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TSX: RVX

BETonMACE:
Prespecified Cognition Assessment Results

December 6th, 2019

Forward Looking Statement

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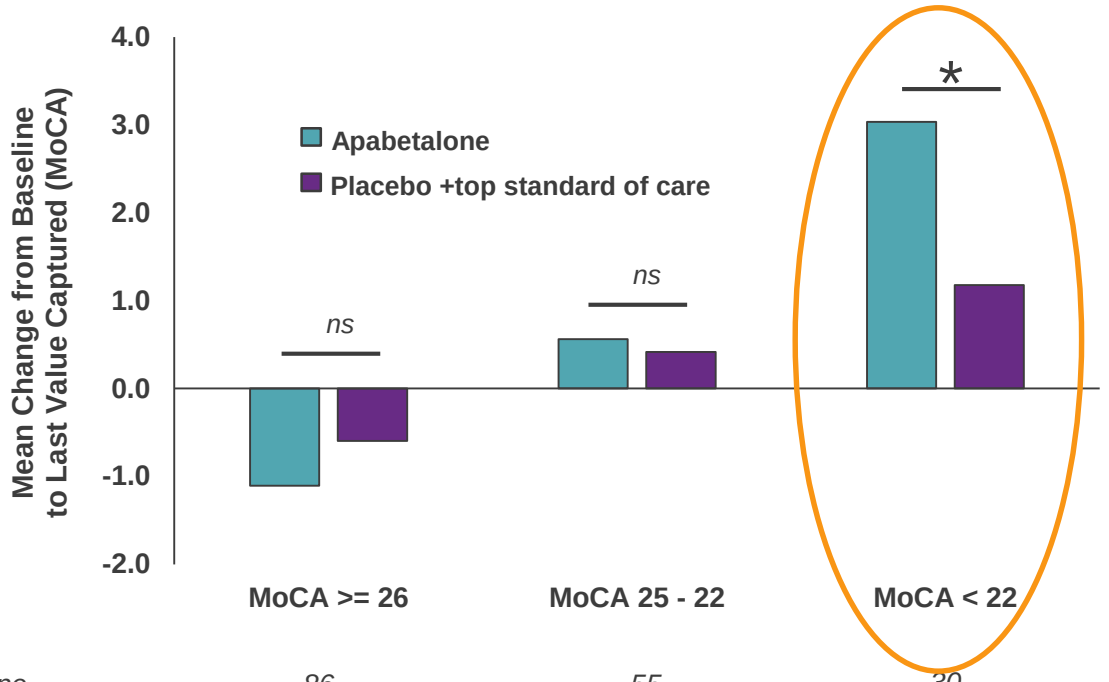
Executive Summary

- **Cognition assessment by Montreal Cognitive Assessment (MoCA) was a prespecified exploratory endpoint in BETonMACE (patients 70 yrs or older)**
  - BETonMACE inclusion criteria was type 2 diabetes patients with a recent acute coronary syndrome (ACS) and low HDL cholesterol **on top standard of care therapies**
  - Diabetes increases the **risk of developing dementia (2x)***
  - Coronary heart disease and heart failure are associated with **a 27% to 60% increased risk of cognitive decline, cognitive impairment, or dementia***
  - There are currently **NO treatment strategies** for addressing **vascular cognitive dementia**
- **Apabetalone treatment illustrated statistically significant improvements versus placebo (+ top standard of care) in patients with a baseline MoCA <22 :**
  - **158% relative improvement in cognitive function** in treated group compared to top standard of care placebo (comparing the mean change from baseline of the treated vs. untreated groups)
  - **Significant and trending changes across treatment duration in ALP and HDL (biomarkers associated with cognitive risk)** were observed in patients with a baseline MoCA<22

** 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*

BETonMACE Cognition Findings - MoCA



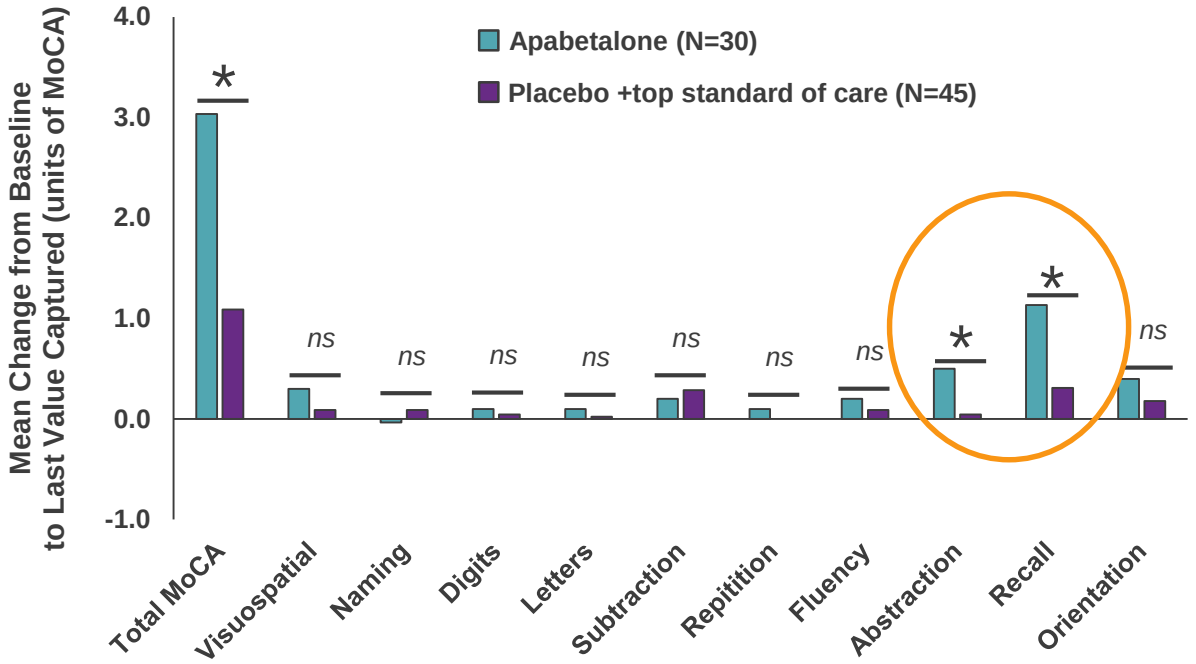
No.	MoCA >= 26	MoCA 25 - 22	MoCA < 22
Apabetalone	*86*	*55*	*30*
Placebo	*101*	*72*	*45*

*treatment p-value calculated using two-sided t-test; * p=0.02*

- Apabetalone treatment **illustrates a statistically significant (*p=0.02) improvement versus placebo** in MoCA in patients with a **baseline MoCA below 22**
  - **158% relative improvement in cognitive function** over top standard of care placebo
  - **Study duration was the same between treatment groups**

Preliminary Data; RVX Internal Analysis; November 2019

MoCA Domains in Patients with Baseline MoCA <22

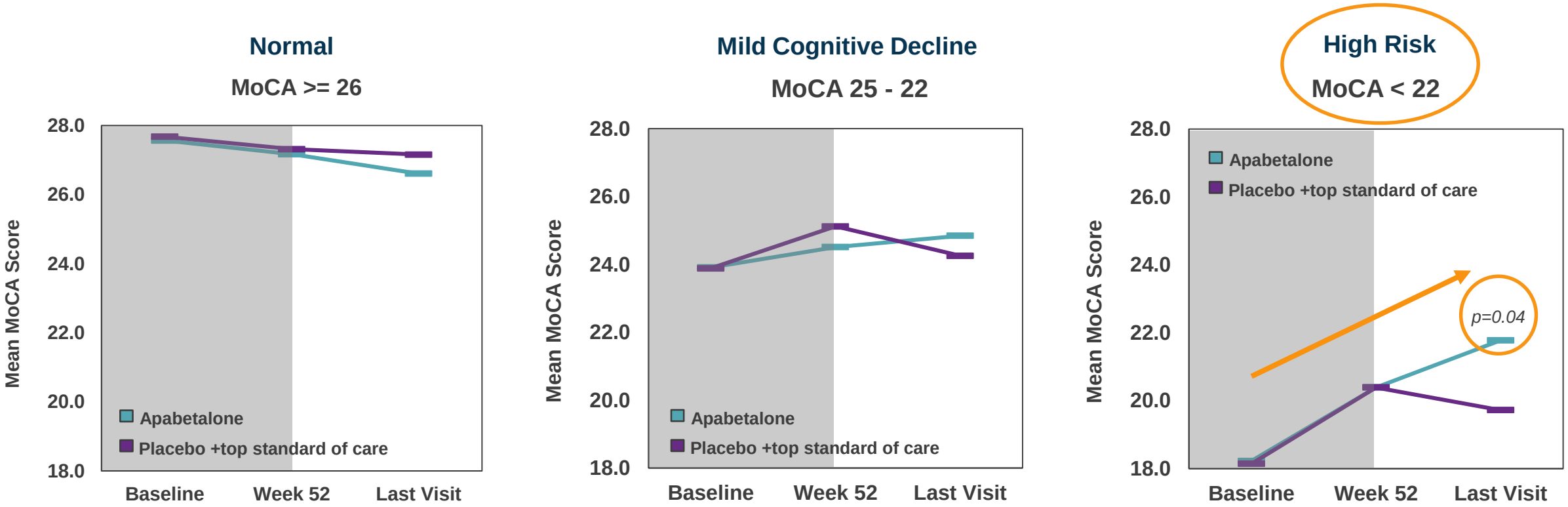


*treatment p-value calculated using two-sided t-test; * p<0.05*

- Analysis of MoCA domains illustrates **a statistically significant improvement (*p<0.05) in the abstraction (conceptual thinking) and recall (memory) domains** in patients with a baseline MoCA < 22 with apabetalone treatment

BETonMACE Cognition Findings – Additional Analysis

- Apabetalone treatment illustrates a **trend in the improvement of cognition** when baseline MoCA was lower (MoCA < 22)



treatment p-value calculated using two-sided t-test; p<0.05

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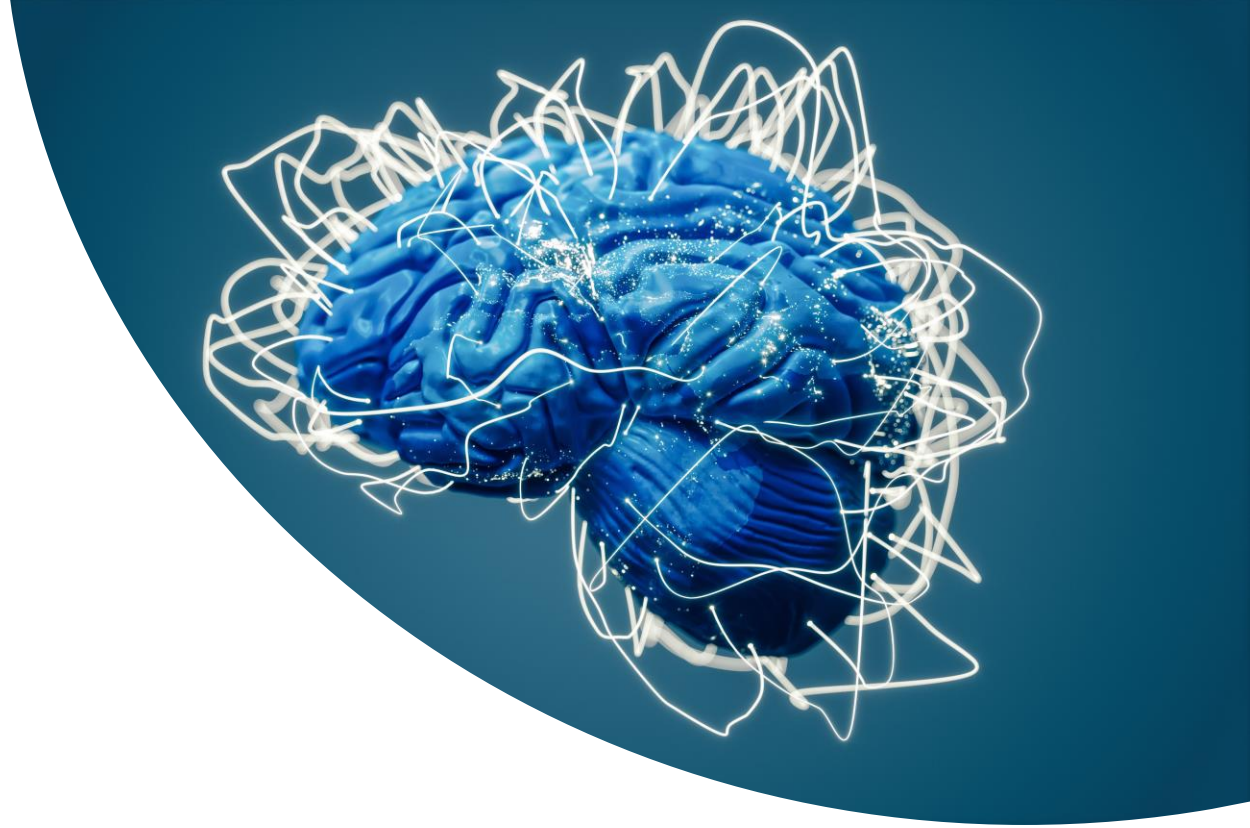
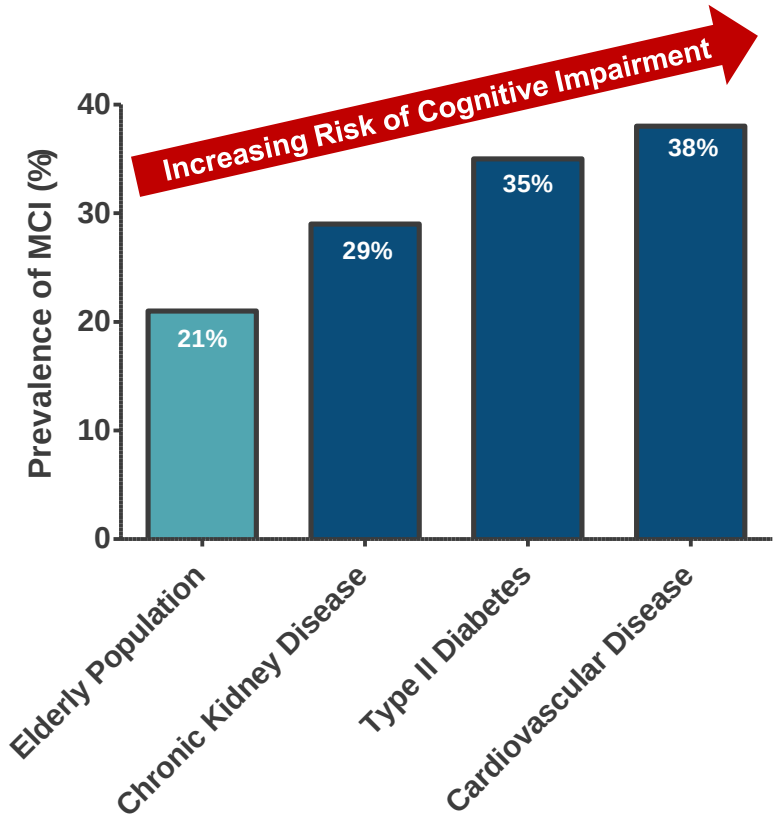


Apabetalone: A New Approach to Neurodegeneration

BET Inhibition a Potential New Approach to Neurodegeneration

- **Alzheimer's disease and vascular cognitive dementia** are one of the **largest health burdens worldwide**
- There are currently **NO treatment strategies** for addressing **vascular cognitive dementia**
- Current landscape of Alzheimer's drugs has not yielded marked improvements on cognition
  - Major focus on amyloid and tau burden
  - Protein based therapies – **expensive** – single target approach
- The **commercial opportunity** and **accretive pipeline value** for any therapy that improves cognitive function would be **highly valuable**

Cardiovascular Disease, Diabetes and Dementia



Source: Meta-analysis of global studies assessing the prevalence of MCI in elderly populations with known risk factors for MCI, including T2DM, CVD and CKD

- Traditionally, **CVD, Diabetes and Chronic Kidney Disease patients have been neglected** in cognitive function trials
- The **prevalence of Mild Cognitive Impairment (MCI) increases** with an increase in **vascular disease** risk factors
- Patients in the **BETonMACE** study are therefore at **higher risk for cognitive impairment**
- **Neurodegenerative risk in diabetes and CVD** is thought to be caused by transcriptional disturbances at the epigenetic level

BETonMACE Cognition Subgroup Method Assessment

- In BETonMACE, **cognition assessment by MoCA** is a **prespecified exploratory endpoint** comparing **change from baseline between treatment groups**
- **MoCA** was performed in **patients 70 years and older** at time of randomization and was scheduled to be **administrated at randomization**, after **52 weeks** of treatment and at **last visit** of the trial
- MoCA was performed in approximately **19%** (n= 469) of the **total population** at baseline and the average treatment duration in BETonMACE was 27 months
- **Subgroups** of patients with **MoCA** score **≥26, 25 – 22 and <22** at baseline were analyzed
- Changes in the **individual MoCA domains** were also **analyzed**

Apabetalone as a Therapeutic for Cognitive Dementia

- **Apabetalone's mechanism of action potentially improves cognition by impacting numerous peripheral pathways that may underlie disease with potential beneficial effects on the neurovascular unit as well as peripheral mediators with roles in the brain**
  - **increases levels of ApoA-I and HDL** which are inversely correlated with increased risk of Alzheimer's Disease and positively correlated with cognitive function
  - **reduces the expression of complement and inflammatory mediators** which play key roles in neuroinflammation and may contribute to cognitive decline
  - **reduces the expression of alkaline phosphatase** in the serum which is increased in Alzheimer's disease patients

Apabetalone Impacts the Pathways that Drive Disease

Apabetalone reduces the expression of multiple components of the **complement cascade**

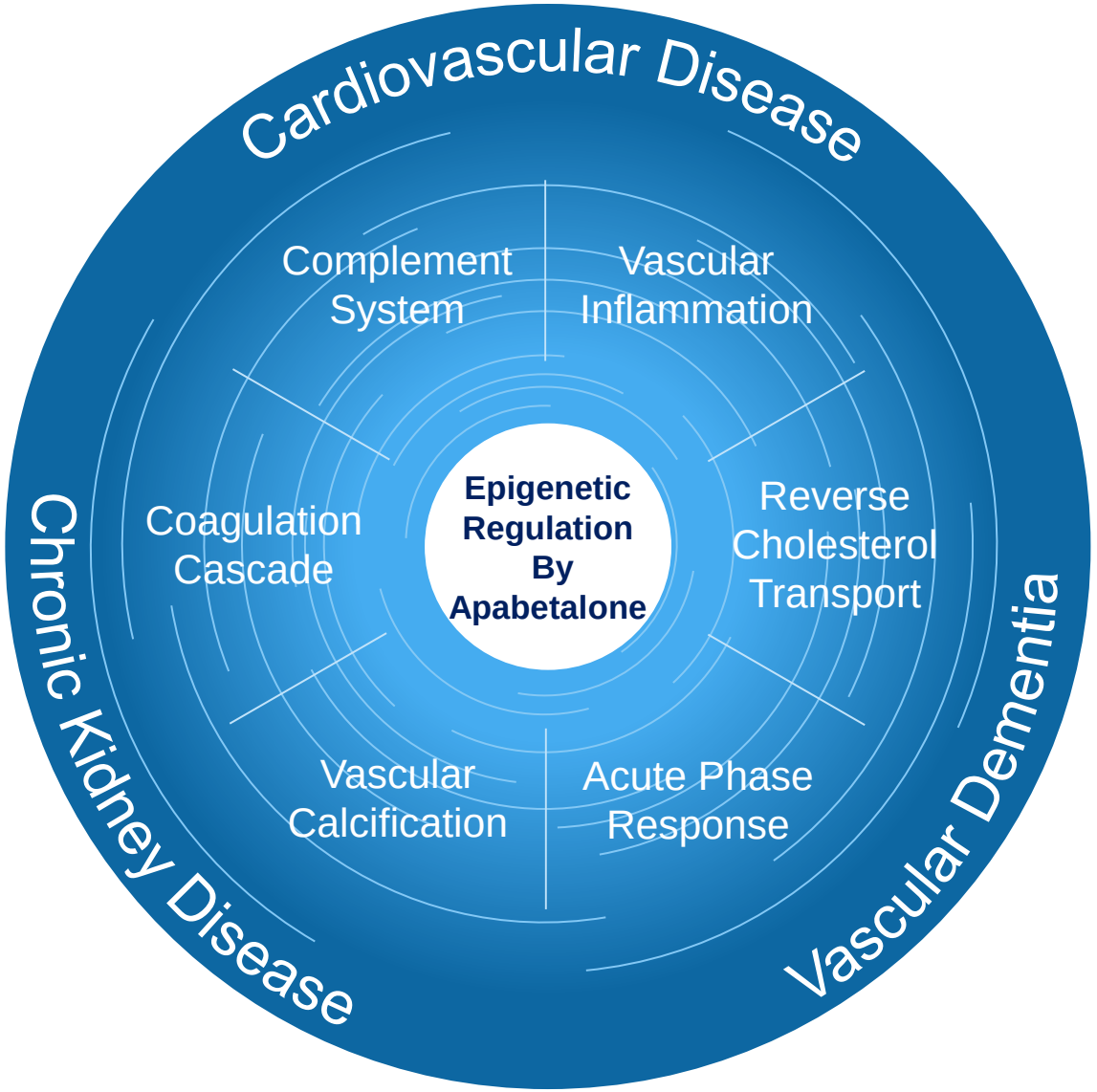
Wasiak et al. 2017

Apabetalone reduces the expression of several factors within the **coagulation system**

Wasiak et al. 2017

Levels of ALP, osteopontin and other drivers of **vascular calcification and fibrosis** are lowered by apabetalone

Gilham et al. 2019



Treatment with apabetalone **reduces mediators that drive endothelial activation**, monocyte recruitment and plaque destabilization

Tsujikawa et al. 2019

Apabetalone contributes to remodeling of the **HDL proteome and lipidome**, including increased ApoA-1 and HDL particle size

Jahagirdar et al. 2014

Apabetalone reduces markers of **systemic inflammation** including acute phase reactants

Wasiak et al. 2019 (Under Review)

Summary

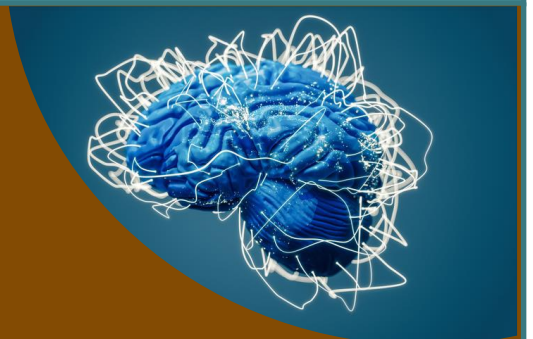
- BETonMACE: CVD Primary endpoint was narrowly missed **with consistent positive trend in key endpoints, including <u>Cognitive Function</u>**

Strengthening Opportunities Through Positive Findings & Synergy

Narrow MACE (with CHF)
24% Hazard Reduction
(95% CI; 0.60-0.95)
p=0.02

Renal Subgroup
eGFR < 60 at Baseline
50% Hazard Reduction
(95% CI; 0.26-0.96)
p=0.03

Apabetalone & SGLT2i
(Empagliflozin)
66% Hazard Reduction
(95% CI; 0.12-1.01)
p=0.05



Cognitive Function
Improved 158% in treated
vs. placebo
(MoCA < 22 subgroup)
p=0.02

Source: RVX Internal Analysis – Non-QC'd

Near Term Commercialization Steps

In the near term we will continue our multi-point approach to progressing our corporate commercial value. This approach involves aggressive exploratory development of the following:

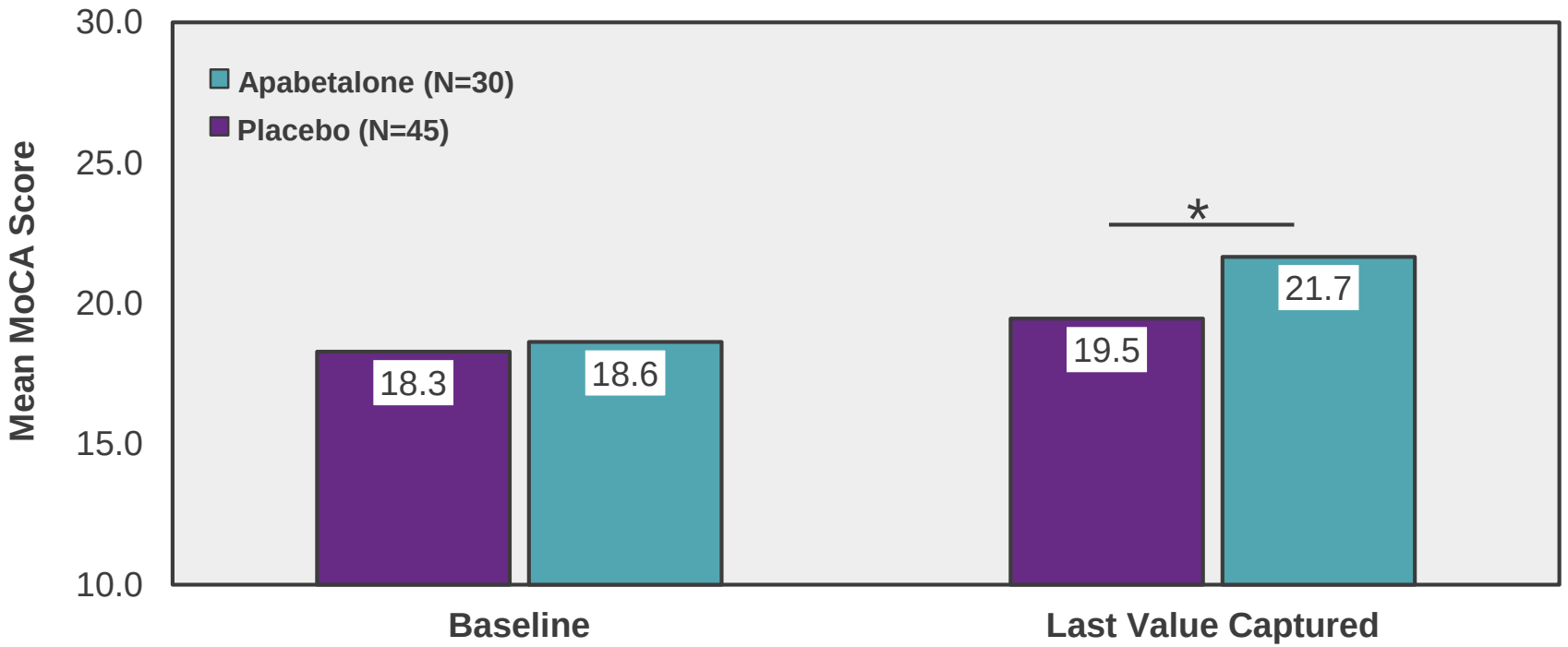
- Breakthrough Therapy status filings, both FDA and EMA, over the next 90-120 days
- SGLT2i partnering discussions, one has already been initiated, key patent already filed
- Renal partnering discussions ASAP
- Congestive Heart Failure partnering discussions ASAP, already initiated
- Orphan partnering discussions initially focused on PAH and HIV only at this time. PAH enrollment has already commenced. HIV funding being derived from a yet to be named US based organization
- MoCA partnering discussion in progress


Appendix

MoCA in Patients with Baseline MoCA <22

Baseline versus Last Value Captured

- **Study duration was the same between treatment groups**



Placebo = 702 days

Apabetalone = 701 days

*treatment p-value calculated on change from baseline using two-sided t-test; * p<0.05*

- Apabetalone treatment **illustrates a statistically significant improvement versus placebo** in MoCA in patients with a **baseline MoCA below 22**

BETonMACE Cognition Subgroup – Baseline Demographics

Baseline Characteristic	All Patients	MoCA ≥ 26	MoCA 25 - 22	MoCA < 22
	N=469	N=224	N=148	N=97
Age (yr), median (min, max)	73 (69, 88)	73 (70, 88)	73 (69, 85)	74 (70, 86)
Age ≥ 80 yr, no. (%)	40 (8.5%)	16 (7.1%)	16 (10.8%)	8 (8.2%)
Male sex, no. (%)	300 (64.0%)	144 (64.3%)	101 (68.2%)	55 (56.7%)
Race or ethnic group, no. (%)				
Native American	11 (2.3%)	0 (0.0%)	6 (4.1%)	5 (5.2%)
Asian	9 (1.9%)	4 (1.8%)	1 (0.7%)	4 (4.1%)
Other	28 (6.0%)	8 (3.6%)	9 (6.1%)	**11 (11.3%)**
White	421 (89.8%)	212 (94.6%)	132 (89.2%)	**77 (79.4%)**
Region of the world, no. (%)				
Asia	9 (1.9%)	4 (1.8%)	1 (0.70%)	4 (4.1%)
Europe	356 (75.9%)	193 (86.2%)	**108 (73.0%)**	**55 (56.7%)**
Latin America	104 (22.2%)	27 (12.0%)	**39 (26.4%)**	**38 (39.2%)**
Body weight (kg), median (IQR)	80.0 (71.0 – 91.0)	81.0 (74.0 – 91.0)	80.0 (70.8 – 92.0)	**72.2 (67.0 – 90.0)**
BMI, median (IQR)	28.7 (25.8 – 32.1)	28.7 (26.4 – 32.2)	29.2 (25.6 – 32.3)	27.9 (25.1 – 31.9)
Statin, no. (%)				
Atorvastatin	233 (49.7%)	111 (49.6%)	76 (51.4%)	46 (47.4%)
Rosuvastatin	236 (50.3%)	113 (50.4%)	72 (48.6%)	51 (52.6%)

p<0.05 indicated in bold compared to MoCA≥ 26; chi-square test for categorical variables and Mann-Witney test for continuous variables

BETonMACE Cognition Findings – Baseline Demographics
by treatment group

Baseline Characteristic	MoCA ≥ 26		MoCA 25 - 22		MoCA < 22	
	Placebo (n=119)	Apabetalone (n=105)	Placebo (n=83)	Apabetalone (n=65)	Placebo (n=53)	Apabetalone (n=44)
Age (yr), median (min, max)	73 (70, 88)	73 (69, 82)	73 (70, 85)	73 (69, 82)	75 (70, 86)	73.5 (70, 85)
Age ≥ 80 yr, no. (%)	8 (6.7%)	8 (7.6%)	9 (10.8%)	7 (10.8%)	6 (11.3%)	2 (4.5%)
Male sex, no. (%)	72 (60.5%)	72 (68.6%)	55 (66.3%)	46 (70.8%)	30 (56.6%)	25 (56.8%)
Race or ethnic group, no. (%)						
Native American	0 (0.0%)	0 (0.0%)	5 (6.0%)	1 (1.5%)	3 (5.7%)	2 (4.5%)
Asian	2 (1.7%)	2 (1.9%)	1 (1.2%)	0 (0.0%)	2 (3.8%)	2 (4.5%)
Other	4 (3.4%)	4 (3.8%)	3 (3.6%)	6 (9.2%)	**1 (1.9%)**	**10 (22.7%)**
White	113 (95.0%)	99 (94.3%)	74 (89.2%)	58 (89.2%)	**47 (88.7%)**	**30 (68.2%)**
Region of the world, no. (%)						
Asia	2 (1.7%)	2 (1.9%)	1 (1.2%)	0 (0.0%)	2 (3.8%)	2 (4.5%)
Europe	102 (85.7%)	91 (86.7%)	59 (71.1%)	49 (75.4%)	32 (60.4%)	23 (52.3%)
Latin America	15 (12.6%)	12 (11.4%)	23 (27.7%)	16 (24.6%)	19 (35.8%)	19 (43.2%)
Body weight (kg), median (IQR)	81.0 (72.0 – 90.8)	81.0 (75.0 – 92.1)	**77.0 (68.3 – 90.0)**	**83.7 (74.0 – 94.0)**	74.0 (70.0 – 87.4)	71.0 (62.2 – 90.0)
BMI, median (IQR)	28.7 (26.4 – 32.1)	28.9 (26.4 – 32.2)	28.6 (25.6 – 32.2)	29.6 (25.6 – 32.3)	28.4 (25.6 – 31.9)	27.1 (24.9 – 31.4)
Statin, no. (%)						
Atorvastatin	61 (51.3%)	50 (47.6%)	41 (49.4%)	35 (53.8%)	24 (45.3%)	22 (50.0)
Rosuvastatin	58 (48.7%)	55 (52.4%)	42 (50.6%)	30 (46.2%)	29 (54.7%)	22 (50.0)

p<0.05 indicated in bold compared between treatment groups; chi-square test for categorical variables and Mann-Witney test for continuous variables

BETonMACE Cognition Subgroup – Baseline Clinical Chemistry

Baseline Chemistry	All Patients	MoCA ≥ 26	MoCA 25 - 22	MoCA < 22
	N=469	N=224	N=148	N=97
Serum glucose, mg/dL	7.4 (6.1 – 9.3)	7.3 (6.3 – 8.9)	7.4 (6.2 – 9.8)	7.6 (5.7 – 10.1)
eGFR, ml/min/1.73m2 †	70.0 (56.0 – 85.0)	71.0 (57.0 – 88.3)	72.0 (56.5 – 85.0)	**65.0 (50.0 – 80.0)**
eGFR < 60, no. (%)	149 (31.8%)	67 (29.9%)	44 (29.7%)	**38 (39.2%)**
Total cholesterol, mmol/L	3.3 (2.8 – 3.9)	3.3 (2.8 – 4.0)	3.3 (2.7 – 3.9)	3.3 (2.8 – 3.9)
LDL cholesterol, mmol/L	1.6 (1.2 – 2.2)	1.6 (1.3 – 2.1)	1.7 (1.2 – 2.2)	1.6 (1.3 – 2.1)
HDL cholesterol, mmol/L	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)
Triglycerides, mg/dl	1.7 (1.3 – 2.2)	1.7 (1.4 – 2.2)	1.6 (1.2 – 2.1)	1.6 (1.2 – 2.1)
Alkaline phosphatase, U/L	76.0 (62.0 – 92.0)	76.0 (62.0 – 92.0)	76.0 (61.0 – 90.0)	80.0 (64.0 – 95.0)
Alanine aminotransferase, units/L	19.0 (14.0 – 26.0)	20.0 (15.0 – 26.0)	18.0 (14.0 – 25.0)	19.0 (14.0 – 25.0)
Total bilirubin, µmol/L	9.6 (7.5 – 13.0)	9.6 (7.5 – 12.9)	9.4 (7.6 – 13.0)	9.8 (7.8 – 13.8)
hsCRP, mg/L	2.4 (1.1 – 5.9)	1.9 (1.1 – 4.6)	2.3 (0.7 – 4.0)	**4.4 (3.0 – 10.0)**
NLR	2.7 (2.2 – 3.7)	2.7 (2.1 – 3.7)	3.0 (2.2 – 3.8)	2.6 (2.2 – 3.6)
HbA1c, (%)	7.0 (6.3 – 8.1)	7.0 (6.3 – 8.1)	7.1 (6.3 – 8.0)	7.1 (6.4 – 8.6)

† Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft Gault method

p<0.05 indicated in bold compared to MoCA≥ 26; chi-square test for categorical variables and Mann-Witney test for continuous variables
Results shown as median (IQR)

BETonMACE Cognition Findings – Baseline Clinical Chemistry

by treatment group

Baseline Chemistry	MoCA ≥ 26		MoCA 25 - 22		MoCA < 22	
	Placebo (n=119)	Apabetalone (n=105)	Placebo (n=83)	Apabetalone (n=65)	Placebo (n=53)	Apabetalone (n=44)
Serum glucose, mg/dL	7.2 (6.0 – 8.9)	7.6 (6.5 – 8.7)	7.1 (6.1 – 9.6)	7.6 (6.2 – 10.1)	7.3 (5.6 – 10.2)	7.8 (5.9 – 10.0)
eGFR, ml/min/1.73m2 †	69.0 (55.0 – 86.5)	73.0 (60.0 – 90.0)	70.5 (55.3 – 85.8)	73.0 (58.0 – 83.0)	63.0 (48.0 – 75.0)	68.5 (52.0 – 81.8)
eGFR < 60, no. (%)	42 (35.3%)	25 (23.8%)	26 (31.3%)	18 (27.7%)	24 (45.3%)	14 (31.8%)
Total cholesterol, mmol/L	3.3 (2.9 – 4.0)	3.3 (2.8 – 3.9)	3.4 (2.9 – 3.9)	3.2 (2.7 – 3.8)	3.5 (2.9 – 3.9)	3.0 (2.7 – 3.6)
LDL cholesterol, mmol/L	1.6 (1.3 – 2.1)	1.6 (1.2 – 2.2)	1.7 (1.3 – 2.2)	1.7 (1.2 – 2.1)	1.7 (1.4 – 2.1)	1.5 (1.2 – 2.0)
HDL cholesterol, mmol/L	**0.90 (0.8 – 1.0)**	**0.86 (0.8 – 1.0)**	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)	0.9 (0.8 – 1.0)
Triglycerides, mg/dl	1.8 (1.4 – 2.3)	1.7 (1.4 – 2.2)	1.6 (1.2 – 2.0)	1.6 (1.2 – 2.1)	1.7 (1.5 – 2.2)	1.5 (1.2 – 2.0)
Alkaline phosphatase, U/L	77.0 (61.0 – 91.0)	76.0 (63.0 – 92.0)	76.0 (61.0 – 93.5)	74.0 (62.0 – 84.0)	77.0 (66.0 – 92.0)	81.0 (59.8 – 101.3)
Alanine aminotransferase, units/L	20.0 (15.3 – 27.8)	19.0 (14.8 – 26.0)	19.0 (15.0 – 27.0)	18.0 (14.0 – 23.0)	19.0 (15.0 – 25.0)	19.0 (13.5 – 25.5)
Total bilirubin, µmol/L	9.9 (7.6 – 13.0)	9.6 (7.3 – 12.5)	9.3 (7.2 – 13.5)	9.4 (7.9 – 11.8)	9.8 (8.5 – 13.8)	9.6 (7.2 – 14.1)
hsCRP, mg/L	**1.3 (0.8 – 2.3)**	**3.2 (1.7 – 5.8)**	2.3 (0.4 – 4.7)	2.1 (1.1 – 3.7)	5.2 (3.3 – 10.3)	2.2 (0.8 – 5.1)
NLR	2.5 (2.1 – 3.5)	2.8 (2.1 – 3.7)	3.0 (2.3 – 3.8)	3.0 (2.2 – 3.9)	2.5 (2.2 – 3.6)	2.9 (2.1 – 3.8)
HbA1c, (%)	7.1 (6.3 – 8.2)	6.9 (6.3 – 7.8)	7.0 (6.2 – 7.9)	7.3 (6.4 – 8.1)	7.0 (6.4 – 8.5)	7.3 (6.5 – 8.9)

† Estimated glomerular filtration rate (eGFR) was calculated using the Cockcroft Gault method

p<0.05 indicated in bold compared to MoCA≥ 26; chi-square test for categorical variables and Mann-Witney test for continuous variables
Results shown as median (IQR)

MoCA Subject Disposition and Subgroup Breakdown

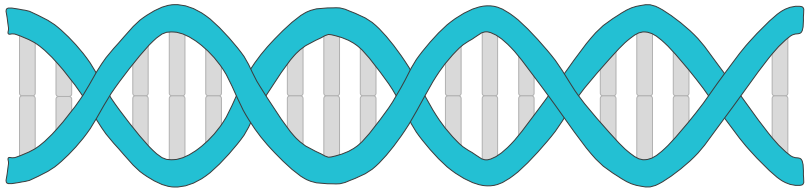
Number of Patients Completing Each Visit

Time Point	All Patients		MoCA ≥ 26 Normal		MoCA 25 – 22 Mild Impairment		MoCA < 22 Moderate to Severe Impairment	
	Placebo	Apabetalone	Placebo	Apabetalone	Placebo	Apabetalone	Placebo	Apabetalone
Baseline MoCA	255	214	119	105	83	65	53	44
Week 52 MoCA	211	165	100	82	71	55	40	28
Week 100 MoCA	103	82	53	39	30	29	20	14
LVC MoCA	218	171	101	86	72	55	45	30

- The **LVC** method was used in the cognition assessment from BETonMACE to ensure the **largest possible number of patients** were included in the analysis **after baseline**

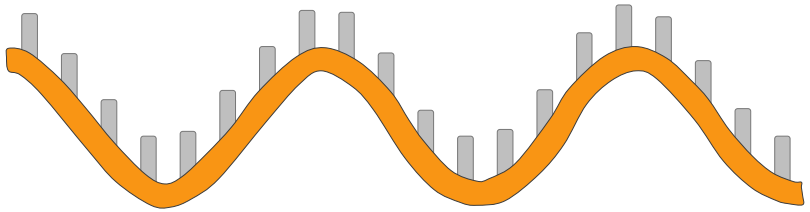
Apabetalone Mechanism of Action

DNA



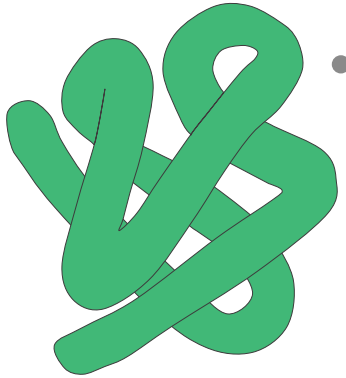
Transcription

RNA



Translation

Protein



Genome Editing

Altering the sequence of DNA itself and then reintroducing **modified genes** into the body

*There are currently **no FDA-approved** therapies based on gene editing*

Transcriptional Regulation

Adjusting the levels of **multiple** disease proteins by modulating their expression at the gene level

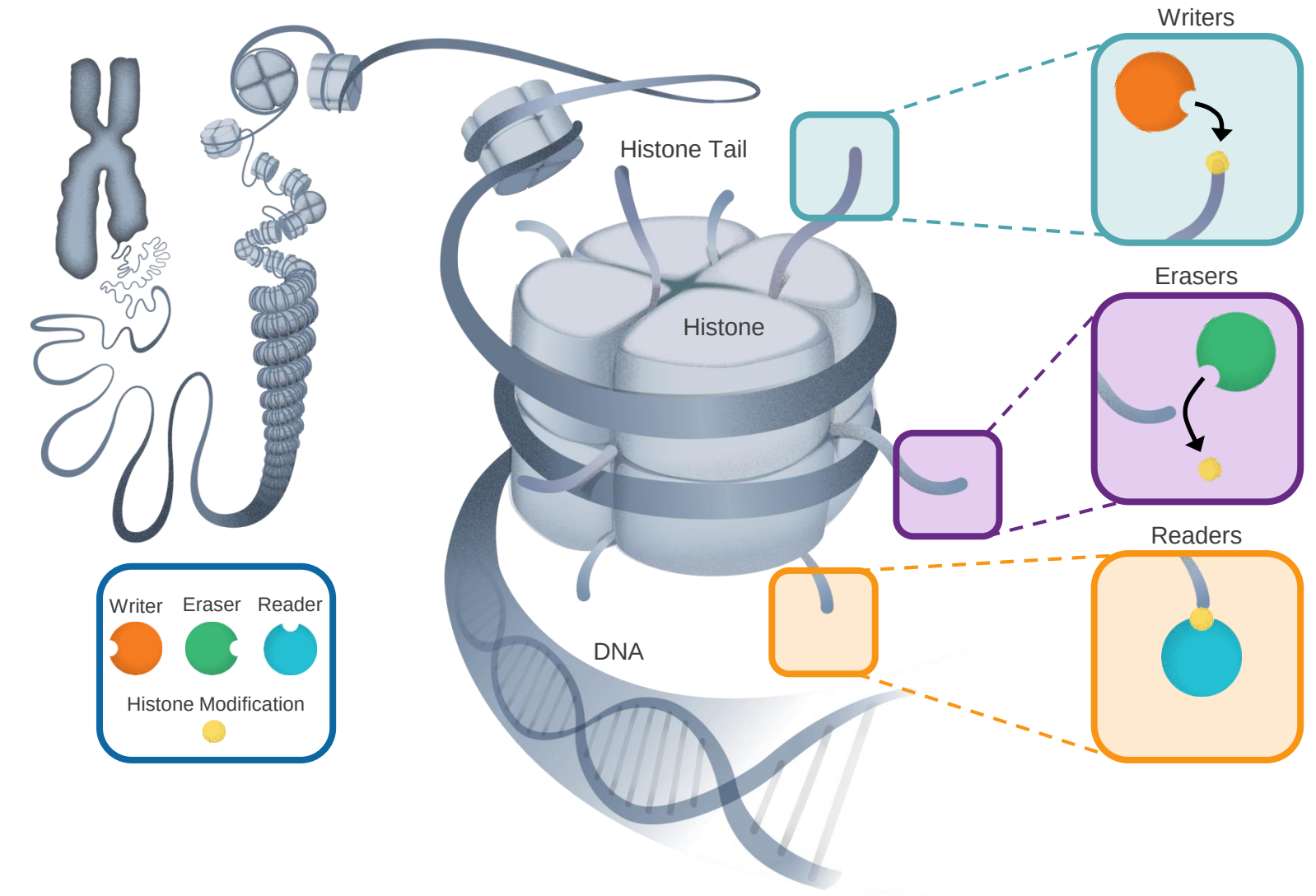
***Apabetalone**, acting upstream of traditional pharmaceuticals, represents a **paradigm shift** in the treatment of chronic disease*

Protein Inhibition

Reducing or blocking the activity of **one** disease protein by using an inhibitor or antibody

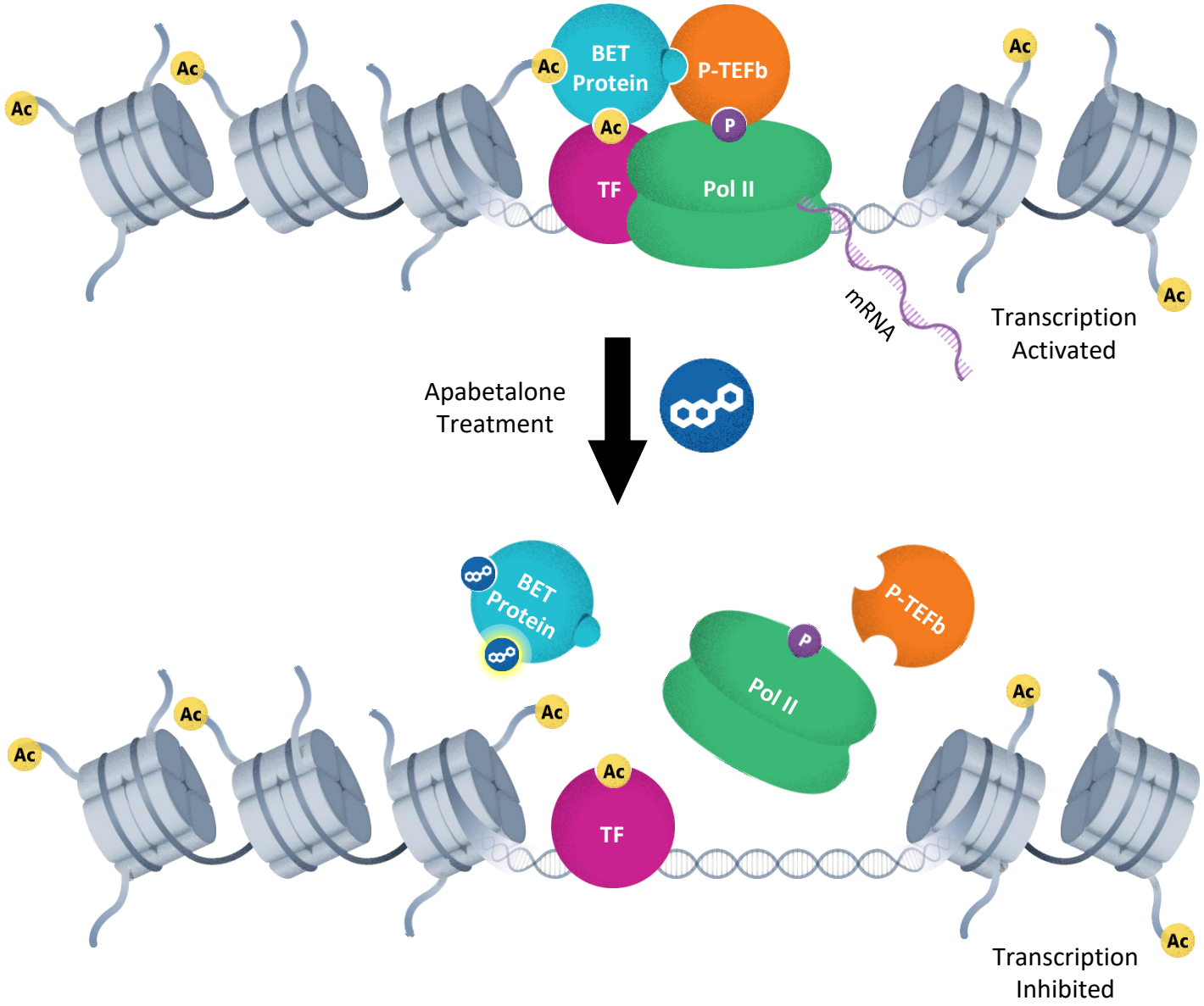
*Almost all **current therapeutics** function via protein inhibition*

Epigenetics Regulate Gene Activity

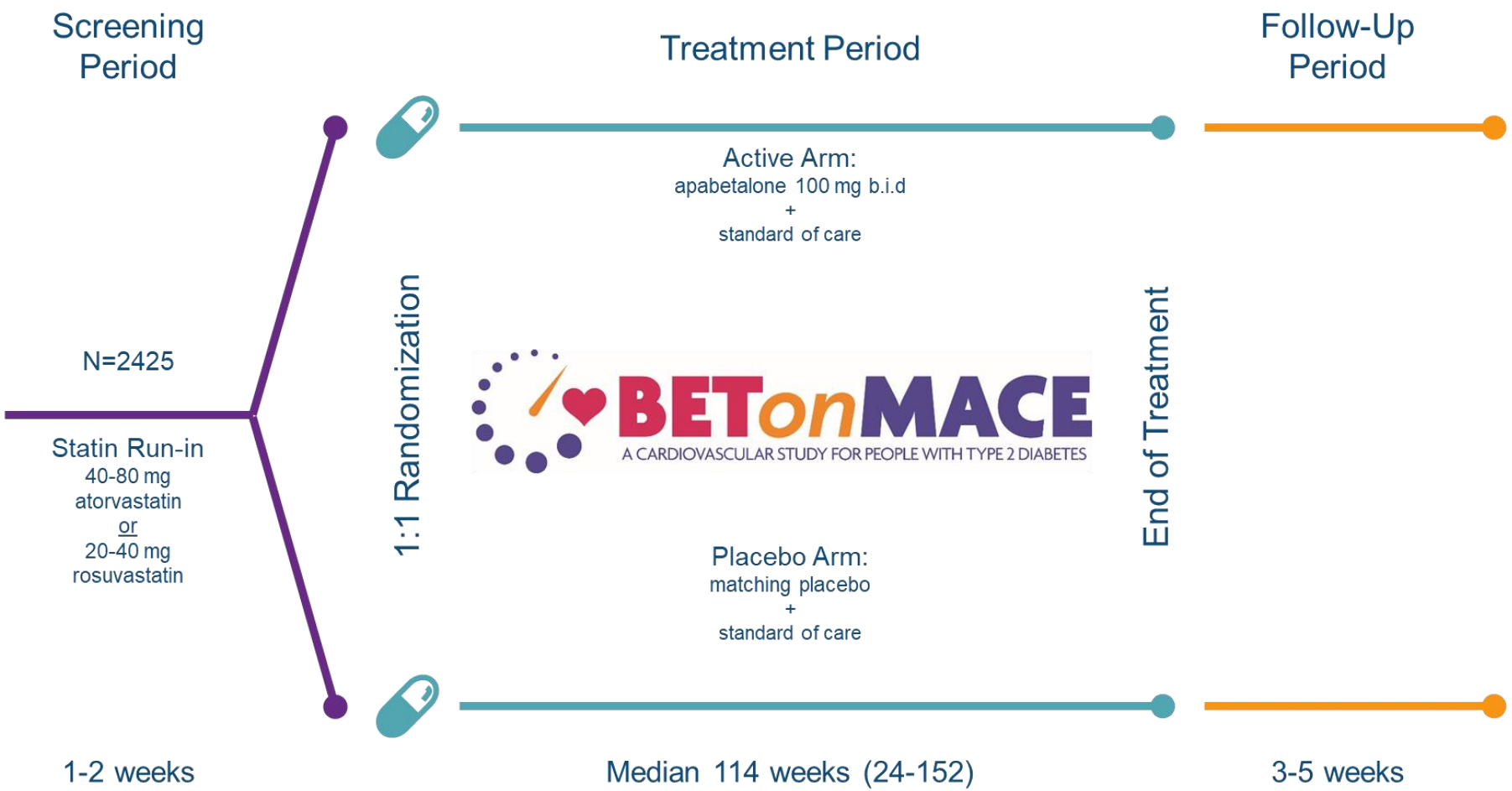


- Epigenetics refers to **modifications** to chromatin that regulate it's activity
- Transcription is regulated by **addition, removal, or recognition** of these modification
- **Acetylation** is associated with **active transcription** regions of chromatin
- **Bromodomain and Extraterminal Domain (BET)** proteins bind to acetylated histones and recruit additional transcription factors to drive gene expression

Apabetalone Mechanism of Action



BETonMACE Study Design



BETonMACE Study Parameters

Primary Objective

- To evaluate if treatment with apabetalone as compared to placebo increases time to the first occurrence of triple MACE. Triple MACE is defined as a single composite endpoint of CV death or non fatal MI or stroke.

Key Inclusion Criteria

- Type 2 Diabetes Mellitus
  - HbA1c >6.5% or history of diabetes medications
- Acute coronary syndrome 7-90 days prior to the screening visit
  - Unstable angina (Limited to 25% of total participants) or acute myocardial infarction
- Low HDL cholesterol
  - <40 mg/dL (1.04 mmol/L) for males; <45 mg/dL (1.17 mmol/L) for females at the screening visit

Primary Endpoint

- Time to first occurrence of adjudication-confirmed triple MACE

Key Secondary and Exploratory Endpoints

- Change in kidney function in chronic kidney disease sub-population
  - Baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.7m^2
- Change in Montreal Cognitive Assessment (MoCA)
  - Evaluated in at-risk sub-population (≥70 years old at randomization)