



## **Resverlogix Corp.**

BET inhibition for Global Vascular Risk

BIO-EUROPE Spring 2018

Amsterdam, The Netherlands

March 14<sup>th</sup>

TSX: RVX

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# Apabetalone Development Highlights



## Main Subject Matter

- Apabetalone, the only-in-class BET inhibitor (BETi), reduces key risk factors for high risk cardiovascular and renal patients resulting in reduction of Major Adverse Cardiac Events (MACE), observed renal improvement markers

## Advanced Mechanism

- Epigenetic modulation of gene expression makes BETi a novel approach
  - No known BETi competitor for next 9 plus years

## Confirmed Science

- Proteomics, genomics, pathway analysis, mechanism of action are all very well understood

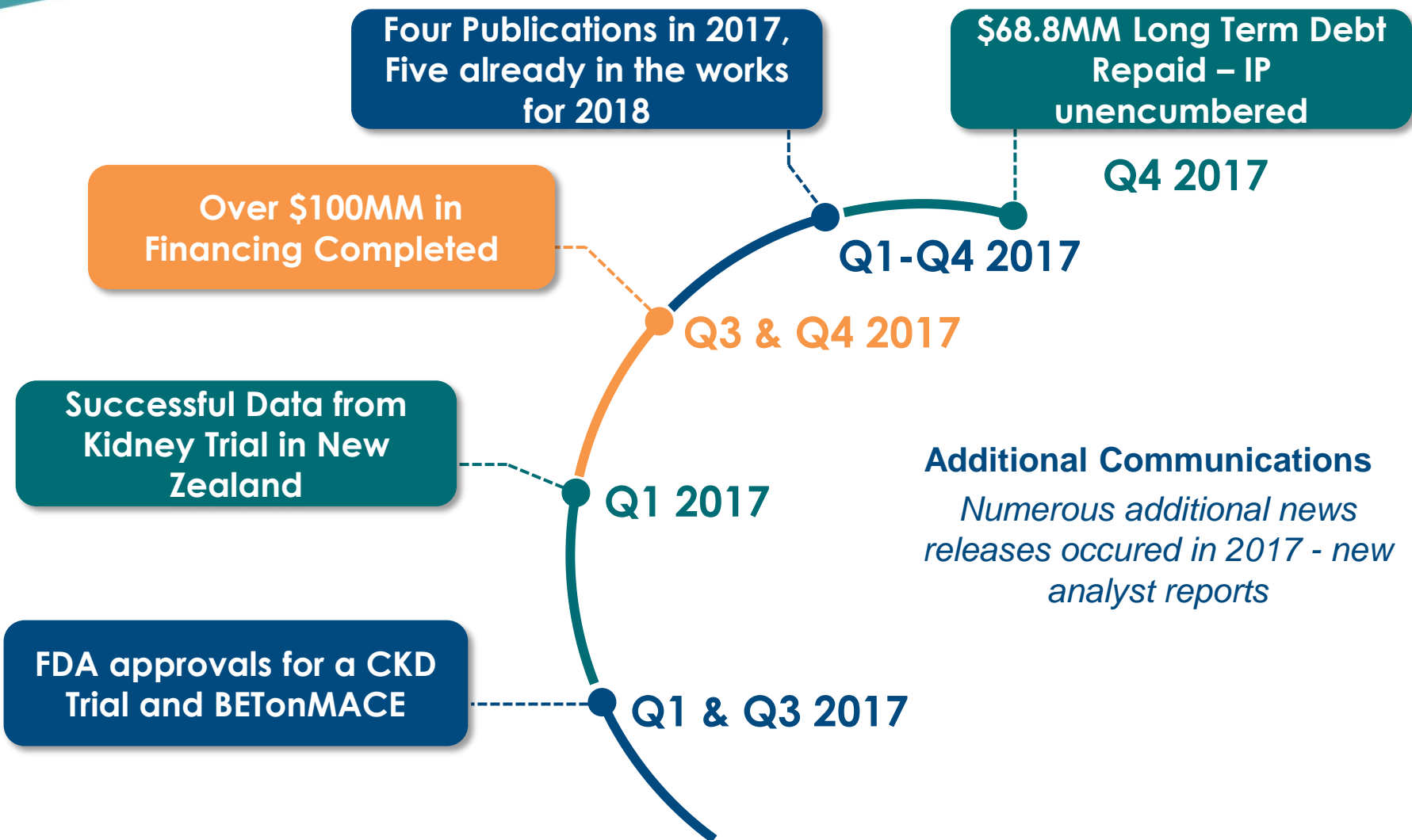
## Clinical Evidence

- Phase 2b data – up to 62% RRR of MACE in high risk CVD patients
- Phase 3 BETonMACE trial 98% enrolled
  - CVD/CKD risk biomarkers tracked to date - positive

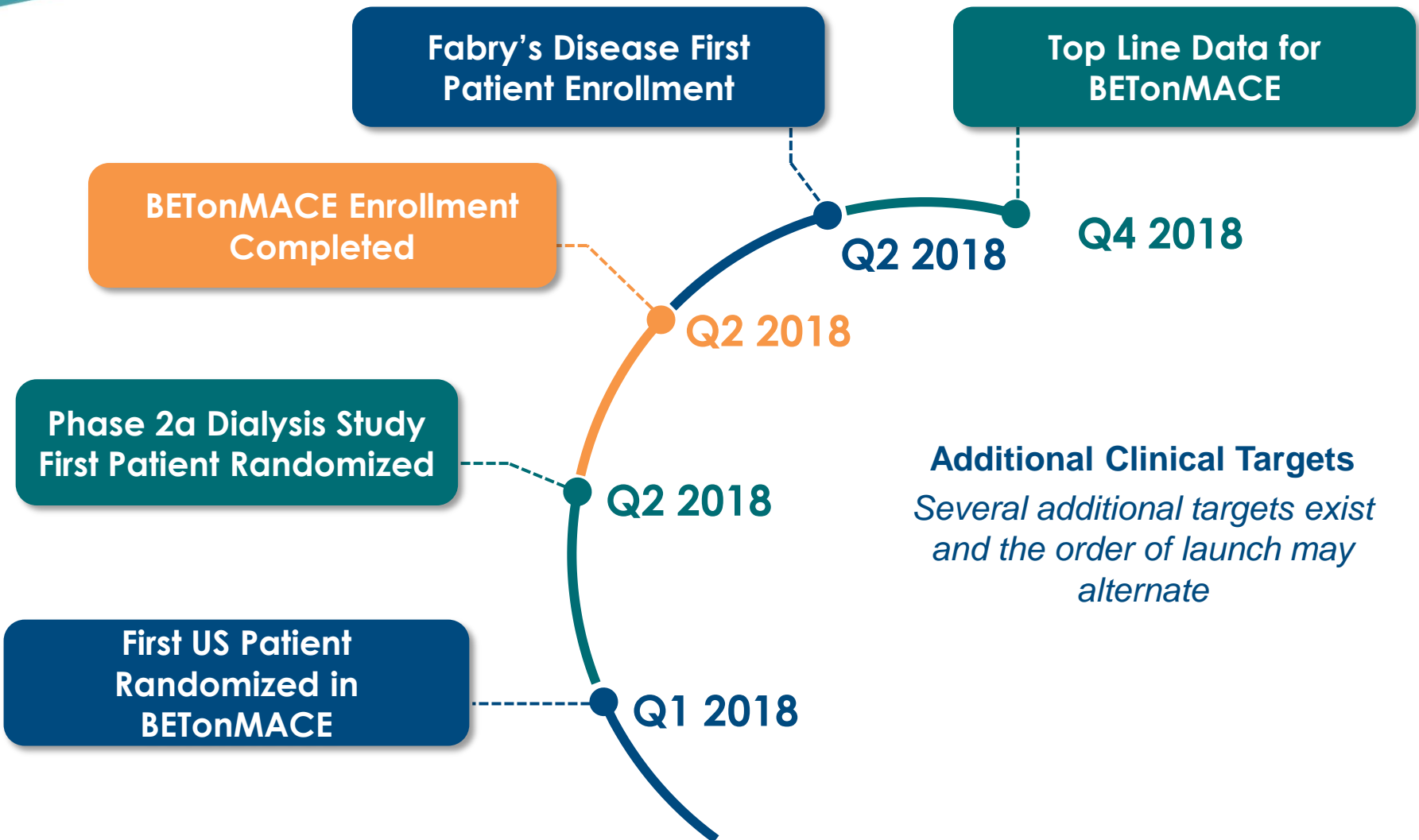
## Corporate Expansion

- Resverlogix corporate goal is to expand commercial partner program

# 2017 Major Accomplishments



# Upcoming Clinical Year Estimates



# BET Literature Impact Growing: CVD and Renal Risk

## RVX-208, an Inducer of ApoA-I in Bromodomain Antagonist

Kevin G. McLure<sup>1</sup>, Ewelina Kulikowski<sup>1</sup>, Christopher Halliday<sup>1</sup>, Ravi Jahagirdar<sup>1</sup>, Dean Gilham<sup>1</sup>, Laura M. Tsujikawa<sup>1</sup>, Michael Sweeney<sup>2</sup>, Norman C. Wong<sup>1</sup>

Data in Brief 8 (2016) 1280–1288

Contents lists available at ScienceDirect



journal homepage

Data Article

Data on gene and protein expression induced by apabetalone in primary human whole blood and primary hepatocytes

Sylvia Wasiak<sup>a</sup>, Dean Gilham<sup>a</sup>, Christopher Halliday<sup>a</sup>, Ravi Jahagirdar<sup>a</sup>, Kevin G. McLure<sup>a</sup>, Peter R. Young<sup>a</sup>, Ewelina Kulikowski<sup>a</sup>, Jan O. Johansson<sup>a</sup>, Norman C. Wong<sup>a,\*</sup>

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Am J Cardiovasc Drugs  
DOI 10.1007/s40256-017-0250-3

### ORIGINAL RESEARCH ARTICLE

## Selective BET Protein Inhibition with Apabetalone and Cardiovascular Events: A Pooled Analysis of Trials in Patients with Coronary Artery Disease

Stephanie C. Stotz<sup>1</sup>, Ravi Jahagirdar<sup>1</sup>, Kevin G. McLure<sup>2</sup>, Jan O. Johansson<sup>3</sup>, Michael Sweeney<sup>4</sup>, Norman C. Wong<sup>5</sup>



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Article in Press

## Benefit of Apabetalone on Plasma Proteins in Renal Disease

[Sylvia Wasiak<sup>5</sup>](#), [Laura M. Tsujikawa<sup>5</sup>](#), [Christopher Halliday](#), [Stephanie C. Stotz](#), [Dean Gilham](#), [Ravi Jahagirdar](#), [Kamyar Kalantar-Zadeh](#), [Richard Robson<sup>6</sup>](#), [Michael Sweeney](#), [Jan O. Johansson](#), [Norman C. Wong](#), [Ewelina Kulikowski](#)✉

J. of Cardiovasc. Trans. Res.  
DOI 10.1007/s12265-017-9755-z

ORIGINAL ARTICLE

## Downregulation of the Complement Cascade *In Vitro*, *In Mice* and in Patients with Cardiovascular Disease by the BET Protein Inhibitor Apabetalone (RVX-208)

Sylvia Wasiak<sup>1</sup>, Dean Gilham<sup>1</sup>, Laura M. Tsujikawa<sup>1</sup>, Christopher Halliday<sup>1</sup>, Cyrus Calosing<sup>1</sup>, Ravi Jahagirdar<sup>1</sup>, Jan Johansson<sup>2</sup>, Michael Sweeney<sup>2</sup>, Norman C. Wong<sup>1</sup>, Ewelina Kulikowski<sup>1</sup>✉

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## Autoimmune Disease<sup>5</sup>

Ravi Jahagirdar, Sarah Attwell, Suzana Marusic, Alison Bendele, Narmada Shenoy, Kevin G. McLure, Dean Gilham, Karen Norek, Henrik C. Hansen, Raymond Yu, Jennifer Tobin, Gregory S. Wagner, Peter R. Young, Norman C. W. Wong, and Ewelina Kulikowski

Resverlogix Corporation, Calgary, Alberta, Canada (R.J., S.A., K.G.M., D.G., K.N., H.C.H., R.Y., J.T., G.S.W., P.R.Y., N.C.W.W., E.K.); Hooke Laboratories Inc., Lawrence, Massachusetts (S.M.); Bolder BioPATH Inc., Boulder, Colorado (A.B.); and Aravasc Inc., Sunnyvale, California (N.S.)



# BET Literature Impact Growing: Neurodegenerative Risk



*Current Alzheimer Research*, 2016, 13, 985-995

## The BET-Bromodomain Inhibitor JQ1 Reduces Inflammation and Tau Phosphorylation at Ser396 in the Brain of the 3xTg Model of Alzheimer's Disease



Marco Magistri, Dmitry Velmeshev, Madina Makhmutova, Prutha Patel, Gregory C. Sartor, Claude-Henry Volmar, Claes Wahlestedt and Mohammad Ali Faghihi\*



Contents lists available at [ScienceDirect](#)

## Biochemical and Biophysical Research Communications

journal homepage: [www.elsevier.com/locate/ybbrc](http://www.elsevier.com/locate/ybbrc)



## The BET/BRD inhibitor JQ1 attenuates diabetes-induced cognitive impairment in rats by targeting Nox4-Nrf2 redox imbalance



Ershun Liang<sup>a</sup>, Min Ma<sup>b</sup>, Lei Wang<sup>c</sup>, Xue Liu<sup>a</sup>, Jinfeng Xu<sup>d</sup>, Mingxiang Zhang<sup>a, \*\*</sup>, Ruixue Yang<sup>a, \*</sup>, Yuxia Zhao<sup>a</sup>

OPEN

Citation: *Transl Psychiatry* (2017) 7, e1239; doi:10.1038/tp.2017.202

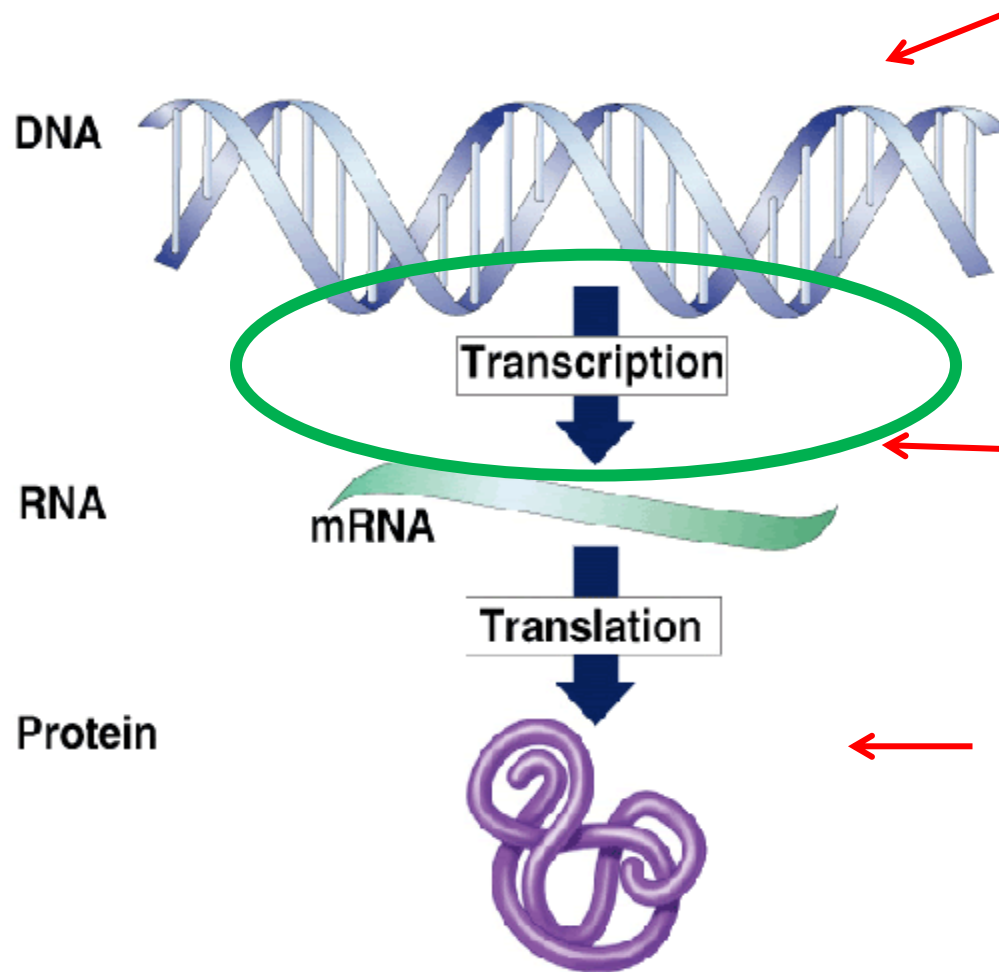
[www.nature.com/tp](http://www.nature.com/tp)

### ORIGINAL ARTICLE

## The BET/BRD inhibitor JQ1 improves brain plasticity in WT and APP mice

E Benito<sup>1</sup>, B Ramachandran<sup>2</sup>, H Schroeder<sup>1</sup>, G Schmidt<sup>3</sup>, H Urbanke<sup>1</sup>, S Burkhardt<sup>1</sup>, V Capece<sup>1</sup>, C Dean<sup>2</sup> and A Fischer<sup>1,4</sup>

# Unique Mechanism of Action



## Genome Editing

The mechanism is based on cutting and pasting undesired/desired sequences into or out of the DNA, thereby altering the gene sequence and then re-introducing the modified DNA into the body.

**CRISPR – gene editing within a cell sub population**

## Transcriptional Regulation

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

**Apabetalone – reduces expression of disease mediators**

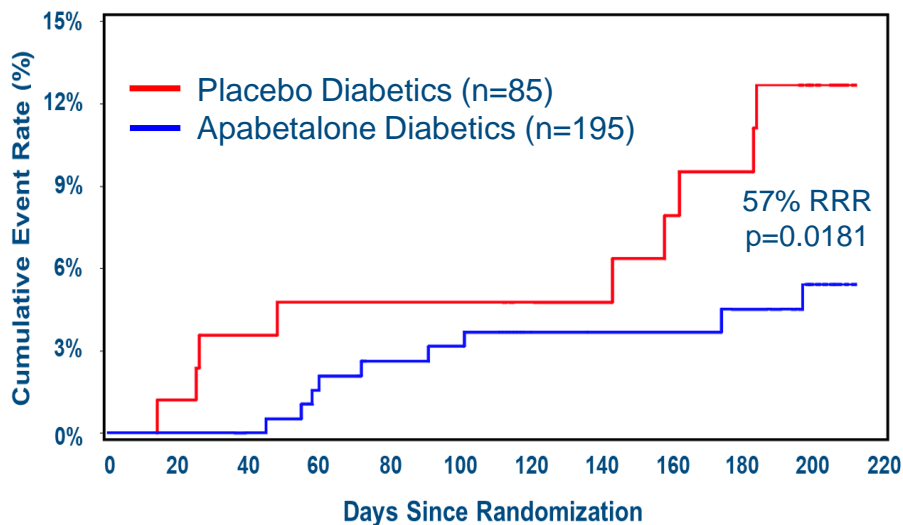
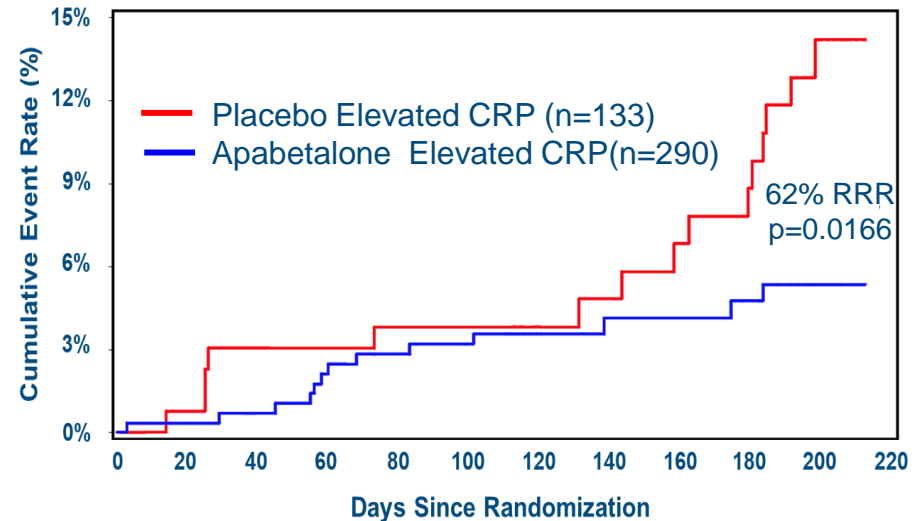
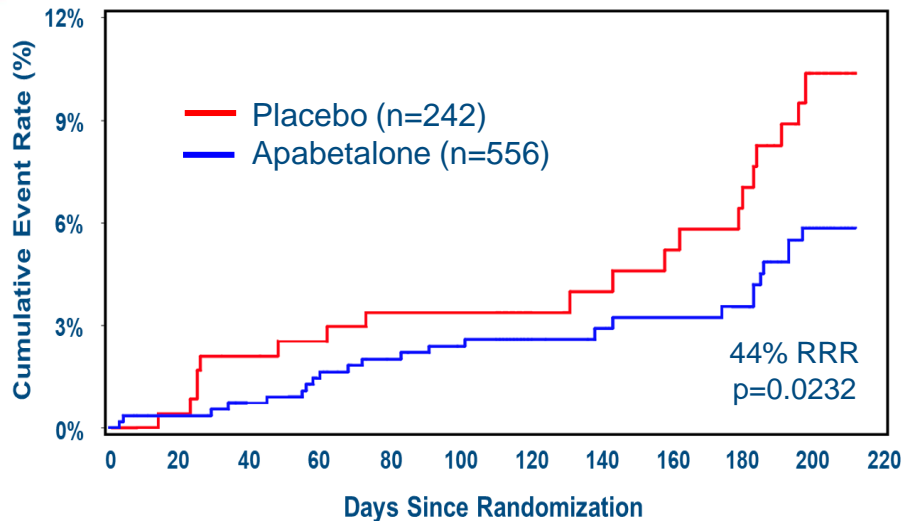
## Protein Targeting

Focus on reducing or blocking the activity of **one** disease protein by using an inhibitor or antibody

**Antibody or Inhibitor – blocks activity of one mediator of disease**



# Nicholls et al. 2017: American Journal of Cardiovascular Drugs



**MACE:** Major Adverse Cardiac Events including: death, myocardial infarction, stroke, coronary revascularization, hospitalization for acute coronary syndrome or heart failure

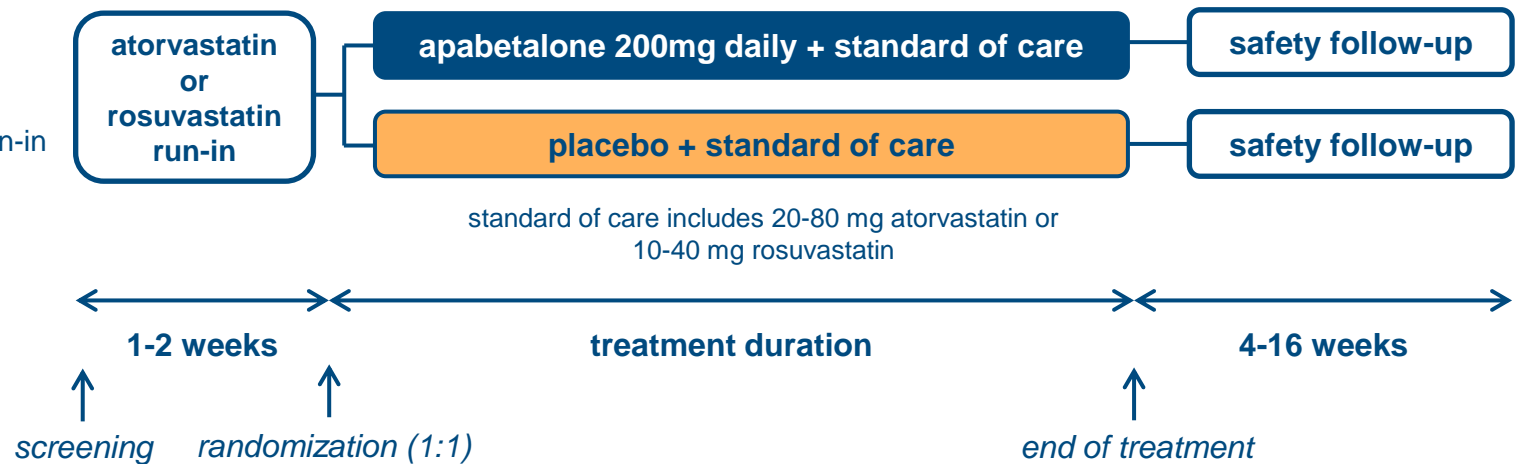
Decrease in MACE was most profound in patients who had a higher level of inflammation such as patients with diabetes

# BETonMACE CV Outcomes Study Design



2,400 + subjects

- double blinded
- 1-2 week statin run-in



**The study is an event-based trial and continues until 250 narrowly defined MACE events have occurred**

## **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: 1) CV death or 2) non-fatal MI or 3) stroke.

## **Key inclusion criteria**

- Type II Diabetes Mellitus
  - HbA1c > 6.5% or history of diabetes medications
- CAD event 7 days - 90 days prior to screening
  - Myocardial infarction (MI), unstable angina or percutaneous coronary intervention
- HDL <40 mg/dL for males and <45 mg/dL for females

## **Primary Endpoint (CVD)**

Time from randomization to the first occurrence of adjudication-confirmed triple MACE defined as a single composite endpoint of: 1) CV Death or 2) Non-fatal MI or 3) Stroke.

## **Secondary Endpoint (RENAL)**

- Time from randomization to the first occurrence of adjudication-confirmed MACE including revascularization and unstable angina
- Changes in apoA-I, apoB, LDL-C, HDL-C, and TG
- Changes in HbA1c, fasting glucose, and fasting insulin
- Changes in ALP and eGFR

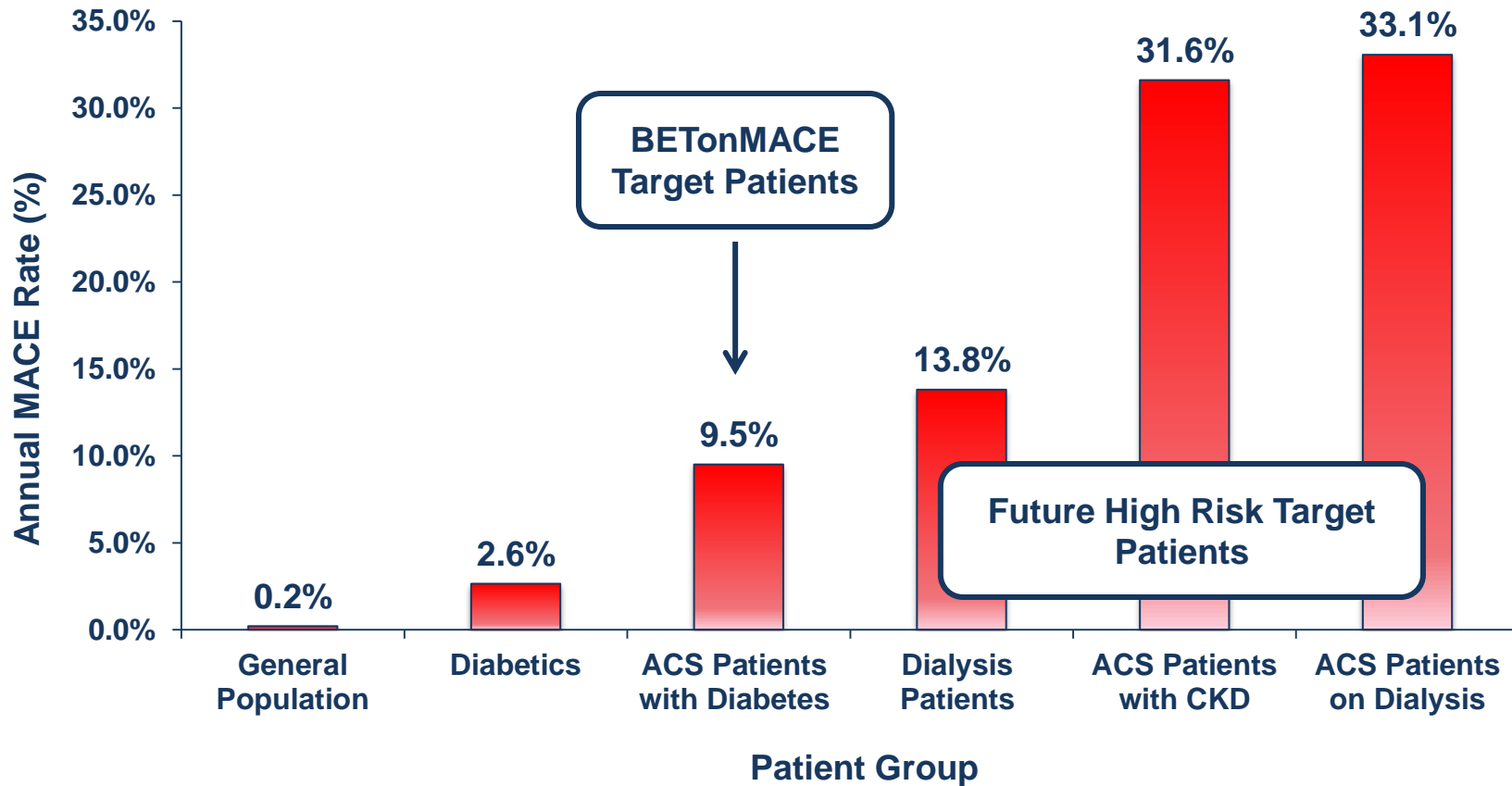
## **Exploratory Endpoint (NEURO)**

- MoCA test on all patients 70 and over
- All patients and those with <26

- ~ 98% enrolled
- CKD Subgroup: ~11% of patients have eGFR<60 at screening
- Cognition Subgroup: ~18% of patients have completed MoCA at Baseline; Target patients are those with baseline MoCA  $\leq 25$  ) approx. 275 patients
- Projected primary MACE rate still 8.0 per 100 patient years on top of aggressive standard of care (low LDL) = strong unmet need
- Even with aggressive statin therapy very high events illustrates CVD risk is more than just LDL

# Patient Enrichment Strategy

**Relative Annual Major Adverse Cardiac Event (MACE) Rates  
In Various Patient Groups**



Sources: Calculated from CDC Heart Disease Facts; Holden, SE. et al. 2015; White, WB. et al. 2013; Kim, H. et al. 2015; Cardarelli, F. et al. 2008; Okada, T. et al. 2008



# Market Opportunity Pathways



## Diabetes/ACS

- BETonMACE derived 2,400 patients
- MACE reduction
- **2-3 Million patients**



## CKD/ESRD

- BETonMACE sub population derived 300-400 patients
- Improved renal function in sub-group
- Reduced MACE
- Future trials in CKD Stage 3-4  
Diabetic Nephropathy  
ESRD
- **6+ Million Patients**



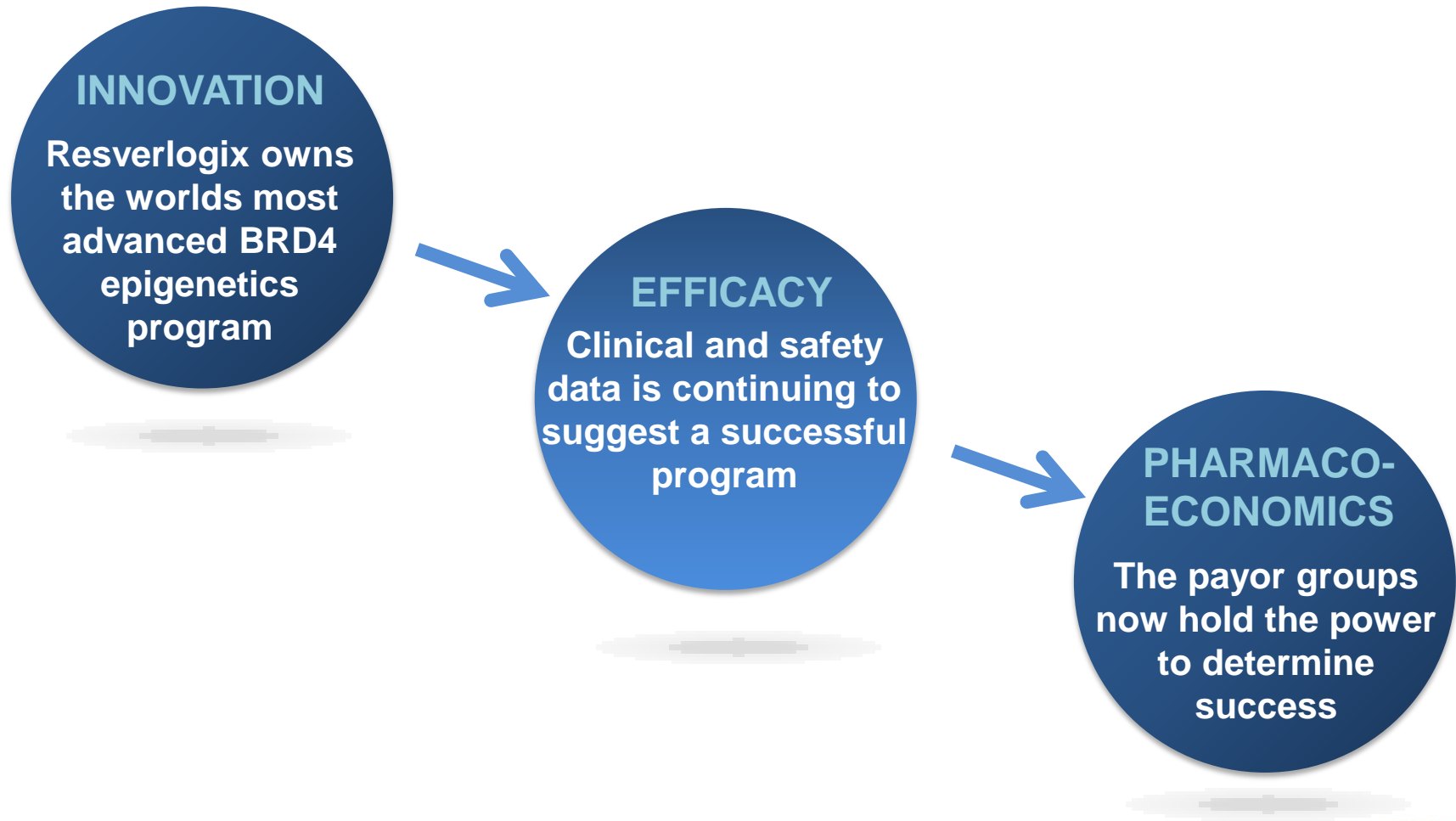
## Expanded Programs

- BETonMACE sub-population data analysis
- Cognition and dementia
- **4+ Million Patients**



Improving Global Vascular Risk

## THREE KEY DEVELOPMENT TARGETS ARE IN PLACE



# Payer KOL Outreach: Key Payer Support



Organization	Lives Covered	MACE Reduction: Unmet need in Recent ACS and T2DM patients	MACE Reduction: Unmet need in CKD patients	ICER Threshold per annum
Payer 1	55 M	Moderate to High	Moderate to High	\$ < 100,000
Payer 2	65 M	Moderate to High	Moderate to High	\$ < 200,000
Payer 3	37 M	Moderate to High	Moderate to High	\$ < 100,000
Payer 4	40 M	Moderate to High	Moderate to High	\$ < 150,000
Payer 5	11 M	Moderate to High	Moderate to High	\$ < 150,000

- 5 Payers - **208 million** lives covered, Key C Suite executives contacts – President, Chief Medical Directors, COO, Executive VP Pharmacy
- Pricing bands support average ICER Target Threshold of approximately **\$140,000-\$200,000** USD
- Pricing bands support annual US price of **\$5,000 - \$8,000** based on new enriched high risk patients

## Highlights

- Novel, first in class, technology – no competitor 8 – 10 years
- Clear science and clinical data supporting strong rationale for risk reduction
- Growing BET literature publications in CVD / Renal risk
- Strong KOL Payers and Prescriber support
- Transformative science and unprecedented commercial opportunity