Cognitive Evaluation of Treatment Effects of the Bromodomain Inhibitor Apabetalone: Baseline Data of the Cognition Substudy of the BETonMACE Phase 3 Cardiovascular Trial

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Disclosures

Dr. Cummings has provided consultation to Acadia, Avanir, Axsome, BiOasis, Biogen, Boehinger-Ingelheim, Bracket, Eisai, Genentech, Lilly, Lundbeck, Medavante, QR, Resverlogix, Roche, and Samus pharmaceutical and assessment companies.

Dr. Cummings has stock options in Prana, Neurokos, ADAMAS, MedAvante, QR pharma.

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This lecture will include reference to unapproved medications.
Cardiovascular Disease, Diabetes and Dementia

• **Diabetes** increases the risk of developing dementia (2 x)

• **Coronary heart disease** and heart failure are associated with a **27% to 60% increased risk** of cognitive decline, cognitive impairment, or dementia

• We hypothesize;
  • That dementia risk in diabetes and CVD is caused by transcriptional disturbances at the epigenetic level

Epigenetics including BET Bromodomains

• The Epigenetic code refers to secondary modifications to chromatin components that regulate its activity
• Transcription is regulated by addition, removal or recognition of these modifications
• Acetylation is associated with active transcriptional regions of chromatin
• BET bromodomains bind to acetylated lysines on histones and recruit additional transcription factors
Apabetalone is a BET Inhibitor

BET proteins bind acetylated lysine (Ac) on histones via bromodomains (BD), and recruit transcriptional machinery to drive expression of BET sensitive genes which drives neuroinflammation and other key markers of cognitive decline. Apabetalone inhibits BET proteins, causing release from chromatin and downregulation of BET sensitive gene expression.

Transcription and translation of proteins related to:
(i) Neuroinflammation
(ii) Neurovascular calcification
(iii) Complement

Regulation of genes, proteins and pathways associated with neuroinflammation and neurodegeneration
Differentiation: BET Mechanism of Action

**CRISPR: Genome Editing**
Mechanism is based on editing undesired/desired sequences into or out of DNA, thereby altering the gene sequence and re-introducing the modified DNA

**Apabetalone**
Mechanism is based on changing the levels of disease causing proteins by modulating their expression at the gene level

**Traditional Drug Therapies**
Focus on modifying the activity of one disease protein by using an inhibitor or antibody

- **CRISPR – gene editing within a cell sub population**
- **Apabetalone – regulates expression of disease mediators**
- **Antibody or Inhibitor – blocks activity of one mediator of disease**
The BETonMACE Study

• BETonMACE is a phase 3 study to evaluating the effects of apabetalone on the reduction of major adverse cardiovascular events in type II diabetes patients with a recent Acute Coronary Syndrome and low levels of HDL-C

• A pre-specified secondary analysis of BETonMACE will examine the effects of apabetalone on cognitive function using the Montreal Cognitive Assessment (MoCA) in patients older than 70 years at randomization

• To date, over 2,400 patients have been randomized

• Results are anticipated to report in H1 2019
Inclusion criteria
• Type II Diabetes Mellitus
• CAD event 7 days - 90 days prior to
• Low HDL; < 45 mg/dL for males and < 45 mg/dL for females

Primary Endpoint
Time to first occurrence narrowly defined MACE (cardiovascular death, non-fatal MI and stroke)
Secondary Endpoint
Change in MOCA

The study is an event-based trial and continues until 250 MACE have occurred
Cognition Subgroup Methods

- Patients at least 70 years of age
- MoCA is administrated at randomization, yearly and at termination of the trial
- Cognition assessment by MOCA is a pre-specified variable comparing change from baseline in both treatment groups, adjusted for age, sex, education, and baseline MoCA score
- A subgroup of patients with MoCA score ≤25 at baseline will also be analyzed
# BETonMACE Cognition Subgroup Baseline Characteristics

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Patients Randomized with Baseline MoCA Completed</th>
<th>Patients Randomized with Baseline MoCA ≤ 25</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Median (min, max)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>455</td>
<td>73 (69, 88)</td>
</tr>
<tr>
<td>Sex (male, %)</td>
<td>64.8%</td>
<td>66.2%</td>
</tr>
<tr>
<td>Education (≤12 years, %)</td>
<td>66.2%</td>
<td>66.2%</td>
</tr>
<tr>
<td>MoCA</td>
<td>25 (7, 30)</td>
<td>23 (7, 25)</td>
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<tr>
<td>Concomitant Statins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>224</td>
<td>49.2%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>231</td>
<td>50.8%</td>
</tr>
</tbody>
</table>

† results from visit 2/week 0, whereas all other values are from visit 1/screening; *subpopulation only
Cardiovascular Disease, Diabetes and Dementia

- Diabetes increases the risk of developing dementia
- Coronary heart disease and heart failure are associated with an increased risk of cognitive decline, cognitive impairment, or dementia
- We hypothesize;
  - That dementia risk in diabetes and CVD is caused by transcriptional disturbances at the epigenetic level
- Cognition assessed by MoCA in phase 3 high risk CVD and diabetes trial over on average 20 months, anticipated to report H1, 2019 (~450 patients)

Summary and Conclusions

• Cognition assessment by MoCA is being evaluated in participants ≥70 years of age in BETonMACE, a phase 3 trial testing the cardiovascular efficacy of a first-in-class BET-inhibitor – apabetalone

• This analysis will provide insights about the potential for BET inhibition to modulate cognitive function in elderly patients with ASCVD and diabetes
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