TO001 - Free Communication
Session S 38 Cardiovascular and renal protection - effects of SGLT2 inhibitors and GLP-1 receptor agonists in people with CKD and type 2 diabetes

EFFECTS OF THE BET-INHIBITOR APABETALONE ON CARDIOVASCULAR EVENTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND ACUTE CORONARY SYNDROME, ACCORDING TO PRESENCE OR ABSENCE OF CHRONIC KIDNEY DISEASE. A BET ON MACE TRIAL REPORT.

Kamyar Kalantar-Zadeh, Kausik K Ray, Stephen J Nicholls, Henry N Ginsberg, Kevin, Buhr, Jan O Johansson, Ewelina Kulikowski, Peter P Toth, Norman Wong, Michael Sweeney, Gregory G Schwartz, on behalf of the BETonMACE investigators

Presented by
Kam Kalantar-Zadeh, MD, MPH, PhD
Professor and Chief, Division of Nephrology, Hypertension, and Kidney Transplantation
University of California Irvine, Orange, California, USA

ERA-EDTA
June 9, 2020
### BETonMACE Committees

#### Clinical Steering Committee

<table>
<thead>
<tr>
<th>Chair</th>
<th>S. J. Nicholls</th>
<th>H. Ginsberg</th>
<th>K. Kalantar-Zadeh</th>
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<tbody>
<tr>
<td>P. Toth</td>
<td>K. Buhr (Independent Statistician)</td>
<td>G. G. Schwartz</td>
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<tr>
<td>Non-Voting</td>
<td>M. Sweeney</td>
<td>N. C. W. Wong</td>
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#### Clinical Events Committee

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<thead>
<tr>
<th>Chair</th>
<th>J. McMurray</th>
<th>Pardeep Jhund</th>
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#### DSMB

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<tr>
<th>Chair</th>
<th>E. Lonn</th>
<th>D. Waters</th>
<th>P. Watkins</th>
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<tbody>
<tr>
<td>J Currier</td>
<td>M. Szarek</td>
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#### Contributions from 13 countries at 195 sites:

<table>
<thead>
<tr>
<th>Country</th>
<th>Lead Investigator(s)</th>
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<tbody>
<tr>
<td>Argentina</td>
<td>A. Lorenzatti, M. Vico</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>M. Milanova</td>
</tr>
<tr>
<td>Croatia</td>
<td>Z. Popovic, G. Melicevic</td>
</tr>
<tr>
<td>Germany</td>
<td>H. Ebelt</td>
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<tr>
<td>Hungary</td>
<td>R. G. Kiss</td>
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<tr>
<td>Israel</td>
<td>B. Lewis</td>
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<tr>
<td>Mexico</td>
<td>E. Bayram-Llamas</td>
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<tr>
<td>Poland</td>
<td>M. Banach</td>
</tr>
<tr>
<td>Russia</td>
<td>S. Tereschenko</td>
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<tr>
<td>Serbia</td>
<td>M. Pavlovic</td>
</tr>
<tr>
<td>Slovakia</td>
<td>D. Pella</td>
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<td>Taiwan</td>
<td>C. E. Chiang</td>
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</tbody>
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**BETonMACE Background & Rationale**

- Bromodomain and extraterminal proteins are epigenetic regulators of gene transcription.

Epigenetics refers to **modifications** to chromatin that regulate its activity.

Transcription is regulated by **addition, removal, or recognition** of these modifications.

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 is a selective bromodomain and extra-terminal (BET) protein inhibitor targeting bromodomain 2 and is hypothesized to have potentially favorable effects on pathways related to atherothrombosis.
BET Protein Inhibition with Apabetalone Favorably Impacts Pathways Implicated in Cardiovascular and Kidney Disease

- Treatment with apabetalone reduces mediators that drive endothelial activation, monocyte recruitment and plaque destabilization.
  - Tsujikawa et al. 2019

- 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 alkaline phosphatase and other drivers of vascular calcification are lowered by apabetalone.
  - Gilham 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
Phase 2 Trials Suggest Potential CV Benefit with Apabetalone

- MACE (major adverse cardiovascular events) including death, myocardial infarction, coronary revascularization, and hospitalization for cardiovascular causes.
- Other characteristics associated with greater effect of apabetalone in pooled Phase 2 were low HDL-C and high hsCRP.
- Data shown are aggregate from the following trials: ASSERT; ASSURE; SUSTAIN. Nicholls Am J Cardiovasc Drugs 2018
# BETonMACE Inclusion and Exclusion Criteria

## Key Inclusion Criteria
- **Type 2 Diabetes Mellitus**
  - HbA1c >6.5% or history of diabetes medication use
- **Acute coronary syndrome 7-90 days prior to the screening visit**
  - Unstable angina (limited to 25% of 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

## Key Exclusion Criteria
- **Planned further coronary revascularization** at time of screening visit
- **Previous or current diagnosis of severe heart failure** (New York Heart Association Class IV)
- **Coronary artery bypass grafting** within 90 days prior to Visit 1.
- **Severe renal impairment** as determined by any one of the following:
  - eGFR <30 mL/min/1.7m² at screening visit
  - Need for dialysis
- **Evidence of cirrhosis** from liver imaging or biopsy, or liver transaminases (ALT or AST) >1.5x the upper limit of normal range at screening visit

BETonMACE Study Endpoints

- **Primary Endpoint**
  - Time to first occurrence of CV death or non-fatal MI or stroke
    - Pre-specified sensitivity analysis excluding deaths of undetermined cause from endpoint

- **Key Secondary Endpoints**
  - Time to first 4-part MACE: primary endpoint + hospitalization for CV events* 
  - Total (first and recurrent) non-fatal MI or stroke, and CV death 
  - Time to first CV Death or Non-fatal MI 
  - Time to first coronary heart disease death or non-fatal MI 
  - Individual components of primary endpoint 
  - All-cause death 
  - Hospitalization for congestive heart failure (CHF)

*Unstable angina or urgent or emergency coronary revascularization at least 30 days after the index ACS

Statistical Assumptions

- A sample size of 2,400 randomized subjects was predicted to yield 80% power for the primary analysis under the following assumptions:
  - Total number of events: 250
  - 2-sided type 1 error rate: $\alpha=5\%$
  - 10.5% event rate in the placebo arm at 18 months
  - 30% relative risk reduction (7.47% event rate at 18 months in the apabetalone arm)

**BETonMACE Study Design**

**Screening Period**
- N=2425
- Statin Run-in
  - 40-80 mg atorvastatin
  - or
  - 20-40 mg rosvustatin
- 1-2 weeks

1:1 Randomization

**Treatment Period**
- Active Arm:
  - apabetalone 100 mg b.i.d + standard of care
- Placebo Arm:
  - matching placebo + standard of care
- Median of 26.5 months

**Follow-Up Period**
- Placebo
  - n = 1,206
- Apabetalone
  - n = 1,212
- 3-5 weeks

**End of Treatment**

# BETonMACE Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Apabetalone (n=1212)</th>
<th>Placebo (n=1206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs</td>
<td>62.0</td>
<td>62.0</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>74.8</td>
<td>74.0</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.2</td>
<td>30.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>89.4</td>
<td>87.8</td>
</tr>
<tr>
<td>eGFR Mean ± SD, mL/min/1.73m²</td>
<td>104.9</td>
<td>101.7</td>
</tr>
<tr>
<td>Duration of diabetes, yrs</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Index acute coronary syndrome, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>73.0</td>
<td>74.0</td>
</tr>
<tr>
<td>STEMI</td>
<td>38.4</td>
<td>38.6</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>34.1</td>
<td>35.1</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>26.7</td>
<td>25.0</td>
</tr>
<tr>
<td>PCI for index ACS</td>
<td>79.8</td>
<td>79.2</td>
</tr>
<tr>
<td>Time from index ACS to randomization, days</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

BETonMACE Primary Efficacy Endpoint

- CV Death, Non-Fatal MI and Stroke (Total number of events = 274)

Median follow-up of 26.5 months

Primary Endpoint:
Placebo = 12.4%
Apabetalone = 10.3%

Prespecified Primary End Point Sensitivity Analysis
Excluding Deaths of Undetermined Cause

CV Death (excluding death of undetermined cause), non-fatal MI, or stroke

Hazard ratio, 0.79 (95% CI, 0.62-1.01), P=0.06

No. at Risk
Placebo: 1206, 1135, 1101, 937, 641, 383, 108
Apabetalone: 1212, 1150, 1113, 949, 671, 396, 107

## Primary Endpoint in Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Apabetalone</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of events/patients (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23/305 (7.5%)</td>
<td>32/313 (10.2%)</td>
<td>0.79 [0.46, 1.36]</td>
<td>0.70</td>
</tr>
<tr>
<td>Male</td>
<td>102/907 (11.2%)</td>
<td>117/893 (13.1%)</td>
<td>0.84 [0.64, 1.10]</td>
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<tr>
<td><strong>Statin</strong></td>
<td></td>
<td></td>
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<tr>
<td>Rosuvastatin</td>
<td>62/591 (10.5%)</td>
<td>71/586 (12.1%)</td>
<td>0.86 [0.62, 1.22]</td>
<td>0.67</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>63/621 (10.1%)</td>
<td>78/620 (12.6%)</td>
<td>0.78 [0.56, 1.09]</td>
<td></td>
</tr>
<tr>
<td><strong>LDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>48/595 (8.1%)</td>
<td>78/597 (13.1%)</td>
<td>0.60 [0.42, 0.86]</td>
<td>0.024</td>
</tr>
<tr>
<td>≥ Median</td>
<td>77/618 (12.5%)</td>
<td>71/606 (11.7%)</td>
<td>1.06 [0.77, 1.46]</td>
<td></td>
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<tr>
<td><strong>Hemoglobin A1c</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; Median</td>
<td>51/563 (9.1%)</td>
<td>60/595 (10.1%)</td>
<td>0.88 [0.60, 1.28]</td>
<td>0.79</td>
</tr>
<tr>
<td>≥ Median</td>
<td>73/639 (11.4%)</td>
<td>85/599 (14.2%)</td>
<td>0.82 [0.60, 1.12]</td>
<td></td>
</tr>
<tr>
<td><strong>Estimated glomerular filtration rate</strong></td>
<td></td>
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<tr>
<td>&lt; 60</td>
<td>13/124 (10.4%)</td>
<td>35/164 (21.3%)</td>
<td>0.50 [0.26, 0.96]</td>
<td>0.032</td>
</tr>
<tr>
<td>≥ 60</td>
<td>112/1084 (10.3%)</td>
<td>114/1041 (11.0%)</td>
<td>0.94 [0.73, 1.22]</td>
<td></td>
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</tbody>
</table>
BETonMACE Summary

- Apabetalone did not have a significant effect on incidence of the primary endpoint (CV death, non-fatal MI or stroke)
  - Lower than anticipated event rate in placebo group (9.7% observed, 10.5% predicted at 18 months)
  - Study was powered on a 30% reduction in risk of primary endpoint, and was underpowered to detect a smaller event reduction

- Apabetalone was generally well tolerated with an overall incidence of adverse events similar to that in the placebo group. However, discontinuation of treatment due to elevated liver function tests was more frequent with apabetalone.
## Baseline Demographic Data of the CKD Subgroup

<table>
<thead>
<tr>
<th></th>
<th>eGFR ≥ 60 (CKD Stage 3-4)</th>
<th>eGFR &lt; 60 (eGFR &lt;60)</th>
<th>P-value</th>
<th>Placebo (eGFR &lt;60)</th>
<th>Apabetalone (eGFR &lt;60)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>N=2,125</td>
<td>N=288</td>
<td></td>
<td>N=164</td>
<td>N=124</td>
</tr>
<tr>
<td><strong>Age (yr)</strong></td>
<td>61 (54-67)</td>
<td>71 (65-76)</td>
<td>&lt;0.001</td>
<td>70.6 (7.9)</td>
<td>69.8 (7.9)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,628 (76.6)</td>
<td>168 (58.3)</td>
<td>&lt;0.001</td>
<td>91 (56%)</td>
<td>76 (63%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>1,879 (88.4)</td>
<td>235 (81.6)</td>
<td>&lt;0.001</td>
<td>136 (83%)</td>
<td>95 (79%)</td>
</tr>
<tr>
<td>Asian</td>
<td>28 (1.3)</td>
<td>11 (3.8)</td>
<td></td>
<td>5 (3.1%)</td>
<td>6 (5.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>218 (10.3)</td>
<td>42 (14.6)</td>
<td>&lt;0.001</td>
<td>13 (8.0%)</td>
<td>14 (11.6%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>30.6 (4.9)</td>
<td>27.4 (3.9)</td>
<td>&lt;0.001</td>
<td>27.6 (4.1)</td>
<td>27.3 (3.6)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>1,876 (88%)</td>
<td>263 (91)</td>
<td>0.15</td>
<td>91%</td>
<td>91%</td>
</tr>
<tr>
<td><strong>Duration of diabetes (yr)</strong></td>
<td>8.2 (7.3)</td>
<td>11.3 (9.1)</td>
<td>&lt;0.001</td>
<td>11.9 (9.1)</td>
<td>10.5 (9.2)</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73 m²</strong></td>
<td>110.8 (35.4)</td>
<td>48.6 (8.8)</td>
<td>&lt;0.001</td>
<td>median eGFR 49 (41 – 56)</td>
<td>median eGFR 51 (41 – 56)</td>
</tr>
</tbody>
</table>

*Note: 186 patients with CKD Stage 3 and 102 patients with CKD Stage 4 in the CKD subgroup*
BETonMACE CKD Group - Results

- CKD vs. non-CKD patients were older (71 vs. 61 years, P<0.001) with more females (42% vs. 23%, P<0.001) and self-identified non-white patients (18% vs. 12%, P<0.001).

- CKD patients had a longer mean duration of diabetes (11.3 vs. 8.2 years, P<0.001) and were less likely to be treated with metformin (69% vs. 84%, P<0.001) and SGLT2 inhibitors (6% vs. 13%, P=0.001).

- CKD patients had higher serum alkaline phosphatase (91 vs. 81 U/L, P=0.02) and lower alanine aminotransferase (23 vs. 26 U/L, P=0.01).
<table>
<thead>
<tr>
<th></th>
<th>eGFR &lt; 60</th>
<th></th>
<th>eGFR ≥ 60</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Apabetalone</td>
<td>Placebo</td>
<td>Apabetalone</td>
</tr>
<tr>
<td></td>
<td>Evt/n (%)</td>
<td>Evt/n (%)</td>
<td>Evt/n (%)</td>
<td>Evt/n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR (95% CI)</td>
<td></td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>MACE</td>
<td>35/164 (21.3)</td>
<td>13/124 (10.5)</td>
<td>0.50 [0.26,0.96]</td>
<td>114/1041 (11.0)</td>
</tr>
<tr>
<td>MACE + HCHF</td>
<td>41/164 (25.0)</td>
<td>16/124 (12.9)</td>
<td>0.48 [0.26,0.89]</td>
<td>132/1041 (12.7)</td>
</tr>
<tr>
<td>Components</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>17/164 (10.4)</td>
<td>6/124 (4.8)</td>
<td>0.47 [0.18,1.21]</td>
<td>38/1041 (3.7)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>20/164 (12.2)</td>
<td>9/124 (7.3)</td>
<td>0.60 [0.27,1.34]</td>
<td>74/1041 (7.1)</td>
</tr>
<tr>
<td>Non-fatal Stroke</td>
<td>6/164 (3.7)</td>
<td>2/124 (1.6)</td>
<td>0.55 [0.11,2.79]</td>
<td>11/1041 (1.1)</td>
</tr>
<tr>
<td>HCHF</td>
<td>14/164 (8.5)</td>
<td>3/124 (2.4)</td>
<td>0.26 [0.07,0.94]</td>
<td>34/1041 (3.3)</td>
</tr>
</tbody>
</table>
BET on MACE CKD group - Results

• Under placebo, CKD patients exhibited higher CVD prevalence, i.e.
  – 35/164 (21.3%) vs. 114/1041 (11.0%) (HR=2.40, 95% CI [1.67, 3.44]) for ischemic CVD/MACE
  – 14/164 (8.5%) vs. 34/1041 (3.3%) (HR=3.19, 95% CI [1.66, 6.12], P<0.001) for HCHF.

• Under apabetalone, CKD group showed dramatic event reductions compared to placebo:
  – HR=0.50 (95% CI [0.26, 0.96], P=0.034) for MACE
  – HR=0.26 (95% CI [0.07, 0.94], P=0.028) for HCHF

• The Kaplan-Maier curves show the much more pronounced CVD risk reduction in the CKD vs. non-CKD group with early and widening curve-separation over the 36 months treatment period.
Kaplan-Meier Estimates by CKD/Non-CKD for MACE
Apabetalone Compared to Placebo

MACE: Composite of CV death, non-fatal MI and stroke

CKD Group (eGFR < 60)

Placebo Events - 35/164 (21.3%)
Apabetalone Events - 13/124 (10.5%)
Hazard Ratio = 0.50 [95%CIs: 0.26,0.96]

Non-CKD Group (eGFR ≥ 60)

Placebo Events - 13/124 (10.5%)
Apabetalone Events - 13/124 (10.5%)
Hazard Ratio = 0.50 [95%CIs: 0.26,0.96]
Kaplan-Meier Estimates by CKD/Non-CKD for MACE
Apabetalone Compared to Placebo

Hospitalizations for Congestive Heart Failure (HCHF)

CKD Group (eGFR < 60)
- Apabetalone
- Placebo

Non-CKD Group (eGFR ≥ 60)
- Apabetalone
- Placebo

Hazard Ratio = 0.26 [95% CIs: 0.07, 0.94]

No. at Risk
- eGFR < 60: 288, 262, 252, 219, 153, 89, 20
- eGFR ≥ 60: 2125, 2058, 2025, 1744, 1213, 739, 216

Months

0 6 12 18 24 30 36
Kaplan-Meier Estimates by CKD/Non-CKD for MACE
Apabetalone Compared to Placebo

Composite of CV death, non-fatal MI, stroke and hospitalizations for Congestive Heart Failure (HCHF)

CKD Group (eGFR < 60)
Placebo Events - 41/164 (25.0%)
Apabetalone Events - 3/124 (12.9%)
Hazard Ratio = 0.48 [95% CIs: 0.26, 0.89]

Non-CKD Group (eGFR ≥ 60)
Placebo Events - 41/164 (25.0%)
Apabetalone Events - 3/124 (12.9%)
Hazard Ratio = 0.48 [95% CIs: 0.26, 0.89]
Safety of Apabetalone in CKD Patients

- Apabetalone was well tolerated with similar number a subjects in both groups experiencing AE’s [119 (72.6%) and 88 (71.0%) in the placebo and apabetalone groups, respectively].

- A significantly lower number of subjects in the apabetalone group had serious adverse events (29% vs 43% p=0.02).

- The majority of this difference was in cardiovascular SAE’s (12% vs 25%) reflecting the efficacy results of the apabetalone.

- Only two subjects in each group had hepatic transaminases greater than 5X ULN on close laboratory monitoring requiring discontinuation of study therapy.
Limitations of the CKD Study

- Relatively small portion of the parent trial: 288 CKD patients out of 2,425
- Less balanced randomization among 288 CKD patients
- Limited to CKD Stages 3a and 3b (given exclusion criteria of eGFR<30 ml/min/1.73)
- Lack of urine data: No albuminuria data were collected
- eGFR changes over time were not different
- Non-diabetic CKD patients were not studied
Conclusions

• This is the first cardiovascular outcomes trial assessing the potential of epigenetic modification with BET protein inhibition “apabetalone” and shows promise.

• In this Phase III RCT, diabetic CKD patients with a recent acute coronary syndrome (ACS) exhibited a high prevalence of CVD (2.4 times for MACE and 3.2 for HCHF).

• Apabetalone reduced this enormous cardiovascular risk by 50% in diabetic CKD patients with prior ACS.

• Apabetalone offers a safe and effective oral pharmacotherapy for reducing cardiovascular risk in form of major cardiac events in patients with diabetes, CKD Stage 3, and prior ACS.

• Additional studies using apabetalone in CKD patients are warranted.