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\(^{(3)}\)

---

\(^{(2)}\) Neurobiology of Disease 37 (2010) 67–76
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
### Alzheimer’s disease

- **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**

- **399 subjects with probable mild-moderate AD**
  - MMSE 14-26
  - Stable background AcheI’s or memantine

- **Primary Endpoint:** ADAS-cog11
- **Key-secondary:** none

- **Secondary Endpoints:** MRI volumetric measures, ADCS-ADL, MMSE, NPI

- **Subjects with diabetes were excluded**

- **20 mg/day discontinued at 6 months due to an increase in AEs of confusion and falls**

### Diabetic nephropathy

- **60mg/day x 6d → 20 mg/day x 6 months**
- **Placebo (PBO) x 6 months**

- **110 subjects with Type 2 diabetes and persistent albuminuria**

- **Primary Endpoint:** UACR
- **Key-secondary:** none

- **Secondary Endpoints:** eGFR, serum creatinine, markers of RAGE inhibition

- **Subjects with diabetes**

- **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?
FDG-PET study: APP-Tg mice (>6 mo old) study
TTP488 10 mg/kg po QD or vehicle x 4 weeks

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

Mean Change in ADAS Cog11 at M18

- placebo
- azeliragon 5 mg/day

Baseline Fasting Glucose

<100 mg/dL  ≥100 mg/dL

n= 38 41 13 11

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)


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

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

Primary Endpoints to be analyzed as independent studies

Secondary Endpoints to be analyzed as one study

---

A-Study

405 Patients
Readout April 2018

B-Study

475 Patients
Terminated

A-Study

47 Patients HbA1c ≥6.5%

B-Study

47 Patients HbA1c ≥6.5%

Terminated

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

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

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

Historical data from Thomas RG et al. Alz Dementia 2016
Back to First-Principles

Phase 2B

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

Phase 3

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)

- 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
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%).

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

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 July 2019

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