



# vTv Therapeutics (VTVT)

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September 2019

NASDAQ: VTVT

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**Clinical stage pipeline** of novel small molecule drug candidates targeting significant unmet medical needs: **Diabetes and Alzheimer's disease**



**Positive phase 2 results** in **type 2 diabetes (T2D)** with two novel oral candidates

Ongoing phase 2 study in **type 1 diabetes (T1D)** with TTP399 with **positive Part 1 readout**

**Topline results** from Part 2 expected in **Q1 2020**



Conducting clinical trial in subjects with **mild Alzheimer's disease and type 2 diabetes** that consists of sequential phase 2 and phase 3 studies operationally conducted under a single protocol



**Significant, long-term financial sponsor** in MacAndrews and Forbes

# Distinguished Management Team



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President, Chief Executive Officer



**Jeff Kindler, J.D.**  
Executive Chairman



**Rudy Howard, B.A., C.P.A.**  
Executive Vice President, Chief Financial Officer



**Rob Andrews, Ph.D.**  
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**Robin Abrams, J.D.**  
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**Imogene Dunn, Ph.D.**  
Senior Vice President, Biometrics and Regulatory



**Carmen Valcarce, Ph.D.**  
Executive Vice President, Chief Scientific Officer



**Sam Rollins, Ph.D., J.D.**  
Senior Vice President, Intellectual Property



**Aaron Burstein, Pharm.D.**  
Senior Vice President, Clinical Development



# Robust Pipeline of Novel Product Candidates



PROGRAM	INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	PARTNER
Azeliragon (RAGE)	Alzheimer's Disease					
TTP399 (GKA)	Type 1 Diabetes					
TTP399 (GKA)	Type 2 Diabetes					
TTP273 (Oral GLP-1r)	Type 2 Diabetes					 华东医药 HUADONG MEDICINE Asia
HPP593 (PPAR-δ)	Mitochondrial Diseases					 Reneo Worldwide
HPP737 (PDE4i)	COPD					 NEWSQARA 恒翼生物医药 Asia
Nrf2/Bach1 Program	Undisclosed					

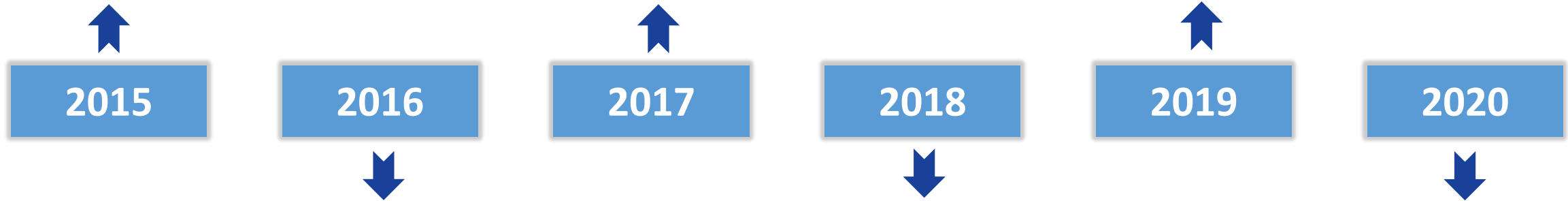
# Delivering on Milestones



- ✓ IPO raised \$117M with following goals:
  - Conduct phase 3 studies in AD
  - Conduct 2 phase 2 studies in T2D
  - Out-license certain pipeline programs

- ✓ Partnered with JDRF on TTP399 in T1D
- ✓ Out-licensed PPARd program to Reneo Pharmaceuticals
- ✓ Out-Licensed Pacific Rim rights for GLP-1R program to Huadong Medicine

- ✓ Initiated Part 2 of TTP399 phase 2 T1D study
- ✓ **Reported positive results from Part 1 of TTP399 phase 2 T1D study in June 2019**
- **Initiate phase 2 clinical trial with azeliragon in subjects with mild AD and T2D\***



- ✓ **Reported positive TTP399 phase 2 6-month study in T2D**
- ✓ Reported positive TTP273 phase 2 3-month study in T2D

- ✓ Initiated phase 2 study of TTP399 in T1D
- ✓ Reported azeliragon phase 3 studies in AD
- ✓ Out-licensed Pacific Rim rights for PDE4 program to Newsoara Biopharma

- Report results from Part 2 of TTP399 phase 2 T1D study\*
- Report results from phase 2 trial with azeliragon in subjects with mild AD and T2D\*

\*ongoing /planned



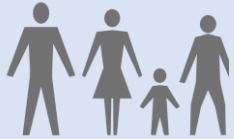
## Type 1 Diabetes Program

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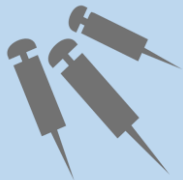
**TTP399**  
**Liver-Selective Glucokinase Activator (GKA)**



**T1D is an autoimmune disease** in which the pancreas stops producing insulin, the hormone that controls blood-sugar levels <sup>(1)</sup>



Estimated **30 million** people suffer from T1D globally in 2017 <sup>(1)</sup>



**Insulin** is the current standard of care administered by multiple **daily injections** or **insulin pumps**



**No FDA-approved oral therapies in the US** that improve glycemic control in T1D. **SGLT-i recently approved in EU for T1D with label limitations:**

- Approved for T1D patients only with BMI  $\geq 27$
- Treatments increase risk of DKA, genital infections and amputations

(1) IDF DIABETES ATLAS 8th edition 2017

# Need for Treatments that Improve Disease Management in T1D

“FDA recognizes there is an unmet need for patients with T1DM to help achieve glycemic goals and improve quality of life and treatment satisfaction”<sup>(1)</sup>

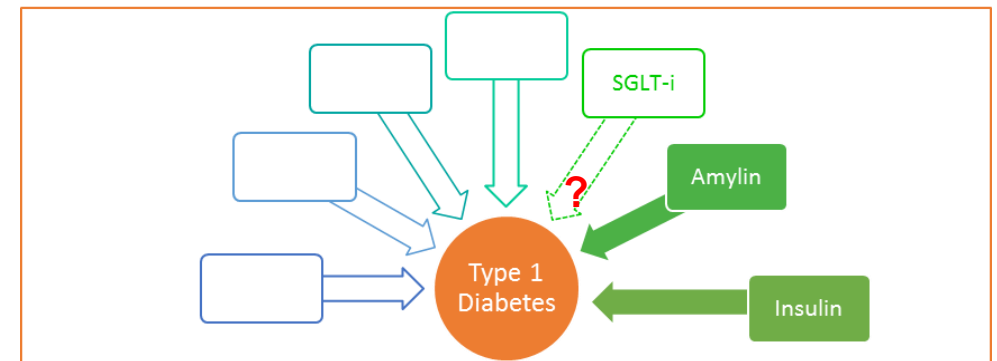
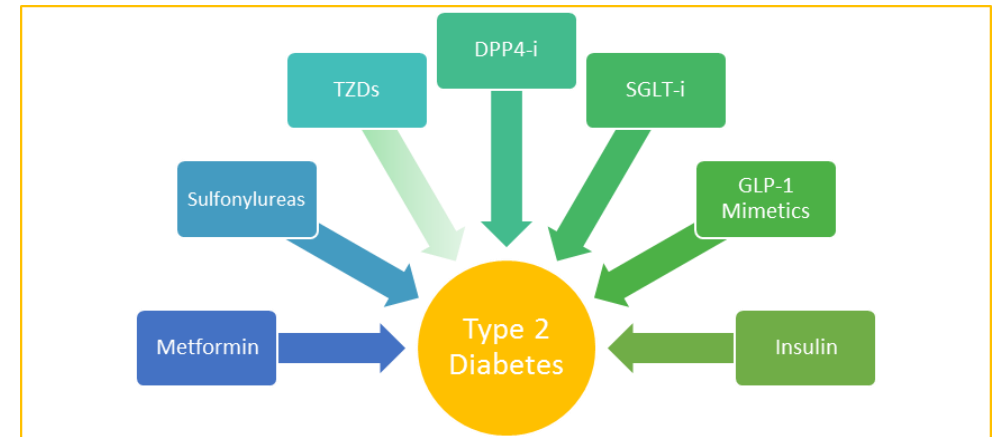
## Goals for new therapies for treatment of T1D:

- Reduce A1C to ease achievement of target goals
- Improve time-in-glycemic range
- Reduce insulin dependence
- Reduce “highs” and “lows”
- Improve overall quality of life
- Oral treatment

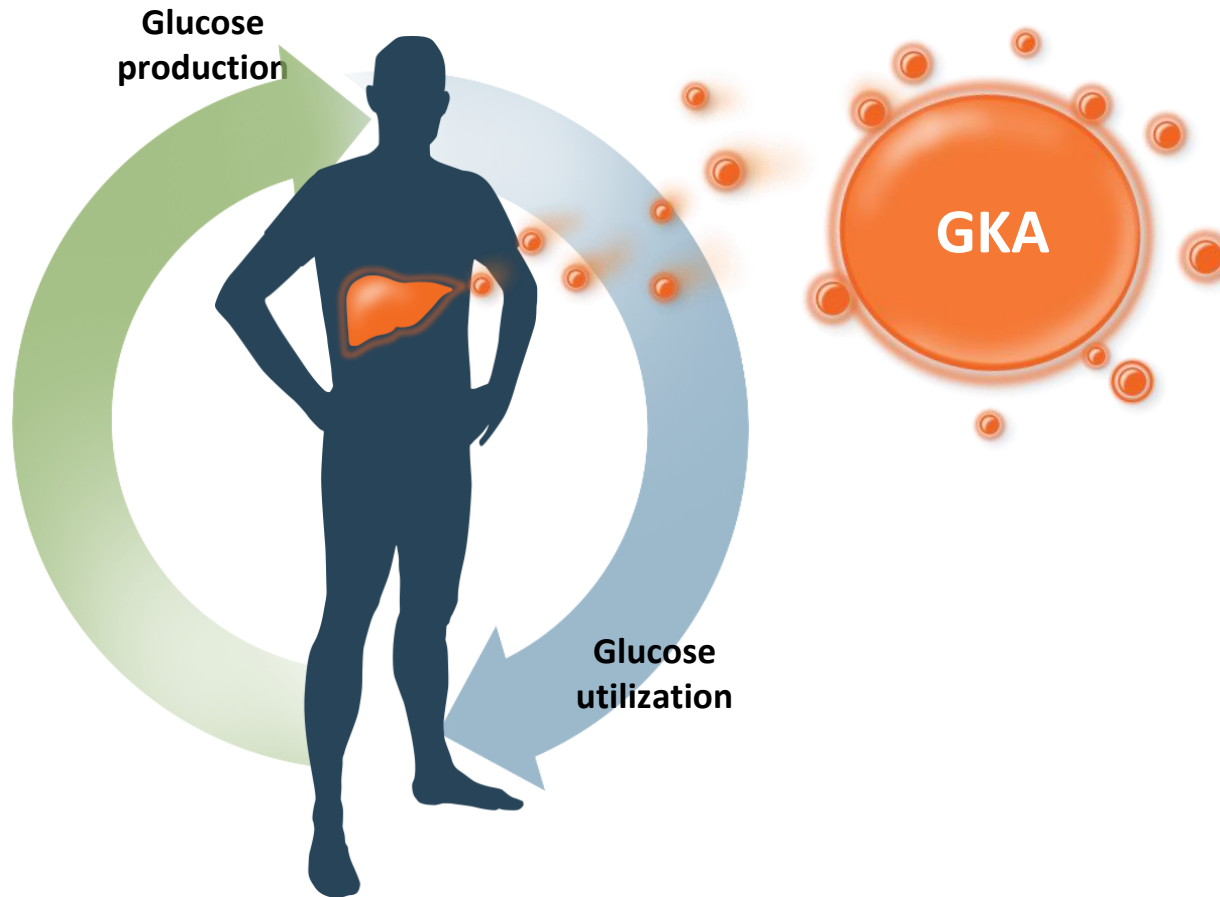
□ ...while not increasing risks of:

- Weight gain
- Hypoglycemia
- Diabetic ketoacidosis (“DKA”)

## Approved Therapies for the Treatment of Diabetes in USA



(1) [FDA Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, January 17, 2019](#)



Activating GK in the **liver restores the balance between glucose production and glucose utilization** by controlling glucose metabolism and gene expression of glucose dependent genes involved in:

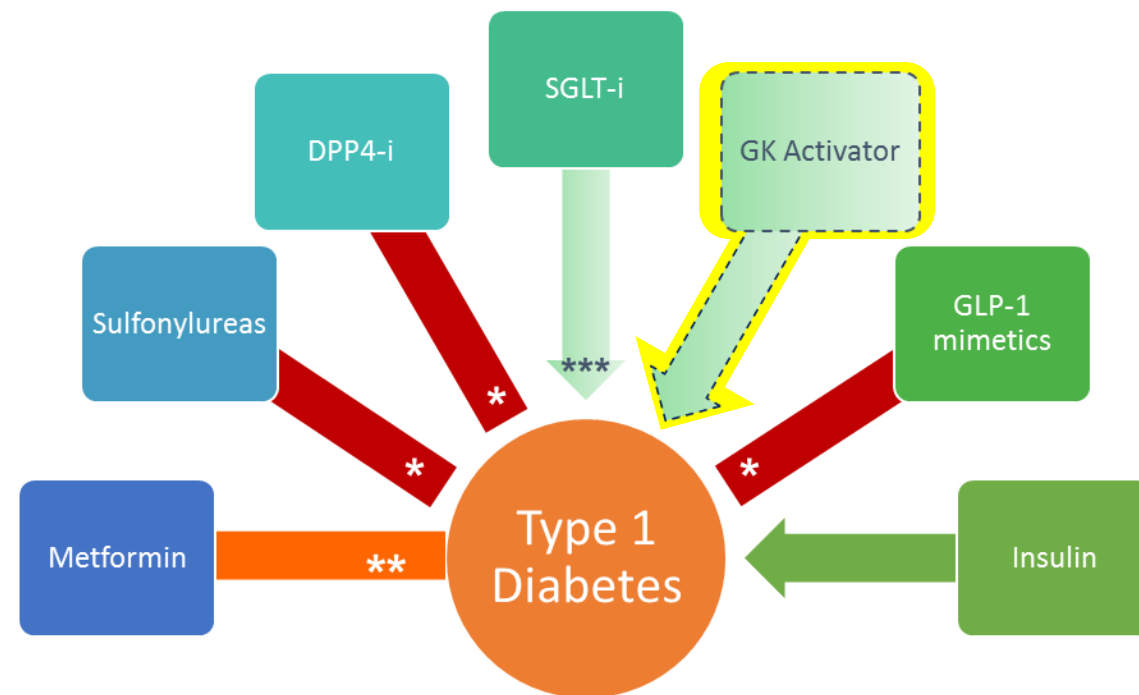
- Glycolysis**
- Gluconeogenesis**
- Lipogenesis**
- Ketogenesis**

**Strong genetic validation** of the target. GK is the **glucose-sensor** of the body.

TTP399: A Novel Hepato-selective GK Activator Being Developed for the Treatment Of Diabetes

## Why Would TTP399 Work in Type 1 Diabetes?

- ❑ People with **type 1** diabetes have **lower GK activity**
- ❑ The mechanism of action of TTP399 **does not require increased insulin secretion**
- ❑ **Increasing glucose utilization** by the liver will **reduce** production of **ketone bodies**



- \* MoA **dependent on insulin secretion**; limited effect in T1D
- \*\* No effect on T1D
- \*\*\* Limited effect, with increase in DKA risk

Diabetes Care 2019 Jan; 42(Supplement 1): S90-S92.  
<https://doi.org/10.2337/dc19-S009>



## Phase 1 (Sentinels)

### Study Design:

- Open-label
- **7 day** dose escalation up to 1200mg QD
- **5** adult subjects with T1D on CSII and CGM

**March 2018**

### TTP399 was well tolerated

- No incidents of severe hypoglycemia or DKA
- Indications of **improved glycemic control, while reducing insulin dose**
  - Increase % time in range
  - Reduce % time in hyperglycemia without increasing % time in hypoglycemia



## Phase 2-Part 1 (Learning Phase)

### Study Design:

- Double-blind Placebo control
- **12 weeks** dosing 800mg QD
- **~20** adult subjects with T1D on CSII and CGM
- **Primary Endpoint:** change in HbA1c

**June 2019**

### Positive Results Reported June 2019



## Phase 2-Part 2 (Confirming Phase)

### Study Design:

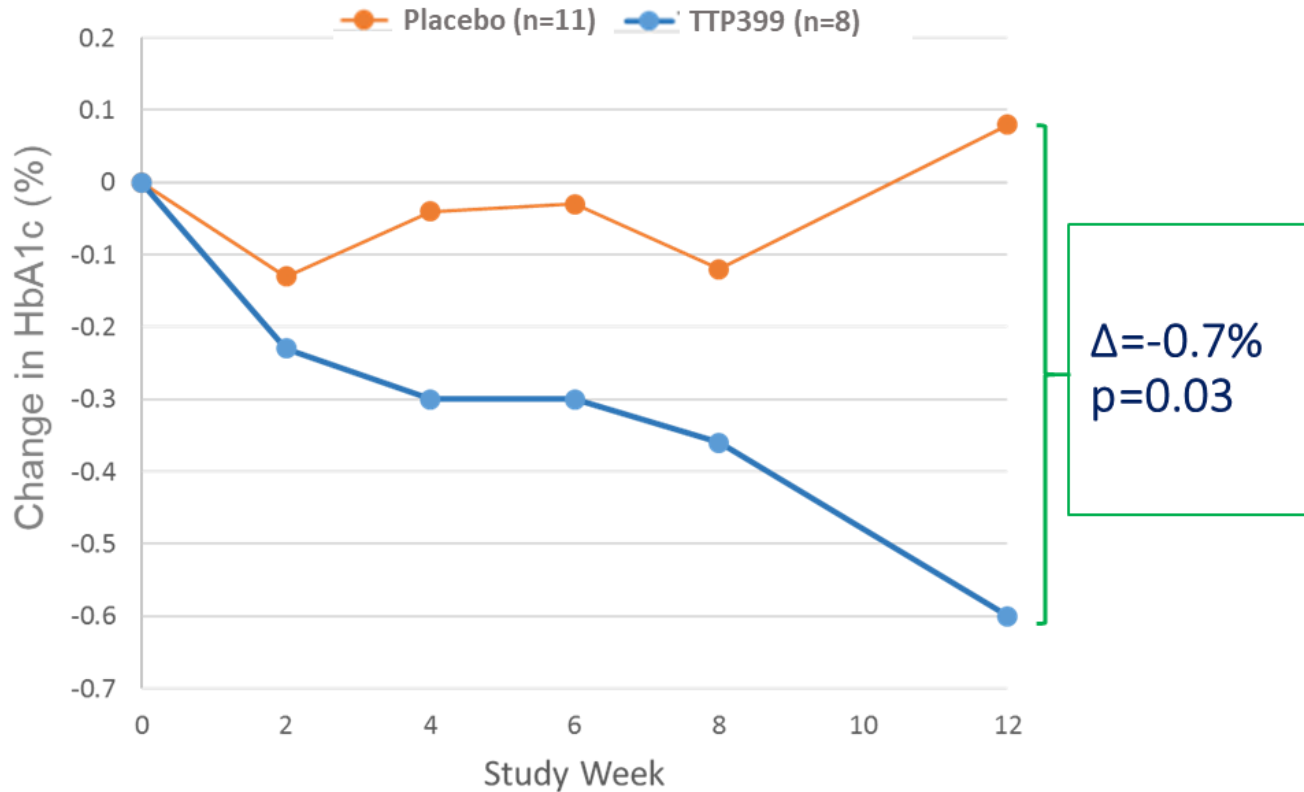
- Double-blind Placebo control
- **12 weeks** dosing 800mg QD
- **~90** adult subjects with T1D (all comers)
- **Primary Endpoint:** change in HbA1c

**Q1 2020**

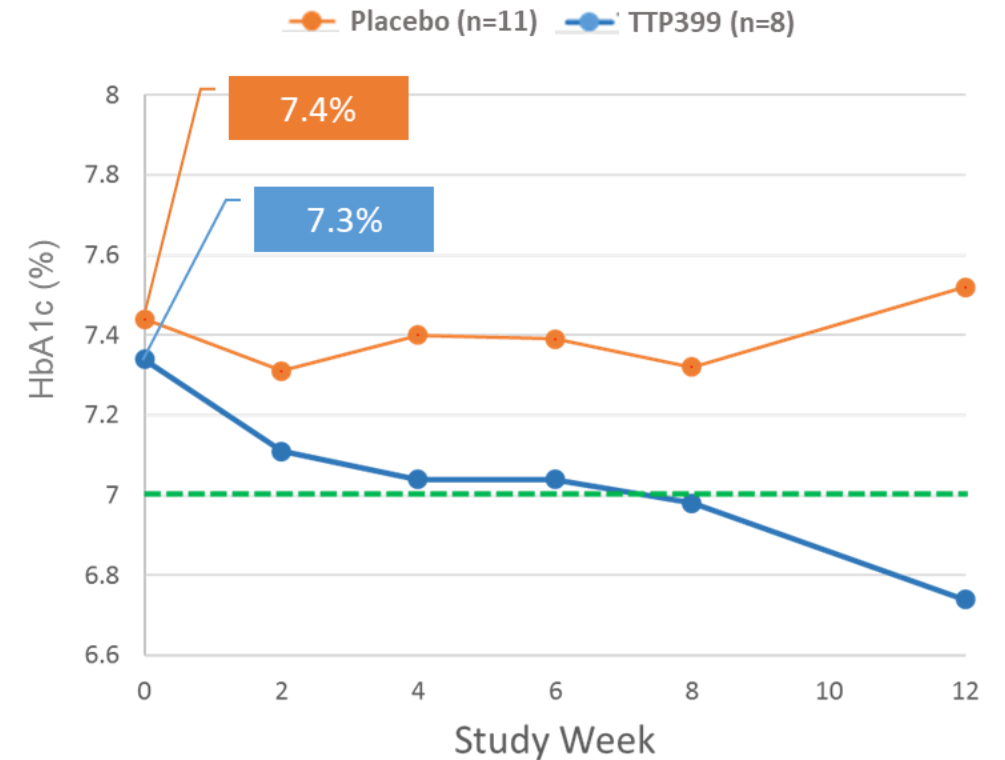
### Results expected in Q1 2020

1. ClinicalTrials.gov Identifier: NCT03335371  
2. Subjects with Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM)

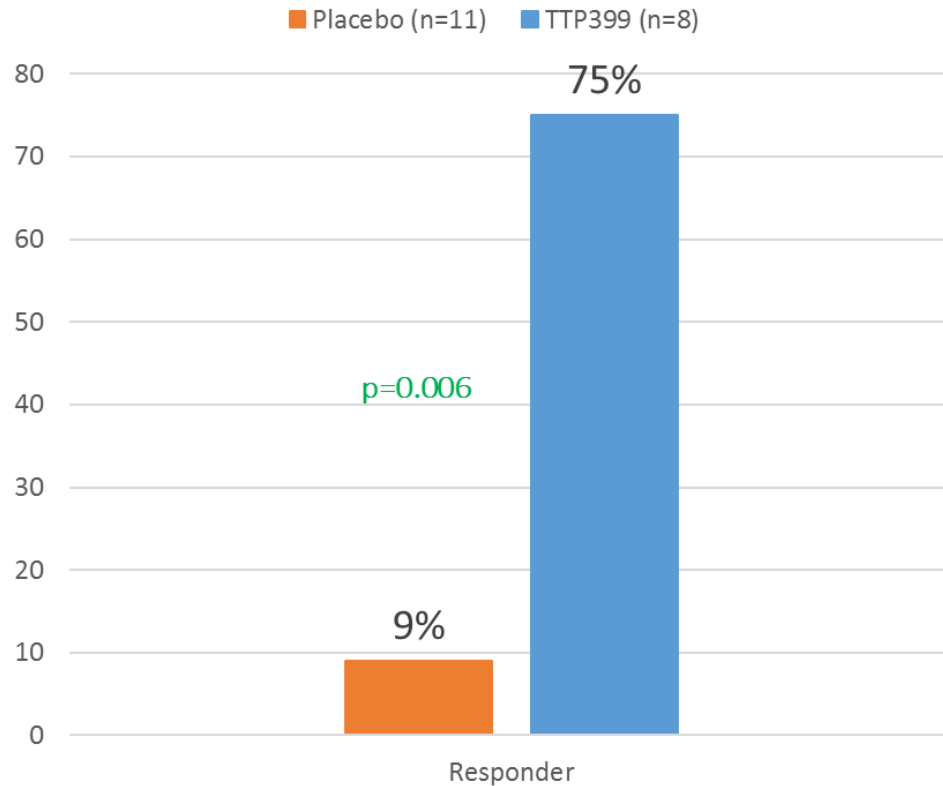
## Change in HbA1c



## HbA1c



### Responder Analysis

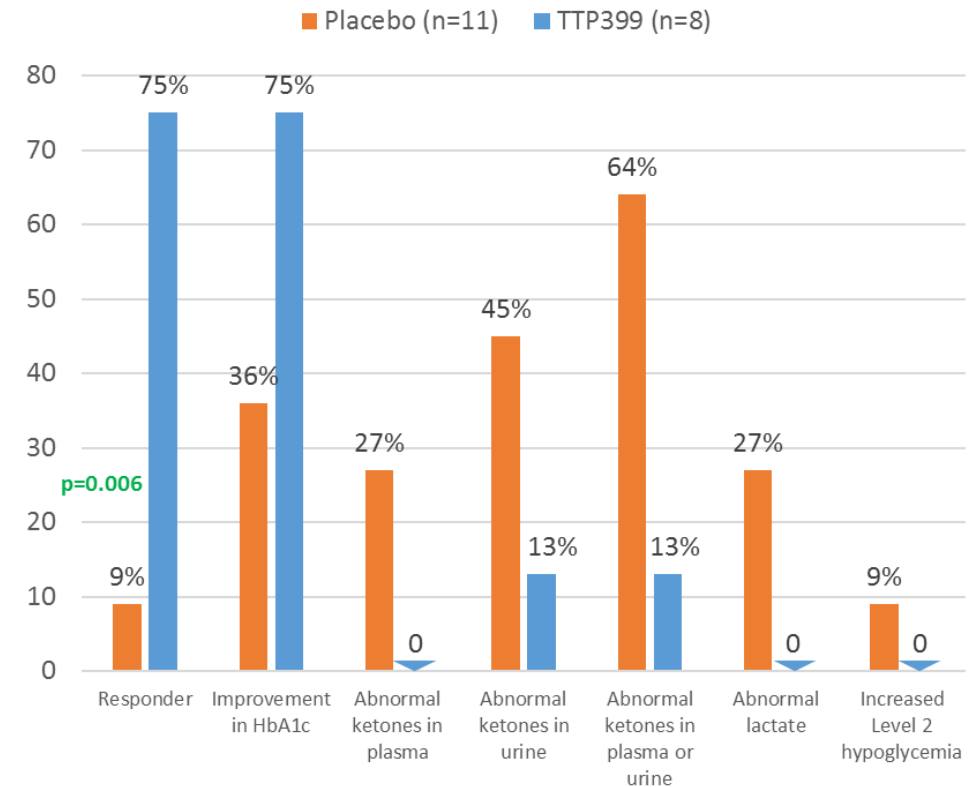


### Responder definition:

Proportions of subjects with: improvement in HbA1c and without predefined risks:

- Abnormal ketones in urine or plasma
- Abnormal lactate in plasma
- Increase in time in level 2 hypoglycemia (glucose <54 mg/dl)

### Responder Analysis and Individual Criteria



### Safety:

- No SAEs
- No reported hypoglycemia
- No Diabetic Ketoacidosis (DKA)
- Similar profiles for reported TEAEs between TTP399 and placebo

# Competitive Landscape in T1D



Product	MOA	Efficacy	Safety	T1D Status
<b>ZYNQUISTA</b> (sotagliflozin)  <i>Sanofi &amp; Lexicon</i>	SGLT1/SGLT2 Inhibitor	<b>0.36 to 0.41% A1c reduction</b> (pbo subtracted) in 24 week phase 3 studies (baseline A1c 8.2%-8.3%)*	DKA Adverse events (% of subjects): <b>3.4 – 3.8% active</b> vs <b>0 – 0.4% placebo*</b>	<ul style="list-style-type: none"> <li>• <b>FDA did not approve NDA in current form in Mar 2019</b></li> <li>• FDA Advisory Committee did not recommend due to risk/benefit assessment in Jan 2019 <sup>(1)</sup></li> <li>• EU approved with limitation in use to patients with BMI ≥ 27</li> </ul>
<b>FARXIGA</b> (dapagliflozin)  <i>AstraZeneca</i>	SGLT2 inhibitor	<b>0.37% to 0.42% A1c reduction</b> (pbo subtracted) in 24 week phase 3 studies (baseline A1c 8.53%) **	DKA Adverse events (% of subjects): <b>1% to 2%</b> vs <b>1% placebo**</b>	<ul style="list-style-type: none"> <li>• <b>FDA did not approve NDA in current form in July 2019</b></li> <li>• EU approved with limitation in use to patients with BMI ≥ 27</li> </ul>
<b>JARDIANCE</b> (empagliflozin)  <i>Lilly &amp; BI</i>	SGLT2 inhibitor	<b>0.28% to 0.54% A1c reduction</b> (pbo subtracted) in 24 week phase 3 studies ***	DKA Adverse events (% of subjects): <b>0.8% to 4.3%</b> vs <b>1.2% placebo***</b>	<ul style="list-style-type: none"> <li>• Two Phase 3 trials completed</li> </ul>

\*Diabetes Care. 2018 Sep;41(9):1970-1980. doi: 10.2337/dc18-0343 and Diabetes Care. 2018 Sep;41(9):1981-1990. doi: 10.2337/dc18-0342

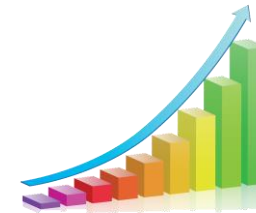
\*\*The Lancet 2017; 5:864-876 [https://doi.org/10.1016/S2213-8587\(17\)30308-X](https://doi.org/10.1016/S2213-8587(17)30308-X)

\*\*\*Diabetes Care 2018 Oct; dc181749. <https://doi.org/10.2337/dc18-1749>

(1) FDA Briefing Document, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, January 17, 2019

## Next Milestone

Part 2 of the 12-week phase 2 Simplici-T<sub>1</sub> study is ongoing with expected **read out in Q1 2020**



## Market Opportunity

Estimated **30 million** people suffer from T1D globally<sup>(1)</sup>



## Clinical Evidence

Evidence from 12 clinical studies conducted to date point to a **benefit of TTP399** in patients with T1D or T2D in both **glycemic control** and **safety profile**



## Underserved Population

**Insulin** is the current standard of care with **risks of DKA, hypoglycemia and weight gain**

(1) IDF DIABETES ATLAS 8th edition 2017



## Alzheimer's Disease Program

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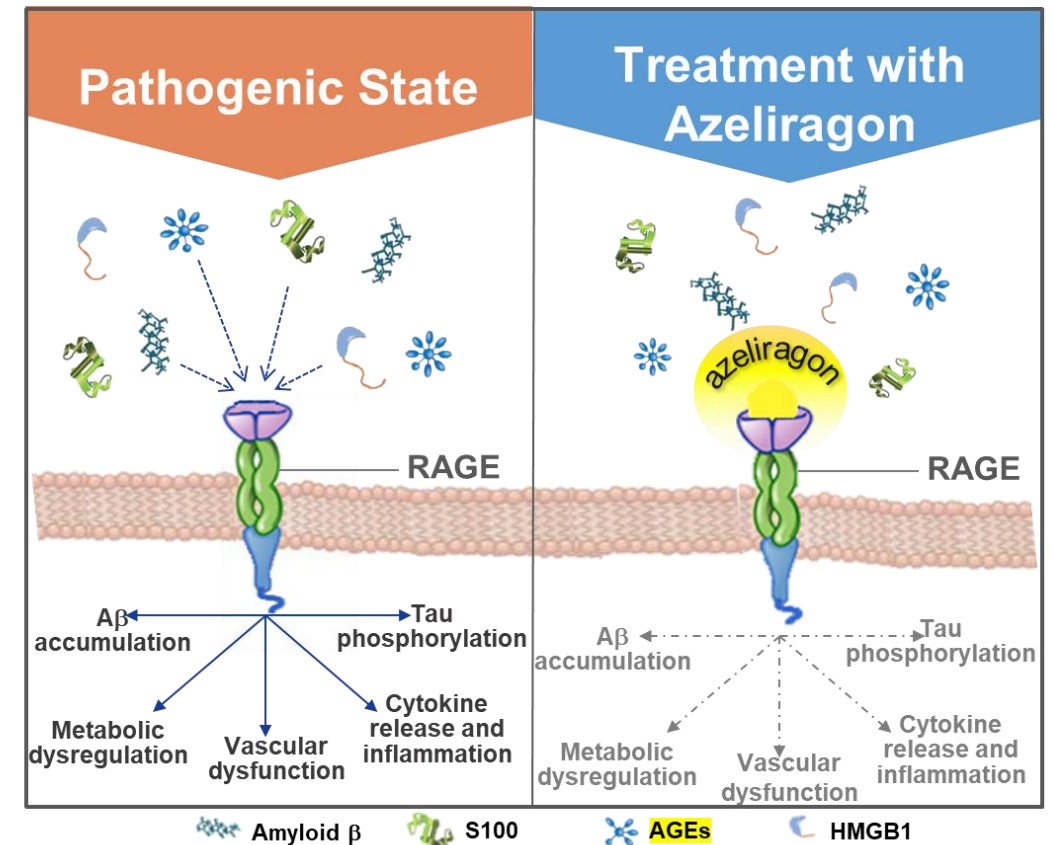
AZELIRAGON

Antagonist of RAGE (Receptor for Advanced Glycation Endproducts)

## RAGE

- Receptor for Advanced Glycation Endproducts (RAGE) is expressed at low levels in healthy tissues (except skin and mucus membranes)
- **Increases** in the concentration of **RAGE ligands (AGEs, HMGB1, S100 and Ab)** induce **RAGE expression**
- **The interaction of AGEs (or other ligands) with RAGE** leads to sustained **cellular damage and inflammation**

## Azeliragon antagonizes RAGE, blocking ligands from binding to the receptor



## RAGE in Alzheimer's Disease and Diabetes

- RAGE protein is increased in autopsied AD brains compared to controls with no AD<sup>(1)</sup>
- Increases in RAGE protein and percentage of RAGE-expressing microglia parallel the severity of disease<sup>(1)</sup>
- Patients with AD and diabetes show **increased hippocampal immuno-staining for RAGE protein**<sup>(2)</sup>
- **AGE** accumulation parallels the development of **cognitive impairment and dementia in individuals with diabetes**<sup>(3)</sup>

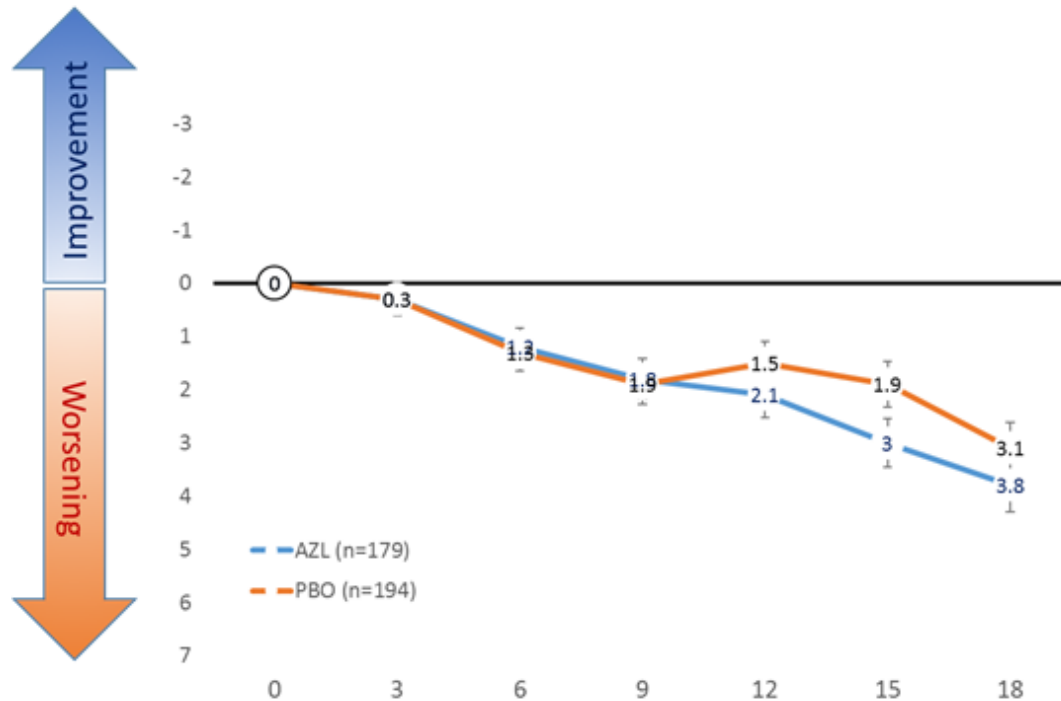
(1) Lue L-F. *Curr. Drug Targets CNS Neurol. Disord.* 2005 Jun;4 (3):249-66. (2) Valente T. *Neurobiology of Disease* 37 (2010) 67-76. (3) Dhananjayan et al. (2018) *Advance Glycation, Diabetes and Dementia* <https://doi.org/10.1016/B978-0-12-809454-9.00009-3>

# Potential Beneficial Effect on Cognition in Patients with Elevated HbA1c



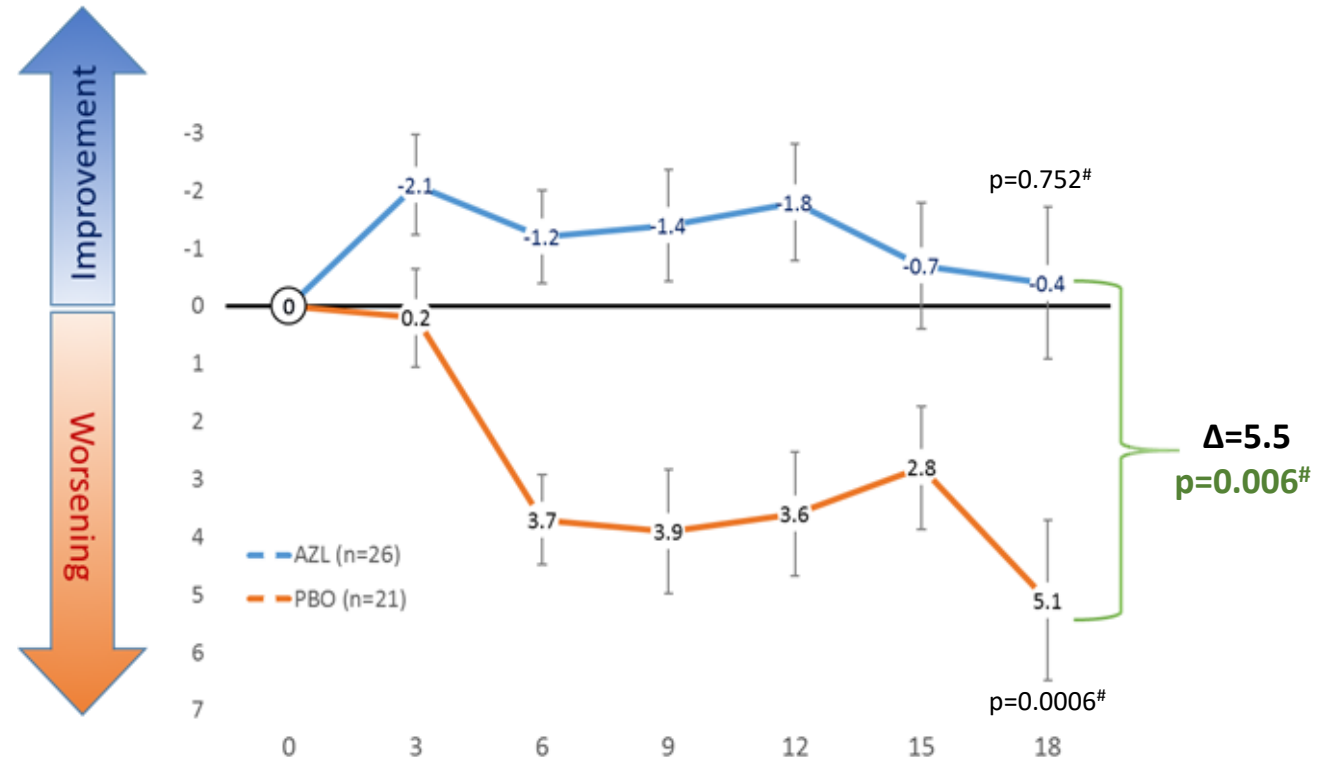
## STEADFAST A-Study (FAS)

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  $\geq$  6.5% at anytime during the study)

Results are LSMeans  $\pm$  SE based on MMRM model.

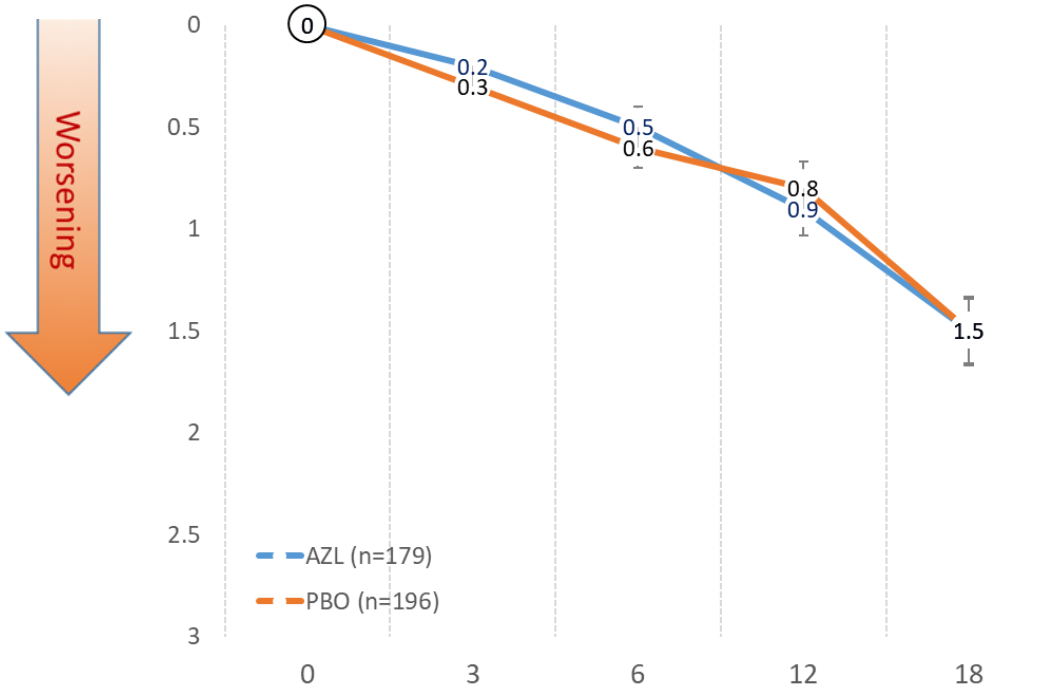
\*All p values are nominal. FAS = Full Analysis Set

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

# Potential Beneficial Effect on Function in Patients with Elevated HbA1c

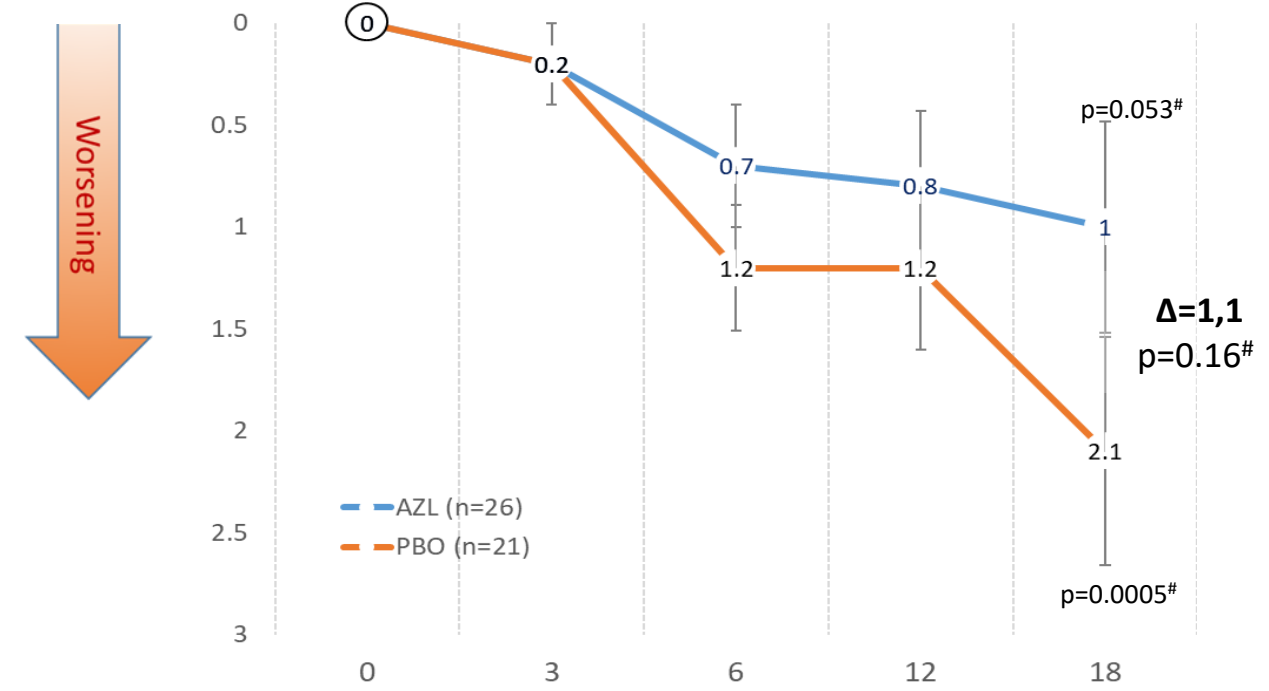
## STEADFAST A-Study (FAS)

Change from Baseline in CDR-SB



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

Change from Baseline in CDR-SB



- Functional improvement cannot be explained by improvement in glycemic control

Analysis of Patients with Diabetes (HbA1c  $\geq 6.5\%$  at anytime during the study)

Results are LSMean  $\pm$  SE based on MMRM model.

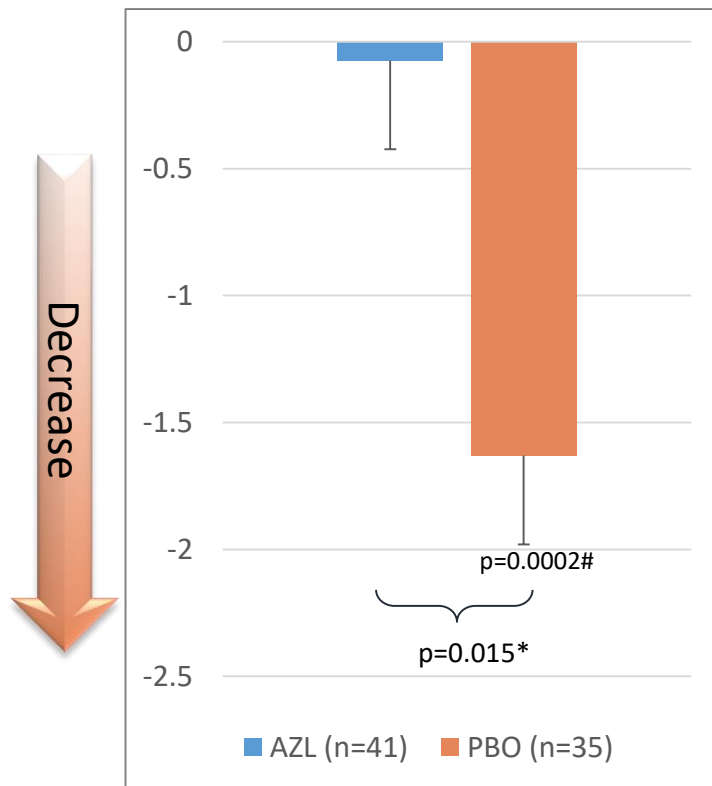
\*All p values are nominal. FAS = Full Analysis Set

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# Change in MRI Brain Volume at Month 18 in the Diabetes Subgroup: Less Brain Atrophy in the AZL-treated Group

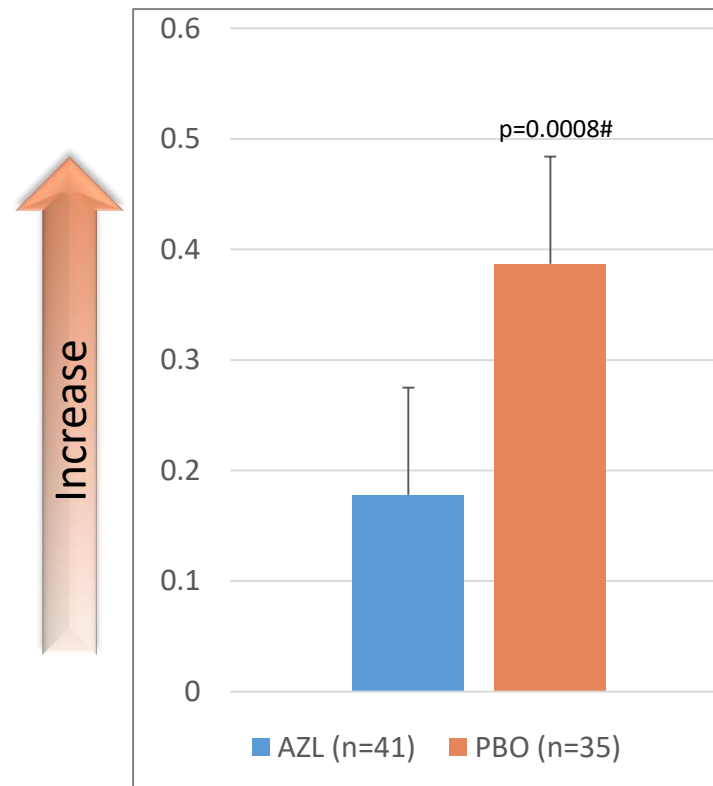
## ADA-T2D Subgroup

### Change in Whole Brain Volume (%)



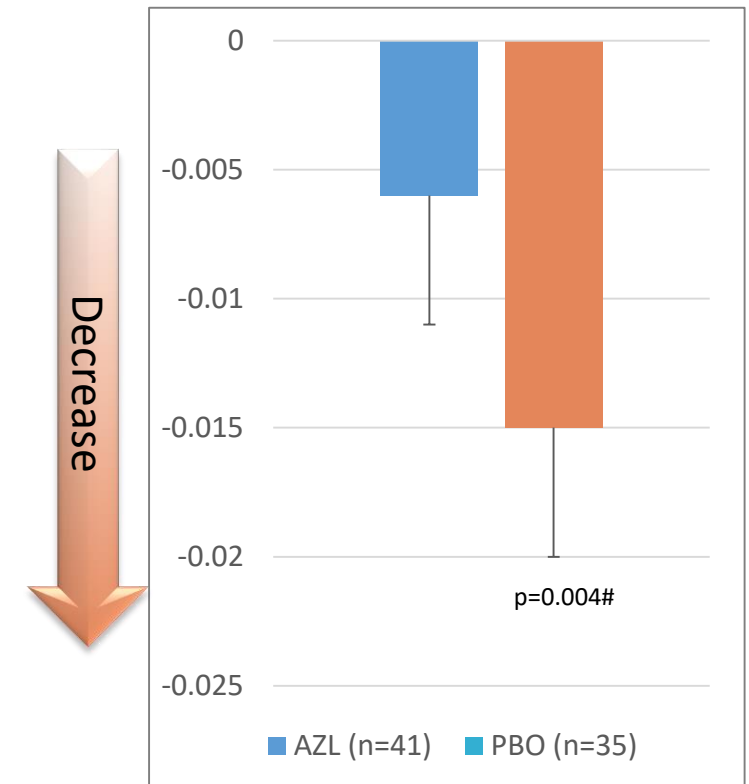
## ADA-T2D Subgroup

### Ventricular Enlargement (%)



## ADA-T2D Subgroup

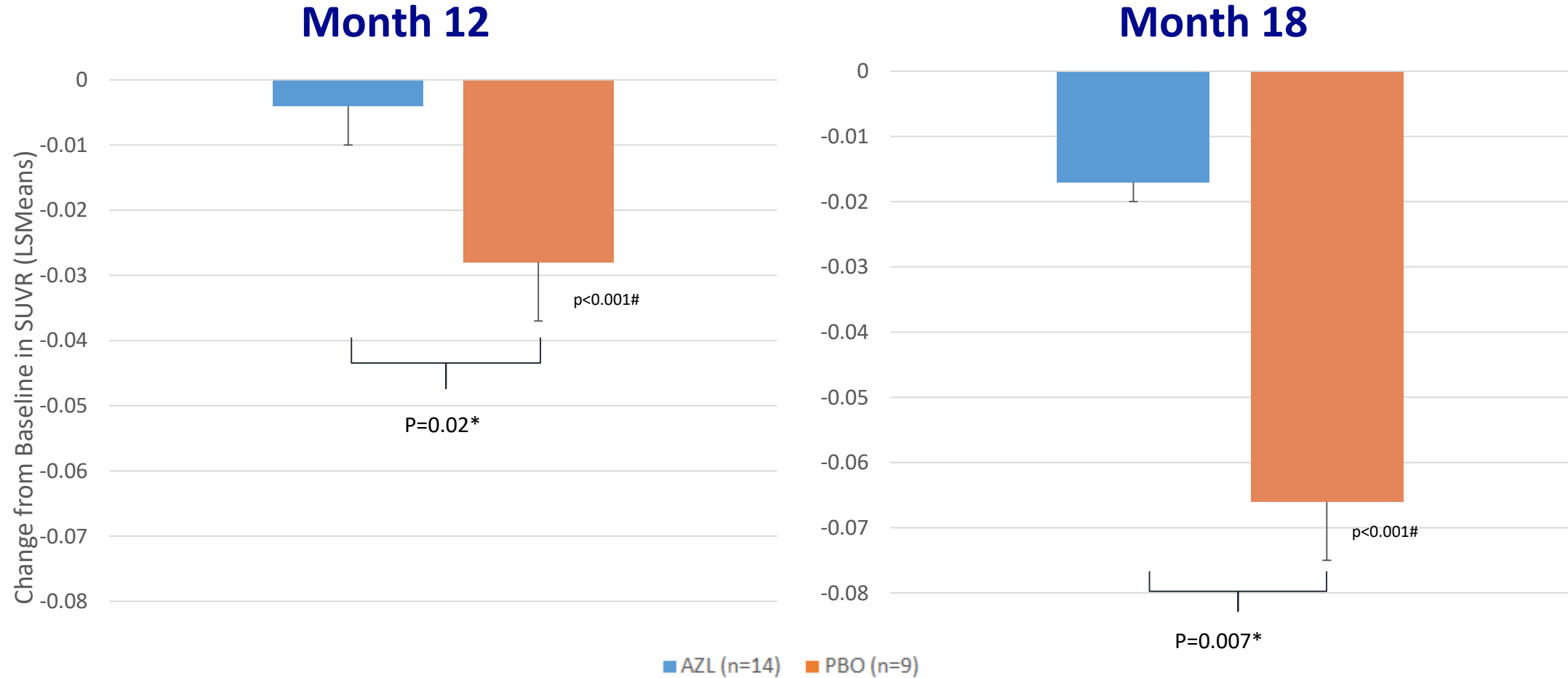
### Change in Total Hippocampus Volume (%)



Analysis of Patients with Diabetes (HbA1c ≥ 6.5% at anytime during the study). \*\*Results are change from baseline LSMMeans ± SE ANCOVA adjusted for baseline, FAS.  
#1-sample test nominal significance indicating worsening. \*All p values are nominal

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

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

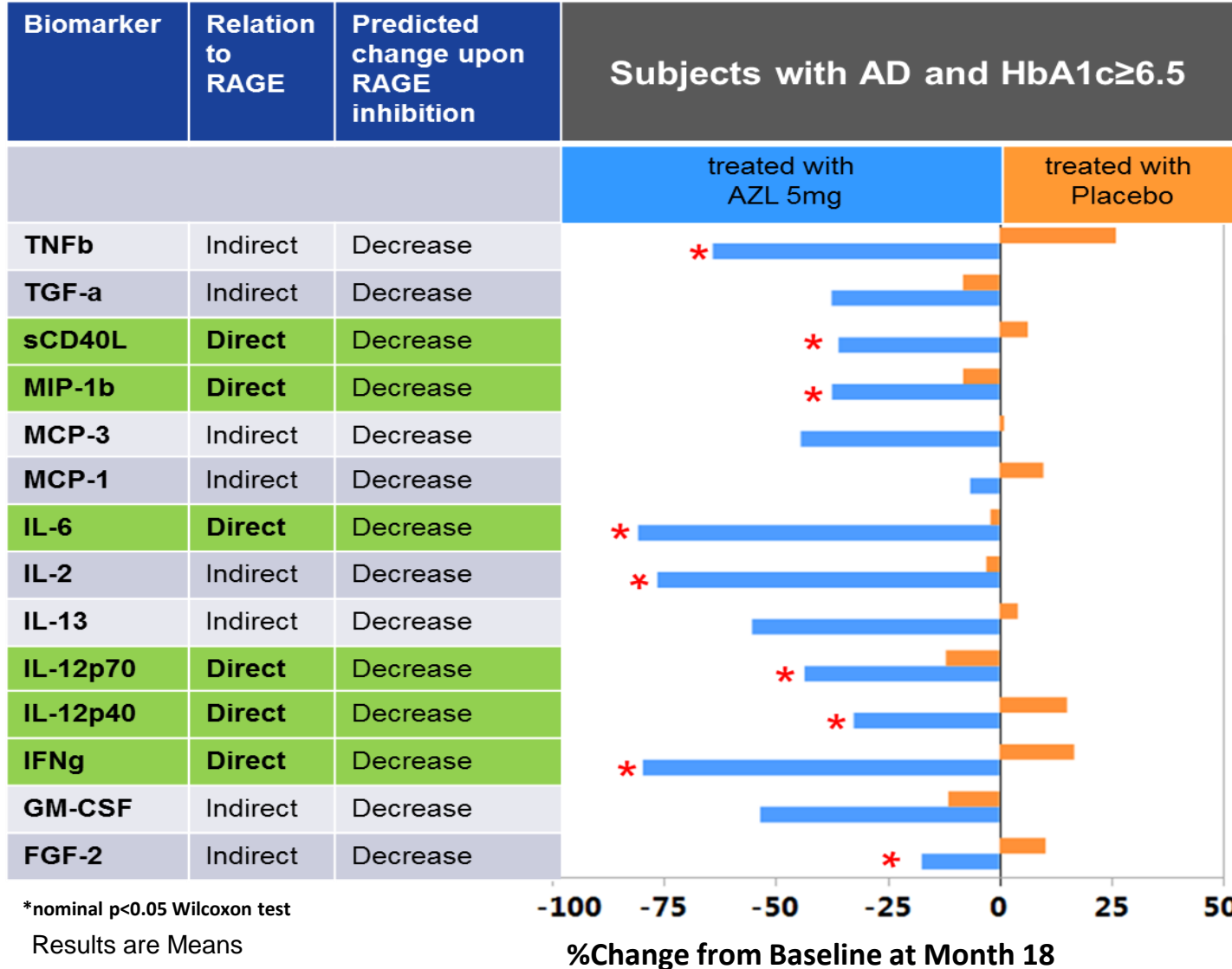


- SUVR composite (unweighted combination of frontal, anterior/posterior cingulate, lateral parietal, lateral temporal, and hippocampus)

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

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

# Decreases in Inflammatory Biomarkers Consistent with RAGE Inhibition



## 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<sup>1</sup>

<sup>1</sup>Based on Ingenuity software predictions

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

## 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 adult subjects with mild Alzheimer's disease and HbA1c  $\geq$  6.5%
- Primary Endpoint: ADAS-cog14
- Secondary Endpoints: CDR-sb, FAQ, Amsterdam-IADL, MMSE

**Study start June 2019**  
**Results expected 4Q2020**



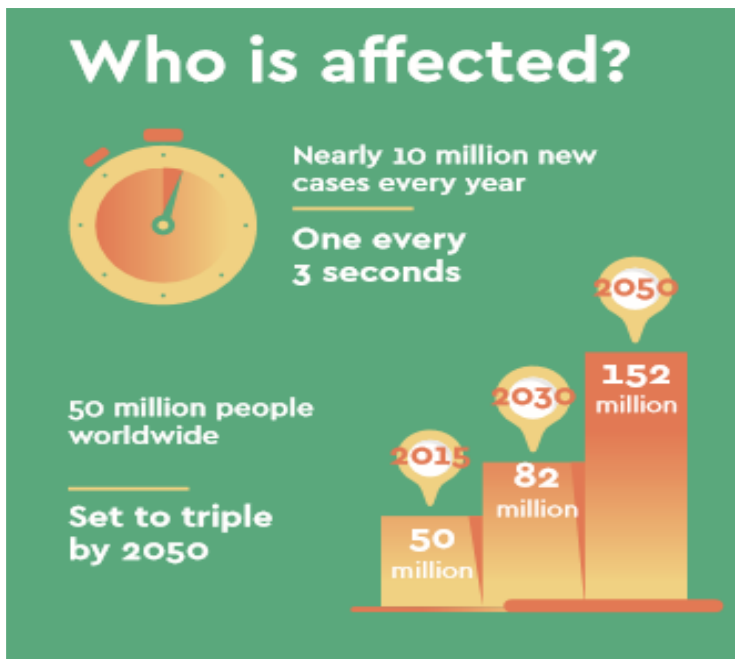
## Phase 3

(Design may be adjusted based on Part 1 results)

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

**Study start expected 1Q2021**

## Dementia and AD<sup>(1)(2)</sup>

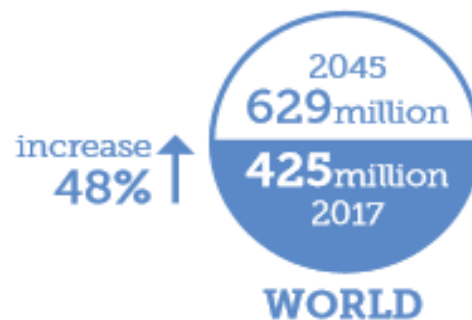


Alzheimer's disease is the most common form of dementia and may contribute to 60–70% of cases

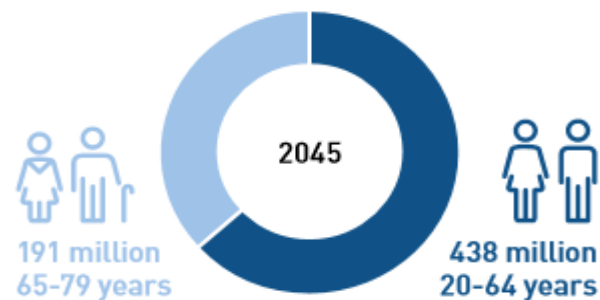
5.8 MILLION Americans are living with Alzheimer's

BY 2050, this number is projected to rise to nearly 14 MILLION

## Diabetes<sup>(3)</sup>



Diabetes by age (20-79 years)

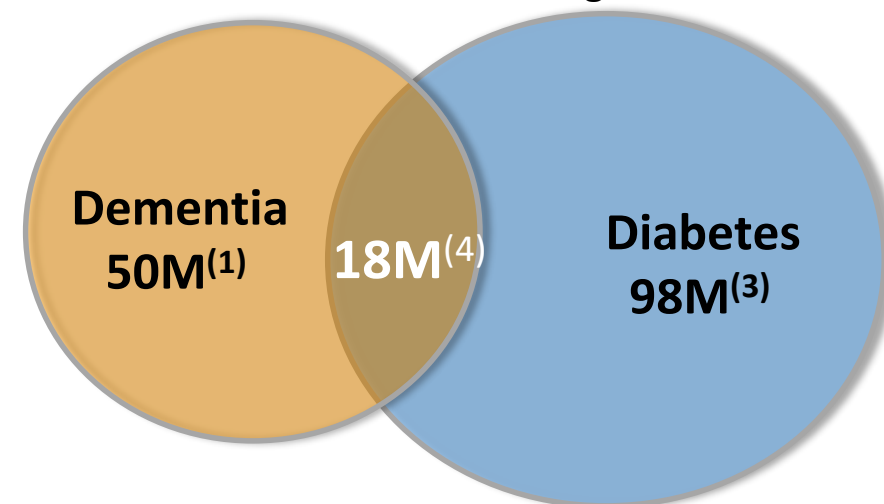


## Diabetes & Dementia

Since the late '80s, case-control and prospective epidemiologic studies around the world have reported an association between T2D and dementia *Type 2 Diabetes and Dementia (2018)* <https://doi.org/10.1016/B978-0-12-809454-9.00001-9>

Number of People Living with Dementia

Number of People ≥65 Living with Diabetes



(1) Globally, number of people with dementia in 2017 (source: *Dementia, key facts, WHO, 2017*)  
 (2) 2019 Alzheimer's Disease Facts and Figures (source: Alzheimer's Association)  
 (3) Globally, number of people with diabetes 65-79 years of age (source: *IDF Diabetes Atlas 8th Edition*)  
 (4) Assumption based on 37% estimate of Medicare beneficiaries age 65 and older with dementia who also have diabetes in the US (Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures)

# Azeliragon: Addressing Significant Unmet Medical Need in Alzheimer's Disease

## Next Steps

Conducting **start-up activities** for a clinical trial in subjects with mild AD and T2D that consists of sequential phase 2 and phase 3 studies operationally conducted under a single protocol



## Market Opportunity

Nearly 40% of Medicare beneficiaries age 65 and older with dementia also have diabetes<sup>(1)</sup>



## Clinical Evidence

Results of **STEADFAST** subgroup analysis in subjects with Type 2 diabetes indicate a **potential benefit of treatment with azeliragon**



## Underserved Population

**No new treatments** for AD/dementia amid growing senior population and rising diabetes pandemic

<sup>(1)</sup> Alzheimer's Association. 2018 Alzheimer's Disease Facts and Figures



# Partnerships

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Creating Value with Program Licenses

## Type 2 Diabetes Unmet Needs in China

- Over 100 million people with diabetes\*
- China's diabetes drug market projected to reach \$20B USD by 2025\*
- Opportunity to introduce new drug classes to a market that has historically lagged behind in access to innovative drugs



## Huadong Medicine Co., Ltd

- One of the largest pharmaceutical companies in China
- A strategic focus in diabetes; >20 candidates in development

## GLP-1r Program Exclusive License Agreement in China and Other Pacific Rim Territories

- In December 2017, vTv granted an exclusive license to Huadong to develop, manufacture and commercialize vTv's GLP-1r agonist program in China and 15 other regions in the Pacific Rim excluding Japan
- Huadong will develop the GLP-1r program for type 2 diabetes in its territory
- vTv is eligible to receive future development and commercialization milestones as well as royalties on sales of approved products
- vTv will utilize the pre-clinical and clinical data generated by this collaboration to continue the development and to seek partners in ROW

\*Morgan Stanley China Healthcare Report; Diabetes 2025: China's Antidiabetic Market Set to Triple (October 4, 2017)

## COPD Market in China

- 8.6% (~100 million) COPD patients in China<sup>(1)</sup>
- Annual sales of top 2 products (Seretide and Spiriva) greater than \$132M USD
- Total COPD market at \$4.5B USD

NEWSOARA  
恒翼生物医药

## Newsora Biopharma Co., Ltd.

- Newsora was established in 2018 to in-license innovative drug candidates for development and commercialization with focus in China and/or Asia Pacific region
- Hangzhou TigerMed, a public company (stock ChiNext: 300347), is a significant investor in Newsora
- CEO and founder Dr. Benny Li has more than 20 years of extensive drug research, development and regulatory experience with global leading pharmaceutical companies such as Takeda and Alcon

## PDE4 Program Exclusive License Agreement in China and Other Pacific Rim Territories

- In May 2018, vTv granted an exclusive license to Newsora to develop, manufacture and commercialize vTv's PDE4 Inhibitor program in China and 14 other regions in the Pacific Rim excluding Japan
- Newsora will develop the PDE4 program for COPD and one other indication in its territory
- vTv is eligible to receive future development and commercialization milestones as well as royalties on sales of approved products
- vTv will utilize the pre-clinical and clinical data generated by this collaboration to continue the development and to seek partners in ROW

<sup>(1)</sup>The Lancet Respiratory Medicine, 2018: DOI, April 09, 2018



## Reneo Pharmaceuticals, Inc.

- San Diego-based clinical stage pharmaceutical company focused on the development of therapies for patients with genetically defined orphan diseases
- Founded by Mike Grey, an experienced VC and entrepreneur with deep biotech experience, and a strong team who have worked together and collaborated on previous successful programs
- Funded by multi-national investor group including Pappas, Rivervest, Lundbeckfonden Ventures and New Enterprise Associates

## PPAR- $\delta$ Program Worldwide Exclusive License Agreement

- In December 2017, vTv granted an exclusive worldwide license to Reneo to develop, manufacture and commercialize vTv's PPAR- $\delta$  program
- Reneo is developing the program to treat genetically defined rare mitochondrial diseases such as fatty acid oxidation disorders (FAOD) and primary mitochondrial myopathies (PMM)
- vTv holds an equity interest in Reneo and is eligible to receive future development and commercialization milestones as well as royalties on sales of approved products



vTv is a small and nimble company that has integrated innovative science with clinical drug discovery in challenging areas like **Diabetes and Alzheimer's disease**



vTv has a novel pipeline of programs including its **liver-selective GKA** for type 1 and type 2 diabetes and its **RAGE program** for mild Alzheimer's disease and type 2 diabetes



vTv has a track record of **strategic partnerships** with leading biopharmaceutical companies, academic institutions and patient advocacy groups