AABC/ISTAART Joint Webinar:
Biotech Innovation in New Therapeutic Approaches to Alzheimer’s Disease
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Judy Walker, MD, FRCPC
Chief Medical Officer
Accera, Inc.

John Didsbury, PhD
President & CEO,
Chairman of the Board
T3D Therapeutics

Mark Gurney, PhD
Chairman & CEO
Tetra Discovery Partners, Inc.
Judy Walker MD FRCPC – mini bio

• Neurologist trained in Canada
• Medical monitor at Quintiles (New Jersey) and led a project management group. 1999-2001
• Head of Neurology for ROW at Serono, Geneva. 2001-2004
• Head of Medical Affairs for Teva Neuroscience (Kansas City, MO). 2004-2008
• VP Quintiles Strategic Drug Development group, UK.
• Chief Medical Officer, Accera since April 2017
• Extensive experience in Alzheimer’s Drug Development throughout her career.
Alzheimer's as a metabolic disease

ACCERA’S APPROACH TO AD
Mitochondrial Cascade Hypothesis of AD: Mitochondrial Dysfunction due to APOE4, Aβ, ROS, aging, diet etc. contribute to disease progression

In Alzheimer’s damaged mitochondria cannot utilize glucose(1)

- Amyloid and other factors inhibit mitochondrial function resulting in early and progressive glucose hypometabolism in cerebral neurons.

Brain Metabolism: The Brain Relies Almost Exclusively on Glucose as an Energy Substrate

Brain Metabolism

- 2% of body weight
- 120-130 g glucose/day
- Uses 25% of total body glucose
- Receives 15% of cardiac output
- Uses 20% of total body oxygen

FDG PET


AD is characterized by declines in the cerebral metabolic rate of glucose (CMRglc)

Regional declines in CMRglc Occur Early in AD

- Hypometabolism is most notable in the posterior cingulate, parietal, temporal, and prefrontal cortices

- Regional low CMRglc can be detected decades before clinical signs of dementia

- Found in APOE4(+) subjects at risk for AD

- Mean age of subjects: 30.7

Studies have Demonstrated that the Metabolic Defect in AD is Specific to Glucose and the Alzheimer’ Brain is now Oxidizing Substrates other than Glucose to Meet its High Energy Demands

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Middle Age</th>
<th>Normal Elderly</th>
<th>Early Onset AD</th>
<th>Late Onset AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{O}_2 )</td>
<td>1.58 ±0.18*</td>
<td>1.54 ±0.11*</td>
<td>1.49 ±0.04*</td>
<td>1.45 ±0.10*</td>
<td>1.27±0.12*</td>
</tr>
<tr>
<td>Gluc</td>
<td>0.26 ±0.04*</td>
<td>0.26 ±01*</td>
<td>0.26 ±0.01*</td>
<td>0.12 ±0.01*</td>
<td>0.14 ±0.03*</td>
</tr>
<tr>
<td>Glucose Ox Ratio</td>
<td>0.99 ±0.02</td>
<td>1.01 ±0.02</td>
<td>0.97 ±0.02</td>
<td>0.50 ±0.02</td>
<td>0.66 ±0.03</td>
</tr>
</tbody>
</table>

Adapted from {Hoyer, 1992 #31}, Glucose Ox Ratio = (Gluc x 6)/\( \text{O}_2 \)
*Cerebral metabolic rate (\( \mu \text{mol/g x min} \))

The authors conclude:
“This abnormal metabolic pattern may bring the cerebral glucose metabolism into focus as the point of primary metabolic damage in DAT and raises the questions as to which substrates other than glucose is (are) utilized from the remaining oxygen for energy generation” *

Ketone metabolism is preserved in AD, even when glucose metabolism is defective

“.... these results suggest that increasing energy availability to glucose-deficient brain regions by increasing glucose (18F-FDG) uptake or by providing alternative energy substrates such as ketones is a potential complementary strategy for the treatment of early AD.”

Treatment Hypothesis: Can addressing Glucose Hypometabolism improve Cognitive Function in Patients with Alzheimer's disease

THE PROBLEM IN ALZHEIMER’S DISEASE

In Alzheimer’s damaged mitochondria cannot utilize glucose
A series of genetic and environmental factors inhibit glycolysis and mitochondrial function resulting in early and progressive glucose hypometabolism in the neurons and brain.

TREATMENT HYPOTHESIS

If the AD brain is having difficulty metabolizing glucose, can we provide the brain with another substrate that it can metabolism in place of glucose and will this improve symptoms of the disease?
Update on ketosis in Alzheimer’s disease

KETOSIS
Ketone Bodies are the Brain’s Natural Backup Fuel

- Normally produced under conditions of low glucose availability, such as ketogenic diets or fasting
- Can provide up to 60 percent of your brain's energy needs
- Production of ketone bodies is suppressed by carbohydrate in the diet

KETONE BODIES ARE MORE THAN A FUEL SOURCE
### Neuroprotection by Ketogenic Diets

<table>
<thead>
<tr>
<th>Injury</th>
<th>Lesion</th>
<th>Species</th>
<th>Outcome</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Transgenic APP expression</td>
<td>Mice</td>
<td>Reduced Aβ levels</td>
<td>1</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>Transgenic SOD1 mouse</td>
<td>Mice</td>
<td>Increased motor neuron counts</td>
<td>2</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>Controlled cortical impact</td>
<td>Rats</td>
<td>Reduced contusion volume</td>
<td>3</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Human PD patients</td>
<td>Human</td>
<td>Improved motor function</td>
<td>4</td>
</tr>
<tr>
<td>KA-induced seizures</td>
<td>Kainic acid</td>
<td>Mice</td>
<td>Increased cell survival</td>
<td>5</td>
</tr>
<tr>
<td>GLUT1 haploinsufficiency</td>
<td>Glucose deprivation</td>
<td>Human</td>
<td>Decrease seizure frequency</td>
<td>6</td>
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<tr>
<td>Ischemia</td>
<td>Cardiac arrest induced ischemia</td>
<td>Rats</td>
<td>Protection from neurodegeneration</td>
<td>7</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Human AD patients</td>
<td>Human</td>
<td>Improve cognitive performance</td>
<td>8</td>
</tr>
</tbody>
</table>

### Neuroprotection by Ketone Bodies Alone

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Injury</th>
<th>Lesion</th>
<th>Species</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection of acetoacetate</td>
<td>Glutamate toxicity</td>
<td>Inhibition of glycolysis by iodoacetate</td>
<td>Rat, cell culture</td>
<td>Neuroprotection</td>
</tr>
<tr>
<td>Infusion of 4mM BHB, 5mM ACA</td>
<td>Glutamate toxicity</td>
<td>Incubation with 5mM glutamate</td>
<td>Cell culture</td>
<td>Increased cell survival</td>
</tr>
<tr>
<td>Infusion of BHB</td>
<td>Glutamate toxicity</td>
<td>Glutamate and iodoacetate treatment</td>
<td>Rats</td>
<td>Neuroprotection and reduced lipid peroxidation</td>
</tr>
<tr>
<td>1mM BHB 1mM ACA</td>
<td>Glutamate toxicity</td>
<td>Glutamate treatment</td>
<td>Cell culture</td>
<td>Increased mitochondrial efficiency</td>
</tr>
<tr>
<td>4mM BHB</td>
<td>Hypoxia</td>
<td>2hr exposure to hypoxia</td>
<td>Cell culture</td>
<td>Increased cell survival</td>
</tr>
<tr>
<td>Infusion BHB</td>
<td>Hypoxia</td>
<td>Carotid artery ligation</td>
<td>Mice</td>
<td>Maintained ATP and low lactate</td>
</tr>
<tr>
<td>Infusion BHB</td>
<td>Ischemia</td>
<td>Occlusion of middle cerebral artery</td>
<td>Mice</td>
<td>Reduced cerebral infarct area</td>
</tr>
<tr>
<td>Infusion BHB</td>
<td>Traumatic brain injury</td>
<td>Controlled cortical impact</td>
<td>Rats</td>
<td>Restored ATP levels after CCI</td>
</tr>
<tr>
<td>Ketogenic agent</td>
<td>Alzheimer’s disease</td>
<td>Memory problems in Alzheimer’s disease</td>
<td>Human</td>
<td>Improved cognitive performance</td>
</tr>
<tr>
<td>BHB treatment</td>
<td>Alzheimer’s disease</td>
<td>Aβ in cell culture model of AD</td>
<td>Cell culture</td>
<td>Increased cell survival</td>
</tr>
<tr>
<td>BHB infusion</td>
<td>Parkinson’s disease</td>
<td>MPTP lesioning</td>
<td>Mice</td>
<td>Improved neuronal survival, improved mitochondrial efficiency</td>
</tr>
<tr>
<td>BHB treatment</td>
<td>Parkinson’s disease</td>
<td>Rotenone treatment of cells</td>
<td>Cell culture</td>
<td>Increased cell survival</td>
</tr>
<tr>
<td>Ketogenic agent</td>
<td>Aging</td>
<td>Cognitive decline with age</td>
<td>Dog</td>
<td>Improved cognitive performance</td>
</tr>
</tbody>
</table>
KETOSIS AS A TREATMENT FOR AD
Support for Mechanism of Action: Recent studies continue to support ketosis as a treatment for Alzheimer’s disease

Yin et al (2016)\(^1\) demonstrated that Ketone bodies:

- Blocked amyloid-beta 42 entry into neurons
- Rescued mitochondrial complex I activity, reduced oxidative stress, and improved synaptic plasticity
- When administered peripherally significantly reduced amyloid burden and greatly improved learning and memory ability in a symptomatic mouse model of AD

Ketogenic Diets Require Strict Compliance

Very low carbohydrate and protein intake

• No bread
• No pasta
• No pizza
• No rice

Compliance in AD

• AD patients have change in food selection toward sweet, carbohydrate-rich foods making compliance difficult1,2,3

Accera’s tricaprilin is an 8-carbon medium chain triglyceride

Medium Chain Triglycerides (MCTs) are specialized lipids

- MCTs are fatty acids consisting of 5-12 carbons that do not occur in the normal diet
- Undergo obligate oxidation to **generate ketone bodies**
- MCTs are self-affirmed GRAS and have undergone extensive its toxicology studies

Accera’s tricaprilin is an 8 carbon MCT

- A structured lipid in which the fatty acids are all C8
- C8 fatty acids are not subject to esterification and are transported to the liver via the portal vein
- These provide an energy rich substrate for the production of ketone bodies
- Human dose is several folds lower than NOAEL levels in rat and dog studies.

Tricaprilin (Caprylic triglyceride)

- Molecular formula: $\text{C}_{27}\text{H}_{50}\text{O}_{6}$
- Molecular weight: 470.68

Structural formula
Accera’s Phase 2a Study: Tricaprilin administration results in rapid improvement in metabolism & cognition

**Design**
- 20 mild to moderate AD patients
- Mean age 74.7 years
- Single dose crossover design

**Results**
- AC-1202 significantly elevated serum ketone bodies
- AC-1202 significantly improved ADAS-cog in ApoE4(-) patients after single dose (p < 0.05)
- BHB serum levels correlated with improved memory (p < 0.05)
- APOE4 non carriers ADAS-Cog scores improve in 90 minutes
- Rapid improvement is likely due to switch in neuronal metabolism to utilize the available ketone bodies

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Accera’s Phase 2b Study: Multi-center, double-blind placebo-controlled study in subjects with mild-to-moderate Alzheimer’s disease

Design: n= 152, 90 Day intervention, Primary endpoint ADAS-Cog\(^1\)

AC-1202\(^2\): 20 g QD, orally

± AChEi

(> 75 %)

N = 152

Placebo

Double - blind

(3 months)

2 week

washout

Conducted at top clinical trial sites in the US

- Performed at 23 clinical trial sites
- Single pre-specified analysis of APOE ε4 non-carriers (as seen in P2a study)
- Full service CRO: CRC (Cognitive Research Corporation)
- Published in peer-reviewed journal\(^1\)

2. Phase 2b study used a slightly different formulation (AC-1202) but the API and dose were the same.
Phase 2b Study: Change from baseline in ADAS-Cog scores in APOE ε4 non-carriers (a pre-specified analysis)

Pre-specified sub-group analysis in 55 APOE ε4 (-) patients

- Effect size of 3.4 pts in ADAS-Cog seen at 90 days
- Persistence of effect after washout

<table>
<thead>
<tr>
<th>Time point</th>
<th>Score Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 45</td>
<td>4.77</td>
<td>0.0005</td>
</tr>
<tr>
<td>Day 90</td>
<td>3.36</td>
<td>0.015</td>
</tr>
<tr>
<td>Day 104</td>
<td>2.08</td>
<td>0.154</td>
</tr>
</tbody>
</table>

N=29 ApoE4(-) AC-1202; N=26 ApoE4(-) Placebo
Phase 2b Study: Strongest effect observed in dosage compliant APOE4 non-carrier patients

<table>
<thead>
<tr>
<th>Time point</th>
<th>Score Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 45</td>
<td>6.26</td>
<td>0.0011</td>
</tr>
<tr>
<td>Day 90</td>
<td>5.33</td>
<td>0.0063</td>
</tr>
<tr>
<td>Day 104 Washout</td>
<td>3.26</td>
<td>0.1070</td>
</tr>
</tbody>
</table>

Mean Change from Baseline Improvement

AC-1202 per protocol (n=18)
AC-1202 dosage compliant (n=16)
Placebo per protocol (n=19)
Placebo dosage compliant (n=19)
Phase 2b Study: Serum βHB levels correlated with improvement in ADAS-Cog scores among APOE4 non-carriers
Accera’s Phase 2/3 Study (NOURISH AD):

**Primary arm**

- **286 APOE ε4 (-) Subjects Randomized**
  - AC-1204 20 grams Once daily (N=143)
  - Placebo Once daily (N=143)
  - 6 months
    - Week 26 Primary Endpoint ADAS-Cog Key Secondary ADCS-CGIC
    - Optional 26 Week Open Label Study

**Exploratory arm**

- **128 APOE ε4 (+) Subjects Randomized**
  - AC-1204 20 grams Once daily (N=64)
  - Placebo Once daily (N=64)
  - 6 months
    - Week 26 Primary Endpoint ADAS-Cog Key Secondary ADCS-CGIC
    - Optional 26 Week Open Label Study

Run by Accera’s clinical operations team with a leading CRO: INC Research
- Conducted at 80 US sites
- Secondary endpoints include:
  - Alzheimer’s Disease Co-operative Study – Activities of Daily Living
  - Quality of Life – Alzheimer’s Disease
  - Resource Utilization in Dementia.
  - Clock Draw Interpretive Scale
  - Mini-Mental State Exam (MMSE)

Exploratory arm included at the request of the FDA to:
- Ensure no efficacy in APOE ε4 carriers after a longer duration
- Ensure no safety concerns

Full Results to be presented at CTAD 2017
Summary

- Accera is developing novel approaches to Alzheimer’s disease based on metabolic defects present in the disease
- Under “normal” conditions the brain runs almost exclusively on glucose
- In mild AD, CMRglc decreases yet metabolism of ketone bodies remains intact
- Ketone bodies act as signaling metabolites with protective properties
- Defective metabolism is an attractive target in Alzheimer's drug development
Acknowledgements – Thanks to the Accera staff!
BACK UP SLIDES
Phase 2b Study: No change from baseline in ADAS-Cog scores in APOE4 carriers

Pre-specified sub-group analysis in 69 APOE ε4 (+) patients

- APOE ε4 carriers showed no statistical difference between placebo and active at any time point

<table>
<thead>
<tr>
<th>Time point</th>
<th>Score Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 45</td>
<td>0.05</td>
<td>0.964</td>
</tr>
<tr>
<td>Day 90</td>
<td>0.12</td>
<td>0.921</td>
</tr>
<tr>
<td>Day 104</td>
<td>-0.25</td>
<td>0.845</td>
</tr>
</tbody>
</table>

N=38 ApoE4(+) AC-1202; N=31 ApoE4(+) Placebo
Ketone bodies can bypass some defects in mitochondrial function in AD

**APOE4 non-carriers**

- Primary block in mitochondrial function by Aβ occurs pyruvate dehydrogenase (PDH) preventing the utilization of glucose (1)
- Ketone bodies provide acetyl-CoA independent of PDH

**APOE4 carriers**

- Block in mitochondrial function by Aβ occurs pyruvate dehydrogenase (PDH) preventing the utilization of glucose
- Further block at Complex III and IV by APOE4 (2)
- Ketone bodies can’t bypass block in ETC

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Alzheimer’s disease: What causes Glucose Hypometabolism?

1. Neuronal damage - cellular/synaptic loss
2. Low expression of energy generation genes in AD
3. Activities of Aβ
4. Activities of ApoE4 protein inhibiting mitochondrial function
5. Defects in mitochondrial transport
6. Brain Insulin Resistance
7. Deleterious effects of glucose on the brain leading to mitochondrial dysfunction

High "Normal" Blood Glucose is Associated with Lower CMRglc

**Design**
- 124 cognitively normal subjects
- Mean age 64 years
- 61 APOE4(-)
- 63 APOE4(+)

**Results**
- Both groups showed lower CMRglc correlated with higher fasting glucose
- Pattern of reduced CMRglc was confined to areas associated with AD

Glucose Hypometabolism is Progressive in AD and Correlates with Cognitive Decline

- Decline in CMRglc ranges from 17-24% across the brain
- Represents a serious problem for the brain which relies on glucose.

Ketone Bodies as Signaling Metabolites

Ketone Bodies act as Histone De-acetylase (HDAC) Inhibitors and Activate HCAR2

The Brain’s Utilization of Ketone Bodies Varies Directly with Blood Concentrations

<table>
<thead>
<tr>
<th>Blood BHB (mM)</th>
<th>CMR (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3-0.5</td>
<td>3-5%</td>
</tr>
<tr>
<td>1.5</td>
<td>18%</td>
</tr>
<tr>
<td>6</td>
<td>60%</td>
</tr>
</tbody>
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Support for Mechanism of Action: Independent studies continue to support ketosis as a treatment for Alzheimer’s disease

- **Krikorian et al. (2012)** demonstrated improved memory performance that correlated with urine ketone levels
- Randomly assigned 23 older adults with Mild Cognitive Impairment to either a high carbohydrate or very low carbohydrate diet for six weeks.
- For the low carbohydrate subjects:
  - Verbal memory performance improved (p = 0.01)
  - Weight reduced (p < 0.0001)
  - Waist circumference reduce (p < 0.0001)
  - Fasting glucose reduced (p =0.009)
  - Fasting insulin (p = 0.005)
  - Ketone levels were positively correlated with improved memory performance (p = 0.04)

**Table:** Post-intervention dietary parameters by group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High Carb</th>
<th>Low Carb</th>
<th>t(21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy, kcal</td>
<td>1592 (395)</td>
<td>1042 (347)</td>
<td>3.55</td>
<td>0.001</td>
</tr>
<tr>
<td>Carb, g</td>
<td>197 (53)</td>
<td>34 (18)</td>
<td>9.94</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protein, g</td>
<td>58 (12)</td>
<td>67 (19)</td>
<td>1.32</td>
<td>0.20</td>
</tr>
<tr>
<td>Fat, g</td>
<td>61 (24)</td>
<td>69 (27)</td>
<td>0.74</td>
<td>0.49</td>
</tr>
<tr>
<td>Urinary ketone, mg/dl</td>
<td>0</td>
<td>5.4 (3.3)</td>
<td>4.54</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Note:** High carb = high carbohydrate group. Low carb = low carbohydrate group.
Urinary ketone = acetoacetic acid. Data represent unadjusted, mean (SD) daily values.

**Figure 1.**
Pre- and post-intervention memory performances for the low and high carbohydrate groups as measured by the Verbal Paired Associate Learning Test (Krikorian, 1996). Values are unadjusted means of the cumulative number of correct immediate recall responses summed across four learning trials. Vertical bars represent standard error. The ANCOVA analysis indicated improved learning for the low carbohydrate subjects, F(1,20) = 6.45, p = 0.01, Cohen’s f = 0.26.

Castellano et al (2017)\(^1\) demonstrated that moderate exercise increases ketone body uptake in the brain:

- Exercise has been proposed to reduce risk of developing AD\(^2\)
- 10 Patients diagnosed as having probable or possible AD dementia were trained to walk on a motorized treadmill 3 days/week for 12 weeks
- Measurement of Glucose uptake was measured with FDG-PET
- Measurement of Ketone uptake was measured with Ketone-PET
- Compared to the Baseline, after Walking, CMRacac was three-fold higher (0.6±0.4 versus 0.2±0.1mol/100 g/min; \(p = 0.01\)).
- CMRglu was unchanged after Walking (28.0±0.1mol/100 g/min; \(p = 0.96\)).
- Plasma acetoacetate concentration and the blood-to-brain acetoacetate influx rate constant were also increased by 2–3-fold (all \(p\leq0.03\))
- There was a trend toward improvement in the Stroop–color naming test (−10% completion time, \(p = 0.06\)) and performance on the Trail Making A&B tests (\(p\leq0.01\))

Support for Mechanism of Action: Recent studies continue to support ketosis as a treatment for Alzheimer’s disease

Vandenberghe et al (2016)\(^1\) demonstrated that caprylic triglyceride is more ketogenic than other MCTs:

- Caprylic triglyceride was more ketogenic than C8/C10 blends for both Cmax and AUC
- Capric triglycerides are weakly ketogenic
- Coconut oil is weakly ketogenic

Vandenberghe C et al 2016. ACUTE PLASMA KETONE RESPONSE TO COCONUT OIL ALONE OR IN COMBINATION WITH DIFFERENT MEDIUM CHAIN TRIGLYCERIDES
Animal Model: Administration of MCTs improved mitochondrial function and cognition in aged beagles


Phase 2b Study: Enrolled patients were typical mild to moderate AD patients

<table>
<thead>
<tr>
<th>Safety population</th>
<th>Treated, N = 86</th>
<th>Placebo, N = 66</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>76.9 (± 8.9)</td>
<td>76.8 (± 7.4)</td>
</tr>
<tr>
<td>Median</td>
<td>78.0</td>
<td>78.0</td>
</tr>
<tr>
<td>Range</td>
<td>52 -93</td>
<td>51 -89</td>
</tr>
<tr>
<td><strong>AD medications n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aricept</td>
<td>43 (50)</td>
<td>28 (42.4)</td>
</tr>
<tr>
<td>Exelon</td>
<td>11 (12.8)</td>
<td>11 (16.7)</td>
</tr>
<tr>
<td>Namenda</td>
<td>32 (37.2)</td>
<td>31 (47)</td>
</tr>
<tr>
<td>Reminyl/Razadyne</td>
<td>3 (3.5)</td>
<td>9 (13.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotyped population</th>
<th>Treated, N = 67</th>
<th>Placebo, N = 57</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APOE Genotype n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total E4 (+)</td>
<td>38 (56.7)</td>
<td>31 (54.4)</td>
</tr>
<tr>
<td>Total E4 (-)</td>
<td>29 (43.3)</td>
<td>26 (45.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Treated, N = 77</th>
<th>Placebo, N = 63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline MMSE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>19.68 (± 4.48)</td>
<td>19.48 (± 4.37)</td>
</tr>
<tr>
<td>Median</td>
<td>20.00</td>
<td>20.00</td>
</tr>
<tr>
<td>Range</td>
<td>10 - 28</td>
<td>8 - 29</td>
</tr>
<tr>
<td><strong>Baseline ADAS-Cog</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± SD)</td>
<td>23.88 (± 9.17)</td>
<td>23.35 (± 8.7)</td>
</tr>
<tr>
<td>Median</td>
<td>23.67</td>
<td>23.00</td>
</tr>
<tr>
<td>Range</td>
<td>7 – 54.33</td>
<td>11.33 – 62.00</td>
</tr>
</tbody>
</table>

*Some patients were on multiple medications

Summary of efficacy results

More compliant patients did better

APOE4 carriers did not respond

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ITT w/LOCF</th>
<th>Per Protocol</th>
<th>Dosage Compliant</th>
<th>E4(-) ITT w/LOCF</th>
<th>E4(-) Per Protocol</th>
<th>E4(-) Dosage Compliant</th>
<th>E4(+) ITT w/LOCF</th>
<th>E4(+) Per Protocol</th>
<th>E4(+) Dosage Compliant</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>1.227</td>
<td>0.956</td>
<td>1.076</td>
<td>1.614</td>
<td>1.963</td>
<td>1.472</td>
<td>0.989</td>
<td>0.145</td>
<td>0.833</td>
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<td>AC-1202</td>
<td>-0.312</td>
<td>-0.563</td>
<td>-1.182</td>
<td>-1.747</td>
<td>-2.426</td>
<td>-3.854</td>
<td>0.846</td>
<td>1.433</td>
<td>0.909</td>
</tr>
</tbody>
</table>
• Dr. Didsbury is a seasoned Executive Manager with over 27 years of experience within the pharmaceutical and biotechnology industries in both small and large public and private companies.

• Former roles:
  • President of DARA BioSciences, Inc. (NASDAQ:CM – DARA). He played a key role in taking the company public in 2008 through a reverse merger.
  • Head of Strategy and Operations for one of GlaxoSmithKline’s six worldwide drug discovery centers.
  • Assistant Professor of Medicine at Duke University Medical Center and a scientist at Genentech, Inc.
A Transformational Approach to Treating Alzheimer’s Disease

AABC/ISTAART Webinar
19 October 2017
Forward-Looking Statements

Statements contained in this presentation that are not statements of historical fact may be deemed to be forward looking statements. Without limiting the generality of the foregoing, words such as “may,” “will,” “expect,” “believe,” “anticipate,” “intend,” “could,” “estimate” or “continue” are intended to identify forward-looking statements. Readers are cautioned that certain important factors may affect the Company’s actual results and could cause such results to differ materially from any forward looking statements which may be made in this presentation or which are otherwise made by or on behalf of the Company. Factors which may affect the Company’s results include, but are not limited to, product demand, market acceptance, impact of competitive products and prices, product development, commercialization or technological difficulties, the success or failure of negotiations and trade, legal, social and economic risks.
Highlights

1. Innovative Approach - Challenging Current Paradigms to Treat the Disease

2. Possibility of the First Truly Effective Treatment for Alzheimer’s Disease (AD) – Phase 2a Evidence

3. Lower Risk – Investigational New Drug T3D-959 Has All Three Key Facets of a Successful Pharmaceutical Drug
Key Tenet: The Alzheimer’s Brain is Being Starved
Three Major Changes in the Alzheimer’s Brain

1. **Metabolism** Changes – Glucose + Lipids

2. **Structural** Changes – Amyloid Plaques + Tau Tangles

3. **Stress** Changes – Inflammation + ROIs

**Metabolism Changes May Be the Initiating Event**
Metabolism Changes Precede Cognitive Decline

Low glucose metabolism > energy deficiency > brain starvation > cognitive decline

FDG-PET Imaging – Measuring Brain Glucose Metabolism. Warm colored areas indicate regions of higher glucose metabolism.
Glucose Metabolism Link With Cognitive Function

• Diabetics Have 2-Fold Increased Risk of Getting AD

• 37% of AD Patients are Diabetic (vs. 9.4% General Population)

• Multiple Similarities of AD & Type 2 Diabetes: The Common Theme is Insulin Resistance
  o Cognitive Decline
  o Neurodegeneration
  o Amyloid Aggregation and Deposition
  o Inflammation

• Clinical Symptoms of AD Do Not Occur Without Decreases in Brain Glucose Metabolism

• Association – Elevated Blood Sugar > Memory Problems & Lower Brain Volume
Innovative Approach

1. Feedback Loop Interconnected Changes

Metabolism Changes

Stress Changes

Structural Changes

2. Focus Today

Multiple Drug Failures

High Perceived Risk

Investor Recalcitrance

Innovation Stifled

Wrong Intervention Point

T3D-959 Correct Metabolism Dysfunctions

Feed the Starving Brain, Intervene Here

Slow, Stop or Reverse Disease Course

T3D Therapeutics, Inc.
Innovative Approach

Unique Molecule T3D-959

• Central Regulator of Glucose and Lipid Metabolism

• Acting to Restore Normal Metabolism – Overcoming Insulin Resistance

• Accesses the Brain – Penetrating the Blood Brain Barrier

• T3D-959 Target is Highly Expressed in Brain Tissue

• Clear Pre-Clinical and Clinical Evidence of a Strong Brain Pharmacological Effect

• Good API and Drug Product Properties
  • Reliable GMP API Manufacture in Hand
  • Facile Drug Product Preparation
  • Excellent API and Drug Product Stability
  • Orally Delivered as a Once-A-Day Capsule
T3D-959 Mechanism of Action

- Regulating genes to correct dysfunctional glucose and lipid metabolism
- Drug Target:  
  Primary – PPAR delta
  Secondary – PPAR gamma

**Central Regulators of Glucose and Lipid Homeostasis**

**PPARδ (delta)**
- Actions:
  - Insulin sensitivity/signaling
  - Fatty acid oxidation/catabolism
  - Cholesterol transport
  - ↑ HDL
  - Reduction in adiposity, ↓ TGs
  - ↓ Inflammatory signaling
  - Macrophage differentiation

**PPARγ (gamma)**
- Actions:
  - Insulin sensitivity/signaling
  - Glycogen synthesis
  - Adipogenesis
  - Anti-oxidation
  - ↓ Inflammatory signaling
  - ↑ BDNF, NGF, Klotho
Other Metabolic Approaches

- Rosiglitazone (PPAR gamma agonist)
- Pioglitazone (PPAR gamma agonist) – TOMORROW Trial Ongoing
- Inhaled Insulin – SNIFF Trial Ongoing

[ Rosiglitazone – Success in Phase 2, Failure in Phase 3 ]
- Restricted target expression in the brain (PPAR gamma)
- Poor brain penetration of Rosiglitazone (pgp substrate)
- Improper dose selection
- ApoE genotype-specific differential response
T3D-959 is Distinctly Different

- Flawed comparisons to “failed” PPAR γ-selective agent (Rosiglitazone/Avandia)
- The Primary Target of T3D-959 is PPAR δ (delta)
- All ‘PPARs’ are not the same:
  - PPAR δ is ubiquitously found in the brain, PPAR γ is not
  - PPAR δ regulates energy expenditure, PPAR γ regulates energy storage
  - PPAR δ activates the key memory and learning wnt pathway, gamma does not
  - PPAR δ restores memory and spatial learning in animal models, gamma does not
  - PPAR δ plays helps maintain cholesterol homeostasis, gamma does not
- T3D-959 has better pre-clinical brain exposure than Rosiglitazone (or Pioglitazone)
  - 30 to 35% of rat plasma concentration of T3D-959 is found in rat brains
- Initial safety data indicates we should be able to use higher doses than Rosiglitazone
- T3D-959 has a different chemical structure. It is an indane acetic acid derivative not a thiazolidinedione. Rosiglitazone and Pioglitazone are racemic mixtures.
T3D-959 Target Rationale

• **PPAR delta null mice are AD-like:**
  a) cognitive impairment,
  b) impaired canonical wnt signaling pathway,
  c) tau hyper-phosphorylation,
  d) increased inflammation in cerebral cortex,
  e) altered myelination,
  f) altered brain phospholipid composition,
  g) increased oxidative stress,
  h) brain atrophy

• **PPAR delta activation Effective in AD animal models**
  a) Complete rescue of cognitive impairment,
  b) Reduced amyloid burden,
  c) Reduced brain inflammation,
  d) Inhibited production of BACE1,
  e) Increased expression of plaque degrading enzymes,
  f) Inhibition of tau phosphorylation of tau,
  g) Increased gene expression of anti-oxidants catalase and SOD
  h) Inhibition of astrocyte and microglia activation,
  i) Stimulation of the production of acetylcholine.
Pre-Clinical and Phase I Data Supporting Phase 2a Clinical Study

- **Pre-Clinical**
  - Efficacy in i.c. STZ Model of Sporadic AD
  - Rat Brain Penetration Study
  - Rat and Monkey Tox data
  - Safety Pharmacology Studies

- **Phase 1**
  - Single Escalating Dose
  - Multiple Escalating Dose
  - Good PK supporting oral qd dose
  - Good exposures over a broad range of doses
  - Excellent Safety Profile, no adverse effects, no MTD
Exploratory / Feasibility Phase 2a Study of T3D-959 in Mild to Moderate Alzheimer’s Disease Patients

- High Safety Profile – 2-week and 22-week dosing
- Multiple Efficacy Signals – Cognition and Brain Glucose Metabolism
- Successful Dose Range Finding for Subsequent Trials

Translate to Lower Risk
Phase 2a High Safety Profile

- One drug-related AE\(^{(1)}\)
- No changes in clinical labs
- No changes in physical and neurological exams
- No changes in ECGs
- No respiratory rate or orthostatic blood pressure and heart rate changes
- No potential bone marrow effects as monitored with hematology testing
- No potential increases in plasma volume as assessed by the presence or absence of edema
- No weight gain
- No tolerability issues

\(^{(1)}\) First patient enrolled, subject 1001 (30mg) – Self-limited, resolved within 1-day
Multiple Efficacy Signals
1. Cognitive Improvement (ADAS-cog11) in Both Alzheimer’s Patient Subgroups (ApoE4 positive & ApoE4 negative)

<table>
<thead>
<tr>
<th>ApoE4 Negative Patients</th>
<th>Improvement from Baseline at Follow-up</th>
<th>ApoE4 Positive Patients</th>
<th>Improvement from Baseline at Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td>Yes</td>
<td>5.25 pt. avg.</td>
<td>3mg</td>
</tr>
<tr>
<td>10mg</td>
<td>Yes</td>
<td>6.17 pt. avg.</td>
<td>10mg</td>
</tr>
<tr>
<td>30mg</td>
<td>Yes</td>
<td>4.60 pt. avg</td>
<td>30mg</td>
</tr>
<tr>
<td>90mg</td>
<td>No</td>
<td></td>
<td>90mg</td>
</tr>
</tbody>
</table>

- Effective in Both Patient Sub-Groups
- Dosing Trend - Low Dose for One Group (ApoE4 negative), High Dose for the Other Group (ApoE4 positive)
- Highly Competitive Versus Marketed Drugs – e.g. Aricept 1.82 pts. at 6-weeks
Multiple Efficacy Signals

2. Cognitive Improvement (DSST)

*Improvement (regardless of dose or ApoE genotype) is sustained at 21 days (7 days post discontinuation of dosing). Less improvement in moderate patients, as expected*

<table>
<thead>
<tr>
<th></th>
<th>Moderate Patients</th>
<th>Mild Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>2.4</td>
<td>7.0</td>
</tr>
<tr>
<td><strong>ApoE4-</strong></td>
<td>1.7</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>ApoE4+</strong></td>
<td>4.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>
Multiple Efficacy Signals

3. FDG-PET Neuroimaging Data Supports Brain Exposure & Activity

Dose Dependent Increase in the Spatial Extent of Regions of Statistically Significant Change in Relative CMRgl (EOT-BL)

- Statistically Significant Change Even at Lowest Dose (3mg)
- Dose Dependent Change
- Regional Specificity - Affecting Alzheimer’s Regions.

Composite of Trial Subjects by dose group (n=8-9)
Subject 3014: MMSE=25, 3mg dose,
Caregiver=Spouse, stated in letter received 7-days after dosing cessation:

1. “Much more alert & aware of surroundings
2. Much more engaged in conversation at home & in public
3. Critical of my driving…aware of every changing light and tried to direct me as to when to stop & go…critical of other drivers…commented on other driver’s traffic violations, etc.
4. Without prompting, went outside to repair polaris that had disconnected from pool wall…got the necessary tools without asking where they were located
5. Started dispensing vitamins at breakfast. He did this on a daily basis for a number of years but quit 6-8 months ago. Now, routine has resumed.
6. At my daughter’s house in Charlotte, he asked if anyone would like a glass of wine. He got the wine that he had chilled earlier, got the wine opener and opened the wine & then served it. For the last year or more he has not remembered where he has chilled the wine nor where the wine opener was kept. He also has not remembered how to operate my daughter’s wine opener for the last year or more. He asked for no assistance when using it after the trial
7. He has been choosing his clothes to wear without asking for advice.
8. He packed his suitcase (twice) without assistance. He has needed assistance with this task for at least 1 ½ to 2 years.”
Multiple Efficacy Signals

5. Clinical Investigator Impressions

“Our trial site has received **consistently positive reports from patients and their caregivers** in this Phase 2a clinical trial. I would like to congratulate T3D on this successful study. We eagerly anticipate a longer [and larger] trial,”

- **Marc Agronin, MD**, Principal Investigator - Miami
  Jewish Health Systems, Miami, FL

“Since the launch of the T3D-959 study, we have unexpectedly received unsolicited, spontaneous **caregiver submissions of feedback, noting significant improvements** in some of the trial participants. We are excited about these preliminary results and look forward to furthering our understanding of the safety and efficacy of T3D-959 in patients with mild to moderate Alzheimer’s disease.”

- **Santosh Gopalakrishnan MD**, Principal Investigator –
  New Hope Clinical Research, Charlotte, NC

“I am familiar with T3D959 and actually had several patients on it for a Phase 2 clinical trial. This was through New Hope Clinical Research here in Charlotte. I am interested in putting many more people on the trial. **We had several of our patients improve, some dramatically, on the drug. I am the world's leading skeptic and even I was impressed.**”

- **Charles Edwards MD**, Physician – Memory Center, Charlotte, NC
Phase 2a – 22-week Expanded Access Extension: Early indicator of potential long term safety

4 Subjects
- All were ApoE4 positive patients (genotype was determined after dose selection & extension study start),
- Selected dose not optimal for ApoE4 positive patients

Monthly cognitive and safety assessments

At **22-weeks** dosing (15mg q.d.):

- No Adverse Events
- No Safety Signals
- No tolerability issues
- CIBIC+ improvement in all subjects Group avg. = 2.75
T3D-959 – All 3 Facets For a Successful Pharmaceutical Drug

Top Tier Drug Properties

**EFFICACY**
- Phase 2a Cognitive Improvement – Sustained After Dosing Discontinuation
- Phase 2a Increase in Brain Glucose Metabolism
- Evidence of Disease Reversal in Animal Model
- Caregiver-Driven Extension Study

**SAFETY**
- No MTD, No SAEs, No Drug-Related AEs, No Tolerability Issues in Phase 1
- No Safety Signals, No Tolerability Issues in Phase 2a
- No Safety Signals, No Tolerability Issues in 4 patients dosed for 22-weeks
- No prototypical PPAR\(\gamma\) – related side effects

**PRODUCT PROPERTIES**
- Orally Delivered
- Once-Day-Dosing PK
- Brain Penetration
- High Drug Stability
- High Solubility
- Simple Formulation
- Scalable Synthesis
- Low Cost of Goods

Translate to **Lower Risk**
Summary

I. New Approach - Correcting AD Metabolic Dysfunctions - Supported by Early Human Clinical Data

II. T3D-959 MOA >
   a. Potential to Treat Multiple Dementia Forms
   b. Potential Disease-Modification
   c. Potential Monotherapy or Combination agent

III. Therapeutic Utility for Different Seversities and ApoE Sub-Groups

IV. Results Support Future Phase 2b Clinical Testing
   ✓ High Safety/Tolerability (incl. 4 patients dosed 22-weeks w/ no safety signals)
   ✓ Cognitive Tests
   ✓ FDG-PET
   ✓ Metabolomics
   ✓ Unsolicited Caregiver Feedback
   ✓ Clinical Investigator Impressions
Appendix – Additional Information
Interrelationship of Metabolic Defects and AD Pathologies

Insulin and IGF-1 Resistance

Altered Lipid Metabolism

Beta Amyloid Plaques

- ↑ Aβ due to ↓ IDE activity
- ↑ Secretion of Aβ1-42
- ↓ Removal of extracellular Aβ oligomers
- ↓ ATP > ↓ ER/Golgi/trans Golgi fxn > protein misfolding
- ↑ Ceramide > BACE > ↑ Aβ
- ↑ Cholesteryl esters > ↑ Secretion of Aβ
- ApoE4 & Aβ > toxic oligomers
- ApoE4 & Aβ > compete for LRP1 > ↓ Aβ removal
- ↓ HDL > ↑ Aβ oligomerization

Tau Tangles

- ↑ GSK3β > Tau hyperphosphorylation
- ↑ CDK5 > Tau hyperphosphorylation
- ↓ O-GlcNAcylation
- ↓ ATP > ↓ ER/Golgi/trans Golgi fxn > protein misfolding
- Imbalance free cholesterol & cholesterol esters
- ↑ Cholesterol > ↑ tau hyperphosphorylation

Inflammation

- Advanced Glycation Endproducts
- ↑ FOXO1
- ↑ NFkB
- Microglia activation
- Astrocyte activation
- Oligodendrocyte dysfunction

Oxidative Stress

- Mitochondrial Dysfunction > ROS
- ↓ SOD
- ↓ Catalase
- Altered Sphingolipid metabolism > ↑ Ceramide > ↑ ROS

Neurotransmitter Deficits

- Decreased Glucose Transport (↓ GLUTs)
- Decreased acetylcholine metabolites of glucose such as acetyl coenzyme A and succinylic coenzyme A; precursors of acetylcholine
- Altered Sphingolipid metabolism > ↑ Ceramide > ↑ ROS

T3D Therapeutics, Inc.
PPAR Delta Null Mouse Phenotype (AD-like)

- Cognitive impairment
- Impaired canonical wnt signaling pathway – key memory pathway
- Tau phosphorylation
- Increased inflammation in cerebral cortex
- Altered myelination
- Altered brain phospholipid composition
- Inactivation of peroxisomal β oxidation
- Increased oxidative stress (↑malondialdehyde, ↓Mn-SOD, ↓glutathione)
- Brain atrophy
- Significant increase vs. wt mice in cerebral infarct size in a focal cerebral ischemia model

References:
Dr. Mark Gurney

Chairman & CEO of Tetra Discovery Partners, Inc.

• Tetra is a clinical stage biotech developing BPN14770, a negative allosteric modulator of phosphodiesterase-4D, for the treatment of Alzheimer's disease and other dementias, psychiatric disease, and neurodevelopmental disorders including Fragile-X.
• Work in drug discovery and development as Senior Vice President at deCODE genetics, Inc.; Director Genomics, Pharmacia Corporation; Associate Professor, Northwestern University Feinberg School of Medicine; and Assistant Professor, University of Chicago Medical School.
• Developed the SOD1-G93A transgenic mouse model of ALS.
• Authored 117 peer reviewed scientific articles that have been cited over 21,000 times and holds 36 issued patents.
• PhD in neuroscience from the California Institute of Technology and an MBA from the Kellogg Graduate School of Management at Northwestern University.
ISTAART-AABC Webinar

BPN14770 For Early Alzheimer’s Disease
Mark Gurney, PhD
Chairman & CEO
Tetra Discovery Partners Inc.

October 19, 2017
The PDE4 *dunce* mutation in *Drosophila* impairs learning and memory.

PDE4D missense mutations in *humans* cause mental retardation associated with brachydactyly (acrodyssostosis type 2; ACRDY2).
Humanizing mouse PDE4D by mutating UCR2 tyrosine271 → phenylalanine (Y271F) improves potency of BPN14770 to the level observed with the human enzyme.
BPN14770 EFFECTS ON cAMP AND HIPPOCAMPAL LTP

Brain cAMP (1 Hr Post Dose)

- **Humanized PDE4D Mice**
- **Wild-type C57Bl6 Mice**

Hippocampal LTP

- Vehicle
- BPN14770 (100 nM)
- BPN14770 (1 µM)

Prof James O’Donnell, Prof Ying Xu, Chong Zhang, University at Buffalo
BPN14770 IMPROVES LONG TERM MEMORY

Novel Object Recognition (24 Hr Recall)

Hippocampal pCREB

Hippocampal BDNF

Prof James O’Donnell, Prof Ying Xu, Chong Zhang, University at Buffalo
PDE4D TARGET IS PRESENT IN BRAIN REGIONS IMPORTANT FOR MEMORY

Hippocampus
- Important for working memory
- Target of Alzheimer’s disease pathology
- Volume correlates with BDNF levels

Prefrontal Cortex
- Important for planning & executive function
- Long term memory

PET scan of rhesus monkey brain showing $^{11}$C-T1650 tracer bound to PDE4D target

Robert Innis, Victor Pike, Masahiro Fujita, Sanjay Telu, NIMH
PET TRACER DEMONSTRATES BPN14770 ENGAGES PDE4D TARGET IN BRAIN

PET scan showing $^{11}$C-T1650 tracer bound to PDE4D in rhesus monkey brain

PET scan showing displacement of $^{11}$C-T1650 tracer by BPN14770

Strength of PET tracer binding is scaled from blue (lowest) to red (highest)

Robert Innis, Victor Pike, Masahiro Fujita, Sanjay Telu, NIMH
• BPN14770 was dosed as the crystalline material in an HPMC capsule
• The 5 and 15 mg doses achieved projected exposure for efficacy based on humanized PDE4D mice (C_{eff} = 10-30 ng/mL)
• Nausea at the 100 mg dose (arrows) was transient and associated with C_{max} (1,337 ng/mL)
BPN14770 DEMONSTRATED A FAVORABLE TOLERABILITY PROFILE

Elderly Subjects > 60 Years of Age

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Adverse Events</th>
<th>Placebo</th>
<th>BPN14770 Doses</th>
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<tr>
<td></td>
<td></td>
<td>n=15</td>
<td>10mg BID</td>
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<tr>
<td>GI</td>
<td>Overall # subjects in SOC with events</td>
<td>2 (13%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal Discomfort</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>1 (7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Flatulence</td>
<td>1 (7%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td>Overall # subjects in SOC with events</td>
<td>2 (13%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>2 (13%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td></td>
<td>Sinus headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bad Taste</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paresthesia</td>
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</tbody>
</table>

Does not cause diarrhea unlike marketed PDE4 inhibitors such as Otezla™

Nausea and vomiting occur with BPN14770 at single doses of 75 mg or 100 mg in young subjects, well above the projected cognitive dose
BPN14770 IMPROVED MEMORY IN ELDERLY ADULTS

BPN14770 Improved Memory In Elderly Adults After Single Or Multiple Doses

ANCOVA model with treatment as base effect and baseline as a covariate: mean ± SEM, * p < 0.05, ** p < 0.01

Baseline response time = 690 msec
Improvement = 60 msec or 10% faster response time

Pooled analysis: n = 20 active and 10 placebo

Log10 msec Response Time For Correct Responses

Memory Change from Baseline

Day -1  Day 1  Day 3  Day 5  Day 7

Placebo  Pooled 10 & 20 mg bid

BPN14770 Significantly Improved Working Memory (One Card Back Task)
BPN14770 IMPROVES FUNDAMENTAL MECHANISMS OF MEMORY

Supports Potential Utility in Early Alzheimer’s Disease

Donepezil increases acetylcholine

BPN14770 increases cAMP by inhibiting phosphodiesterase-4D (PDE4D)

BPN14770 increases brain derived neurotrophic factor (BDNF)

BPN14770 stabilizes synapses

BPN14770 augments hippocampal long term potentiation (LTP)

Acetylcholine
Other Neurotransmitters
Glutamate

Cholinesterase

DENDRITIC SPINE

PKA
CREB

Reduced BDNF correlates with age-related memory decline, rapid progression of AD