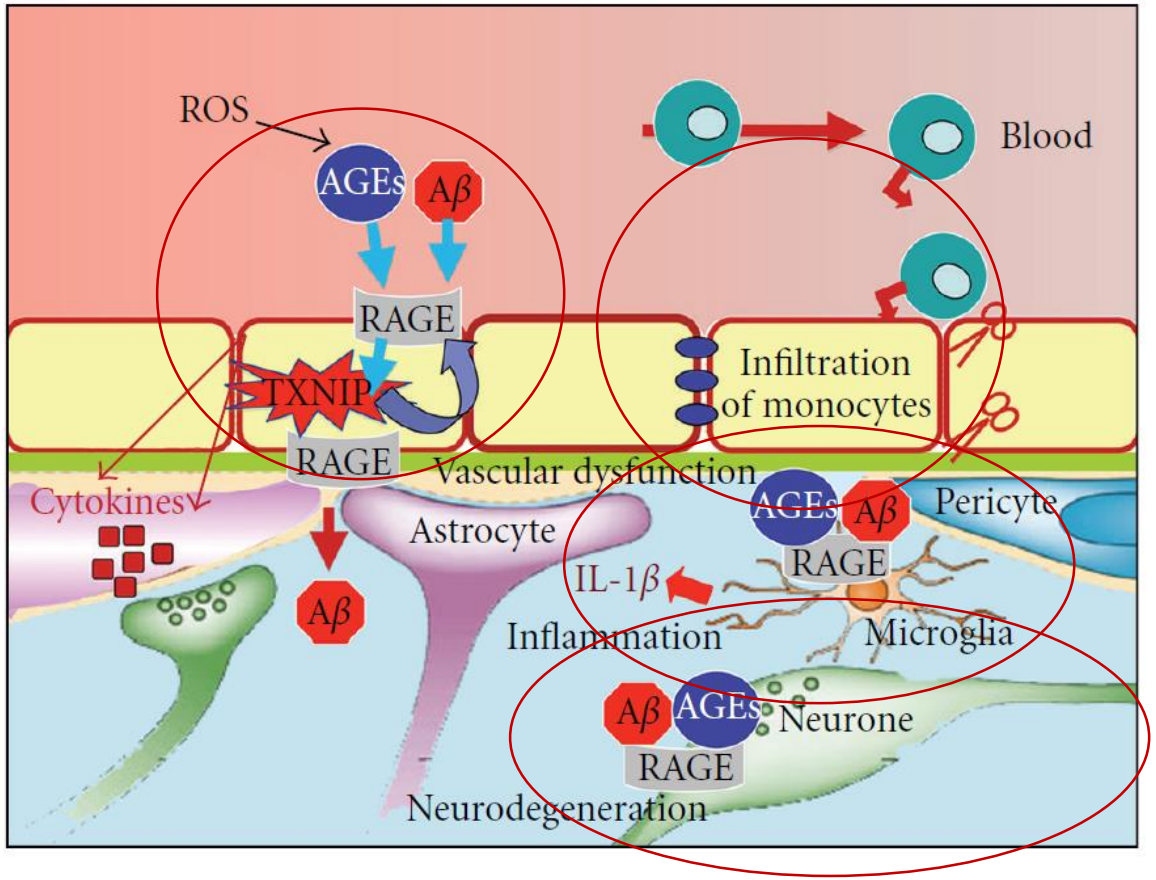




(1) Curr.Drug Targets CNS Neurol.Disord. 2005 Jun;4(3):249-66
(2) Neurobiology of Disease 37 (2010) 67–76
(3) Curr. Alzheimer Res.2008 Oct;5(5):432-7.

Hypothesis for Azeliragon's Mechanism of Action

- Activation of RAGE at BBB → TXNIP expression and resultant:
  - BBB leakage and monocyte infiltration
  - Positive feedback loop whereby activation of RAGE results in enhanced RAGE expression
  - Aβ transport from blood to brain
- RAGE activation in glial cells promoting proinflammatory gene expression
  - Increased Aβ production in brain
  - Neurotoxicity
- RAGE activation in neuronal cells
  - Increased oxidative stress
  - Production of M-CSF
  - Inflammation
- End-result = Neurodegeneration, synaptic loss
- Antagonism of RAGE by azeliragon may reduce inflammation and improve cell survival



Perrone L et al. Int J Alzheimers Dis 2012; doi: 10.1155/2012/734956.

Phase 2 Studies in AD, Diabetic Nephropathy

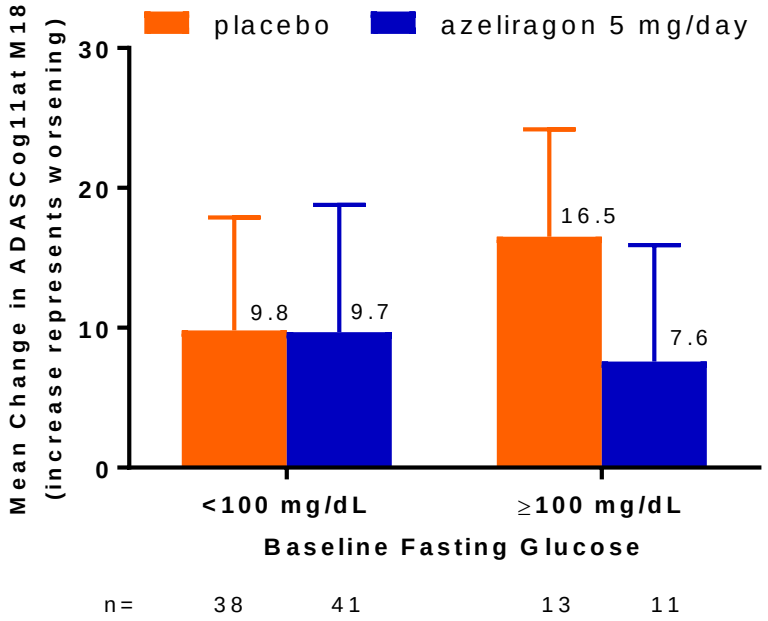
Alzheimer's disease	Diabetic nephropathy
60mg/day x 6d → 20 mg/day x 18 months **15 mg/day x 6d → 5 mg/day x 18 months** **Placebo (PBO) x 18 months**	**60mg/day x 6d → 20 mg/day x 6 months** **Placebo (PBO) x 6 months**
399 subjects with probable mild-moderate AD **MMSE 14-26** **Stable background Achel's or memantine**	**110 subjects with Type 2 diabetes and persistent albuminuria**
Primary Endpoint: ADAS-cog11	**Primary Endpoint:** UACR
Key-secondary: none	**Key-secondary:** none
Secondary Endpoints: MRI volumetric measures, ADCS-ADL, MMSE, NPI	**Secondary Endpoints:** eGFR, serum creatinine, markers of RAGE inhibition
Subjects with diabetes were excluded	Subjects **with** diabetes
20 mg/day discontinued at 6 months due to an increase in AEs of confusion and falls	**20 mg/day completed 6 months** **No increase in AEs of confusion and falls**

Questions following Phase 2 Studies:

- Is the effect on cognition/function dependent on glucose levels?
- Does RAGE antagonism affect glucose metabolism?

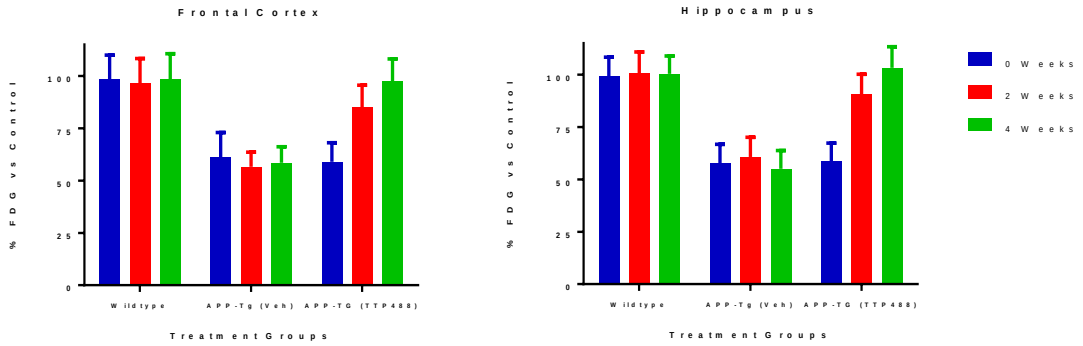
Phase 2b Data and Preclinical FDG-PET Support for Phase 3 Design

Phase 2b: Suggestion of potential differential response in subjects with increased fasting glucose

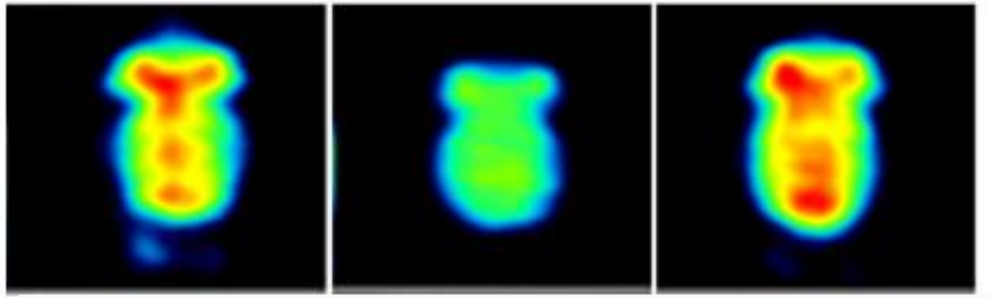


FDG-PET study: APP-Tg mice (>6 mo old) study

TTP488 10 mg/kg po QD or vehicle x 4 weeks



After 4 weeks treatment with TTP488 10mg/kg or vehicle (control)



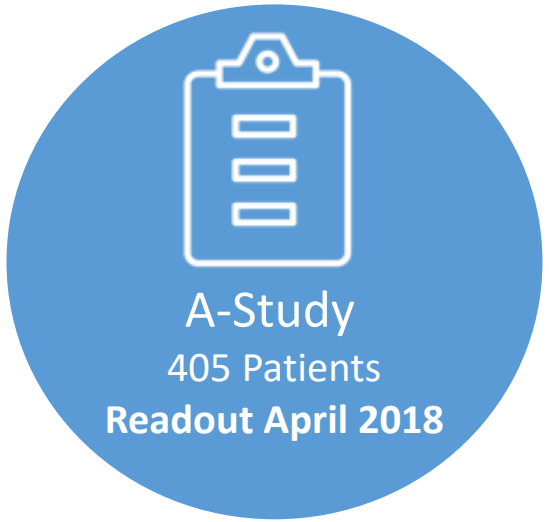
Wildtype | APP-Tg (Veh) | APP-Tg (TTP488)

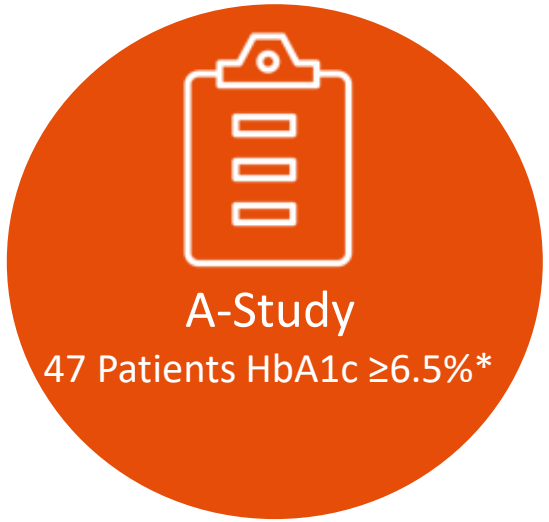
Burstein et al. J Prev Alz Dis 2018;5(2):149-154

Implications on Phase 3 (STEADFAST) Study Design

- Allow inclusion of patients with T2D
- Include FDG-PET sub-study as translation biomarker

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

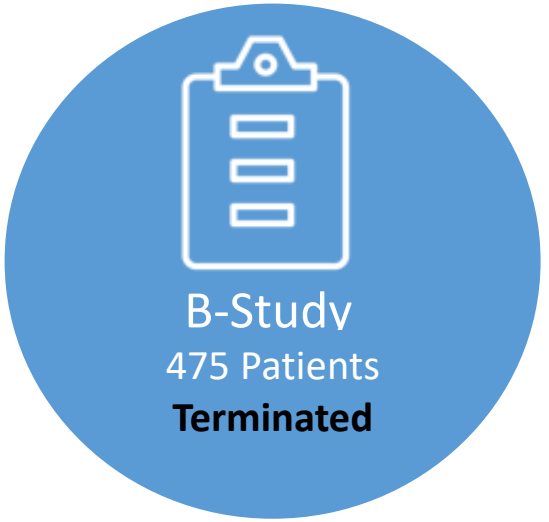
Co-Primary Endpoints: ADAS-cog11 and CDR-SB

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

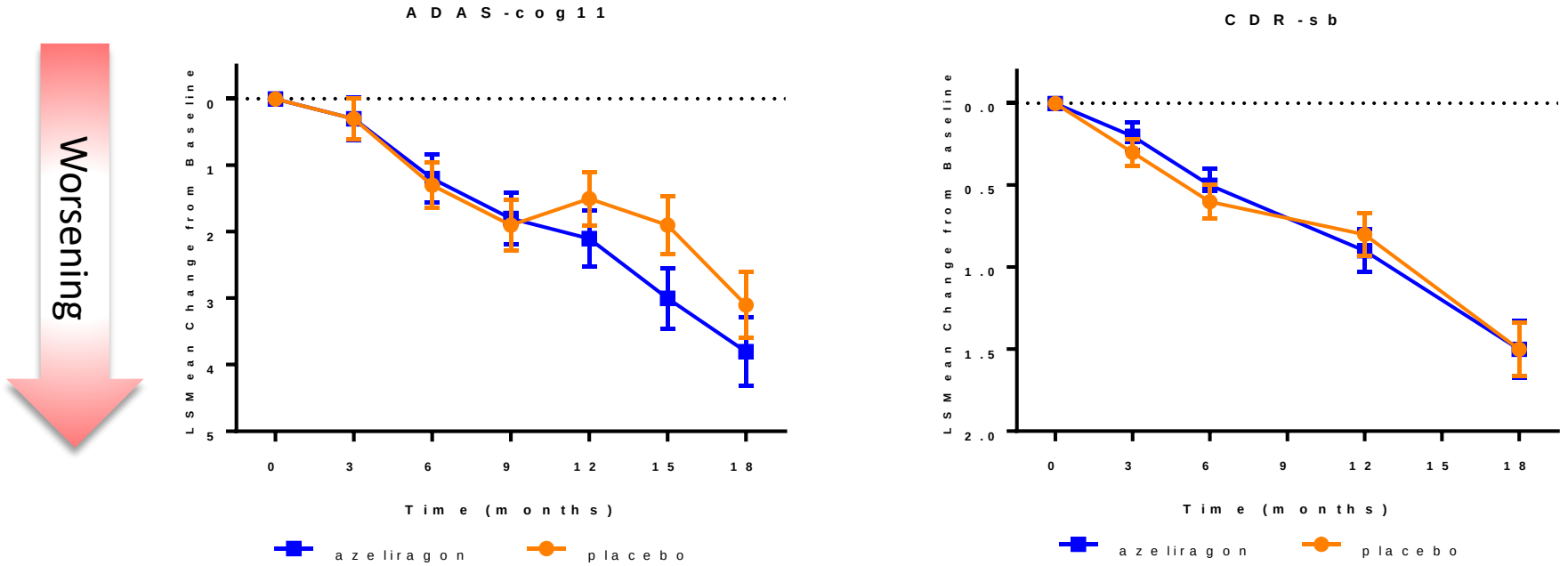
Patients with diabetes were permitted in the study (HbA1c ≤7.7%)



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

A-Study Failed to Demonstrate Statistically Significant Benefit of Azeliragon on Co-Primary Endpoints of ADAS-cog$_{11}$ and CDR-sb

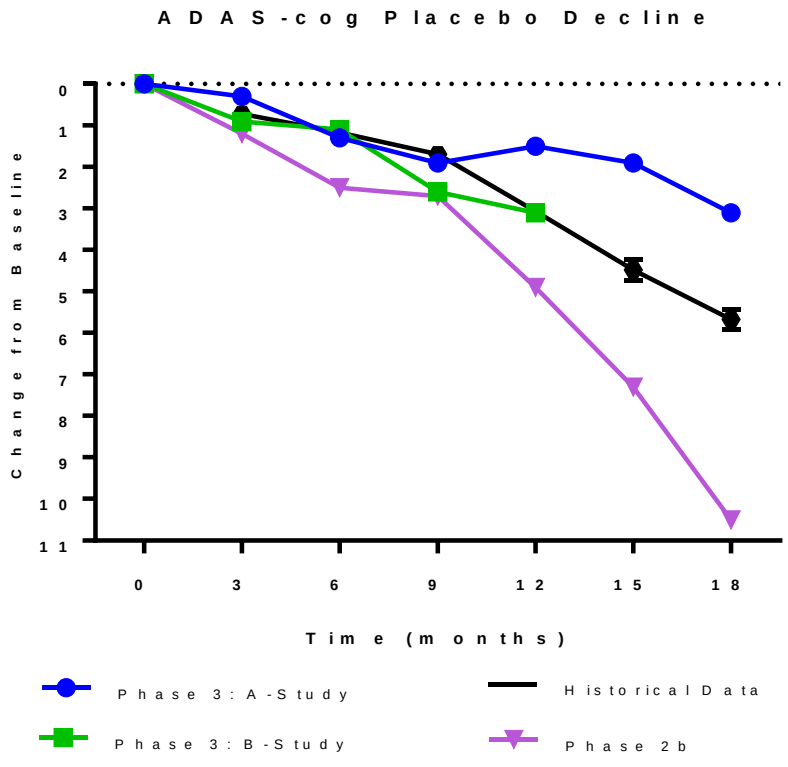
A-Study Final Analysis: Full Analysis Set*, MMRM
Data reported as LSMean (SE)

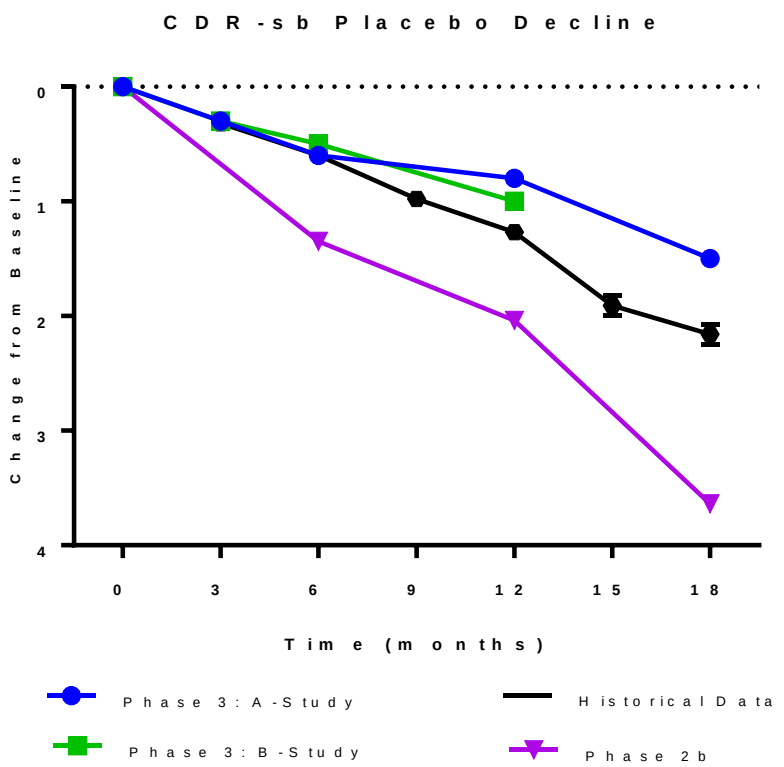


- **B-Study and Open Label studies terminated at time of A-Study Top Line Results**
  - B-Study failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints of ADAS-cog$_{11}$ and CDR-sb

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

Very Different Populations Between Phase 2b and Phase 3 Despite Virtually Identical Inclusion/Exclusion Criteria





Historical data from Thomas RG et al. Alz Dementia 2016

Phase 2B

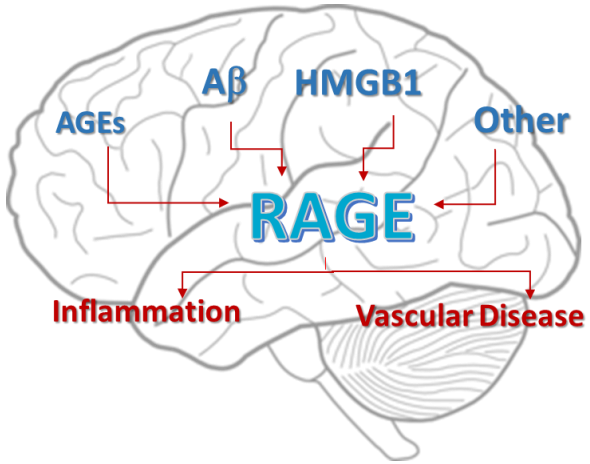
- "Faster progressors"
- Placebo decline ~2x faster than historical data

Phase 3: Part A

- More "Non/slow progressors and improvers"
- Placebo decline ~1/2 that of historical data

Back to First-Principles

Phase 2B	Phase 3
Facts: ❑ "**Faster progressors**" (Placebo decline 10.5 points /18 months) ❑ Azeliragon delayed cognitive and functional decline ❑ Higher glucose predicted more pronounced response **Hypothesis:** ❑ Potential **higher** concentrations of **RAGE/RAGE-ligands** ❑ Potentially **higher** degree of **inflammation and cell death** ongoing	**Facts:** ❑ "Non/**slow progressors**" (Placebo decline 3 points/18 months) ❑ Azeliragon did not affect cognitive or functional decline ❑ Patients with diabetes were included in the study **Hypothesis:** ❑ Potential **lower** concentrations of **RAGE/RAGE-ligands** ❑ Potentially **lower** degree of **inflammation and cell death** ongoing



Hypothesis: High plasma concentrations of RAGE-ligands should identify responders to azeliragon

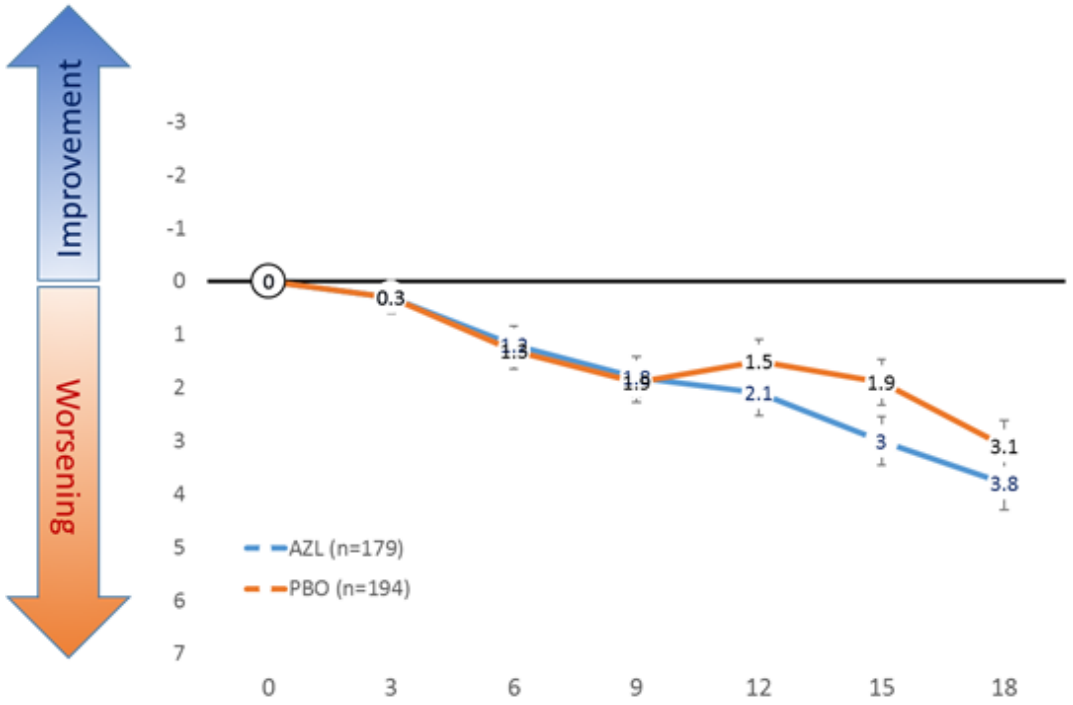
HbA1c chosen as a surrogate marker for AGEs

Post-hoc analysis of patients with HbA1c ≥ 6.5%

Potential Beneficial Effect on Cognition in Patients with Elevated HbA1c

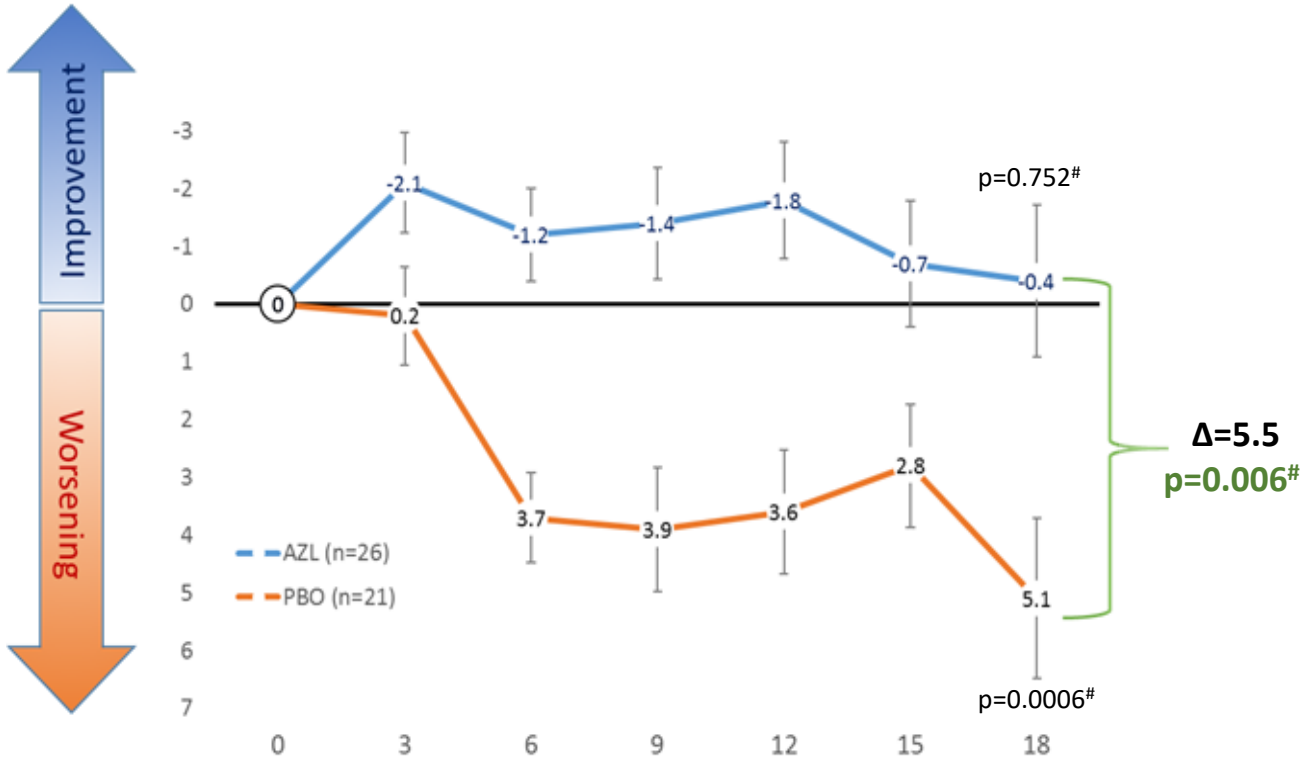
STEADFAST A-Study (FAS)

Change from Baseline in ADAS-cog11 (LSMEANS)



STEADFAST A-Study ADA-T2D Subgroup (FAS)

Change from Baseline in ADAS-cog11 (LSMEANS)



- Cognitive improvement cannot be explained by improvement in glycemic control

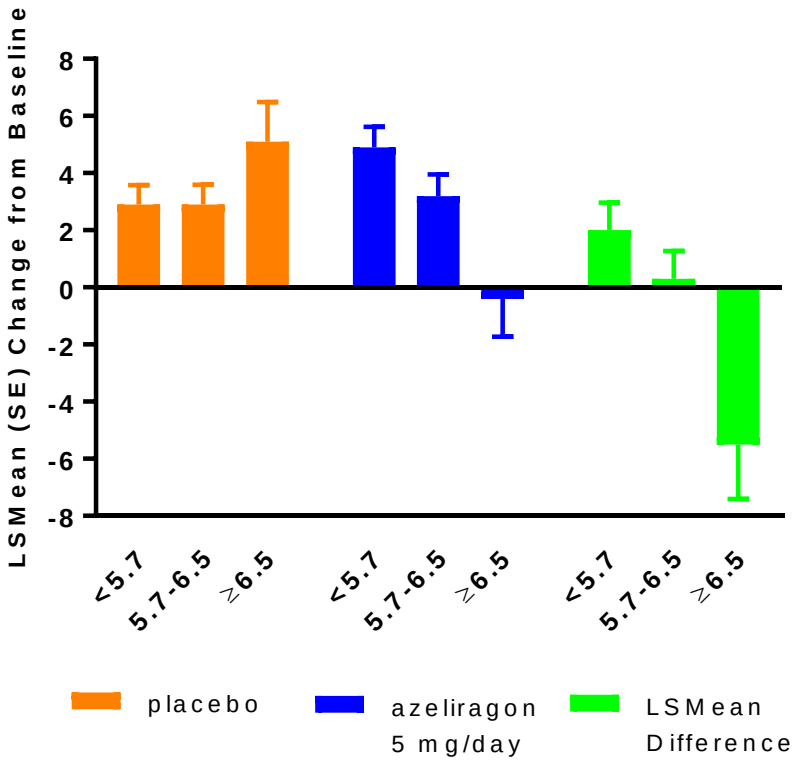
Analysis of Patients with Diabetes (HbA1c ≥ 6.5% at anytime during the study)
Results are LSMeans ± SE based on MMRM model.
***All p values are nominal**. FAS =Full Analysis Set

Data presented on March 30, 2019 at the 14th International Conference on Alzheimer's & Parkinson's Diseases held in Lisbon, Portugal

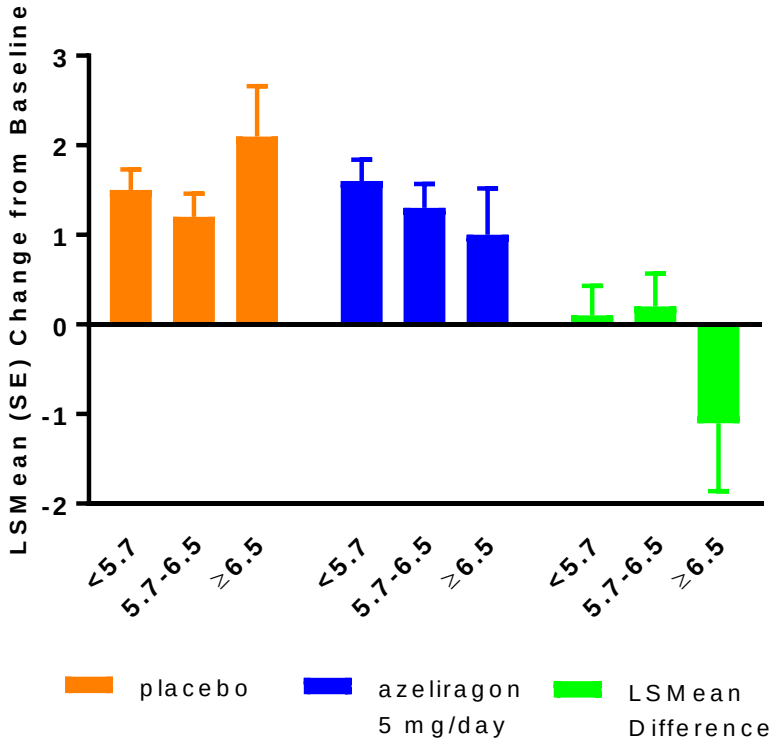
Phase 3 A-Study: HbA1c as Biomarker to Predict Responders
LSMean Change from Baseline to Month 18

Potential for greater magnitude of benefit on ADAS-cog in diabetes (HbA1c ≥ 6.5%) than in pre-diabetes (HbA1c 5.7-6.5%) and non-diabetes (HbA1c < 5.7%)

ADAS-cog11



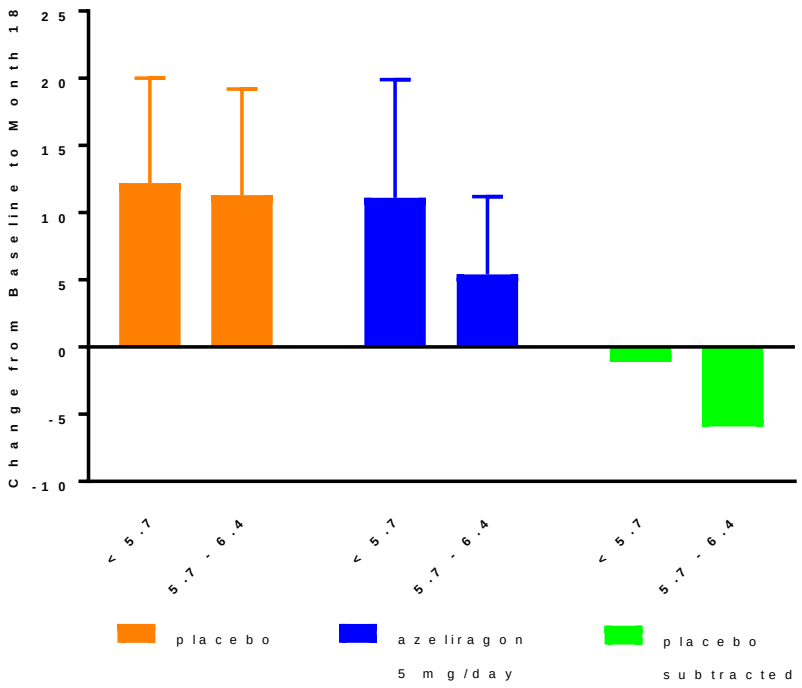
CDR-sb



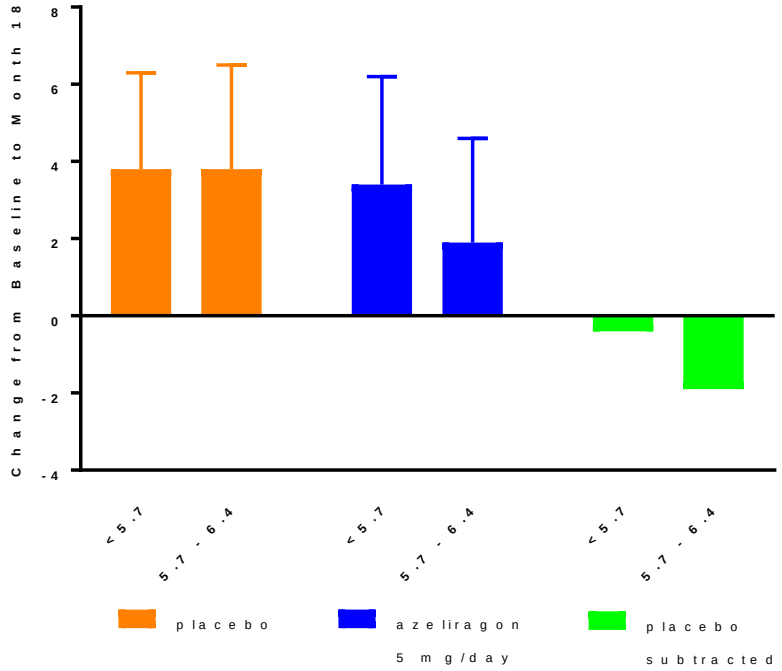
Phase 2b: HbA1c as Biomarker to Predict Responders
Mean Change from Baseline to Month 18, Mild-Moderate Subjects

Potential for greater magnitude of benefit on ADAS-cog and CDR-sb in pre-diabetes (HbA1c 5.7-6.4%) than in non-diabetes (HbA1c < 5.7%)

ADAS-cog11



CDR-sb



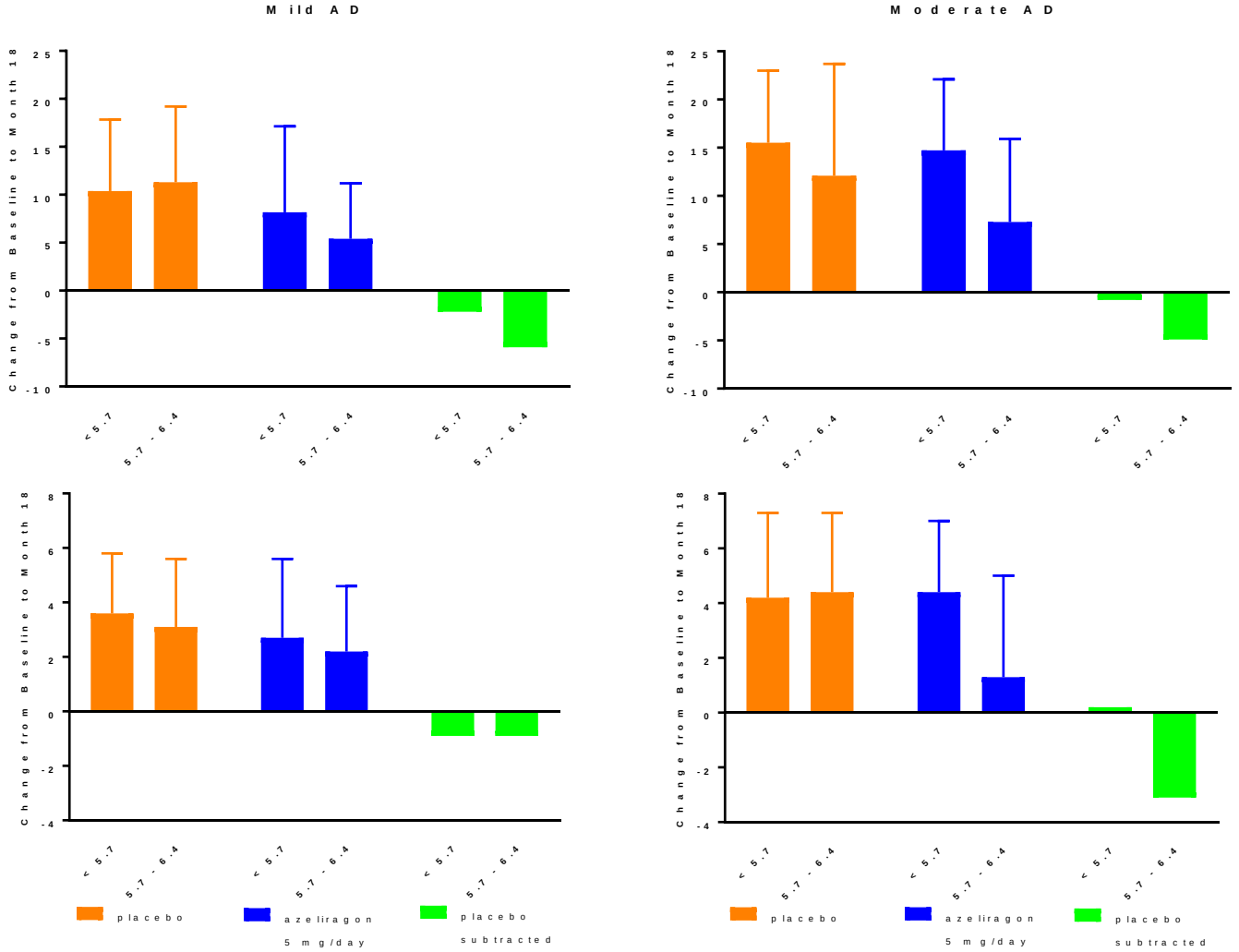
Phase 2b: Support for HbA1c as Biomarker to Predict Responders Mean Change from

Potential for greater magnitude of benefit on ADAS-cog and CDR-sb in pre-diabetes (HbA1c 5.7 – 6.4%) than in non-diabetes (HbA1c < 5.7%)

Effect does not appear to be driven by disease severity

ADAS-cog11

CDR-sb



Future Directions

- Identification of additional subgroups from STEADFAST Phase 3 Trial with plasma markers indicative of increased concentrations of RAGE ligands and/or increased RAGE expression
  - Analysis of baseline plasma samples from STEADFAST for markers of:
    - RAGE ligands: AGEs, HMGB1, S100
    - RAGE: sRAGE
    - Pro-inflammatory cytokines
    - Vascular injury
    - Neurodegeneration / Neural Injury: NfL
- TTP488-305
  - Clinical study to prospectively replicate results of post-hoc subgroup analysis from STEADFAST

TTP488-305: Two Studies Operationally Conducted Under a Single Protocol (NCT03980730)

Study Objectives:

Phase 2:

- Proof of concept study to confirm the findings from the diabetes subgroup of the STEADFAST study

Phase 3:

- Demonstrate safety and efficacy with co-primary endpoints of cognition and function to support possible registration

Phase 2

(Part 1 / Proof of Concept)

- Double-blind, placebo control
- 5mg QD or placebo for 6 months
- ~100 subjects with mild Alzheimer's disease and HbA1c ≥ 6.5%
- Primary Endpoint: ADAS-cog14
- Secondary Endpoints: CDR-sb, FAQ, Amsterdam-IADL, MMSE

Phase 3

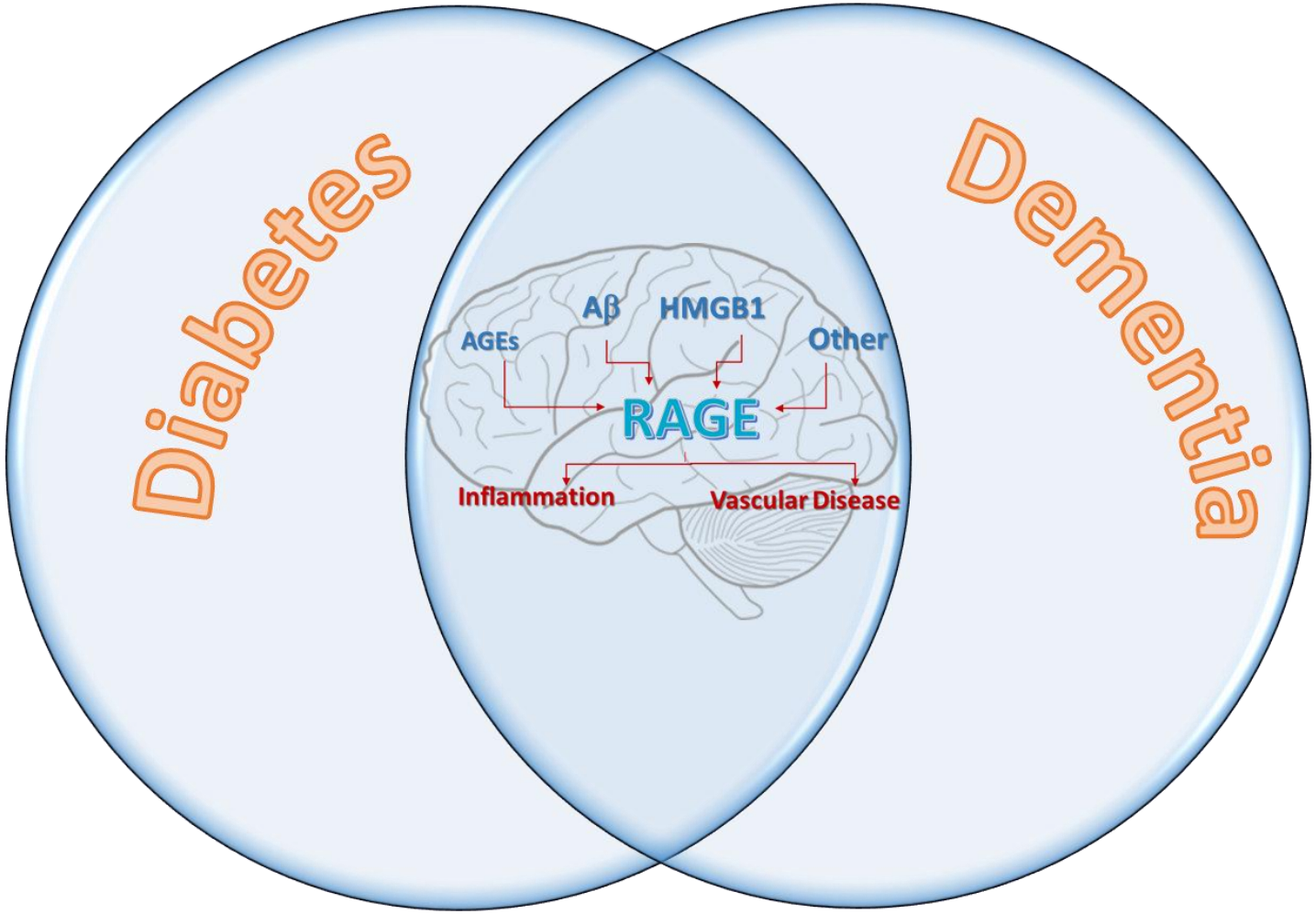
(Design may be adjusted based on Part 1 results)

- Double-blind, placebo control
- 5mg QD or placebo for 18 months
- ~200 subjects with mild Alzheimer's disease and HbA1c ≥ 6.5%
- Co-primary Endpoints:
  - Cognition: ADAS-cog14
  - Function: TBD

Study start: June 2019

Currently enrolling

Thank you!



We greatly appreciate all the patients, families, investigators and staff for their participation in the Phase 2b and Phase 3 STEADFAST studies