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, Boehringer-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.

Dr. Cummings owns the copyright of the Neuropsychiatric Inventory.

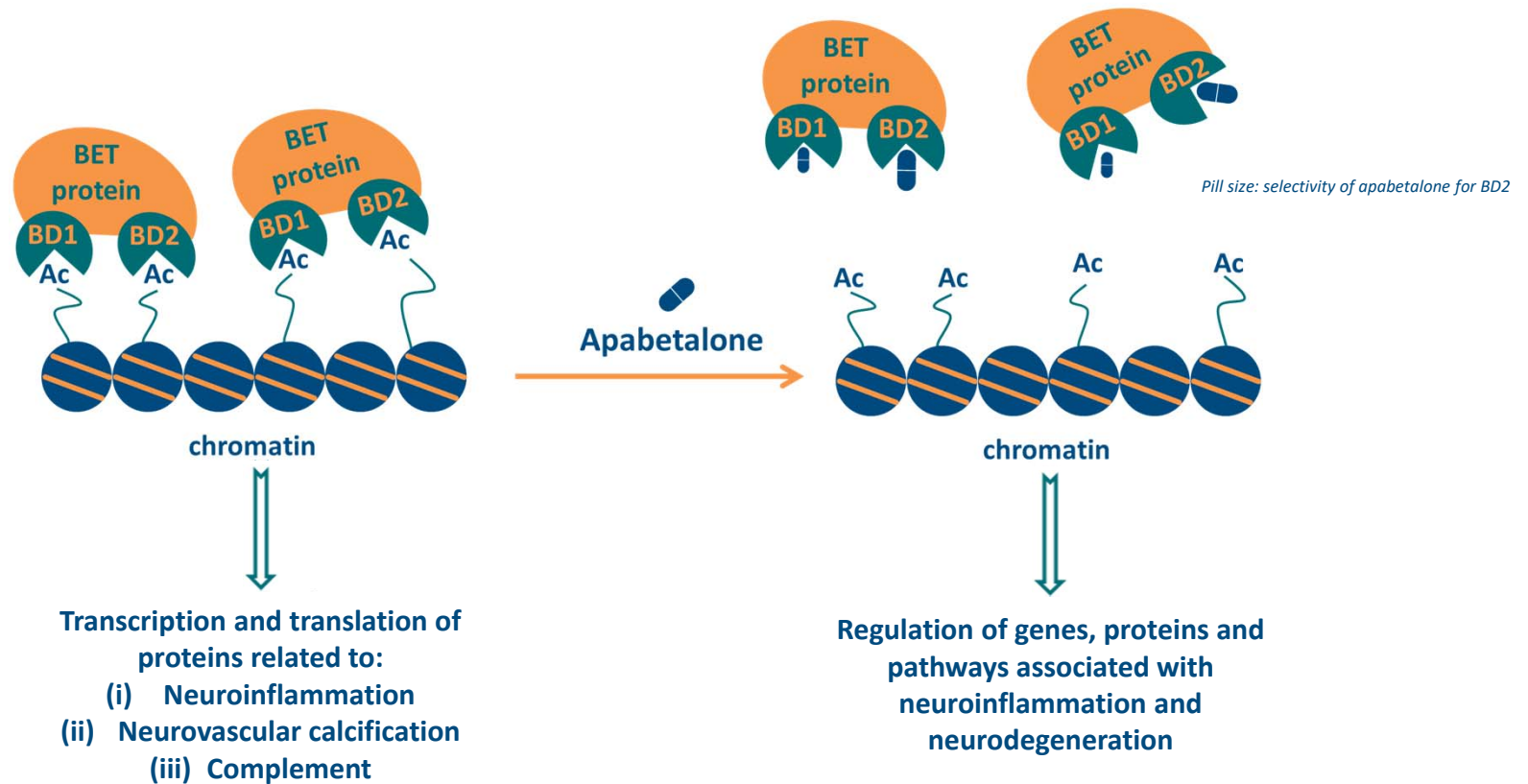This lecture will include reference to unapproved medications

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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

Sources: Saedi, E. et al. 2016; Baumgart, M. et al. 2015; Umegaki, H. 2014; Munshi, MN. et al. 2017; Zilliox, LA. et al. 2016; Ravona-Springer, R. and Schnaider-Beeri, M. 2011; Wolters, FJ. et al. 2018; Deckers, K. et al. 2017; Zheng, L. et al. 2012; Newman, AB. Et al. 2005; Otta, A. et al. 1999
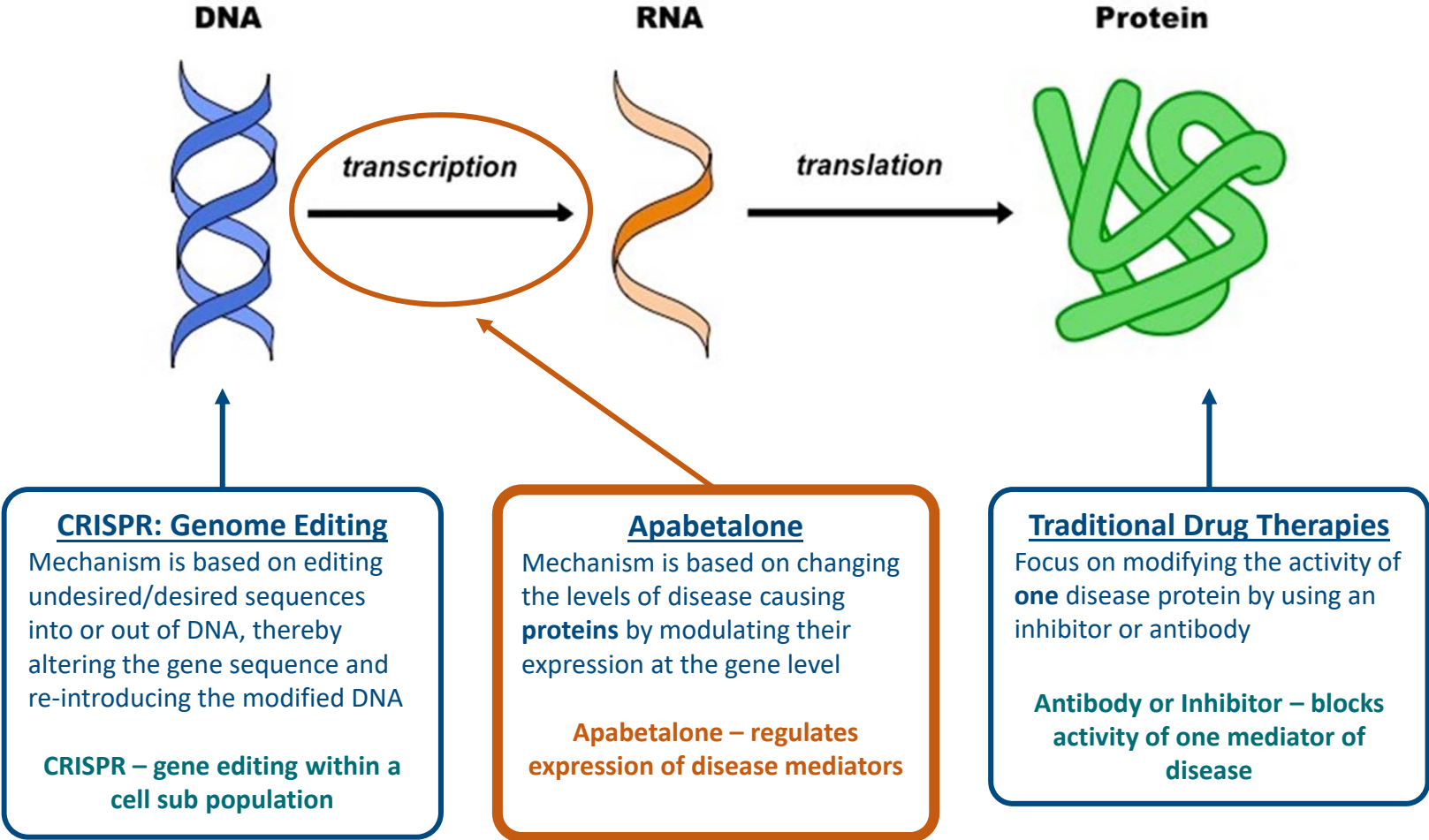
Epigenetics including BET Bromodomains

- 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

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Apabetalone is a select BET Inhibitor small molecule for oral administration

Pill size: selectivity of apabetalone for BD2

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

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.
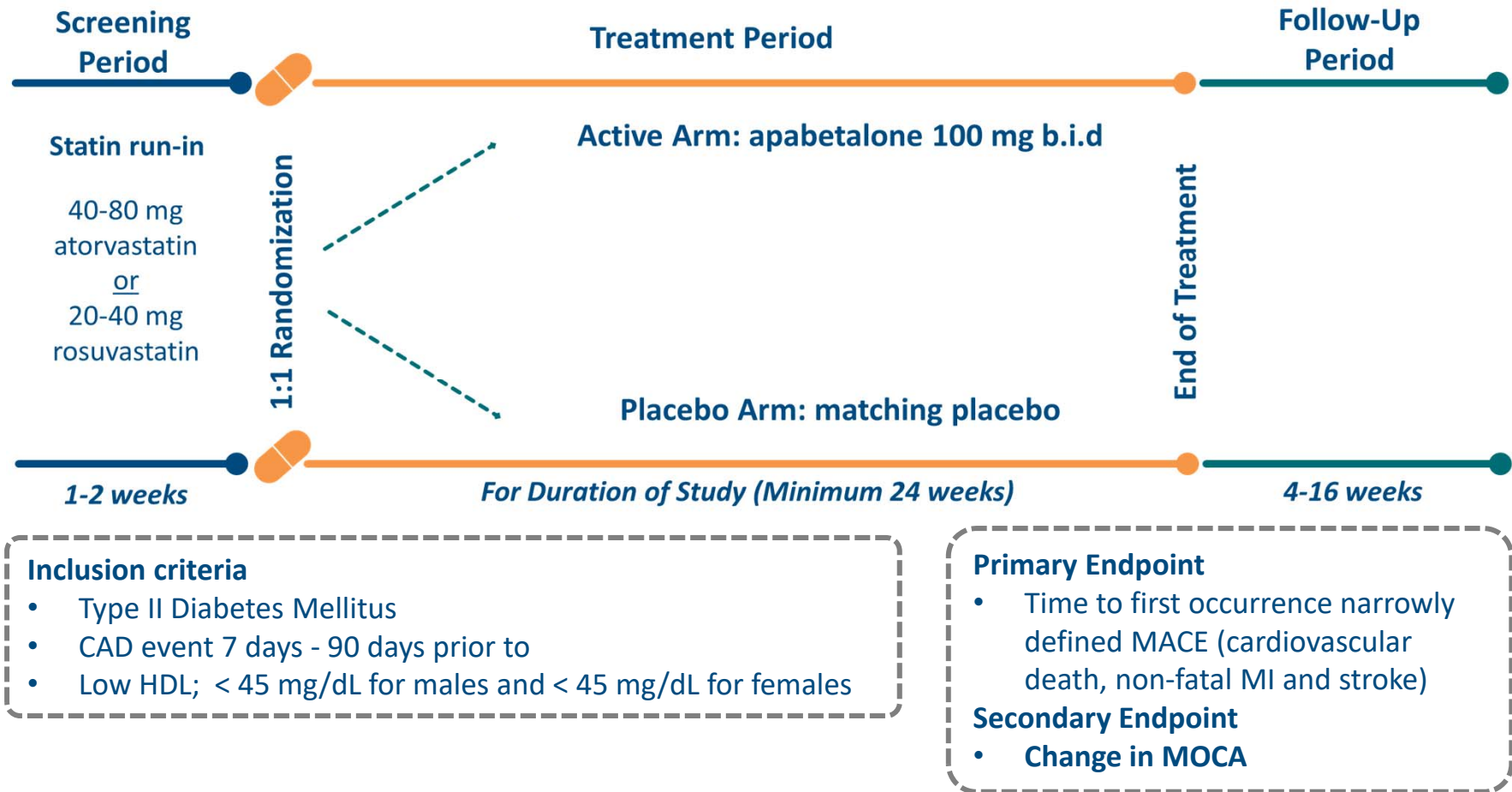
Differentiation: BET Mechanism of Action

DNA — transcription → **RNA** — translation → **Protein**

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

CRISPR – gene editing within a cell sub population

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

Apabetalone – regulates expression of disease mediators

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

Antibody or Inhibitor – blocks activity of one mediator of disease

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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 70 years and older at randomization

- The study is fully recruited with 2,425 patients randomized

- Top line data is expected the summer of 2019

BETonMACE Study Design

Screening Period

Treatment Period

Follow-Up Period

Statin run-in

40-80 mg atorvastatin
or
20-40 mg rosuvastatin

1:1 Randomization

Active Arm: apabetalone 100 mg b.i.d

Placebo Arm: matching placebo

End of Treatment

1-2 weeks

For Duration of Study (Minimum 24 weeks)

4-16 weeks

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
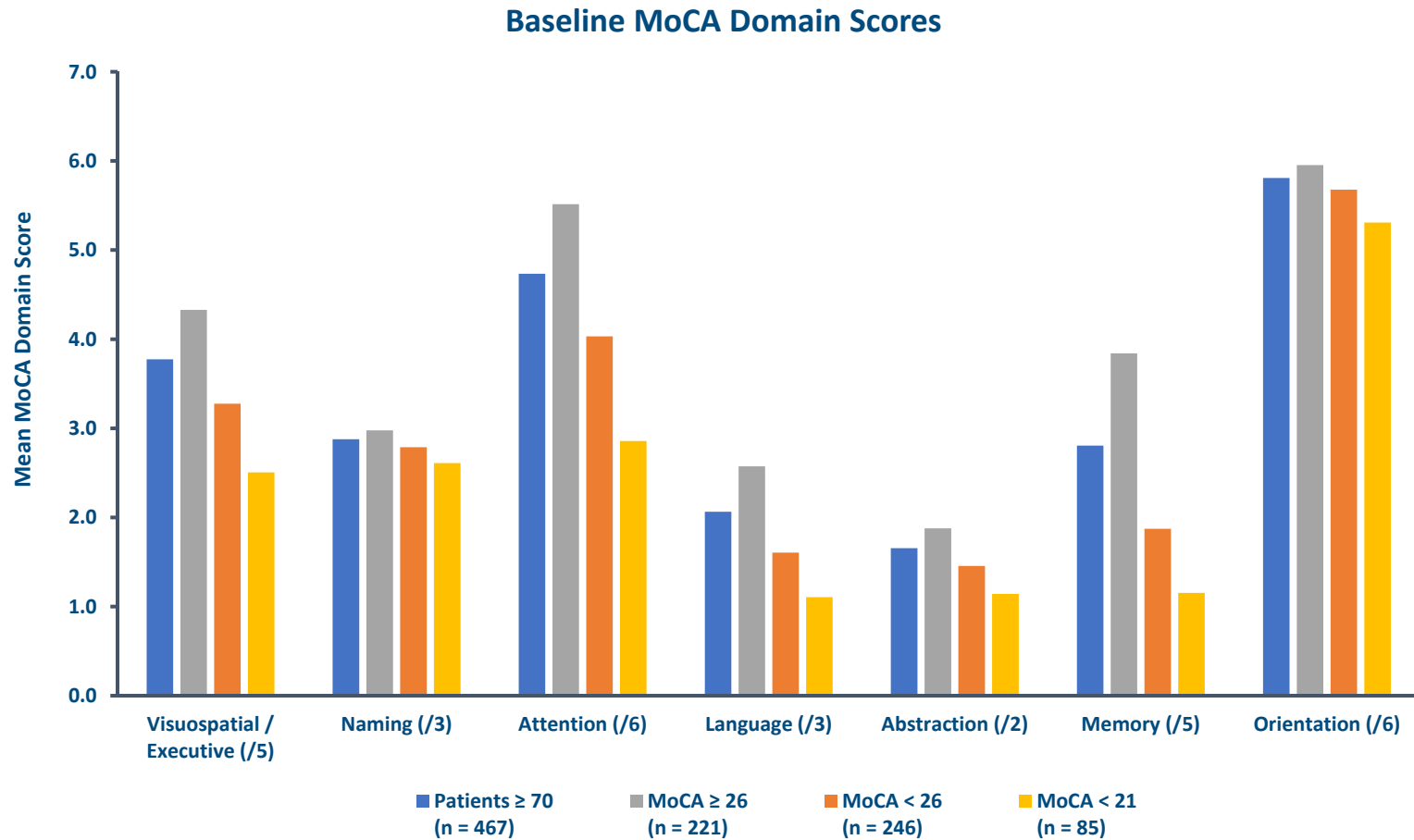**Expected average treatment duration is 26 months**

Cognition Subgroup Methods

- Patients at least 70 years of age at randomization.

- Average treatment duration 26 months (range 14-36 months)

- 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

- Subgroups of patients with MoCA score <26 and <21 at baseline will also be analyzed

BETonMACE Cognition Subgroup
Baseline Characteristics

Clinical Characteristic	Patients Randomized with Baseline MoCA Completed		Patients Randomized with Baseline MoCA <26		Patients Randomized with Baseline MoCA <21	
	N	Median (min, max)	N	Median (min, max)	N	Median (min, max)
Age (yrs)		73 (69, 88)		74 (69, 86)		73 (70, 85)
Sex (male, %)	467	64.0%	246	63.8%	85	57.6%
Education (≤12 years, %)		69.0%		74.0%		81.2%
MoCA		25 (7, 30)		22 (7, 25)		18 (7, 20)
Concomitant Statins						
Atorvastatin	231	49.5%	121	49.2%	41	48.2%
Rosuvastatin	236	50.5%	125	50.8%	44	51.8%

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- 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 26 months, anticipated to be completed Q2, 2019 and reported shortly thereafter (n~467 patients)

Sources: Saedi, E. et al. 2016; Baumgart, M. et al. 2015; Umegaki, H. 2014; Munshi, MN. et al. 2017; Zilliox, LA. et al. 2016; Ravona-Springer, R. and Schnaider-Beeri, M. 2011; Wolters, FJ. et al. 2018; Deckers, K. et al. 2017; Zheng, L. et al. 2012; Newman, AB. Et al. 2005; Otta, A. et al. 1999

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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

- Cognition assessments are pre-specified in statistical analysis plan (SAP) facilitating expedient development to confirmatory registration trial(s)

- This analysis will provide insights about the potential for select BET inhibition to modulate cognitive function in elderly patients with cardiovascular disease and diabetes

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