



# **Resverlogix Corp.**

Bloom Burton & Co. Healthcare Investor Conference

May, 2018

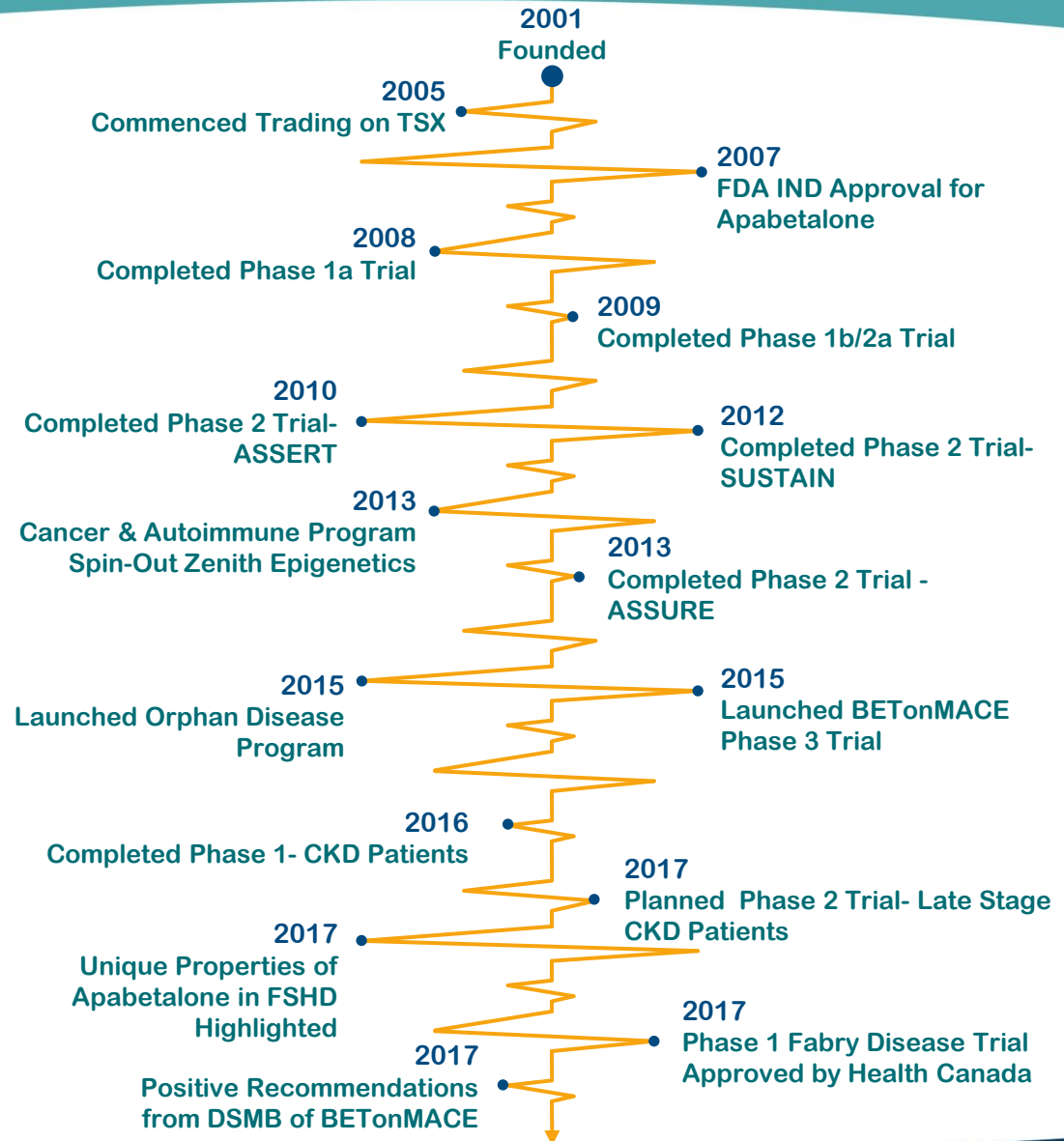
Toronto, ON

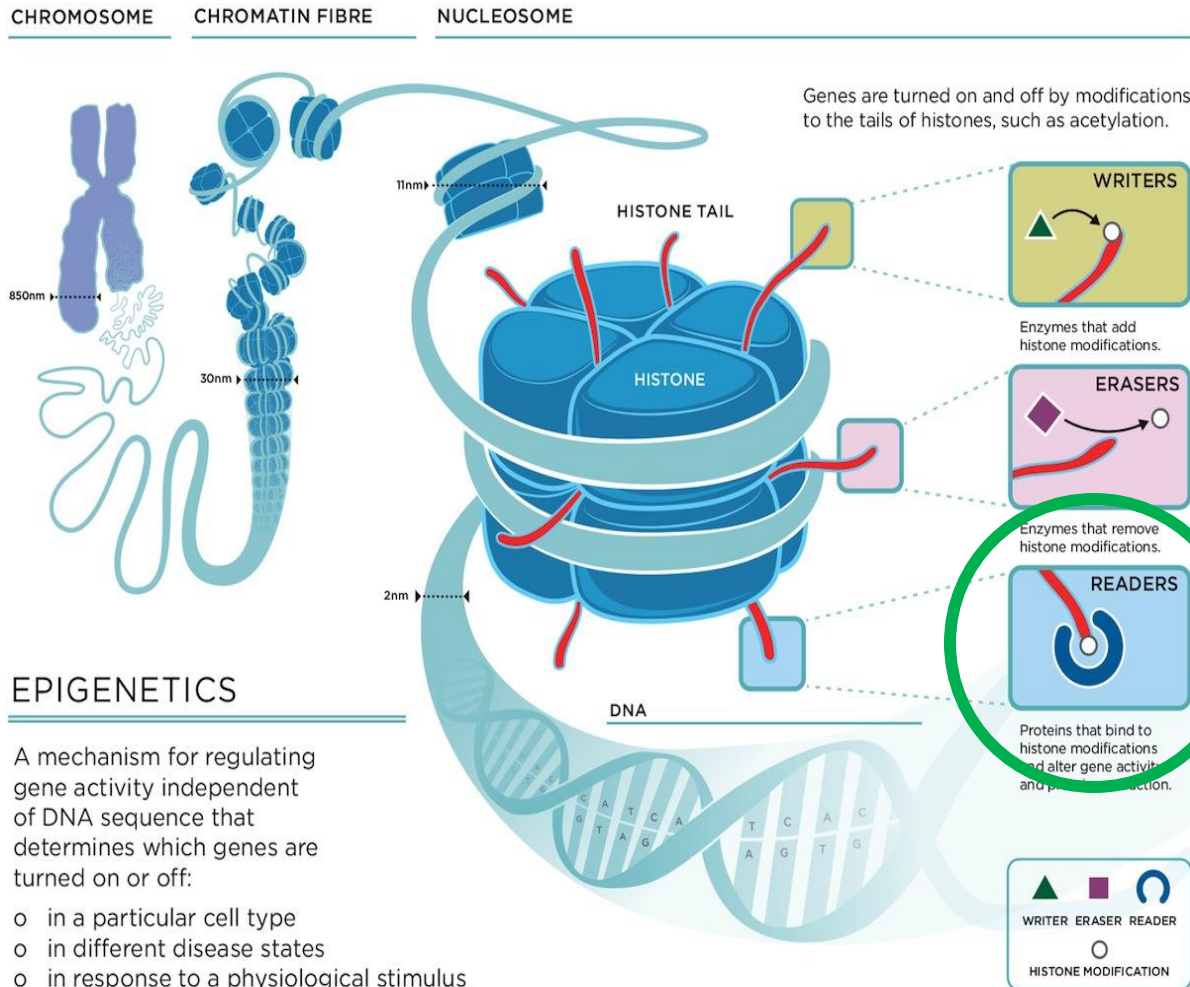
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# About Resverlogix



- Resverlogix Corp. (TSX:RVX) is a Calgary and San Francisco based clinical stage biotechnology company focused on the development of apabetalone
- Apabetalone (RVX-208) is a first-in-class small molecule selective BET bromodomain inhibitor, which acts via an epigenetic mechanism that can turn disease-causing genes off, returning them to a quiescent state
- Apabetalone is the only selective BET bromodomain inhibitor in clinical trials
  - Discovered and synthesized in 2006
  - Selected using a cell based screen for Apolipoprotein A-I induction in liver cells





## EPIGENETICS

A mechanism for regulating gene activity independent of DNA sequence that determines which genes are turned on or off:

- o in a particular cell type
- o in different disease states
- o in response to a physiological stimulus

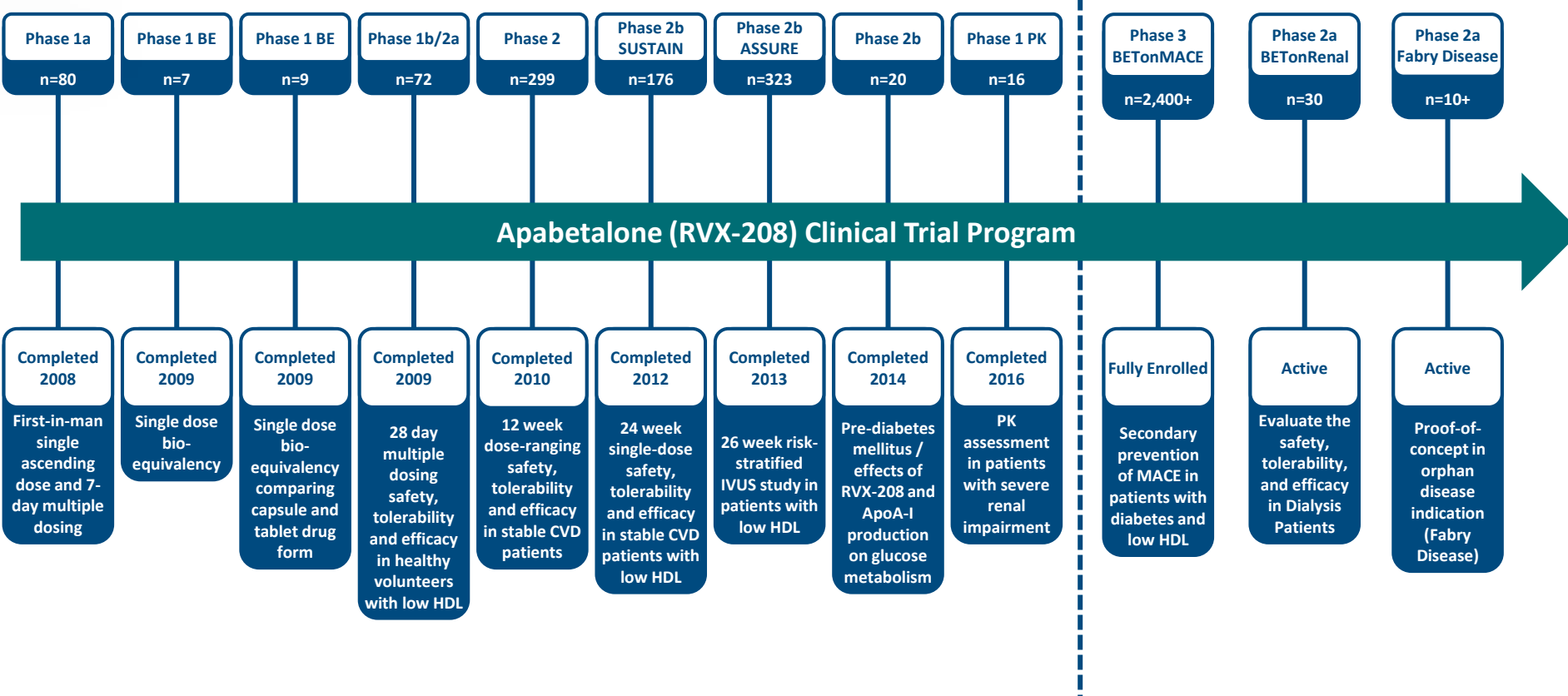
- The epigenetic code refers to modifications to chromatin components that regulate its activity
- Turning genes **on** or **off** is regulated by these modifications
- BET (Bromodomain and Extraterminal Domain) proteins recognize these modifications and turn genes **on**

# Apabetalone Clinical Trials to Date



## Completed Trials

## Ongoing Trials





# BET Literature Impact Growing CVD and Renal Risk

OPEN ACCESS Freely available online

PLOS ONE



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

Kevin G. McLure<sup>1</sup>, Ewelina Kulikowski<sup>1</sup>, Jan O. Johansson<sup>2</sup>, Norman C. Wong<sup>1</sup>, Ravi Jahagirdar<sup>1</sup>, Christopher Halliday<sup>1</sup>, Michael Sweeney<sup>2</sup>, Sylvania Wasiak<sup>1</sup>, Dean Gilham<sup>1</sup>, Richard Robson<sup>6</sup>, Kamyar Kalantar-Zadeh<sup>5</sup>, and Ravi Jahagirdar<sup>1</sup>

Data in Brief 8 (2016) 1280–1288

Contents lists available at ScienceDirect

ELSEVIER journal homepage

Data Article

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

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

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<sup>b</sup> Resverlogix Corp., San Francisco, USA

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>, Kamyar Kalantar-Zadeh<sup>5</sup>, Jan O. Johansson<sup>3</sup>, Alan Goldstein<sup>3</sup>, Norman C. Wong<sup>3</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 System 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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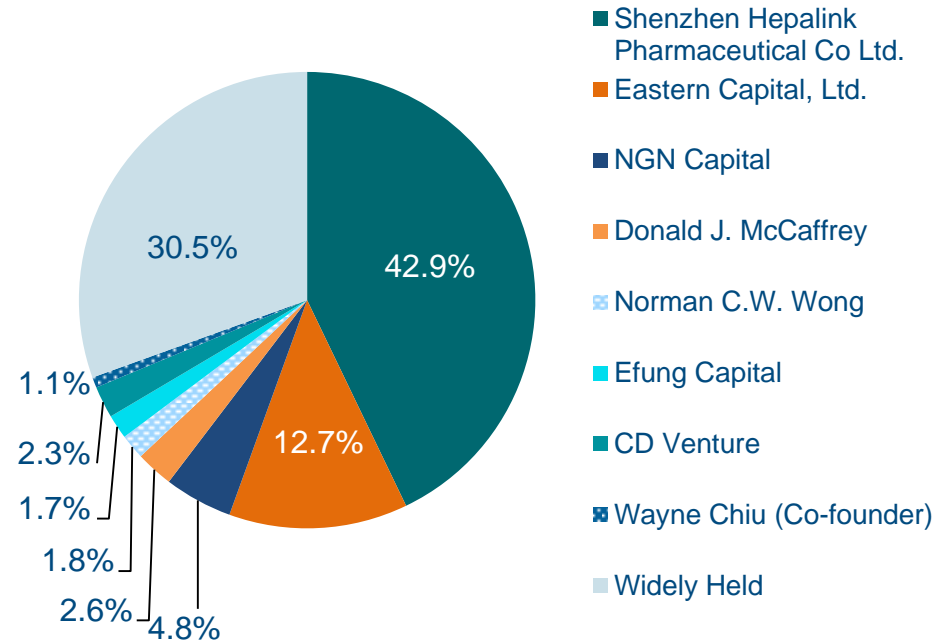
Ravi Jahagirdar, Sarah Atwell, Suzana Marusic, Alison Bendele, Narmada Shenoy, Kevin G. McLure, Dean Gilham, Karen Norek, Henrik C. Hansen, Raymond Yu, Jennifer Tobin, Gregory S. Wagner, Peter R. Young, Norman C. W. Wong, and Ewelina Kulikowski

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.)

- Resverlogix Corp. (TSX:RVX) is a Calgary and San Francisco based clinical stage biotechnology company focused on the development of **apabetalone**
- Apabetalone (RVX-208) is a **first-in-class** small molecule selective BET bromodomain inhibitor, which acts via an epigenetic mechanism that can turn disease-causing genes off, thereby normalizing gene function
  - Apabetalone is the only selective BET bromodomain inhibitor in clinical trials
- Resverlogix has initiated clinical trial work for apabetalone in **three indications**:
  - Cardiovascular Disease (BETonMACE Trial) – Phase 3
  - Chronic Kidney Disease (BETonRENAL Trial) – Phase 2b
  - Fabry's Disease – Phase 2b

<b>Founded</b>	<b>2001</b>
<b>Ticker</b>	<b>TSX: RVX</b>
<b>Market Cap</b>	<b>~C\$250M</b>
<b>Shares Outstanding</b>	<b>175.04M</b>
<b>Cash Burn (Annual)</b>	<b>~C\$40.0M</b>
<b>Finance</b>	<b>US\$30M - Announced April 2018</b>

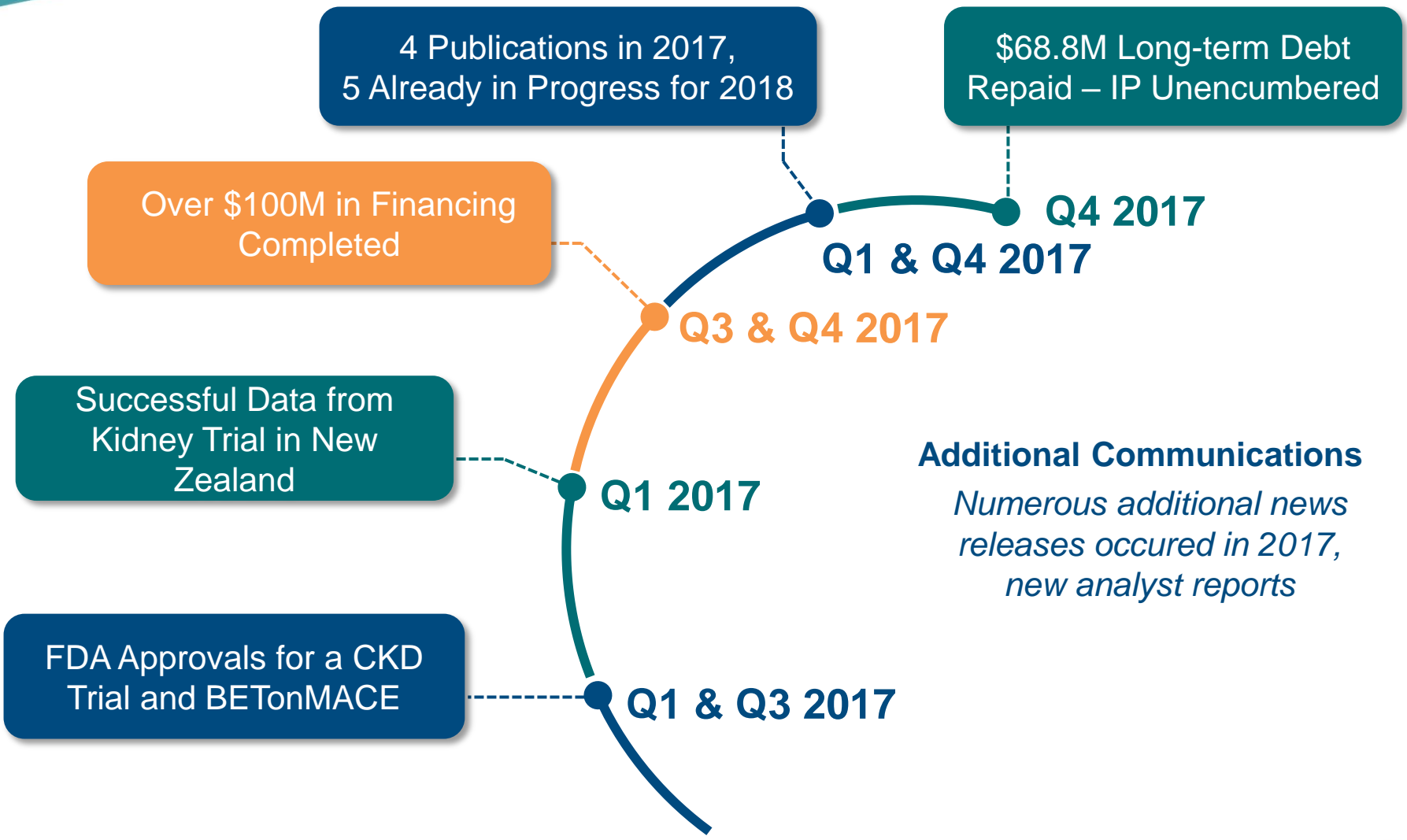
## RVX Top Shareholders



- RVX shareholder base consists of several long term investors who have been supportive over 10 years
- RVX maintains a diversified public market float of approximately 54M shares



# 2017 - Major Accomplishments



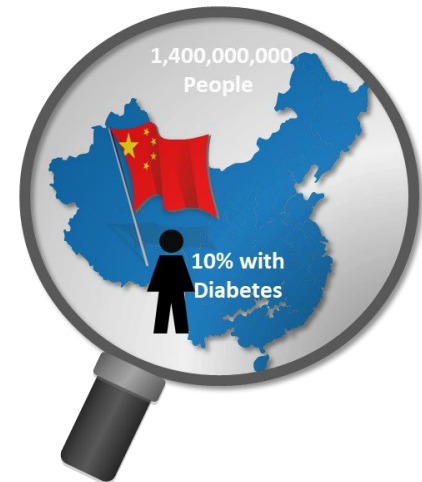
# Shenzhen Hepalink Partnership



Resverlogix's partnership with Shenzhen Hepalink represents the largest single molecule deal in the history of China



Resverlogix – Shenzhen Hepalink Exclusive Licensing Agreement	
<b>Compound</b>	<ul style="list-style-type: none"> <li>• Apabetalone (RVX-208)</li> </ul>
<b>Licensor</b>	<ul style="list-style-type: none"> <li>• Resverlogix Corp.</li> </ul>
<b>Licensee</b>	<ul style="list-style-type: none"> <li>• Shenzhen Hepalink Pharmaceutical Co., Ltd.</li> </ul>
<b>Territories</b>	<ul style="list-style-type: none"> <li>• China, Hong Kong, Taiwan, and Macau</li> </ul>
<b>Indications</b>	<ul style="list-style-type: none"> <li>• Any approved indication</li> </ul>
<b>Deal Structure</b>	<ul style="list-style-type: none"> <li>• US\$35M in equity investments in Resverlogix</li> <li>• &gt;US\$400M in projected future China sales milestones and licensing royalties</li> </ul>
<b>Developmental Costs</b>	<ul style="list-style-type: none"> <li>• Shenzhen Hepalink is responsible for all developmental costs for the licensed territories</li> <li>• This includes the cost of additional clinical trials in the licensed territories, regulatory applications, etc.</li> </ul>

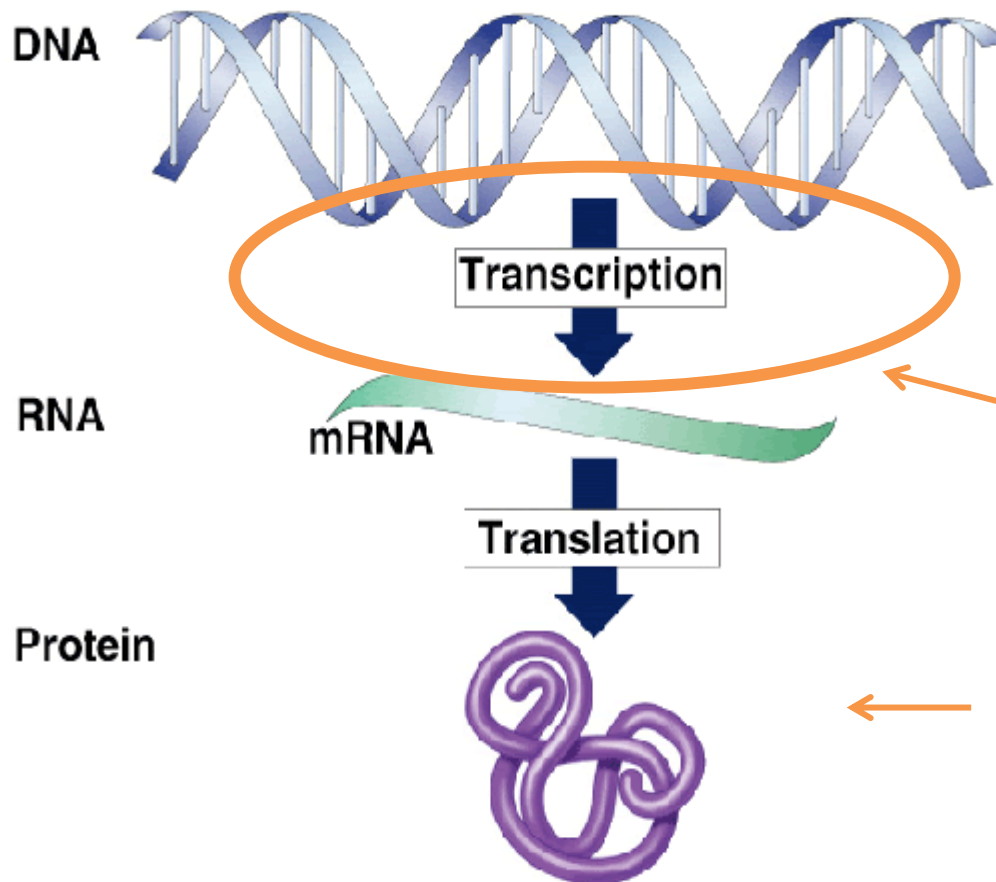


**Hepalink**



## Apabetalone and the BET Platform

# Differentiation: Advanced Mechanism of Action



## CRISPR: 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**

## Apabetalone

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**

## Traditional drug therapies

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

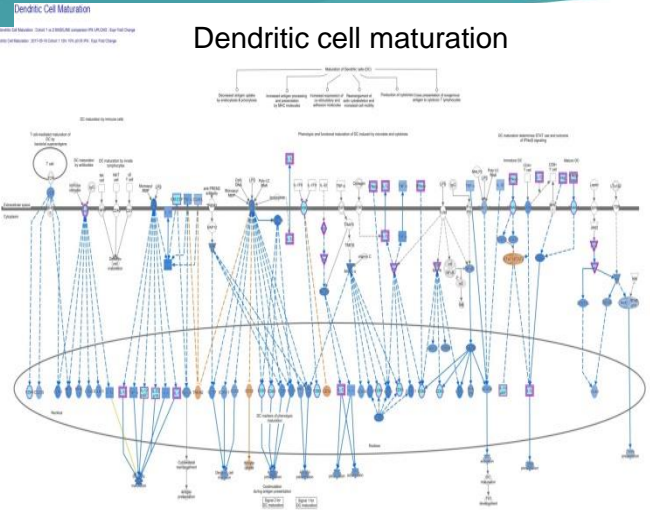
**Antibody or Inhibitor – blocks activity of one mediator of disease**



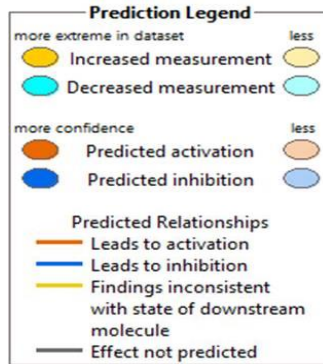
# SOMAscan® Analysis of Plasma Proteome

## IPA Canonical Pathways: Top 5 Pathways Upregulated

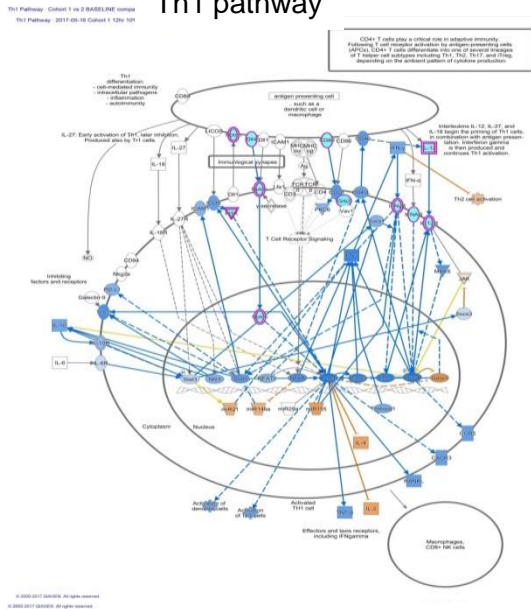
### Dendritic cell maturation



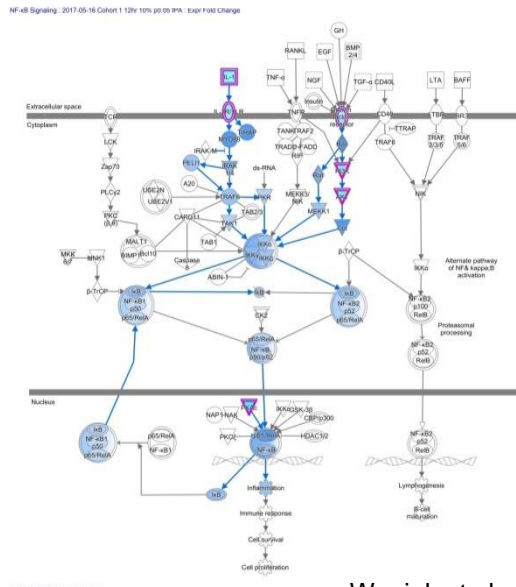
## Apabetalone



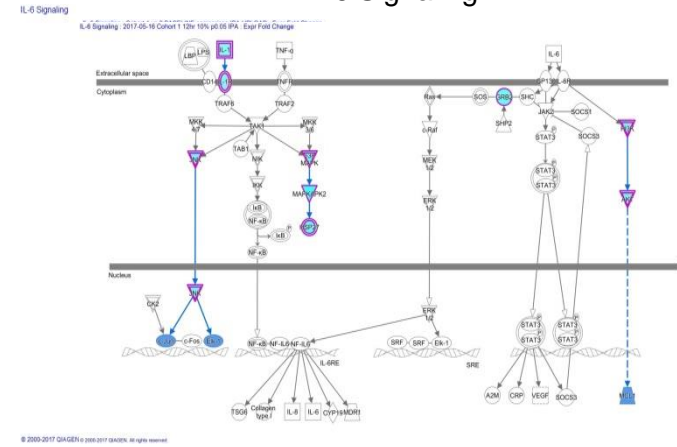
### Th1 pathway



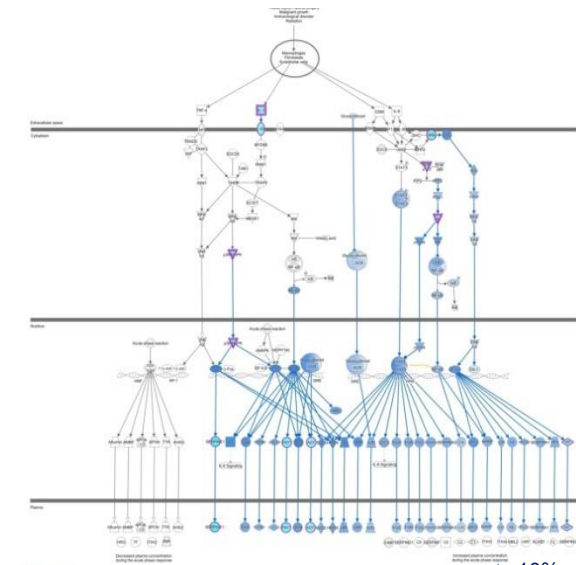
### NF-κB Signaling



### IL6 Signaling



### Acute Phase Response



Wasiak et al., 2017

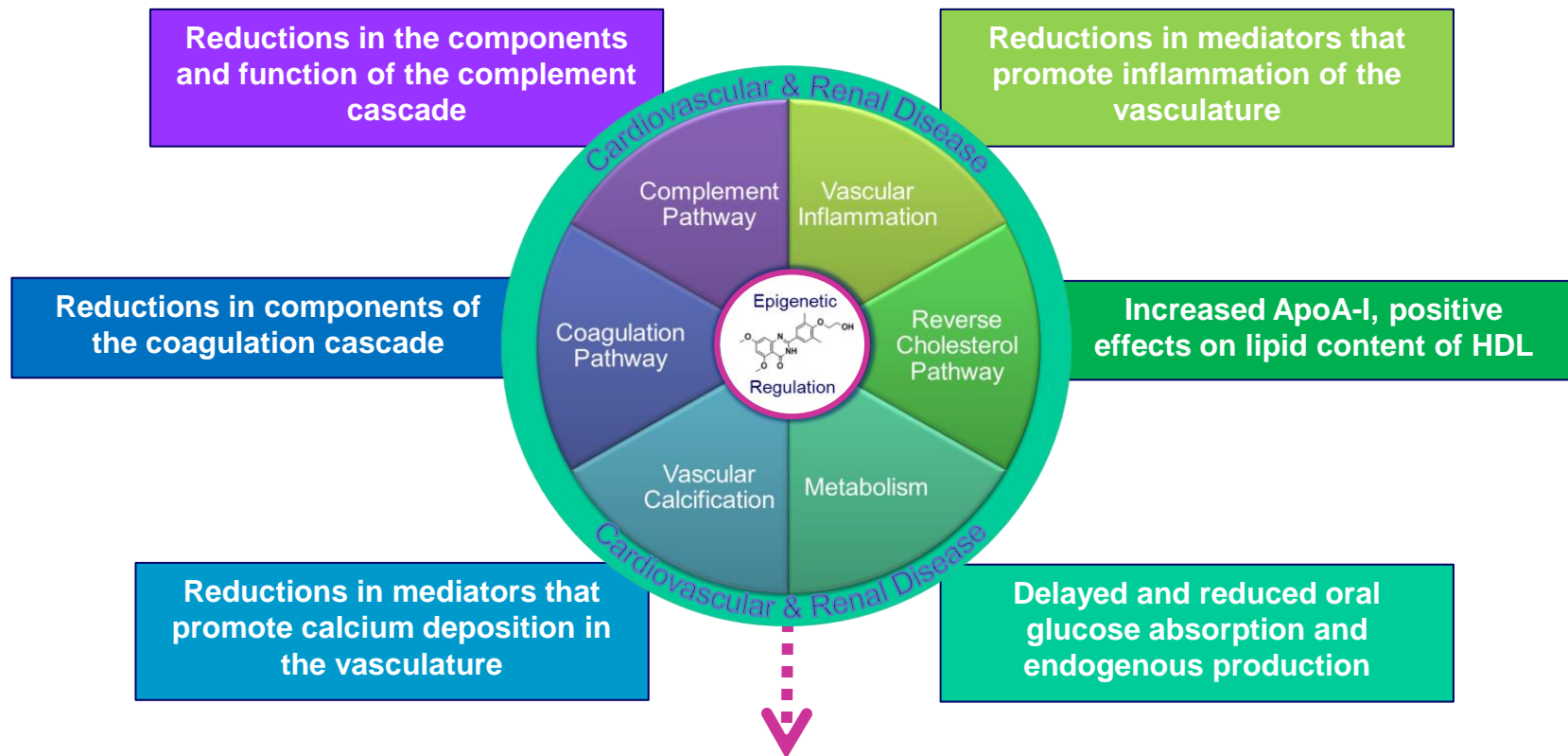
Δ>10% p≤0.05



- Resverlogix has discovered compounds that bind the bromodomains of BET proteins with a **high degree of specificity**.
  - Other BET programs hit multiple targets (BRD2, BRD3, BRD4, BRDT, etc.)
  - Our expertise in medicinal chemistry and epigenetics allows us to identify small molecules that target one or a specified subset of BET proteins
    - Resverlogix's apabetalone product candidate specifically targets BRD4
- Our Phase 2 clinical program provided us with **the only blood bank of BET inhibitor-treated patients in the world**
  - In-depth analysis such as proteomics, genomics, and pathway analysis revealed advanced knowledge of BET activities
  - The resulting knowledge from these activities provided a level of sophistication around BET that surpasses that of many others working in this area
- The specificity of Resverlogix's molecules **avoids side effects seen when multiple targets are affected**
  - BET programs in oncology can tolerate a high degree of side effects due to the nature of the disease being treated
  - Chronic conditions such as cardiovascular disease and renal impairment require treatments with a side-effect profile acceptable for long-term treatment

# BET Inhibition Impacts the Pathways that Drive Cardiovascular Disease and Kidney Diseases

Apabetalone, a bromodomain extra-terminal (BET) protein inhibitor, inhibits BRD4, thereby regulating the expression of genes and restoring the function of pathways underlying the pathogenesis of CVD and kidney disease

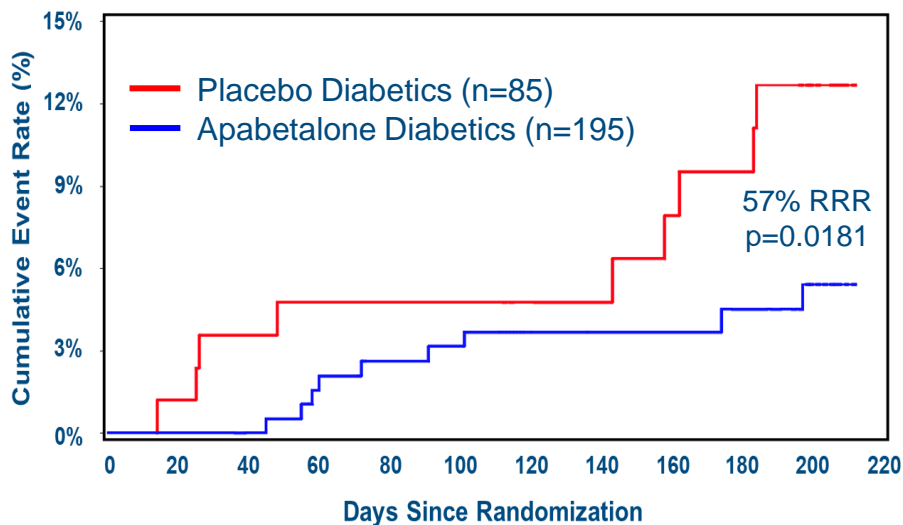
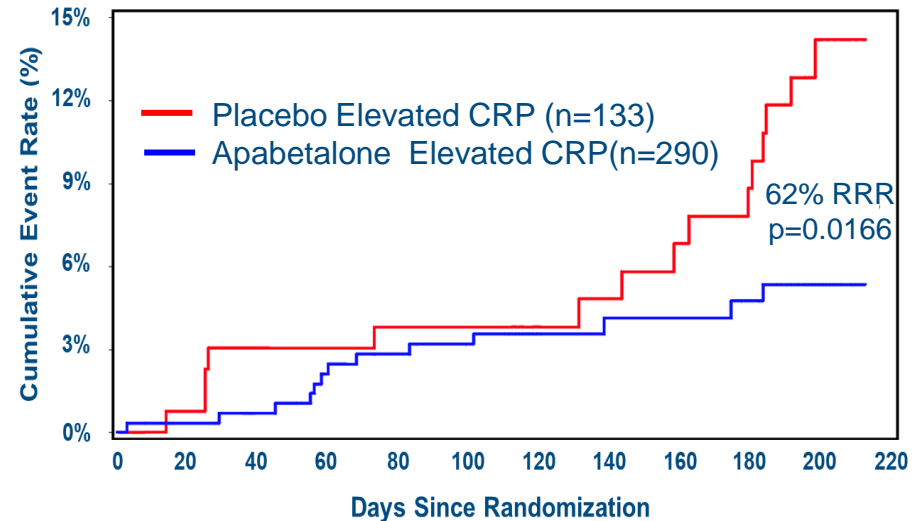
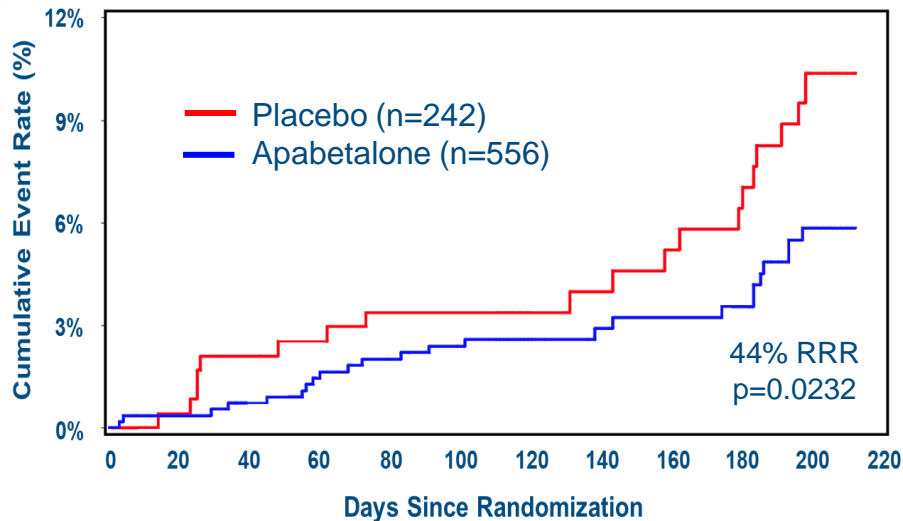


Reduced incidence of cardiac events and renal impairment



# BETonMACE Clinical Program Overview

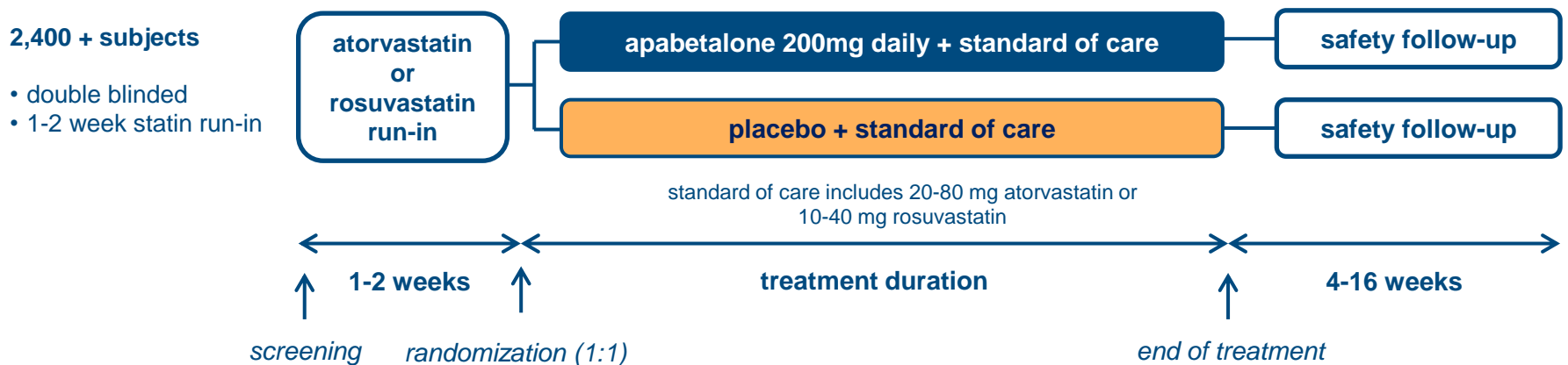
# Nicholls et al. 2017: American Journal of Cardiovascular Drugs



**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

# CVD Program Moving Forward- BETonMACE CV Outcomes Study



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

## 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 < 1.04 for males and < 1.17 for females

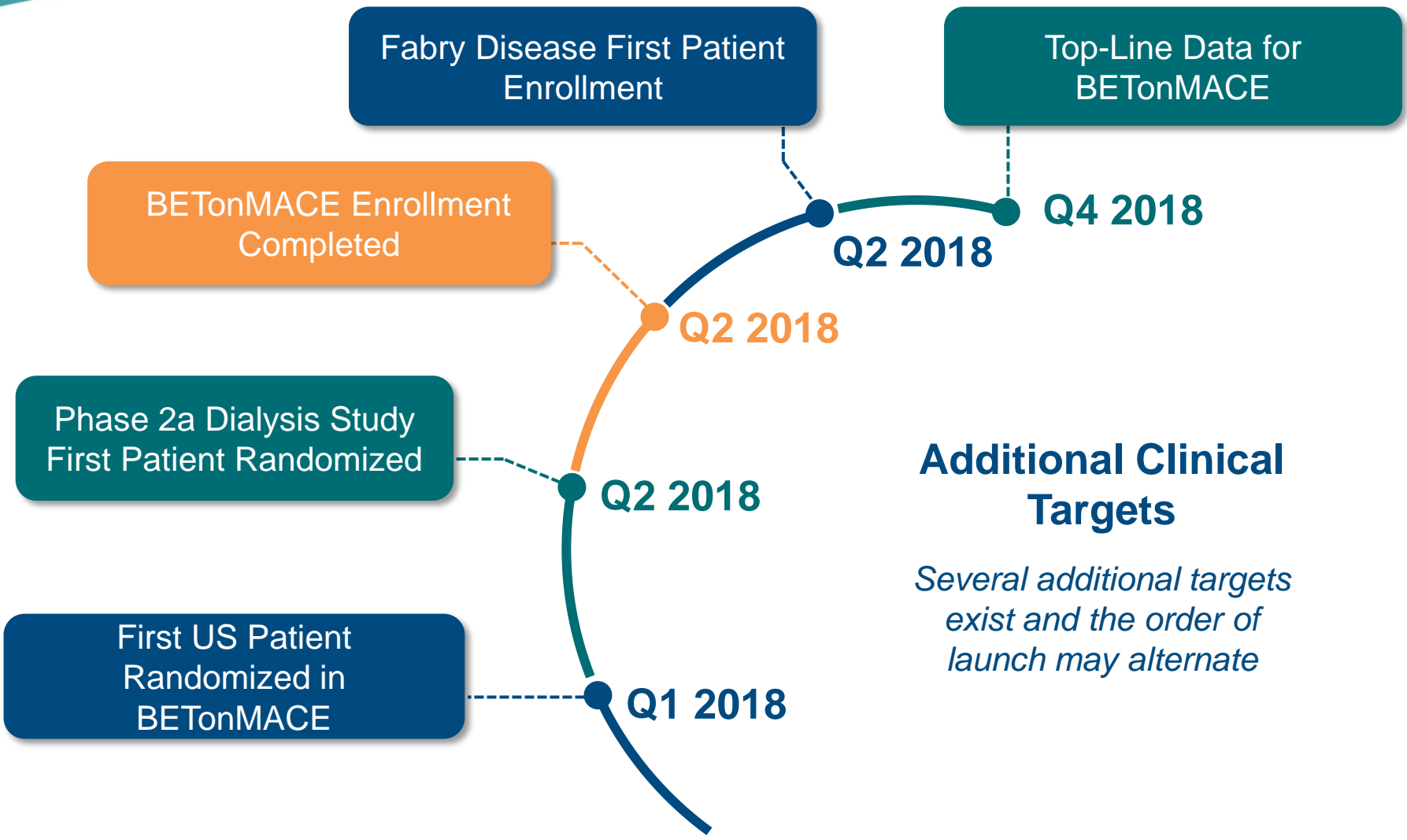


# BETonMACE Commenced November 2015



Apabetalone has already been tested in over 1,800 patients in 19 countries around the world.

# The Upcoming Clinical Year Estimates



## Additional Clinical Targets

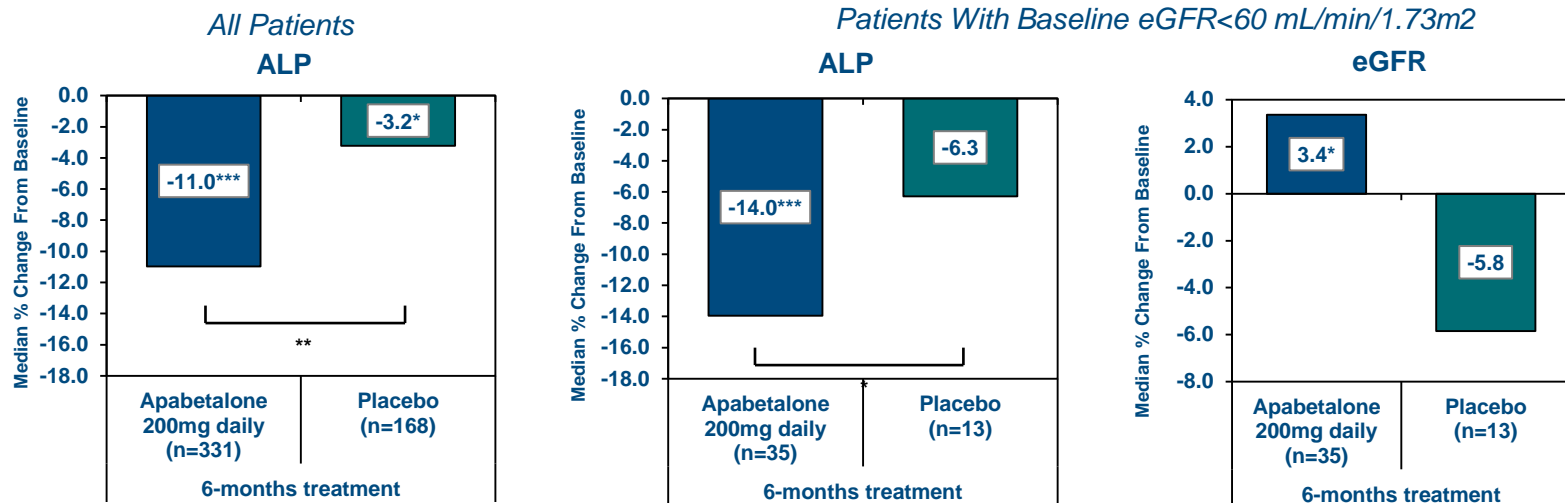
*Several additional targets exist and the order of launch may alternate*



# Chronic Kidney Disease Clinical Program Overview

# Rationale for Kidney Disease Program

- Apabetalone has demonstrated reductions in alkaline phosphatase (a strong marker of CKD risk) and improvements in eGFR in CKD patients (eGFR < 60 mL/min/1.73m<sup>2</sup>) with CVD in the phase 2 ASSURE and SUSTAIN trials.

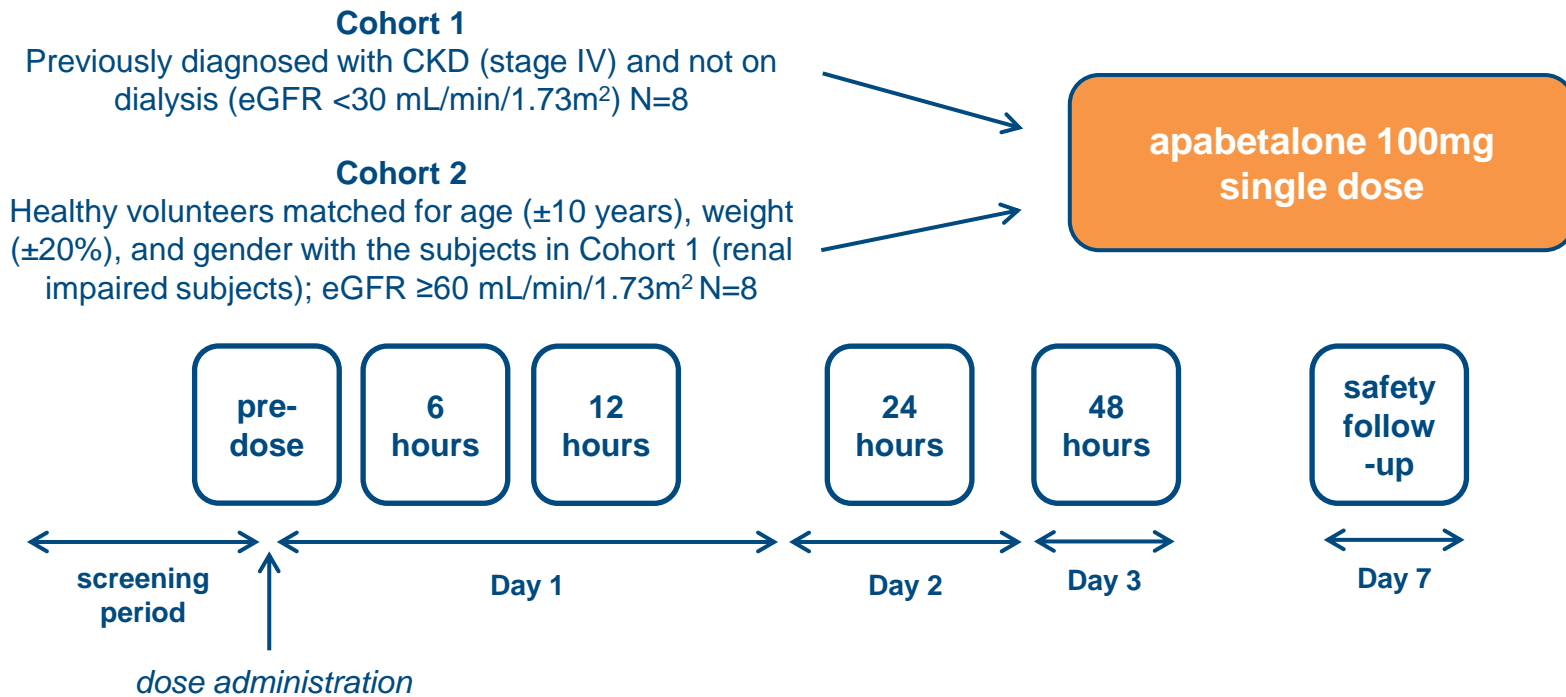


Data Presented in Keynote Address at the 2015 American Society of Nephrology Conference, San Diego

- Resverlogix believes that BET inhibition and apabetalone may have the potential to improve kidney function, as measured by eGFR, in patients suffering from various stages of kidney disease.
- Resverlogix is currently investigating the potential for expansion into specific kidney indications:
  - CKD (Stages 3a and 3b) patients, with a history of CVD (Phase 3 BETonMACE subgroup)
  - High Risk CKD Patients on Dialysis (Phase 2a BETonRenal study)

# Kidney Disease: Phase I Study

A Phase I, open-label, parallel group study to evaluate the safety and pharmacokinetics of a single oral dose of apabetalone (RVX-208) in subjects with severe renal impairment



Trial demonstrated that apabetalone has a highly differential effect on protein levels based on disease status in healthy versus sick cohorts, reducing a variety of plasma proteins and downregulating pathways activated in the CKD cohort



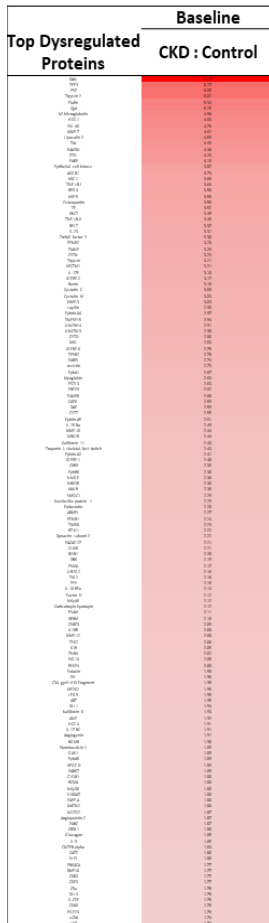
# CKD Program - Phase 1 Data

## Effect of Apabetalone on Differentially Expressed Proteins

289 proteins were different between the plasma of CKD patients and matched controls (red indicates higher protein levels in CKD/control)

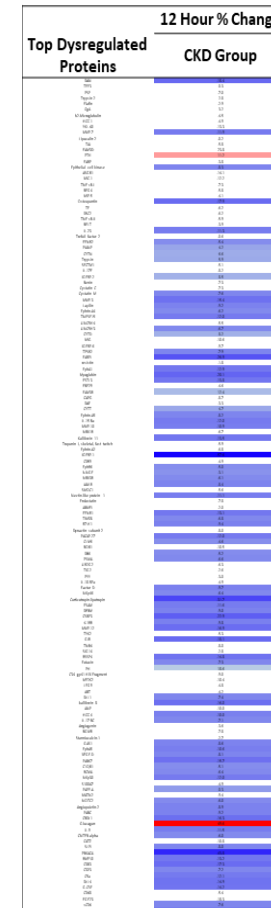
**CKD = Subjects with stage 4 Chronic Kidney Disease**

152 of the 289 differentially expressed proteins in the CKD patients were downregulated at 12 hours following one dose of apabetalone



Blue = downregulated;  
white = no change;  
Red = upregulated

**In CKD patients, one dose of apabetalone reduced CKD and CVD biomarkers that were dysregulated at baseline**



# SOMAscan® Analysis of Plasma Proteome – Phase 1 Trial

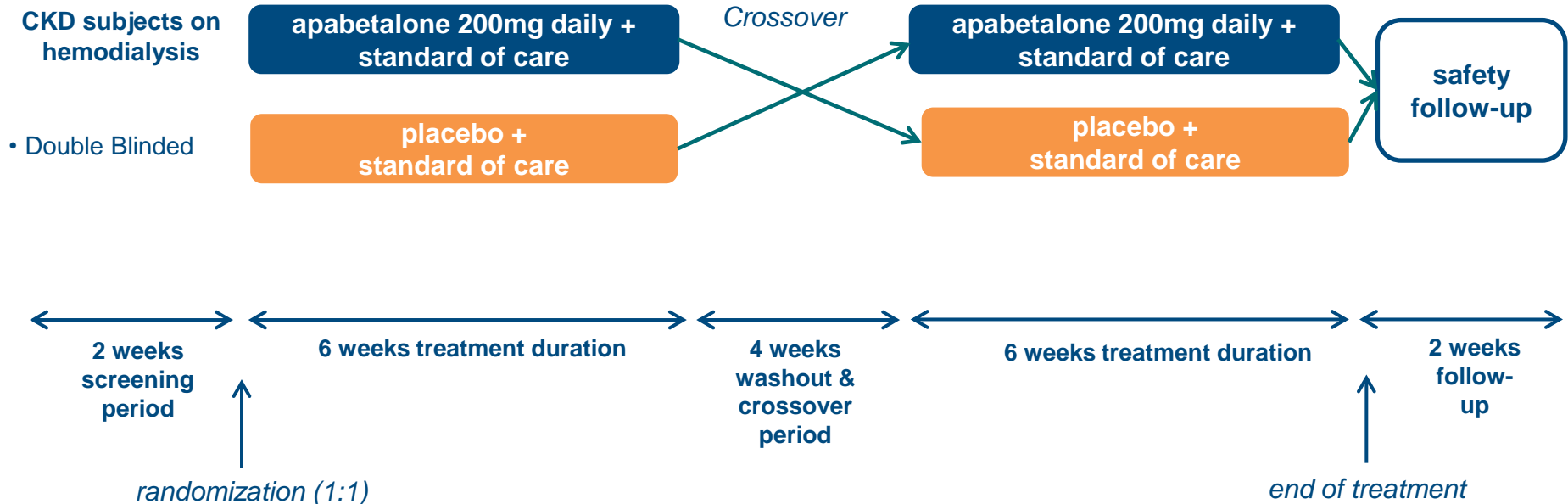
Apabetalone Reduces CVD and CKD Biomarkers



	Protein Name	Gene Symbol	Subjects with CKD (stage IV) (n=8) treated with 100 mg Apabetalone		Matched Control Subjects (n=8) treated with 100 mg Apabetalone	
			% Δ from baseline at 12h	p-value	% Δ from baseline at 12h	p-value
Inflammation	Interleukin-6	IL6		0.05	NS	
	Interleukin-1 alpha	IL1A		0.01	NS	
	Interferon gamma	IFNG		0.04	NS	
	TNF receptor superfamily member 1A	TNFRSF1A		0.05	NS	
	C-reactive protein	CRP		0.04	NS	
	Tumor necrosis factor	TNF		0.02	NS	
Cell Adhesion	P-selectin	SELP		0.04	NS	
	E-selectin	SELE		0.01		0.02
	Intercellular adhesion molecule 1	ICAM1		0.05		0.04
	Vascular cell adhesion protein 1	VCAM1		0.01	NS	
Matrix Remodeling Calcification	Fibronectin	FN1		0.02	NS	
	Stromelysin-1	MMP3		0.02	NS	
	Stromelysin-2	MMP10		0.02	NS	
	Osteopontin	SPP1		0.01		0.04
Thrombosis	Plasminogen activator inhibitor 1	SERPINE1		0.04	NS	
	Tissue-type plasminogen activator	PLAT		0.01	NS	
	Urokinase-type plasminogen activator	PLAU		0.01	NS	
	D-dimer	FGA/B/C		0.05	NS	
	Urokinase plasminogen activator surface receptor	PLAUR		0.02	NS	

Apabetalone reduces markers of inflammation, cell adhesion, matrix remodeling, calcification and thrombosis in the CKD cohort after one dose and 12 hours

# BETonRENAL Dialysis Study Design



- The study is an sequential cross-over trial to evaluate the safety, tolerability, and efficacy of apabetalone in CKD patients on hemodialysis in addition to standard of care
- 30 CKD patients receiving standard regimens of hemodialysis three days per week
- Clinical sites identified and prepared to begin patient enrollment



**Dr. Kamyar Kalantar-Zadeh**  
Chair  
*UC Irvine Chief Nephrology*



**Dr. Marcello Tonelli**  
Member  
*University of Calgary Chair Medical Research*



**Prof. Vincent Brandenburg**  
Member  
*University Hospital RWTH Aachen*



**Dr. Srinivasan Beddhu**  
Member  
*University of Utah*



**Dr. Carmine Zoccali**  
Member  
*University Pisa*



**Dr. Mathias Haarhaus**  
Member  
*Karolinska University Hospital*

# Why Invest in Resverlogix?



- **Phase 3 company** focused on significant unmet need in high-risk CVD patient population with lead therapeutic - **apabetalone**
- **Market leader with significant potential** – targeting high-risk unmet need in several patient groups – Over 10MM patients in top 7 markets
- **Advancing development** of apabetalone in high-risk (dialysis) CKD patients – New phase 2 clinical trials to commence in early 2018
- **Well established safety profile** - to date, over 2,000 patients treated with apabetalone with no significant safety issues
- **Proven track record** of funding development while minimizing shareholder dilution