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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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

For review see Dhananjayan et al. (2018) Advance Glycation, Diabetes and Dementia https://doi.org/10.1016/B978-0-12-809654-9.00009-3
Pre-clinical Evidence with Azeliragon Treatment

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Main Results: Treatment with Azeliragon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat Diabetic Retinopathy</td>
<td>Protection Against Vascular and Neuronal Lesions:</td>
</tr>
<tr>
<td></td>
<td>• Reduces acellular capillaries and improves pericyte/endothelial cell ratio</td>
</tr>
<tr>
<td></td>
<td>• Reduces activated microglia</td>
</tr>
<tr>
<td>Adriamycin Induced Mouse Nephropathy model</td>
<td>Protection from the Development of Massive Albuminuria, Mesangial Expansion and Glomerular Sclerosis</td>
</tr>
<tr>
<td>Alzheimer’s disease Transgenic Mouse model (human APP Swedish and London mutations)</td>
<td>• Reduces amyloid deposition and inflammation in the brain</td>
</tr>
<tr>
<td></td>
<td>• Increase Glucose Uptake in the brain</td>
</tr>
<tr>
<td></td>
<td>• Preserves cognitive/ behavioral function</td>
</tr>
<tr>
<td>CS7BLKS/J-m+/+Lepr db mice (Lepr db)</td>
<td>Dose related decrease in wound closure time and % closure at all doses</td>
</tr>
</tbody>
</table>
**Phase 3 STEADFAST Study Design**

### Two Pivotal Studies Under One Protocol

- **A-Study**
  - 405 Patients
  - Readout April 2018
  - 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

- **B-Study**
  - 475 Patients
  - Terminated
  - Patients with diabetes were included in the study (HbA1c ≤7.7%)

### Notes:

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

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**March 2019**

vTv Therapeutics LLC
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

March 2019

vTv Therapeutics LLC
Cognitive Improvement Cannot be Explained by Improvement in Glycemic Control

### STEADFAST A-Study ADA-T2D Subgroup (FAS)

#### Change in HbA1c (%) 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

### STEADFAST A-Study ADA-T2D Subgroup (FAS)

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

- **AZL (n=26)**
- **PBO (n=21)**
### Demography and Baseline Characteristics: No Notable Imbalance Between Treatment Arms

#### STEADFAST Study ADA-T2D Subgroup

**Demographics (A&B Studies Combined)**

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

#### STEADFAST Study ADA-T2D Subgroup

**Baseline Characteristics (A&B Studies Combined)**

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

AD-T2D=HbA1c ≥6.5% at anytime during the study
ADAD_T2D subgroup
Change in Whole Brain volume (%)

ADA-T2D Subgroup
Ventricular Enlargement (%)

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

ADAD-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

Month 12

Month 18

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 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.
Changes in Biomarker Profile Consistent with RAGE Inhibition

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

¹Based 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

- Decreased: Th1 recruitment

AD and RAGE Inhibition

- Increased: BBB disruption
- Microglia activation
- T cell recruitment
- Ca²⁺ overload

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

- Increased: Th1 recruitment

- Decreased: Ca²⁺ overload

Inhibition: RAGE+AZL

IL-6
 INF-γ
 TGF-β
 IL-12
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
We greatly appreciate all the patients, families, investigators and staff for their participation in STEADFAST