Zacks Small-Cap Research

June 29, 2016
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# Resverlogix Corp. (RVX - TSX)

## *Initiating with CAD$5.00 Target: Successful BETonMACE Provides Material Upside*

Based on our DCF model and a 15% discount rate, RVX is valued at approximately CAD$5.00 per share. Our model applies a 64% probability of apabetalone sales for indications in the BETonMACE trial. Our valuation only includes BETonMACE indication contributions from the US, Europe, & Latin America, as well as royalties from the Hepalink arrangement. It does not recognize potential from orphan or renal indications.

| | |
|---|---|
| Current Price (6/28/2016) | $1.15 |
| **Valuation** | **$5.00** |

## INITIATION

Resverlogix Corp. (RVX.TO) began recruiting and dosing participants in the Phase 3 BETonMACE trial of its lead candidate apabetalone (RVX-208) in high-risk CVD patients with diabetes in November 2015. We believe the trial will take approximately 3 years to complete, targeting topline readout in 2018. With a potential impact on multiple markers for CVD we are optimistic on a materially significant impact on MACE.

The company also may launch orphan disease studies in and renal opportunities in 2016 which may provide for a more rapid approval and access to market.

At the current price, we view Resverlogix shares as undervalued, and in a position to provide long-term upside potential. We initiate RVX at CAD$5.00 per share and believe that expansion into new geographies, the orphan disease program, and renal disease, could provide further upside to our valuation.

## SUMMARY DATA

| | |
|---|---|
| **52-Week High** | **2.52** |
| **52-Week Low** | **1.00** |
| **One-Year Return (%)** | **-47.7** |
| **Beta** | **3.55** |
| **Average Daily Volume (sh)** | **17,097** |
| **Shares Outstanding (mil)** | **105.2** |
| **Market Capitalization ($mil)** | **115.7** |
| **Short Interest Ratio (days)** | **1.17** |
| **Institutional Ownership (%)** | **N/A** |
| **Insider Ownership (%)** | **N/A** |
| **Annual Cash Dividend** | **$0.00** |
| **Dividend Yield (%)** | **0.00** |
| **5-Yr. Historical Growth Rates** | |
| **Sales (%)** | **N/A** |
| **Earnings Per Share (%)** | **N/A** |
| **Dividend (%)** | **N/A** |
| **P/E using TTM EPS** | **N/A** |
| **P/E using 2017 Estimate** | **N/A** |
| **P/E using 2018 Estimate** | **N/A** |
| **Zacks Rank** | **N/A** |

| | |
|---|---|
| **Risk Level** | **Above Average** |
| **Type of Stock** | **Small-Growth** |
| **Industry** | **Med-Biomed/Gene** |

## ZACKS ESTIMATES

### Revenue

(In millions of US$)

| | Q1 (Jul) | Q2 (Oct) | Q3 (Jan) | Q4 (Apr) | Year (Apr) |
|---|---|---|---|---|---|
| 2015 | $0.0 A | $0.0 A | $0.0 A | $0.0 A | $0.0 A |
| 2016 | $0.0 A | $0.0 A | $0.0 A | $0.0 E | $0.0 E |
| 2017 | | | | | $0.0 E |
| 2018 | | | | | $0.0 E |

### Earnings per Share

| | Q1 (Jul) | Q2 (Oct) | Q3 (Jan) | Q4 (Apr) | Year (Apr) |
|---|---|---|---|---|---|
| 2015 | $0.08 A | -$0.04 A | -$0.02 A | -$0.23 A | -$0.21 A |
| 2016 | $0.03 A | -$0.04 A | -$0.08 A | -$0.06 E | -$0.16 E |
| 2017 | | | | | -$0.25 E |
| 2018 | | | | | -$0.26 E |

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## INITIATING COVERAGE

We are initiating coverage of Resverlogix Corp. (TSX: RVX) with a CAD$5.00[1] price target based on our estimates of a 2020 launch of RVX-208 (apabetalone) in Europe and Latin America, followed by a launch in the United States and in partner markets for reduction of major adverse cardiovascular event (MACE) in high-risk populations.

Resverlogix is a clinical stage cardiovascular company with an epigenetic platform technology that modulates protein production. Novel compounds arising from Resverlogix's epigenetic drug development platform function by inhibiting Bromodomain and Extra Terminal domain (BET) proteins and have the potential to impact multiple biologies and diseases. Resverlogix is engaged in the development of novel therapies for important global medical markets in a variety of broad areas of cardiovascular disease (CVD), atherosclerosis, neurodegenerative diseases, renal conditions and potentially other orphan indications.

Apabetalone (RVX-208) has a multifactorial approach and impacts several key biological processes that play a role in vascular disease risk. These processes include vascular inflammation, complement, coagulation, vascular calcification, reverse cholesterol transport (RCT) and metabolic mediators.

Apabetalone is the first selective BET bromodomain inhibitor in clinical trials for high-risk vascular disease. Resverlogix is the first to test apabetalone in the reduction of major adverse cardiac events (MACE) in diabetic and chronic kidney disease (CKD) patients, and has a seven-year head start in the arena of epigenetic small molecules for CVD risk reduction. Analysis of prior Phase 2 clinical trials data ("ASSERT," "ASSURE," and "SUSTAIN") indicated that apabetalone significantly reduces coronary atherosclerosis and major adverse cardiac events in patients with CVD who also have a low level of high-density lipoprotein (HDL) and elevated C-reactive protein (CRP), and other select populations with unmet medical need. Resverlogix is currently underway with its Phase 3 clinical trial "BETonMACE" which seeks to evaluate time to MACE in high-risk type 2 diabetes mellitus subjects with coronary artery disease.

As of January 2016, Resverlogix held approximately USD$30 million in cash on its balance sheet and is spending approximately $2 million per month to fund internal operations, the BETonMACE trial and interest payments. The company carries $41.5 million of debt on its balance sheet which it plans to refinance prior to summer 2017. Resverlogix began enrolling for its Phase 3 BETonMACE trial in late 2015 and while exact expenditures will be based on the total number of patients enrolled, Resverlogix has guided trial costs to be in the range of $45 to $50 million over the anticipated three year duration.

Based on the anticipated length of the trial, the announcement of top-line data is expected to be in late 2018, with subsequent filing of a new drug application (NDA). The company will initially pursue an approval in Europe and Latin America followed shortly after by a filing in the United States. Resverlogix also has a relationship with Hepalink in China and Taiwan which would provide for additional licensing revenue from sales in Asia.

## INVESTMENT THESIS

Cardiovascular disease (CVD) is the number one killer in both North America and the world. With estimated costs of $300 billion in the United States and almost $900 billion worldwide, there is an intense demand for therapies that will address this very important disease. In developed countries, there is an accelerating demographic trend of growth in the older population. Given the high degree of correlation between age and heart disease, as we see faster growth in the developed world's older population, the globe will also experience a substantial increase in heart disease. Based on US Census Bureau data, in just the United States alone, the over 60 population will increase from 69 million in 2016 to over 111 million in 2050. This is a 61 percent increase over this time period and a rate that is double the overall population growth rate.

Below is a population pyramid that illustrated the large population bulge that occurs in the age cohorts from 50 – 60. We also include the US Census Bureau's forecast of population by age cohort in 2050.

[1] Note that Resverlogix financial statements are prepared in US Dollars, however, we generate our valuation price using Canadian dollars to reflect the currency used on the Toronto Stock Exchange.

**Exhibit I – 2016 Population by Age Cohort, United States**

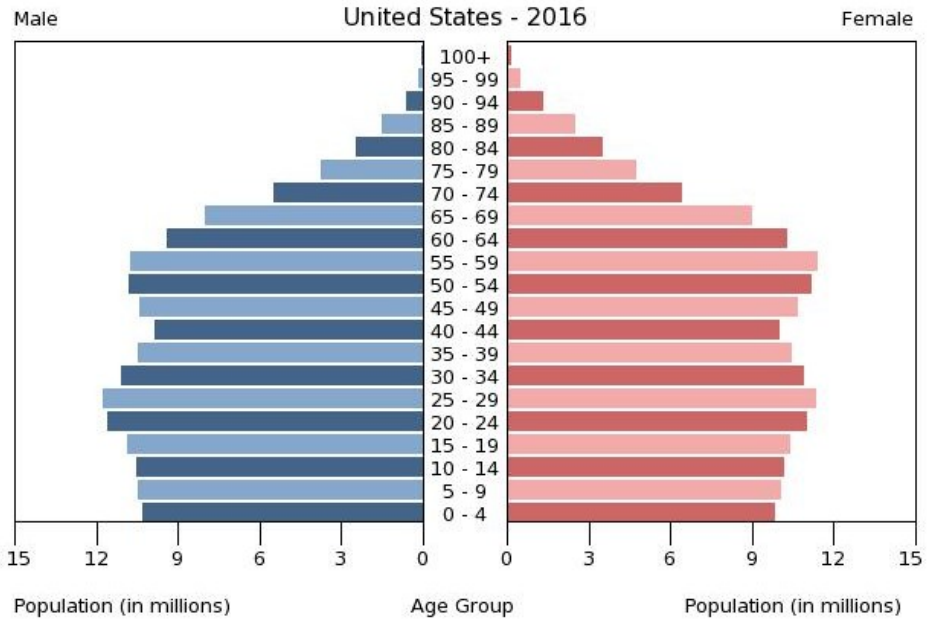
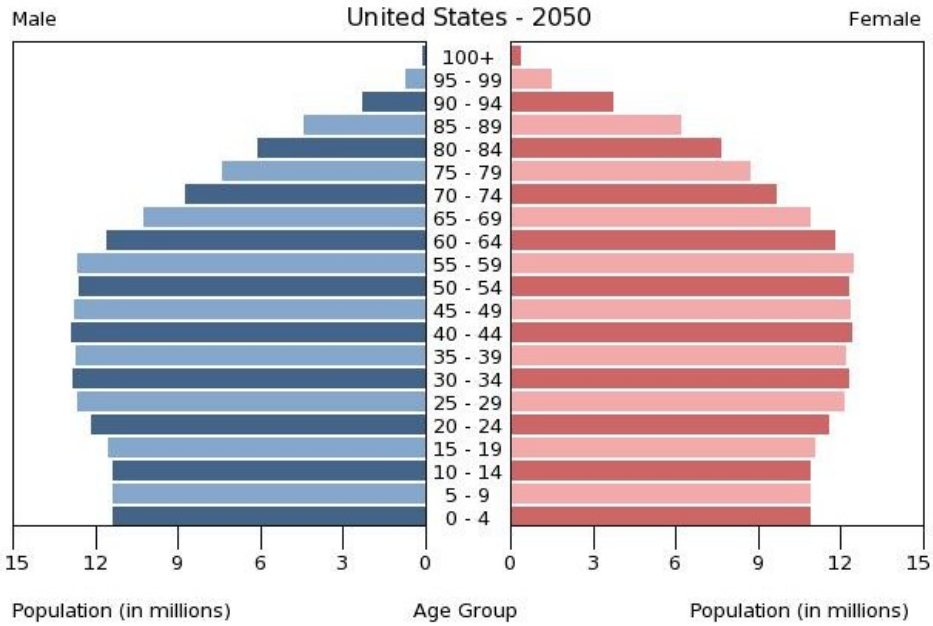



**Exhibit II – 2050 Estimated Population by Age Cohort, United States**




Besides age, several other risk factors for heart disease have increased over time including obesity, diabetes and high cholesterol. These risk factors are expected to increase the incidence of heart disease in the population, which suggests that the incidence of heart disease will grow even faster than the rate of the aging population.

The need and demand for cardiovascular disease treatment is immense and is expanding. The current slate of therapies have only modestly addressed underlying problems, leaving substantial opportunity for therapies that are more effective and address a wider list of underlying biologies.

Resverlogix's lead compound, apabetalone has shown promise in addressing many of the key biomarkers underlying CVD and potentially has applications in other therapeutic areas beyond CVD. The drug is currenly in Phase 3 trials for high risk cardiovascular disease and the company has indicated that there are renal and orphan indications that merit clinical investigation on the horizon, potentially expanding the addressable market for apabetalone. Based on the many completed studies for the compound, there is evidence that it has a positive

impact on several key biologies that are behind CVD risk such as vascular inflammation, complement, coagulation, vascular calcification, RCT and metabolic mediators.

Given the substantial size of the population that is anticipated to suffer from CVD, and the dramatic costs that are expected to be incurred, there is an acute need for therapies to address the growing problem. Even with competing therapies, many of which have not shown promising levels of efficacy or safety, there is a materially large niche for a number of treatements for CVD in the era of personalized medicine. The promising clinical evidence for Resverlogix's apabetalone is supportive of an investment in the company's stock.

In the following sections we provide additional detail regarding the impact of CVD. We further elaborate on the etiology of the disease and provide a backdrop for the method of action for RVX's lead compound. A review of competing therapies is also provided.

**Cardiovascular Disease: #1 Cause of Death Worldwide**

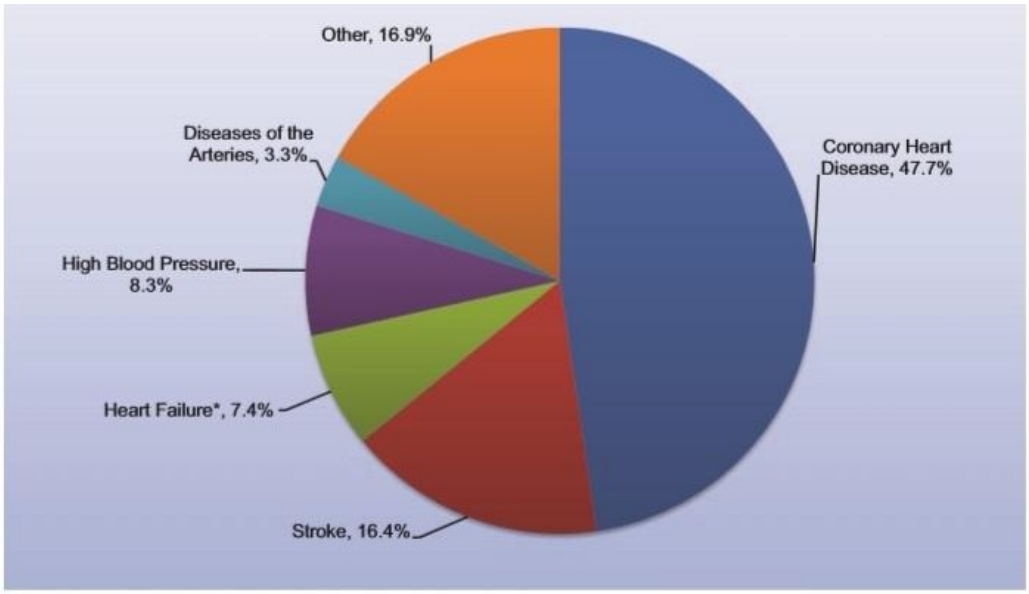
Cardiovascular disease (CVD) refers to a category of diseases that involve the circulatory system including the heart and blood vessels. Several of the key precursors to CVD include heart attack, stroke, angina, aortic aneurysms, and kidney failure among others. These disorders result from several different processes including inflammation, atherosclerosis, thrombosis, and vascular calcification. CVD is also promoted by risk factors including obesity, diabetes, hypertension, diabetes, cigarette smoking, decreased levels of HDL and apolipoprotein A-1 (Apo A-1) levels, as well as elevated levels of inflammatory markers such as CRP.

The American Heart Association reported CVD as the leading cause of death in the world accounting for 17.3 million deaths based on the group's 2015 Heart Disease and Stroke Statistics Update. The disease also accounts for 30% of global deaths which makes CVD the number one cause of death globally, and claiming more lives than all types of cancer combined. By 2030, almost 24 million people are expected to die annually from cardiovascular diseases.

It is important to highlight that in every year since 1900 (excluding 1918 due to the impact of the Spanish Flu pandemic), CVD was consistently responsible for more deaths than any other cause in the United States (Ford et al., 2007 and NVSR – HHS/CDC public use data file, 2013). According to the U.S. CDC, approximately 610,000 individuals die of heart disease in the U.S. every year, which is approximately 1 in every 4 deaths. The American Heart Association pegs the rate at a slightly higher 787,000 deaths per year. CVD is the leading cause of death in both men and women in the U.S., with coronary heart disease being the most common type of CVD resulting in over 370,000 deaths annually (below).

According to the most current statistical update from the American Heart Association, more than 85 million American adults have one or more types of cardiovascular disease, with approximately 44 million of these being 60 years old or greater (Mozaffarian et al., 2015).

**Exhibit III – Deaths Attributable to CVD in the United States, 2011**




*Sources:* National Heart, Lung, and Blood Institute from National Center for Health Statistics;
Heart Disease and Stroke Statistics—2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322.

## The Economic Burden of Cardiovascular Disease

CVD and stroke accounted for 15% of total health expenditures in 2011 in the United States, which is more than any other major diagnostic group (MEPS, 2011). The American Heart Association pegs the amount at $310 billion from heart disease, hypertension, stroke and other CVD. In the U.S., the total direct and indirect costs of CVD and stroke for 2011 were estimated to be about $320 billion per year. This value includes $196 billion of direct expenses associated with the cost of physicians and other health care providers, hospital services, medication, and home health care as well as $125 billion of indirect expenses of lost future productivity due to premature CVD and stroke mortality in 2011 (below). By way of comparison, CVD and stroke direct costs of $196 billion are far higher than that of the National Cancer Institute estimates for cancer in 2011 of $88.7 billion in direct costs.

**Exhibit IV – Estimated Direct and Indirect Costs ($Billions) of CVD and Stroke in United States, 2011**

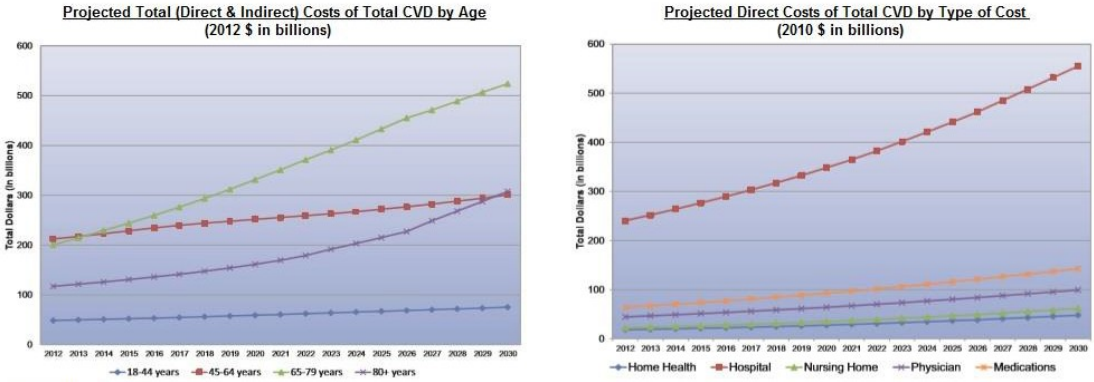
| | Heart Disease* | Stroke | Hypertensive Disease† | Other Circulatory Conditions | Total CVD |
|---|---|---|---|---|---|
| Direct costs‡ | | | | | |
| Hospital inpatient stays | 70.5 | 7.6 | 4.9 | 8.7 | 91.7 |
| Hospital emergency department visits | 4.8 | 1.2 | 1.5 | 0.6 | 8.1 |
| Hospital outpatient or office-based provider visits | 23.1 | 2.0 | 13.5 | 5.9 | 44.5 |
| Home health care | 6.6 | 5.1 | 3.9 | 2.3 | 17.9 |
| Prescribed medicines | 11.3 | 1.7 | 19.0 | 1.5 | 33.5 |
| Total expenditures | 116.3 | 17.5 | 42.8 | 19.0 | 195.6 |
| Indirect costs§ | | | | | |
| Lost productivity/mortality‖ | 99.3 | 16.0 | 3.6 | 5.6 | 124.5 |
| Grand totals | 215.6 | 33.6 | 46.4 | 24.6 | 320.1 |

Numbers do not add to total because of rounding.
CVD indicates cardiovascular disease.
*This category includes coronary heart disease, heart failure, part of hypertensive disease, cardiac dysrhythmias, rheumatic heart disease, cardiomyopathy, pulmonary heart disease, and other or ill-defined heart diseases.
†Costs attributable to hypertensive disease are limited to hypertension without heart disease.

*Sources:* Agency for Healthcare Research and Quality; National Center for Health Statistics; Wendy Max - Institute for Health and Aging (UCSF).
Heart Disease and Stroke Statistics - 2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322.
Estimates prepared by Michael Mussolino, National Heart, Lung, and Blood Institute

The American Heart Association estimates that the total direct medical costs of CVD will increase from $273 billion in 2010 to roughly $818 billion by 2030 in the United States. Of these direct costs, 60% is due to hospital related expenses, 16% to medications, 11% to physicians, 7% to nursing home care, 5% to home health care, and 1% to other costs (bottom right). Indirect costs for all CVDs are estimated to increase from $183 billion in 2012 to $290 billion in 2030, which equates to an increase of 58%. It is projected that by 2030, 44% of Americans will have some form of cardiovascular disease (Heidenreich et al., 2011). Additionally, the estimated cost of CVD worldwide in 2010 was $863 billion, and this cost is estimated to increase to over a trillion dollars by 2030 (Bloom et al., 2011). Below we provide graphic representation of the costs of CVD over time by age cohort and by type of cost from an American Heart Association 2015 report.

**Exhibit V – Projected CVD Costs**

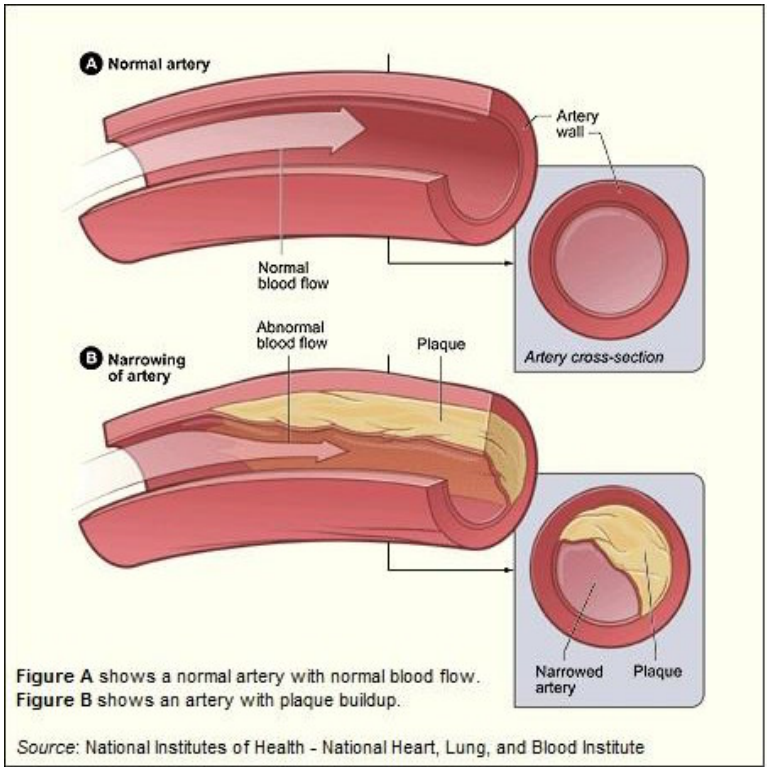



*Sources:* Heidenreich *et al.*, 2011
Heart Disease and Stroke Statistics - 2015 Update: A Report from the American Heart Association. *Circulation.* 2015;131:e29–e322.

**Atherosclerosis: The Silent Killer**

Cholesterol and lipids that are ingested through the diet are transported throughout the body via specialized carriers known as lipoproteins or more specifically, low-density lipoprotein (LDL) cholesterol and HDL cholesterol. LDL is a major cholesterol carrier in the blood and carries produced or absorbed cholesterol from the gut to the other organs throughout the body. Over time, elevated amounts of LDL in the blood can slowly deposit into the walls of arteries forming atherosclerotic plaques. On the other hand, HDL carries cholesterol away from the arteries and back to the liver for excretion from the body through a process called Reverse Cholesterol Transport (RCT). HDL's major lipoprotein is Apo A-1, and there is growing evidence that Apo A-1/HDL removes excess cholesterol from atherosclerotic plaques; thus, not only preventing plaque growth but also promoting the regression of existing plaques. Atherosclerosis develops when there is too much cholesterol being deposited in the arteries and organs by LDL, and/or too little being cleared by HDL and RCT. To date, one of the most successful strategies for preventing CVD is by reducing LDL cholesterol levels through the use of statins. In the following exhibit we show the difference between a normal artery and an artery that has accumulated plaques which leads to atherosclerosis.

**Exhibit VI – Arterial Atherosclerosis**




Atherosclerosis is the major underlying cause of CVD and over time can result in heart attack, stroke, and death. It involves hardening and narrowing of the lumen of arteries due to the accumulation of plaques, which consist of fat, cholesterol, lipids, calcium, white blood cells, and other substances within the walls of these blood vessels. This process can arise due to several factors including diet, smoking, hypertension, elevated lipids, and inflammatory markers. As the disease progresses, the plaques harden, which leads to loss of elasticity and function in the blood vessel, and the restriction of blood flow through arteries. This results in decreased flow of oxygen-rich blood to vital organs and other parts of the body. Atherosclerosis remains a major cause of mortality and morbidity worldwide. Atherosclerosis can affect any artery in the body, and therefore different cardiovascular diseases may develop based on what arteries are involved (NIH-NHLBI):

- Coronary Heart Disease (CHD) or Coronary Artery Disease (CAD) is the most common form of heart disease and occurs if there is a build-up of plaque in the coronary arteries, which are blood vessels that supply the heart muscle. These arteries normally supply oxygen-rich blood to the heart, and once narrowed by plaque, there is restricted blood flow to the cardiac muscle. Additionally, blood clots can also form when atherosclerotic plaques are present and can further impede blood flow. Once blood flow to the heart is reduced, angina (chest discomfort or pain) or myocardial infarction (heart attack) can occur. CHD is the number one killer in the U.S.

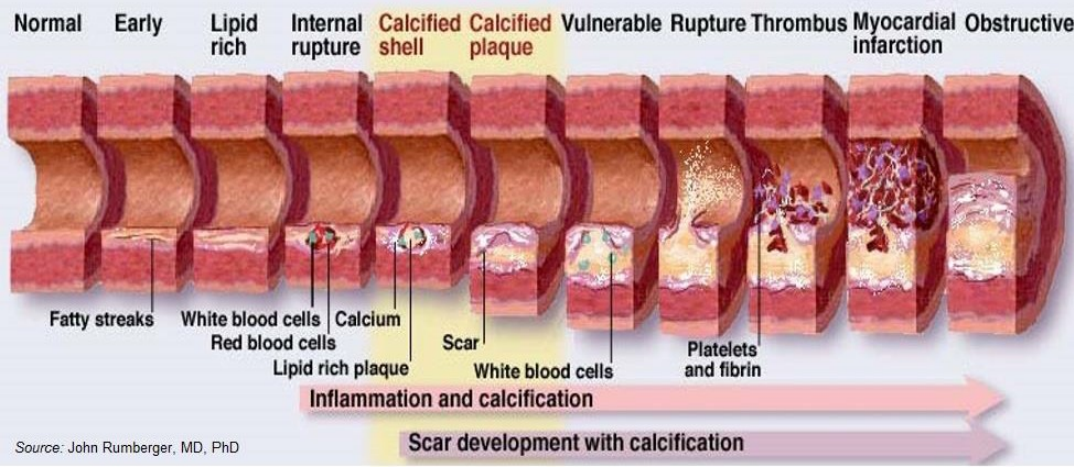
- Stroke, or cerebrovascular accident, occurs when blood flow to the brain is restricted or reduced. It is often caused by a build-up of plaque in the carotid arteries that supply oxygen-rich blood to the brain.

- Peripheral Arterial Disease (PAD) or Peripheral Vascular Disease (PVD) occurs if there is build-up of plaque in the blood vessels that supply oxygen-rich blood to the arms, legs, and pelvis. If blood flow is restricted or reduced, numbness, pain, and infections can ensue.

- Chronic Kidney Disease (CKD) occurs if there is build-up of plaque in the renal arteries, which normally supply oxygen-rich blood to the kidneys. The function of the kidneys is to eliminate waste and excess water from the body, but with CKD progression, kidney function starts to deteriorate and function is slowly lost.

- Other forms of CVD include Heart Failure, Rheumatic Heart Disease, and Congenital Heart Disease.

**Exhibit VII – Progression of Atherosclerosis**




**Current Therapies to Control Cholesterol**

The American Heart Association (AHA) recommends lifestyle modifications such as smoking cessation, daily physical activity, weight management, and healthy dietary choices for reducing CVD risk. However, oftentimes lifestyle modifications are not sufficient and therapeutic agents are introduced to help control cholesterol (as well as other factors such as blood pressure and the activity of platelets) for the reduction of CVD risk.

**Statins (HMG CoA Reductase Inhibitors)**

Physicians recommend statins for most patients with elevated cholesterol based on their clinical efficacy in reducing risk for stroke and heart attack. Statins work in the liver to prevent the formation of cholesterol, and in turn, lower the circulating levels of cholesterol in the blood. Statins are most effective at reducing LDL ("bad") cholesterol, but also have moderate effects on lowering triglycerides ("blood fats") and raising HDL ("good") cholesterol (AHA, 2014).

Statins comprise one of the single largest categories of prescription pharmaceuticals by revenue, with peak worldwide sales prior to major product patent expirations approaching $30 billion at one point. Although the statins have been the most successful therapeutic agent in the world by reducing overall CVD risk by approximately 25-30%, there still remains a large unmet medical need in further reduction of CVD risk. The key patents for Pfizer's Lipitor (atorvastatin), a leading statin with sales of over $13 billion in 2006, expired in 2011, and several of AstraZeneca's Crestor (rosuvastatin) key patents expire over the next few years. With the expiration of these patents, pharmaceutical companies have launched a strategic initiative to introduce a new class of drug, a select BET inhibitor, that will provide additional CAD and CVD risk reduction over standard of care products such as statins. For instance, Resverlogix is actively pursuing the lowering of MACE via the modulation of vascular inflammation, complement, coagulation, vascular calcification, RCT and metabolic mediators with apabetalone in addition to standard of care treatment.

**Selective Cholesterol Absorption Inhibitors**

Selective Cholesterol Absorption Inhibitors are a fairly new class of cholesterol-lowering drugs that work by preventing cholesterol absorption from the intestine. These drugs are most effective at lowering LDL cholesterol, but may also have moderate effects on decreasing triglycerides and raising HDL cholesterol. Ezetimibe (Zetia) was approved in 2002 and is the first drug in this class for the treatment of high cholesterol and particular inherited lipid abnormalities.

**Resins (Bile Acid Sequestrant or Bile Acid-Binding Drugs)**

This is a class of LDL-lowering drugs that works in the intestines by promoting increased cholesterol elimination. The body uses cholesterol to produce bile, which is an acid used to aid the process of digestion. Resins bind to bile so that is no longer available for use during digestion. This triggers the liver to produce more bile, and in turn, more cholesterol is used up during this process with lower cholesterol levels left to circulate through the blood. Resins currently available in the U.S. include cholestyramine (Questran, Questran Light, Prevalite, Locholest, Locholest Light), colestipol (Colestid), and colesevelam HCl (WelChol).

**ACL Inhibitors**

ATP (adenosine triphosphate) citrate lyase (ACL) inhibitors lower cholesterol synthesis in the liver. As a result, expression of LDL receptors is increased, which removes cholesterol from the blood. This approach is appropriate for patients with statin intolerance who suffer from muscle pain and weakness related side effects. Esperion Therapeutics (NASDAQ:ESPR) announced positive results from its Phase 2 clinical trials with its ACL inhibitor, bempedoic acid (ETC-1002). The product is a first-in-class, once-daily oral low-density lipoprotein cholesterol (LDL-C) reducing small molecule designed to lower elevated levels of LDL-C. Bempedoic acid is absorbed rapidly in the small intestine and enters the liver through cell surface receptors different from those transporters that selectively take up statins. Currently, the compound is a Phase 3 development program with expected topline results in fourth quarter 2017.

**Lipid Lowering Drugs**

Lipid Lowering Drugs include fibrates, niacin, and omega-3 fatty acids. Although fibrates (fibric acid derivatives) are not very effective at lowering LDL cholesterol, the drugs are highly effective at lowering triglycerides and in some instances increasing HDL levels. Fibrates currently available in the U.S. include gemfibrozil (Lopid), fenofibrate (Antara, Lofibra, Tricor, and Triglide), and clofibrate (Atromid-S).

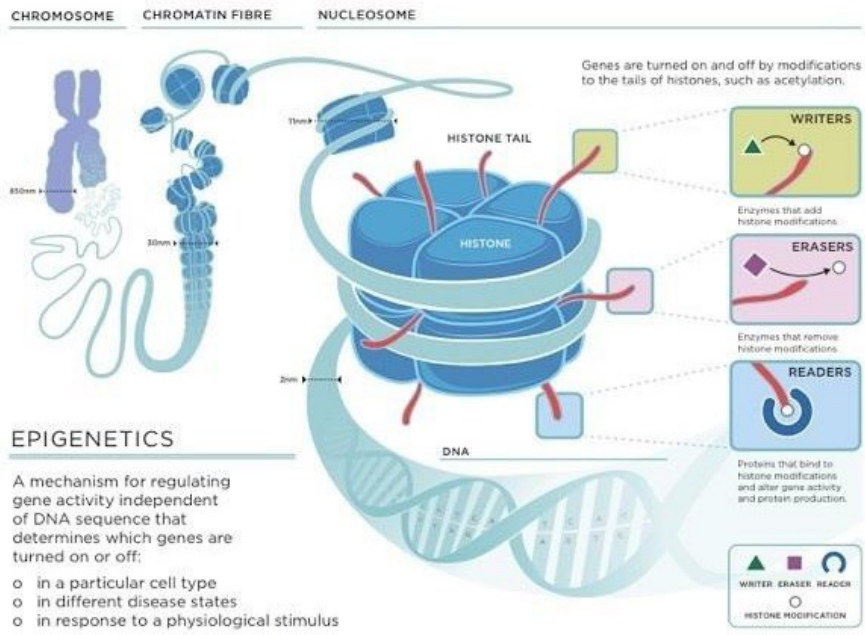
Niacin (nicotinic acid) works in the liver by affecting production of triglycerides (blood fats). There are many side effects related to the drug including itching, flushing, and GI disturbances. Liver functions must be closely monitored as niacin can cause liver toxicity and caution must be exercised in diabetic patients as the drug can result in elevated blood sugar levels. Niacin comes in prescription form and as a dietary supplement.

Omega-3 Fatty Acid Ethyl Esters are derived from fish oils that are chemically modified and purified and are used in conjunction to dietary modifications in order to lower triglycerides in individuals with high triglyceride levels over 500 mg/dL. Serious adverse effects include drug interactions with other medications and supplements. Leading omega-3 fatty acid ethyl esters available in the U.S. include Lovaza and Vascepa.

***Background on Epigenetics***

Biologist Conrad Waddington first defined the term epigenetics in the 1940s as the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being (Waddington, 1942). In other words, epigenetics refers to the study of heritable changes caused by activation or deactivation of gene expression that do not involve alterations in DNA sequence (Dupont *et al*., 2009).

**Exhibit VIII – Characteristics of Epigenetics**




*Source:* Resverlogix, Corp., Richard E. Ballerman

Epigenetics is involved in many normal cellular processes. Epigenetic modifications to DNA or DNA associated proteins (histones) can turn a gene on or off and determine if its activity is high or low, thus dictating which proteins are subsequently transcribed (Simmons, 2008). Examples of these epigenetic modifications include acetylation, methylation, and phosphorylation. These modifications are added to histones by enzymes known as "writers" and removed by enzymes referred to as "erasers."

Over the last decade, early epigenetic approaches focused on these "writers" and "erasers" which involved chemical-to-chemical interactions. One way to turn genes off is via epigenetic silencing, by DNA methylation, histone modifications, and/or RNA-associated silencing, possibly leading to variable expression. The most popular epigenetic therapies aim to reactivate genes that have been silenced via inhibition of histone acetylation and/or DNA methylation (Egger et al., 2004). A more advanced approach to epigenetics involves the protein-to-protein interaction of "readers," which are proteins that that identify a specific pattern of modifications by binding to them and recruiting other proteins to modulate gene activity. For instance, as BET proteins bind, they recruit additional proteins to regulate gene activity. Once the gene becomes activated, messenger ribonucleic acid (mRNA) is synthesized followed by the translation of mRNA into a specific protein.

Epigenetic therapy is emerging as a promising area of biotechnology/medical research and drug development poised to combat diseases of high unmet clinical need. Epigenetic therapy is currently being explored to target cardiovascular, neurological and metabolic diseases, with emphasis on protein and enzyme molecular targets. Since there is evidence that these epigenetic changes are involved in many disease processes, such as certain cancers and certain types of mental retardation, this field has become an area of marked research interest (Egger et al., 2004). However, successful epigenetic therapies must be highly selective towards abnormal cells; otherwise, the activation of gene transcription in healthy, normal cells could render them malignant. Although this is quite a feat, researchers are exploring new ways of targeting atypical cells. Since epigenetic modifications play significant roles in the regulation of cellular processes and in overall health, epigenetics as a field is quickly growing and continues to look promising for the discovery of new medications (Simmons, 2008). The discovery by Resverlogix that RVX-208 is a BET bromodomain inhibitor adds new drive to the promise of epigenetic mechanisms as a source of new therapeutics in order to combat the area of high-risk CVD and other diseases that are impacted by this pathway.

**Resverlogix's Epigenetics Platform Technology**

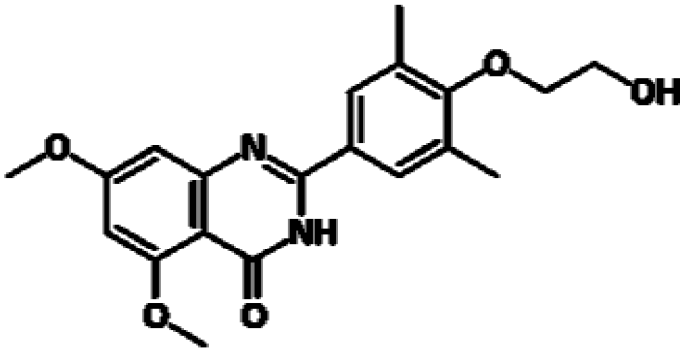
The basis of Resverlogix's epigenetics drug development platform involves targeting Bromodomain and Extra Terminal Domain (BET) proteins with the potential to impact cardiovascular disease, neurodegenerative diseases, diabetes, cancer, and autoimmune diseases. Acetylated lysine, a modified amino acid that is found in histones, binds to the two small bromodomain regions of BET proteins. Resverlogix has discovered BET protein inhibitors that specifically bind to BET bromodomains, thereby preventing them from binding to histones. This leads to modifications in certain gene activity involved in disease processes. Resverlogix is focusing the majority of its research efforts on the BRD2, BRD3, BRD4, and BRDT proteins.

These novel, small molecule compounds identified by Resverlogix function via selective inhibition of BET proteins. They alter the activity of genes that play a key role in disease in relevant cell models, demonstrate oral bio-availability allowing for oral administration in the form of a pill, and demonstrate activity in animal models of human disease. Resverlogix is in the process of identifying and developing compounds for additional clinical indications with proprietary platform activities continuing to add to its growing portfolio of intellectual property needed to support the development of these assets.

**Apabetalone (RVX-208) is a BET antagonist**

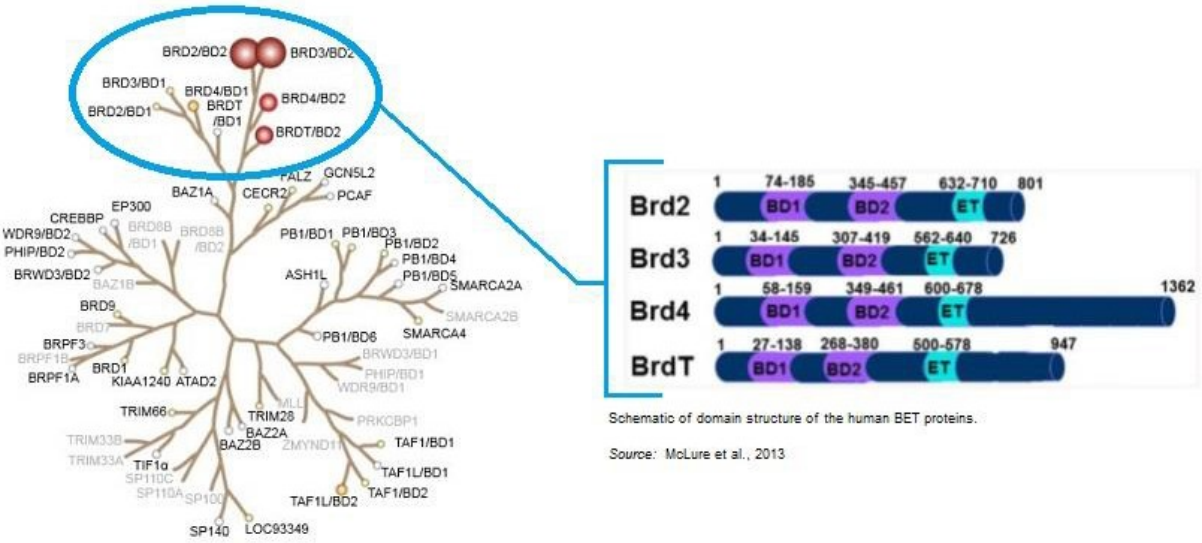
Resverlogix's lead candidate, apabetalone, is a first-in-class, orally active small molecule that selectively inhibits BET proteins.

**Exhibit IX – Chemical Composition of Apabetalone (RVX-208), $C_{20}H_{22}N_2O_5$**




Apabetalone works by binding to the two specialized areas of BET proteins known as bromodomains (BD1 and BD2). Both of these bromodomains can recognize and bind to an acetylated lysine, which is a modified amino acid found on histones bound to DNA. This process is referred to as "reading", which refers to the protein-to-protein interaction of a BET protein finding and binding an acetylated lysine through the actions of the bromodomain. Apabetalone acts via an epigenetic mechanism on BET proteins, specifically BRD2, BRD3, BRD4 and BRDT with increased selectivity for BRD4-BD2.

**Exhibit X – Bromodomains BD1 and BD2**




Schematic of domain structure of the human BET proteins.

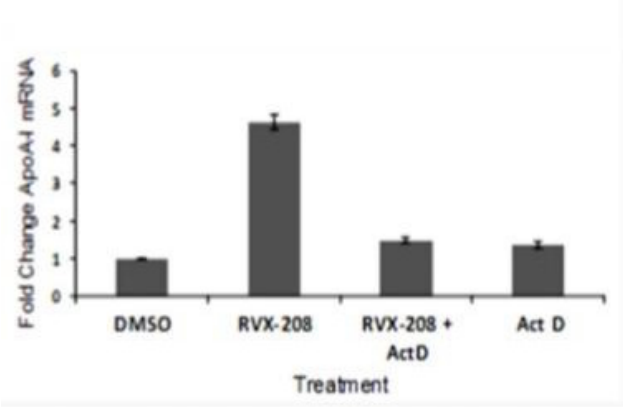
*Source:* McLure et al., 2013

Selectivity of RVX-208 within the human bromodomain family determined using a thermal shift assay.

*Source:* Picaud et al., 2013

By targeting BET bromodomains, apabetalone has a multimodal approach and impacts several key biological processes that play a role in vascular disease risk. Initially, apabetalone binds to the BET protein and triggers a cascade of events. Apabetalone induces Apo A-1 mRNA production in human hepatocyte cell lines leading to an increase in Apo A-1 gene transcription and eventually an increase in endogenous Apo A-1 protein production (McLure et al., 2013). This results in the subsequent synthesis of new HDL particles.

**Exhibit XI – RVX-208 Induction of Apo A-1 mRNA**



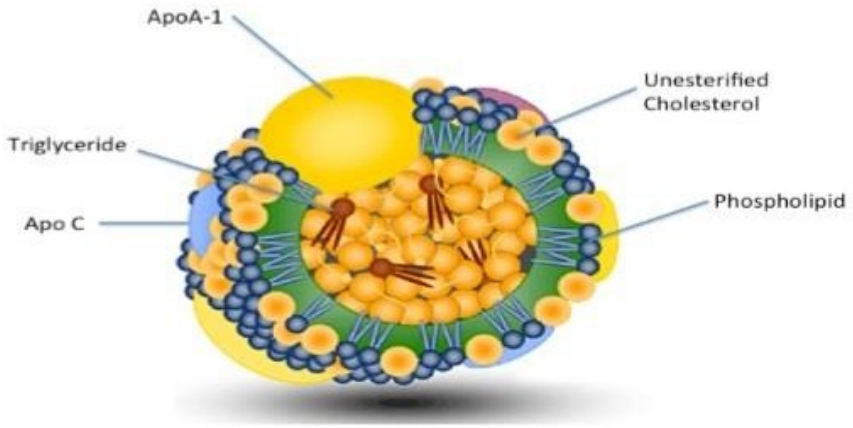

Induction of ApoA-I in the human hepatoma cell line Huh7 by 30 µM RVX-208 is inhibited by Actinomycin D (Act D).

*Source:* McLure et al., 2013

**Apabetalone Targeting Apo A-1, HDL, & Reverse Cholesterol Transport**

Apo A-1 makes up approximately 70% of the protein found in HDL particles ("good cholesterol") and is secreted by the intestines and liver. Apo A-1 is crucial for the synthesis and function of HDL (Zannis et al., 2006), and greater production of Apo A-1 results in the formation of new HDL molecules. The newly formed HDL molecules have increased functionality because they are unfilled and flat, and thus have a greater ability to remove cholesterol out of plaques from arteries and reduce and/or prevent atherosclerosis. These HDL particles can effectively remove plaque via RCT, which is a natural physiologic process by which cholesterol is transported out of arteries and subsequently to the liver for excretion out of the body in bile.

**Exhibit XII - High density lipoprotein (HDL)**




*Source:* Resverlogix, Corp.

**Apabetalone Targets Multiple Biologies**

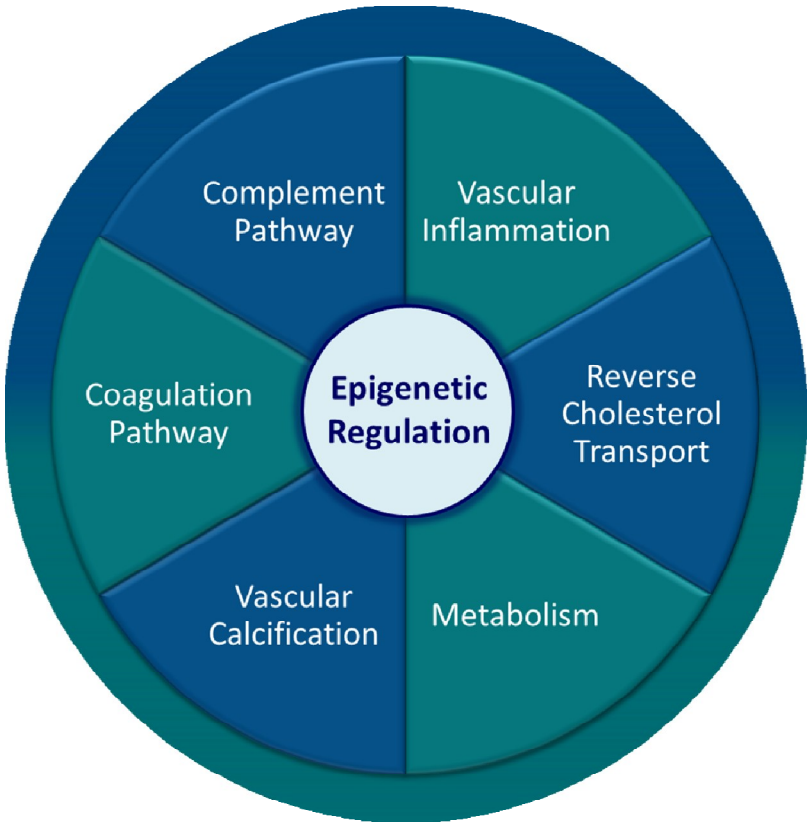
For the first several years of RVX-208 development, Resverlogix focused solely on the RCT mechanism for MACE reduction, and although it is plays an important role in the process, management has now evolved the company's focus to address other aspects of the drug's mechanism of action that are impacted thorough the BET Bromodomain 4 target. Resverlogix believes that apabetalone:

- Reduces key vascular inflammation markers
- Modulates the complement, coagulation and acute phase response cascades, known drivers in CVD and acute cardiac events

- Enhances RCT
- Lowers key markers of metabolic risk

These multimodal aspects of apabetalone explain the overall MACE reduction observed in certain populations within back-to-back clinical trials.

**Exhibit XIII –Apabetalone: The Multimodal Approach[2]**




**The Apabetalone Hypothesis**

In April 2012, Resverlogix announced the mechanism of action by which apabetalone increases Apo A-1 production. The finding provides the opportunity to initiate licensing and partnering in the areas of atherosclerosis, oncology, autoimmune and Alzheimer's diseases where the MoA plays a pivotal role. The value can be further translated into the cancer space, with the connection highlighted by Dr. James Watson between regulation of the BRD4 protein and its relationship with uncontrolled cell division by AML cells.

Apabetalone disrupts the acetylation of specific lysines in the histones found in actively transcribed regions of DNA. The compound is taken up by liver cells, where it binds to a BET protein. The proteins contain two small conserved regions called bromodomains, each of which has a pocket that can bind to or read specific acetylated lysine found at the end of some histones. When this interaction occurs, a different region of the BET protein can recruit other components important for controlling gene transcription. When a BET protein is anchored to chromatin via its bromodomain binding to an acetylated lysine, this complex recruits additional proteins that regulate transcription which can lead to selective increases and decreases in mRNA. Apabetalone binds to the same pocket of the bromodomain as the acetylated lysine of histones and in so doing causes the BET protein to be released from chromatin, thus altering transcription. This action of apabetalone leads to an increase of Apo A-1 mRNA and production of Apo A-1 protein, the key building block of new HDL.

Researchers recognize that high concentrations of plasma HDL are a negative risk factor for coronary heart disease (CHD) and we cite the well-known Framingham study as early evidence (Gordon et al., 1977). Therefore, novel

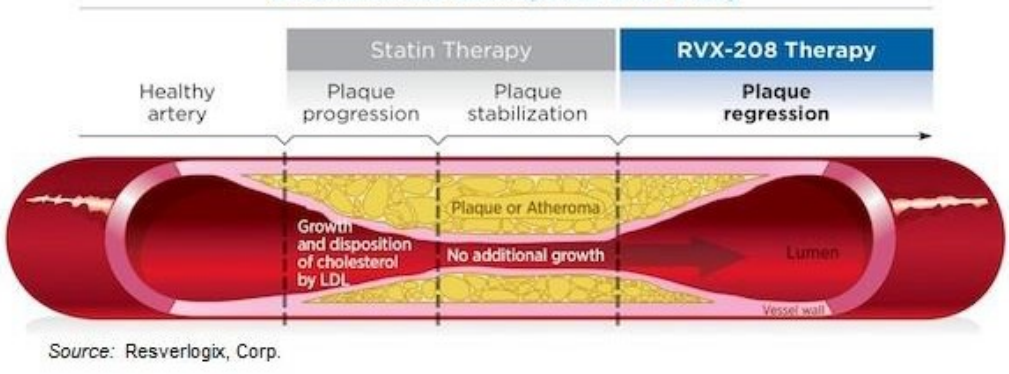
[2] Source: Resverlogix June Presentation

therapies that consistently increase Apo A-1 and HDL to facilitate plaque removal and regression are clearly intriguing. There are a limited number of companies pursuing programs that focus on enhancing Apo A-1. The Medicines Company and Roche are developing recombinant proteins or peptides that exogenously increase Apo A-1. However, these therapies are costly to manufacture and may cause immunological responses for patients when used for longer durations. Therefore, these therapies are likely to have utility as acute or induction-based therapies.

Drugs that target Apo A-1 production and cholesterylester transfer protein (CETP) inhibitors are the only technologies to date that were thought to effectively eliminate and regress atherosclerotic plaque from arteries in high-risk CVD patients. CETP inhibitors are a class of drugs that work by reducing the risk of atherosclerosis by increasing HDL and RCT. To date, these drugs have generally failed in trials either because of excess deaths (Pfizer's torcetrapib), not showing clinically meaningful efficacy despite increases in HDL (Roche's dalcetrapib) or for high-risk atherosclerotic cardiovascular disease (Eli Lilly's evacetrapib).

The other CETP inhibitor currently being tested, Merck's anacetrapib, exhibited encouraging Phase 2b interim results in 2010. The compound is currently participating in two Phase 3 trials that will run until 2017. Apabetalone's ability to increase Apo A-1 production and thus enhance RCT activity could set itself apart from other HDL medications, making it an intriguing candidate for the treatment of atherosclerotic CVD. While the Phase 3 trial is still in process for apabetalone, management believes that the drug is positioned to be one of the most promising drugs in development for the prevention and reduction of atherosclerotic related CVDs.

**Exhibit XIV – Atherosclerotic Development in an Artery**




*Source:* Resverlogix, Corp.

Currently, apabetalone is the first and most clinically advanced BET bromodomain inhibitor in clinical trials for high-risk vascular disease. Management also noted that apabetalone is the first ever and only drug with selectivity for the BRD4-BD2 bromodomain that has been written up by the Structural Genomics Consortium (Picaud et al., 2013). Management also believes the drug has the advantage of a seven-year head start on any other drug in this category.

**Addressing the Unmet Need in CVD**

Cardiovascular disease is the most common cause of death in the world and future projections illustrate that the prevalence of CVD and associated expenses are anticipated to rise dramatically over the next decades. The need for new therapeutics that lower the CV risk is crucial to addressing this unmet clinical need. With the growing knowledge and insight into disease mechanisms, new approaches are being evaluated with the hopes of the discovery of novel therapeutic options for CVD.

Resverlogix is addressing the major problem of the unmet need in cardiovascular management. Over the last several years, there has been a great movement forward in cardiovascular care with statins and other therapies, but these address less than a third of the afflicted population. There are new medications emerging such as the novel LDL modulators like PCSK9 that are designed to lower LDL, yet they only have a small impact on the unmet need in CV management and take up only a small part of the market.

The large market opportunity lies in the 70% of unmet need of unmanaged cardiovascular issues that extend to other indications such as diabetes and kidney disease. According to the International Diabetes Federation, there are 387 million patients worldwide with diabetes, and this number is expected to rise to 592 million by 2035. While the majority of current therapies aim to manage glucose levels in diabetic patients, Resverlogix is taking a unique approach by looking at it from the point of view of reducing MACE – the primary killer in both men and women. In a multinational study, 50% of people with diabetes died of cardiovascular disease, primarily heart disease and stroke

(Moorish et al., 2001). Other sources cite up to 80% of patients with diabetes will develop and possibly die from CVD (Narayan et al., 2003 and Hogan et al., 2003). Furthermore, CKD is an extension of diabetes and also results in high CVD death rates, and may be another area addressed by apabetalone.

**Major Adverse Cardiac Events (MACE)**

Many scientists, key opinion leaders and physicians believe that of all the markers that are analyzed for providing prognostic predictability for cardiovascular risk, MACE is the most crucial. Payer groups and health systems carefully assess MACE when looking at the potential reimbursement of a novel CVD drug. MACE includes several key markers of cardiovascular risk including death, myocardial infarction, stroke, hospitalization for cardiac-related incidents, percutaneous stent procedures, worsening angina, worsening of peripheral artery pain and ischemia. According to the 2015 AHA Statistics report, an estimated 85.6 million American adults (greater than 1 in 3) have one or more types of CVD. Many of these CVD patients will have some type of MACE during or after they have been diagnosed with heart disease. On average, more than 2,150 Americans die of CVD daily, which is approximately 1 death every 40 seconds (Mozaffarian et al., 2015).

The term MACE came into use in the mid-1900s in reference to complications related strictly to percutaneous coronary interventions (PCIs) in hospital settings (Hermans et al., 1993 and Keane et al., 1994). Although there is no standard definition of MACE, it has become the most commonly utilized end point in cardiovascular clinical research today, and is reported for both short and long term outcomes involving various treatment regimens. MACE is used today as a composite of clinical events that typically include safety and effectiveness endpoints. There has been some controversy over the last decade within the medical community regarding the true value of MACE in clinical trials, as there is no standard definition for MACE and individual outcomes vary per study and inconsistencies often arise (Kip et al., 2008). In response, as part of its trial design Resverlogix has provided both a narrow and broad definition of MACE as primary and secondary outcome measures.

**Clinical Overview of Apabetalone**

Resverlogix has completed many clinical trials to date. Apabetalone has been tested in over 1,000 patients in 12 countries, and clinical experience with apabetalone has demonstrated that BET inhibitors can be both safe and effective. Over the years, Resverlogix has gathered information from these studies and shifted focus to target patients with low HDL and diabetes with co-treatment of RVX-208 and rosuvastatin (Crestor®) and atorvastatin (Lipitor®) in its BETonMACE trial.

Prior to the BETonMACE trial, apabetalone has completed two Phase 2b trials named SUSTAIN and ASSURE in collaboration with the Cleveland Clinic. Furthermore, Resverlogix has performed thorough analysis of MACE in the Phase 2b clinical program; 35 MACE events were reported in both the SUSTAIN and ASSURE trials. This analysis demonstrated that treatment with apabetalone was associated with a 55% reduction in MACE. Apabetalone treated patients had a lower level of cumulative events of 6.7% vs. 15.1% (p=0.02) in the placebo treated group. Furthermore, a beneficial effect of apabetalone on patients with diabetes mellitus was accentuated with a reduction in MACE that was lowered by 77% (p=0.01). BETonMACE will continue to focus on MACE reduction as the primary endpoint for the registration study.

**Exhibit XV – Summary of Resverlogix's Clinical Trials[3]**

| Trial | Summary | Patients | Status | Initiated (Calendar) | Data Release (Calendar) |
|---|---|---|---|---|---|
| Phase 3 | Secondary prevention of MACE in patients with diabetes and low HDL | 2,400 + | Enrolling Fall 2015 | Fall 2015 | TBD |
| Phase 2a | Alzheimer's disease | 45-60 | Pending | TBD | TBD |
| Phase 2b | Pre-diabetes mellitus / effects of RVX-208 and ApoA-I production on glucose metabolism | 20 | Completed | Q4 2012 | Q3 2014 |
| Phase 2b ASSURE | 26 week risk-stratified IVUS study in patients with low HDL | 323 | Completed | Q2 2011 | Q2 2013 |
| Phase 2b SUSTAIN | 24 week single-dose safety, tolerability and efficacy in stable CVD patients with low HDL | 176 | Completed | Q3 2011 | Q3 2012 |
| Phase 2 ASSERT | 12 week dose-ranging safety, tolerability and efficacy in stable CVD patients | 299 | Completed | Q4 2009 | Q4 2010 |
| Phase 1b/2a | 28 day multiple dosing safety, tolerability and efficacy in healthy volunteers with low HDL | 72 | Completed | Q3 2008 | Q3 2009 |
| Phase 1 BE | Single dose bio-equivalency comparing capsule and tablet drug form | 9 | Completed | Q3 2009 | N/A |
| Phase 1 BE | Single dose bio-equivalency | 7 | Completed | Q3 2009 | Q4 2009 |
| Phase 1a | First-in-man single ascending dose and 7-day multiple dosing | 80 | Completed | Q4 2007 | Q1 2008 |

**Phase 2 "ASSERT" Clinical Trial: Completed**

ASSERT was a Phase 2, 12-week randomized, double-blind, placebo-controlled, parallel-group, multi-center U.S. dose-finding and safety study of 299 enrolled patients with established stable coronary artery disease (CAD). The primary endpoint of the study was increased plasma Apo A-1 levels after three months of apabetalone dosing compared to the placebo group. Additional goals of the study included evaluation of the safety and tolerability profile of apabetalone, comparing the dose-time response relationship for Apo A-1 and investigating important reverse cholesterol markers involved with HDL activity.

Resverlogix announced top line results of the ASSERT Phase 2 clinical trial in November 2010. Data revealed that the three key biomarkers in the RCT process showed dose dependent and steady improvement. Although the study demonstrated dose dependent increases in Apo A-1, the trial's primary endpoint, the percent change in ApoA-1 from baseline to 12 weeks post-randomization for each treatment arm, was not statistically significant when compared to the control group. In *post-hoc* analysis of the data, the study found that apabetalone had more of an impact on low HDL and low Apo A-1 patients.

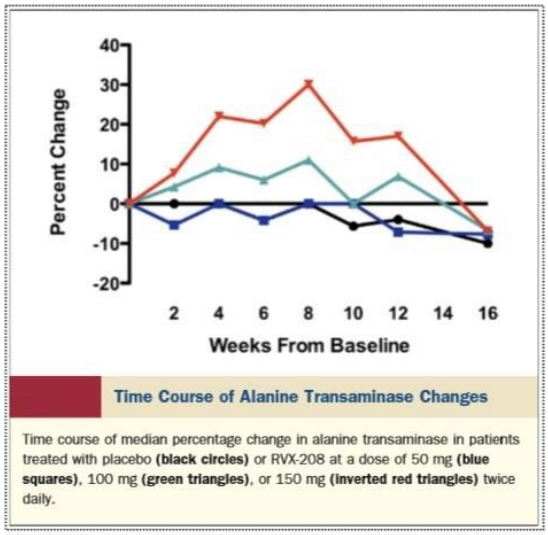
However, the data showed statistically significant increase in HDL cholesterol including alpha1 particles or functional HDL as well as highly statistically significant increases in large HDL particles. In the highest dose cohort, Apo A-1 showed a 5.6% increase with a statistical value of p=0.06 vs. placebo. Across all patients, Apo A-1 showed a trend to increase in higher doses with statistical significance of p=0.035. Apo A-1 as well as other HDL molecules continued to be increasing by the end of the 12-week trial. For example, both the 8.3% HDL cholesterol increase (p<0.01) and the 21.1% large particle HDL increase (p<0.001) were highly statistically significant. In the high-risk sub population of patients who received the newer class of statins and had HDL <45mg/dL, the middle dose of 200 mg saw the most marked increases of 12% in Apo A-1 (p<0.02), 21% in HDL (p<0.015), and 32% in large HDL (p.<0.018) vs. baseline. As per Resverlogix, these pronounced HDL related increases via Apo A-1 production are very important as they take place later in the RCT process and are indicative of the strong potential for plaque regression and/or prevention.

It is important to mention that incidents of elevated alanine aminotransferase liver enzymes (ALTs) in excess of 3 times the upper limit of normal ("ULN") were experienced by 18 of 225 treated patients in ASSERT. One patient out of 45 in the high-risk sub population who received the newer class of statins and had HDL <45 mg/dL experienced

[3] Source: Resverlogix Clinical Trials Summary

ALTs in excess of 3 times ULN. One possible explanation for this finding, suggested by Resverlogix, was that this patient had an elective surgery during the study and was also given two agents post-surgery that are known to cause excessive liver ALT signals. ALTs were highest at week 8 and declined at weeks 10 and 12 across all doses. Resverlogix believes these data point to the possibility of liver adaptation and/or that elevated ALTs are transient. The occurrence of elevated ALTs was less frequent in patients on low and medium doses of statin agents, and RCT biomarker levels remained the same or improved in patients that were receiving high dose statins.

**Exhibit XVI - Alanine Transaminase and Related Biomarker Data**




**Time Course of Alanine Transaminase Changes**

Time course of median percentage change in alanine transaminase in patients treated with placebo **(black circles)** or RVX-208 at a dose of 50 mg **(blue squares)**, 100 mg **(green triangles)**, or 150 mg **(inverted red triangles)** twice daily.

Biochemical Safety Parameters

| Parameter | Placebo (n = 74) | RVX-208 50 mg bid (n = 76) | RVX-208 100 mg bid (n = 75) | RVX-208 150 mg bid (n = 74) | Overall p Value |
|---|---|---|---|---|---|
| ALT or AST >3× ULN | 0 (0) | 3 (3.9) | 8 (10.7) | 7 (9.5) | 0.009 |
| ALT or AST >8× ULN | 0 (0) | 2 (2.6) | 4 (5.3) | 2 (2.7) | 0.28 |
| Total bilirubin >2× ULN | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1.00 |
| CK elevation >3× ULN | 4 (5.4) | 1 (1.3) | 0 (0) | 3 (4.1) | 0.10 |
| Creatinine elevation >1.5× baseline | 0 (0) | 0 (0) | 3 (4.0) | 3 (4.1) | 0.07 |

Values are reported as the n (%) of subjects experiencing laboratory measures of adverse events.
ALT = alanine transaminase; AST = aspartate transaminase; bid = twice daily; CK = creatinine phosphokinase; ULN = upper limit of normal.

*Source:* Nicholls et al., 2011

To summarize, key findings drawn from ASSERT included the following: (1) 200 mg/day of apabetalone was the optimal dose, based on safety and efficacy; (2) those patients with a low level of HDL-C at baseline had a better response for HDL-C and Apo A-1 increases when treated with apabetalone; and (3) the best response was seen in those patients given apabetalone in combination with non-max doses of second generation statins such as rosuvastatin (Crestor®) or atorvastatin (Lipitor®). These observations helped Resverlogix establish a better understanding of apabetalone dosing and more details regarding what target patient population to further examine in the design of “SUSTAIN” and “ASSURE” studies.

**Phase 2b “SUSTAIN” Clinical Trial: Completed**

“The Study of Quantitative Serial Trends in Lipids with Apolipoprotein A-1 Stimulation”, also known as SUSTAIN, was a 24-week, multi-center, double-blind, randomized, parallel group, placebo controlled Phase 2b clinical trial carried out in South Africa and led by investigators at the Cleveland Clinic. The SUSTAIN clinical trial began enrolling and dosing patients in September 2011, with enrollment completed in November 2011 and dosing of patients completed in May 2012. All 176 patients enrolled in the study had established atherosclerotic CVD, low HDL-C and were at a high-risk for recurrent CVD events. All patients had been receiving up to 40 mg atorvastatin (Lipitor®) or 20 mg rosuvastatin (Crestor®). Subjects received 200 mg apabetalone daily or placebo in order to evaluate safety, lipid trends and other biomarkers of reverse cholesterol transport. The purpose of SUSTAIN was to measure changes in Apo A-1, HDL and other lipid parameters vs. placebo as well as to examine safety over an extended period in the patient population with the largest response to apabetalone in the Phase 2 ASSERT trial.

In August 2012, Resverlogix announced that SUSTAIN met both its primary endpoint for apabetalone significantly increasing HDL-C from baseline (p=0.001) and its secondary endpoints of apabetalone increasing levels of Apo A-1 (p=0.002) and large HDL particles (p=0.02), which are both believed to be important in the process of improving reverse cholesterol transport (RCT) activity. These increases in both HDL and Apo A-1 biomarkers seen in the 24-week SUSTAIN trial represents a remarkable increase over the respective HDL and Apo A-1 values observed in the 12-week ASSERT trial. SUSTAIN also showed that apabetalone was safe when administered daily for 6 months and that increases in ALTs (as mentioned above from ASSERT) that were previously reported were transient and uncommon with no new increases seen past week 12 of the 24-week trial. Furthermore, with the help of some experts in the field, Resverlogix has completed detailed analyses on these patients and have found that these ALT elevations were isolated occurrences, generally observed without clinical symptoms and mainly seen in individuals that had underlying pathology (such as Hepatitis A, B or C, or liver disease) and using concomitant medications known to cause ALT elevations (such as high dose acetaminophen or clavulanic acid).

To summarize, key findings drawn from SUSTAIN included the following: (1) patients with both low baseline HDL and low baseline Apo A-1 biomarkers were the best responders to the treatment; and (2) 1 MACE event was observed in treated subjects compared to 6 MACE events in the placebo group. The findings from the SUSTAIN trial provided Resverlogix with important HDL functionality data as well as safety data regarding the transient nature of the early liver signals that were seen in prior studies. Resverlogix believes that this data firmly supports the chronic usage of apabetalone.

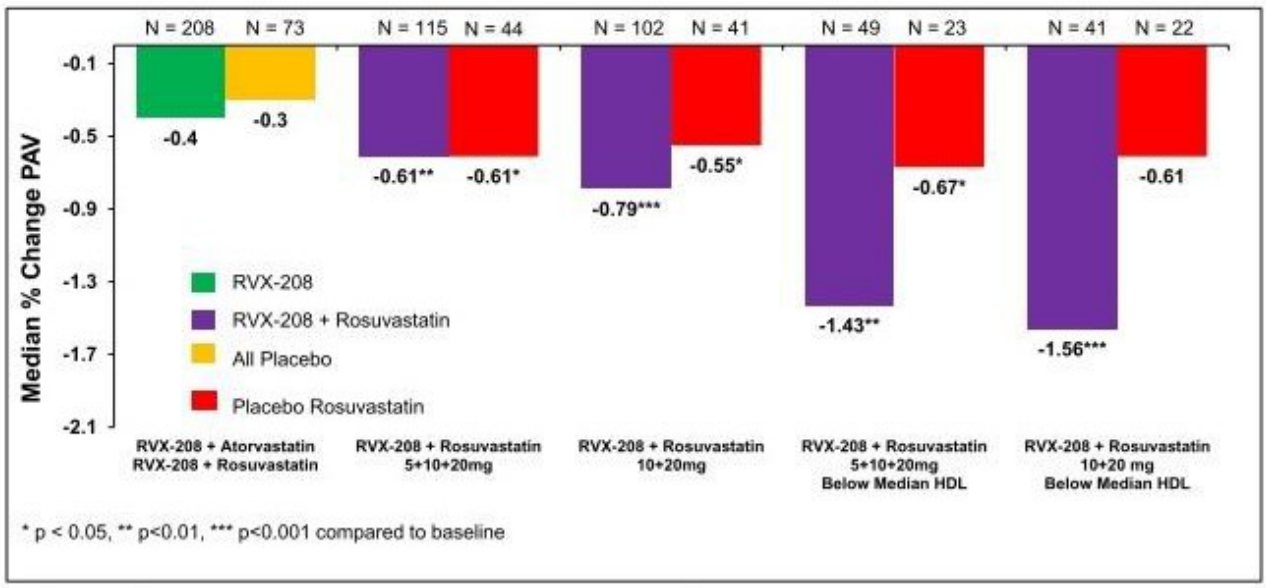
**Phase 2b "ASSURE" Clinical Trial: Completed**

"The Apo A-1 Synthesis Stimulation and Intravascular Ultrasound for Coronary Atheroma Regression Evaluation" trial, ASSURE, was a 26-week, multi-center, double-blind, randomized, parallel group, placebo-controlled Phase 2b trial led by investigators at the Cleveland Clinic. The ASSURE clinical trial began enrolling and dosing of patients in November 2011 with enrollment of all 323 patients completed in September 2012. The purpose of the trial was to assess the early impact of atherosclerosis regression by 100 mg of apabetalone twice-daily therapy in high-risk CVD patients. A total of 281 patients formed the Full Analysis Set (FAS) and each received two Intra-Vascular Ultrasound (IVUS) procedures that provided grey-scale images detailing plaque volume.

In June 2013, Resverlogix announced that ASSURE did not meet its primary endpoint of a -0.6% change in percent atheroma volume (PAV) from baseline to 26 weeks as determined by intravascular ultrasound (IVUS) measurement. The apabetalone treated group had -0.4% plaque regression (p= 0.08). All seven of the secondary IVUS and non-IVUS endpoints were met. These markers included regression of Total Atheroma Volume (TAV) and 10mm worst occluded TAV were met with high statistical significance with p<0.001 and p<0.001, respectively. Additional secondary endpoints such as increases in HDL of 10.7% (p<0.001) and increases in Apo A-1 of 11.7% (p<0.001) were also met.

In September 2013, Resverlogix announced ASSURE's Full Analysis Set (FAS) data showing that the below median HDL (<39 mg/dL) baseline population consisted of 92 patients who were taking either atorvastatin (Lipitor®) or rosuvastatin (Crestor®) with apabetalone. Subjects taking rosuvastatin (Crestor®) and apabetalone had a highly statistically significant Percent Atheroma Volume (PAV) plaque regression of -1.43% as compared to baseline (p<0.002). This PAV regression surpassed the ASSURE's pre-determined PAV endpoint of -0.6% by more than 138% (below). On the other hand, subjects taking atorvastatin (Lipitor®) and apabetalone had a PAV plaque progression of +0.19% with a non-significant probability value as compared to baseline. This reconfirmed previous findings from ASSERT which demonstrated that the best improvements were observed in patients with low HDL-C in combination with the newer generation statin agents.

**Exhibit XVII – Median Percent Change Atheroma Volume**



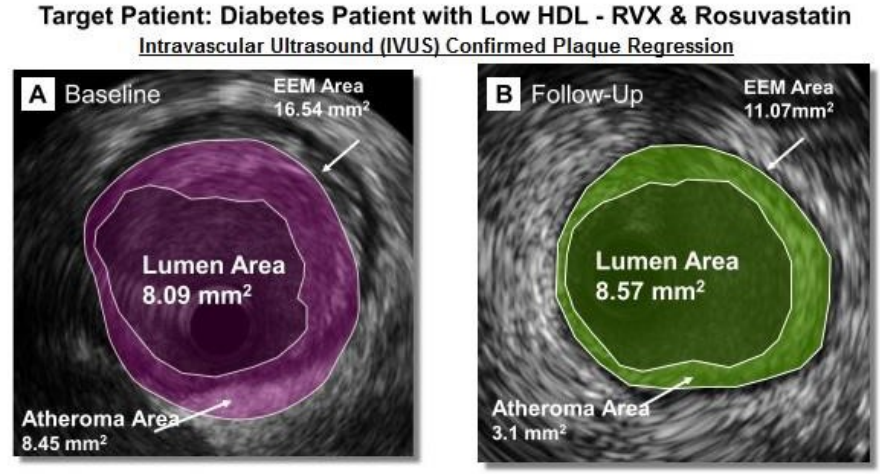

Notes: Median Baseline HDL = 39 mg/dL, N refers to number of patients

Source: RVX data on file – ASSURE FAS Population. Wilcoxon signed-rank test.

On November 4, 2013, Resverlogix announced two new results from ASSURE outlining the effects of apabetalone on vascular inflammation and vulnerability of atherosclerotic plaque rupture. The first observation showed statistically significant improvements in MACE and coronary IVUS plaque measurements in patients with a >2.0 mg/dL serum high sensitivity C-reactive protein (hsCRP) biomarker. The hsCRP biomarker when >2.0 mg/dL indicates an increased state of inflammation and is an established indicator of predicting CVD risk. The incidence of MACE was lower by 63% (p=0.023) vs. placebo in apabetalone treated patients with elevated hsCRP. There was a 60% reduction (p<0.0001) in hsCRP in patients receiving apabetalone vs. baseline and (p=0.054) vs. placebo. To summarize, the potentially greater promising effects of apabetalone on MACE and coronary disease progression were observed in patients with higher levels of systemic inflammation. Resverlogix presented a poster, co-authored by the Cleveland Clinic, in March 2014 at the American Cardiology Congress highlighting these findings.

The second finding arose from a pre-determined endpoint in ASSURE using a new catheter (Volcano Revolution 45 mghz) intended for radiofrequency analysis of the intravascular (IVUS) signal. Catheter data reveals virtual histology IVUS ("VH-IVUS"), which is an emerging technology that helps measure tissue properties of atherosclerotic plaques and provides information regarding the vulnerability of atherosclerotic plaque rupture and its relationship to future CV risk. These VH-IVUS observations illustrated that apabetalone treatment lead to less vulnerability of atherosclerotic plaque rupture (Missel et al., 2008).

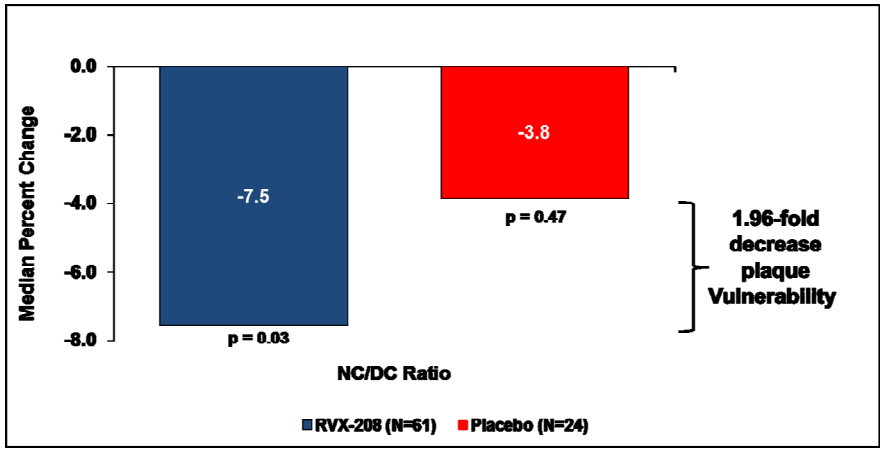
**Exhibit XVIII – VH-IVUS Vulnerability Measurement**




Source: RVX ASSURE Internal assessment change from baseline:
Individual Patient and Individual Coronary Segment FAS Population

This information was used to reflect plaque vulnerability by calculating the ratio of necrotic core to dense calcium (NC/DC). The NC/DC ratio in apabetalone treated patients (n=61) was significantly lower by -7.5% (p<0.03) vs. baseline while those (n=24) given placebo had a non-significant reduction of -3.8% (p=0.47) vs. baseline. The initial VH-IVUS findings show that the actions of apabetalone improved the NC/CS ratio pointing to less vulnerability of the atherosclerotic plaque for rupture.

**Exhibit XIX – NC/DC Ratio**

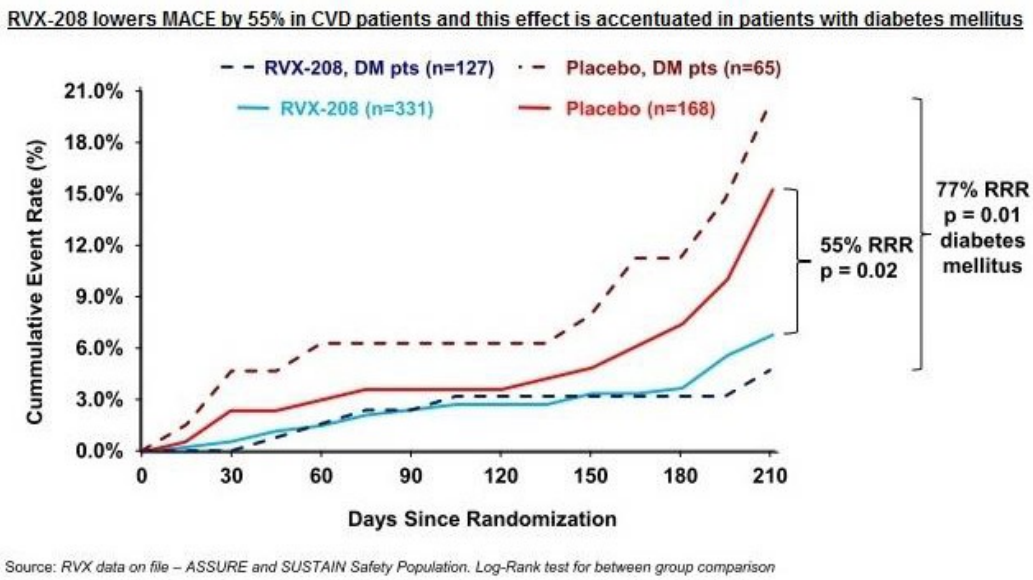


**Pooled ASSURE & SUSTAIN (MACE) Analysis**

In January 2014, Resverlogix announced that when MACE data (n=499) from both SUSTAIN and ASSURE trials were pooled and analyzed by an independent firm, it was found that patients treated with apabetalone over a six-month period had a significant reduction in MACE. According to Resverlogix, patients treated with apabetalone (n=331) had fewer overall major adverse cardiac events of 6.7% vs. 15.1% (p=0.02) in the placebo treated group (n=168). It was also observed that the benefit of RVX-208 treatment (n=179) was most noteworthy in patients with elevated CRP > 2.0mg/dL (n=283), with an overall event rate of 6.4% vs. 20.5% (p=0.007) in the placebo group (n=104). The pooled analysis on MACE is also being investigated in the context of other high-risk populations. The information gathered from the independent MACE analyses will help provide guidance to Resverlogix regarding the future development of apabetalone. Management believes that this early data showing reduction in MACE will be an important factor for apabetalone registration down the road, and that it is promising in showing the potential of apabetalone to help patients that are at high risk for CVD.

In September 2014, Dr. Jan Johansson, Senior Vice President of Medical Affairs of Resverlogix, reported at the European Society of Cardiology (ESC) Congress that CVD patients when treated with apabetalone had a 55% (p=0.02) relative risk reduction (RRR) in MACE. Furthermore, this effect of apabetalone on patients with diabetes mellitus was greatly accentuated with a RRR in MACE that was reduced by 77% (p=0.01) (below). This information is guiding Resverlogix in the planning and design of Phase 3 clinical study BETonMACE.

**Exhibit XX – RVX-208 Impact on MACE**




Source: *RVX data on file – ASSURE and SUSTAIN Safety Population. Log-Rank test for between group comparison*

**Phase 2b Pre-Diabetes Clinical Trial: Completed**

In October 2012, Resverlogix initiated a small exploratory Phase 2 clinical trial in pre-diabetic/metabolic syndrome patients to explore the effects of apabetalone and Apo A-1 production on the metabolism of glucose. Enrollment was completed in December 2013 and patient dosing was completed in March 2014. The trial was conducted in association with Baker IDI Heart & Diabetes Institute in Melbourne, Australia and examined factors such as insulin sensitivity and insulin secretion.

The preliminary results of the trial were announced on July 23, 2014. The investigators hypothesized that the apabetalone induced rise in Apo A-1/HDL-C could potentially affect pancreatic insulin secretion and thus lower blood glucose levels as detected by oral glucose tolerance tests. A total of 23 patients with pre-diabetes mellitus/ metabolic syndrome were given 200 mg apabetalone daily for 4 weeks. Unfortunately, the preliminary results were not in-line with the investigators hypothesis, as there was no statistically significant change in pancreatic insulin secretion or blood glucose levels after four weeks on 200 mg apabetalone. Resverlogix believes that this finding was useful in understanding the ASSURE data because for apabetalone to decrease blood glucose in diabetic patients diabetes, at least 12 weeks of apabetalone treatment is necessary. Further analysis from the data will include HDL abundance, lipidomics, platelet aggregation, monocyte activation and neutrophil adhesion.

**Epigenetics Pooled Database**

Resverlogix's Phase 2b program (SUSTAIN and ASSURE) in high-risk cardiovascular patients with low HDL has provided the company with a proprietary database of key biomarkers that are targeted by apabetalone. According to Resverlogix, this is "the first and largest integrated dataset of multiple vascular risk markers with an epigenetic drug treatment on these specific high target patients." Resverlogix performed a pooled analysis of various vascular risk biomarkers such as RCT markers including Apo A-1, HDL-C, HDL particle numbers, large HDL, HDL particle size; vascular inflammatory markers such as C-reactive protein (CRP); and metabolic markers such as alkaline phosphatase, glucose, HbA1C as well as others markers of epigenetic interest. Resverlogix will continue building the database with the hope of developing a more comprehensive foundation of epigenetics knowledge and to highlight patient groups that will be responders to apabetalone treatment.

**Phase 3 "BETonMACE"**

In October 2015, Resverlogix launched its Phase 3 "Effect of RVX-208 on Time to Major Adverse Cardiovascular Events in High-Risk Type 2 Diabetes Mellitus Subjects with Coronary Artery Disease" (BETonMACE) trial with lead drug apabetalone in high-risk patients with coronary artery disease (CAD) and type 2 diabetes mellitus (DM). The study is a large international multi-center, double-blind, randomized, parallel group, placebo-controlled clinical trial to determine whether treatment with apabetalone in combination with rosuvastatin or atorvastatin increases the time to MACE compared to treatment with rosuvastatin or atorvastatin alone.

The primary endpoint of the BETonMACE trial is designed to show a relative risk reduction of MACE, narrowly defined as a single composite endpoint of CV death, non-fatal myocardial infarction ("MI") and stroke. The study is an event-based trial and will continue until at least 250 MACE events have occurred. MACE will be adjudicated by an independent committee and the study will be monitored by a data safety monitoring board. Management is seeking a 30% reduction in MACE as compared to the placebo arm.

Secondary endpoints include time to first occurrence of the composite broad MACE which includes the addition of hospitalization for CVD events (unstable angina and revascularization procedures), changes in lipoprotein concentrations (HDL and apolipoprotein A-1, changes in diabetes mellitus variables (glucose and glycated hemoglobin), change in alkaline phosphatase ("ALP"), changes in kidney function and additional safety and tolerability of apabetalone.

In order to be eligible to participate in the study, patients must have documented history of type 2 Diabetes Mellitus, experienced a recent (defined as 7-90 days prior to randomization) coronary artery disease ("CAD") event including unstable angina, revascularization procedure or MI and have low levels of HDL (<40 mg/dL for males and <45 mg/dL for females). Standard of care high potency statin therapy shall consist of daily dose of either atorvastatin 40-80 mg or rosuvastatin 20-40 mg. After an initial screening period of 1 to 2 weeks during which subjects will be treated with standard of care statin therapy, subjects will be randomized to either apabetalone 100 mg twice daily or matching placebo with continued statin treatment. This combination treatment period will continue for up to 104 weeks.

Resverlogix believes that a Phase 3 MACE trial could confirm health benefits in CVD, diabetes, and CKD. The main objective of the trial will be to confirm MACE reduction by apabetalone as observed in SUSTAIN and ASSURE pooled analysis and also expand safety assessment. The study will be in a larger prospective setting with high-risk patients that have diabetes mellitus and low HDL-C (< 40 mg/dL for males and < 45 mg/dL for females who are post events). Management also plans to further explore the potential impact that apabetalone may have on inflammation, the complement and coagulation pathways, as well as on platelet improvement in these high-risk patients in the future Phase 3 trial.

As part of the BETonMACE trial, the study will examine a subset of the patients to test for impact on neuro-degenerative diseases and test for cognition. The subset will include patients over the age of 70 and perform a Montreal Cognitive Assessment (MoCA) test. The company anticipates that this could be from 200 to 300+ participants in the trial. This population group is the equivalent of a Phase 2 dementia trial built into BETonMACE.

BETonMACE will initially be conducted in Argentina, Mexico and various European cities with potential expansion into Asia through the partnership with Hepalink. U.S. sites are also a consideration as Resverlogix looks towards FDA approval in this adaptive trial that will target a minimum of 2,400 patients.

**New Paradigm / Development Strategy for Apabetalone**

Cardiovascular disease Phase 3 clinical trials typically extend from two to five years and require testing of a much larger patient pool as compared to most other therapeutic areas, and include anywhere from several hundred to several thousand patients. Due to the large size of the pool of patients in this prospective group, Resverlogix has focused the target population on CVD patients with diabetes, decreased levels of HDL with coronary artery disease and chronic kidney disease (CKD). There is an unmet need in these high-risk patients as they are more likely to suffer from MACE than CVD patients. Resverlogix believes, and we agree, that this is a much more efficient Phase 3 process. This presents as a large savings in both time and cost related expenses due to the higher rate of CVD in the high risk population.

Phase 3 trials in cardiovascular are very expensive, with many above $50 million and some in excess of $100 million in cost. The high cost is due to the large population sizes required to power statistical significance. For normal populations, MACE events are observed at a very low rate, fluctuating around 2% of observations. To generate statistical significance, very large population sizes are required as are extended observation periods. For the high risk population of MACE, which includes those with diabetes and chronic kidney disease, the incidence of MACE is much higher, in excess of 11% providing a much lower threshold to determine efficacy.

Apabetalone has the potential to expand to other indications and Resverlogix plans to conduct subsequent Phase 3 trials in the future. For instance, Resverlogix has mentioned several orphan indications that may be pursued in the undetermined future. This pathway may provide a quicker route to market for the compound.

Resverlogix sees possibility in a successful pharmaceutical partnership or licensing agreement for apabetalone which may help overcome the cost burden, lengthy development time, and high attrition rates, while helping to advance the drug through future clinical trials and drug development stages. Through extensive modeling and ongoing outreach to key opinion leaders (KOLs), management believes that if apabetalone can provide a 30% relative risk reduction of MACE in the Phase 3 trial, the pharmaco-economics of apabetalone could be very compelling for managed care and other payors that will be able to justify a fair price that lowers costs overall. While the outcome and efficacy of the trial, prices for competing therapies and negotiations with payors will ultimately determine the price, we are currently targeting a range of $2,500 to $4,500 per annum.

This range was supported by a study commissioned by Resverlogix that used AstraZeneca's Brilinta (ticagrelor) and Amgen's PCSK9 target drug Repatha (evolocumab) as a benchmark. The study found pricing for these therapies in the $14,000 per year range. It's important to remember that pricing is a sliding scale and that numbers needed to treat (NNT) and the cost to prevent an event must also be taken into consideration. For example, the ODYSSEY LONG TERM trial showed that alirocumab (Sanofi/ Regeneron Pharmaceuticals), an investigational monoclonal antibody that inhibits PCSK9 (proprotein convertase subtilisin/ kexin type 9), was significant in lowering LDL cholesterol by 62% and also exhibited a 50-55% reduction in MACE. These results appear to be promising, but also set a benchmark in the $14,000 per year range. Base on this treatment cost per patient, the cost to prevent an event could exceed $1 million per event as per the analysis of the NNT, in this case 90-92 for alirocumab (vs. 21 for apabetalone from the SUSTAIN and ASSURE trials), based on annualized treatment therapy. Based on projected efficacy, preliminary health economic apabetalone data commands an incremental cost effectiveness ratio (ICER) score between $50,000 and $100,000 per year at based on preliminary pricing estimates of $2,500 to $4,500 per annum. This compares favorably with the statistics provided above in other novel therapeutic approaches in CVD and diabetes. If approved, and if apabetalone value proposition is superior to other novel competitors in high risk diabetes and CVD risk reduction, we believe this could be a very attractive option from the viewpoint of payor groups.

**Intellectual Property**

The company's strategy is to build a strong patent portfolio around its core technology that is important to the development of leading edge medicines. Resverlogix's strategy is to be the first to identify, isolate, and patent therapeutic agents with commercial importance, as well as, to seek out and license intellectual property believed to be useful in connection with potential products.

Resverlogix's intellectual property portfolio covers compositions, methods of use, manufacturing, combinations, and treatments for a number of indications related to its core technology. The company owns and/or has rights to more than 10 patent families, comprising more than 40 issued patents, including 10 in the U.S., as well as more than 50 pending patent applications in different jurisdictions. Resverlogix Corp. announced in April 2015 that it had received two patent approvals in China covering RVX-208, which include a composition of matter patent granted until

February 2027, and a manufacturing patent granted until June 2029. The table below shows a list of issued U.S. patents and pending patent applications related to RVX-208.

**Exhibit XXI – Summary of Patents Held**

| Patent Number | Title | Expiration Date |
|---|---|---|
| US 8,053,440 (Composition claims) | Compounds for the prevention and treatment of cardiovascular disease | August 2030 |
| US 8,889,698 (Use claims) | Compounds for the prevention and treatment of cardiovascular disease | September 2027 |
| US 8,114,995 (Manufacturing) | Methods of preparing quinazolinone derivatives | April 2030 |
| US 8,884,046 (Manufacturing) | Novel compounds useful in the synthesis of benzamide compounds | October 2033 |
| **Application Number** | **Title** | **Filing date** |
| US 13/665,147 (Formulation) | Pharmaceutical Compositions for Substituted Quinazolinones | October 2012 |
| WO 2015/025226 | Compositions and Therapeutic Methods for Accelerated Plaque Regression | August 2014 |
| WO 2015/025228 | Compositions and Therapeutic Methods for Accelerated Plaque Regression | August 2014 |

**Financial Position**

As of January 31, 2016 Resverlogix held approximately $30 million in cash and cash equivalents on its balance sheet. We believe this is sufficient to fund Phase 3 BETonMACE trial activities over the next year. For the first nine months ended January 31, 2016, Resverlogix used approximately $18 million in cash from operations and capital expenditures over the first nine months of its reporting period. We anticipate that Resverlogix will report annual results for the year ending April 30, 2016 in July 2016.

## RISKS

All investments contain an element of risk which reflects the uncertainty of the business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are betting on a new technology that has not yet even been fully defined have a much higher level of perceived risk.

The biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products yet.

For smaller early-stage companies, investing in drug development is an extended process. The timeframe for conducting pre-clinical research to eventually marketing a drug can take from 12 to 15 years or even longer given market conditions. And with, on average, only one in one thousand compounds eventually making it to the market, the risks are substantial.

Even if a company has a strong, experienced team that is developing a therapy with a high likelihood of success and a large addressable market, securing funding may pose a substantial risk. Access to financing comes and goes in cycles. During periods of improving confidence, capital may be easy to access; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their work. If capital is needed to sustain the company and it is not readily available, a company may be forced to suspend operations, sell at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising therapies without a viable route for progressing or force a company to accept onerous terms.

FDA or other governmental regulatory approvals are a material uncertainty to which all drugs must submit before they are legally marketed. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are key elements that can help mitigate this risk. Companies that have had previous success with the FDA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways to approval have been put forth such as the Orphan Drug Act, however, changes in sentiment or perceived safety for epigenetic drugs or for pharmaceuticals in general could change the regulatory environment for the worse and these pathways may be extended or additional requirements may be put in place. For Resverlogix in particular, the risks of regulatory approval are substantial. The company plans to initially seek approval in Europe through the European Medicines Agency (EMA) then expand to Latin America. There is no centralized agency for Latin America as there is in Europe and each country requires its own individual approval process which may take substantial time and resources to secure.

There are also risks particular to epigenetics. Turning on and off genes with potentially pleiotropic consequences may result in outcomes with unintended outcomes. Using agents with hypomethylating and histone-deacetylase inhibitory effects may result in toxicities and the development of second malignancies. Some studies have shown that the use of epigenetic drugs have resulted in tumors (Gaudet, et al., 2003) and genomic instability (Eden, A., Gaudet, F., Waghmare, A. & Jaenisch, R., 2003). While there is no evidence of these outcomes in apabetalone, investors must be aware of adverse events faced by other epigenetic compounds.

In Resverlogix's Phase 2 ASSERT clinical trial, some patients had elevations in serum enzymes which are sensitive markers of liver injury however other clinical laboratory tests indicate there was no impairment in liver function and patients were asymptomatic for liver injury. Most of these liver signals occurred between weeks five and ten with less occurrence between weeks ten and thirteen. In our subsequent Phase 2b clinical trials, SUSTAIN and ASSURE I, increases in alanine transaminases (ALTs) were observed in a small group of patients. Those who had ALT elevations of 3x the upper limits of normal (ULN) all dosed through the trial which potentially illustrated adaptability to the drug. Those who had elevation greater than 5x ULN, a high number of those patients had pre-existing liver condition such as hepatitis and took known agents that cause ALT elevations such as acetaminophen, clavulanic acid, diclofenac, and Augmentin. These increases were all observed within weeks 12 and 24 of the trial. Upon stopping apabetalone, ALT elevations returned to ULN quickly which further illustrates a lack of hepatotoxicity. The company also performed the FDA's liver analysis tool ("eDISH") which further illustrated that

there were no Hy's Law (elevated ALT and total bilirubin) cases. Based on this data, Resverlogix believes that the current therapeutic regimen can be safe with regard to effects on the liver. However, if further tests were to determine such risk did exist, the FDA may require the company to conduct additional clinical trials to address these concerns prior to receiving FDA or foreign regulatory approval for apabetalone. These clinical trials would be expensive and could delay any commercialization of apabetalone and could jeopardize existing development in other indications.

In recent years, contract research organizations (CROs) have taken on a larger role in the development of drug candidates as the complexity and cost of trials has increased. Finding appropriate populations to participate in clinical trials has become increasingly difficult due to the shift to personalized medicine and orphan indications that address a small population. This shift has increased the dependence on these specialized CROs for project management and clinical monitoring services which add additional risks and dependence on third parties into the mix.

Drug price inflation has been a hot topic for many years and has contributed materially to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate. For example, in 1996, new cancer drugs cost roughly $54,000 for each additional year of life they provided. However, by 2013, this amount increased to over $200,000. The inflation rate for established drugs has also been very high. In a Forbes article, Novartis' leukemia drug Gleevec was highlighted. This drug cost $24,000 in 2001 when it was first approved; and 14 years later, in 2015, had risen to a cost of $90,000. This represents a 10% compound annual growth rate over that period. Other price moves such as the 5,000% price hike for Turing Pharmaceutical's Daraprim and Valent Pharmaceuticals 500% and 200% price increase for Isuprel and Nitropress last year combined with similar moves by other companies may create a situation where further increases are unsustainable.

We highlight three risks that come from these pricing increases. First, health care may become unaffordable for a broad segment of the population, reducing the market size to a level what we could otherwise reasonably forecast. Second, sharp price increases will attract the attention of elected officials and regulators who may create legislation and implement regulations that limit drug profitability. Third, the government may impose additional non-price related regulation and disclosure that can increase costs for the industry. We note that Resverlogix has been very sensitive to pricing and has performed thorough pharmaco-economic studies which target pricing that will reduce overall system costs.

While we have discussed a broad variety of risks above, we believe that our valuation metrics have addressed these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

## MANAGEMENT PROFILES

**Donald J. McCaffrey – President, Chief Executive Officer and Co-Founder**

Donald McCaffrey is has over 35 years of business experience including 15 years of drug discovery & development. He has raised over $260 million for research and clinical development in the areas of CV, DM, AD and other serious indications. Under Donald's guidance, Resverlogix was honored with multiple awards, the most prestigious being the 2008 World Economic Forum (WEF) Technology Pioneer award in Davos Switzerland. Mr. McCaffrey spearheaded the development and spin-out of Resverlogix's subsidiary RVX Therapeutics Inc. to Zenith Epigenetics Corp., a newly-incorporated company. Mr. McCaffrey acted as President and CEO of Zenith Epigenetics for the first year and now serves as the Chairman of the Board of Directors Donald's career accomplishments have been recognized by the business community and peers, as he was nominated for Ernst & Young Entrepreneur of the Year three times.

**Dr. Norman C.W. Wong, M.D., FRCP – Chief Scientific Officer and Co-Founder**

Dr. Wong's research interest focus is on the molecular actions of hormones related to the regulation of lipoprotein expression and pathogenesis of diabetes mellitus. His clinical interest encompasses patients with thyroid disease or diabetes mellitus. His most recent successes have come from elucidating the potential therapeutic opportunities for cardiovascular disease by harnessing the regulation of Apolipoprotein A-1 (Apo A-1) gene expression. He has been the author and co-author of more than 275 articles and abstracts and has been invited to sit on more than 40 national or international panels and committees. He has also acted as a consultant to several leading pharmaceutical companies, including Eli Lilly, Merck Frost, GlaxoSmithKline, Solvay Pharmaceuticals and Abbott Laboratories.

**A. Brad Cann, CA – Chief Financial Officer**

Brad has more than 19 years of financial and business experience. Prior to joining Resverlogix, Brad was Executive Vice President and CFO of Royal Host Real Estate Investment Trust, a diversified hospitality trust engaged in hotel ownership, investment, management and franchising, and Canada's second largest hotel REIT. Brad shared responsibility for developing the strategic initiatives of the Trust and leading its executive team in day-to-day operations, as well as investing, financing and real estate transactions. Prior to joining Royal Host, Brad was a business consultant and held senior management positions with several companies including CFO of a sulphur export development company and CFO of an oilfield waste water treatment company. Prior thereto, Brad held various positions with a chartered accounting firm. Brad is a Chartered Accountant and a Chartered Business Valuator, and holds a Bachelor of Commerce from the University of Saskatchewan.

**Dr. Jan O. Johansson, M.D., Ph.D. – Senior Vice President Medical Affairs**

Dr. Johansson has had a distinguished 30 plus year career of which the past 18 years have been in small biotechnology and large pharmaceutical companies with expertise in the CVD therapeutic area. He has served as Chief Medical Officer at Nuvelo, Inc., VP, Clinical Research and Development at Lipid Sciences, Inc. and was Co-founder, VP, Clinical Affairs and Senior Clinical Research Fellow of Esperion Therapeutics, Inc. From 1995 to 1997, Dr. Johansson was a medical advisor with executive responsibilities at Pharmacia bringing one lipid lowering product to the market and heading the apolipoprotein A-1 Milano clinical program. Dr. Johansson earned his M.D. and Ph.D. at the Karolinska Institute in Sweden where he lead a successful career as a tenured associate professor at the Karolinska Hospital and as a practicing physician. He has published more than 50 peer review medical articles, and is a member of the AHA and the European Atherosclerosis Society.

**Dr. Michael Sweeney, M.D. - Senior Vice President of Clinical Development**

Dr. Sweeney, a cardiologist with extensive experience in pharmaceutical product development and marketing, has an impressive 26-year career history. This includes 11 years at Pfizer Inc., holding a variety of senior-level medical and marketing positions, including Senior Director, Urology Global Medical Group Leader and Director of Marketing of the Viagra Worldwide Team. Prior to joining Resverlogix, Dr. Sweeney was Chief Medical Officer and Vice President of R&D at Depomed, Inc. in Silicon Valley. Dr. Sweeney was also the Vice President of Medical Affairs at CV Therapeutics, Inc. Dr. Sweeney holds biochemistry and medical degrees from Liverpool University and an advanced medical research degree from Manchester University in the U.K. Dr. Sweeney also holds post-graduate diplomas in pharmaceutical medicine and pharmaco-epidemiology from the University of London. He is a fellow of the Royal College of Physicians of Edinburgh.

**Kenneth Lebioda, B.A. - Senior Vice President Business & Corporate Development**
Ken has over 30 years' experience in the innovative pharmaceutical industry with leading global companies such as Bristol-Myers Squibb, Hoechst Marion Roussel and Marion Merrell Dow. He held a variety of management positions with these companies in the areas of sales and business development, regulatory affairs, reimbursement and market access. Ken's past contributions include helping to build leading global cardiovascular brands such as Plavix, Pravachol, Cardizem, and Avapro. pharmaco-economics, licensing and commercial development.

**Henrik C. Hansen, Ph.D. - Vice President of Intellectual Property**
Henrik C. Hansen has more than 13 years of experience, from both academia and industry, in basic research, drug discovery, and drug development. His areas of expertise include medicinal chemistry and carbohydrate chemistry, process development, and manufacturing of drug substances and drug products under cGMP for clinical use. Henrik holds a M.Sc. in Chemical Engineering from the Technical University of Denmark and a Ph.D. in Organic Chemistry from Lund University, Sweden. He has authored or co-authored more than 40 articles and meeting abstracts and is listed as inventor of 9 patent families.

**Dr. Ewelina Kulikowski, Ph.D. - Senior Vice President of Research & Development**
Dr. Kulikowski has over 11 years' experience in scientific research and drug development. Dr. Kulikowski joined Resverlogix in 2005 as Director of Research and Development and has been involved in the development of lead drug apabetalone from its discovery, to the IND and into clinical development. Dr. Kulikowski has led projects in oncology, ophthalmology, and vascular inflammation, as well as served as a liaison between the science and business teams. As Director of Business Development and Scientific Affairs, Dr Kulikowski was involved in various aspects of pipeline development including market, reimbursement and pharmacoeconomic surveys, regulatory affairs, commercial and lifecycle management. Most recently, Dr. Kulikowski has led the Neurodegenerative Program and continues to oversee this area of development. In 2004, she received her Doctorate in Oncology from the University of Calgary, AB.

**Clayton Paradis - Vice President of Investor Relations**
Clayton brings 15 years of capital markets and investor relations experience to Resverlogix. Most recently, Clayton led the investor relations function for Penn West Petroleum with shareholders and joint venture partners geographically dispersed throughout North America, Europe and Asia. Prior to his career in investor relations, Clayton worked for Ross Smith Energy Group and CIBC World Markets in equity research as an energy specialist. Clayton is a member of the Canadian Investor Relations Institute (CIRI) and holds an MBA – Finance from the University of Calgary and Bachelor of Management from the University of Lethbridge.

## VALUATION AND RECOMMENDATION

We are initiating coverage of Resverlogix Corp. (TSX: RVX) with a price target of CAD$5.00. Resverlogix's lead clinical stage candidate, apabetalone, is the first selective BET bromodomain inhibitor in clinical trials for high-risk vascular disease. Apabetalone is targeting a very specific patient population with low HDL, diabetes and chronic kidney disease with a high cardiovascular risk for increased MACE. Based on internal analysis conducted by Resverlogix, there are from 3.0 to 4.0 million CVD patients with low HDL and recent ACS in the initial targeted markets of Europe and Latin America. Our research estimates that there are a similar range of these patients in the United States. Resverlogix analysis also shows from 1.8 to 2.0 million individuals with CKD and ACS (non-dialysis) are also potential patients for apabetalone. Our analysis shows a slightly greater number of these individuals in the United States.

Our pricing is dependent on geography, and we select a range slightly narrower than that suggested by the company's analysis. We estimated that apabetalone will be priced between $3,000 and $4,000 per year, but note that increased levels of efficacy shown in the BETonMACE trial may support pricing upside from current levels.

We also value the licensing agreement with Hepalink and assume that the addressable market will be between two and three million patients and that Hepalink will achieve from 40% to 50% penetration into this market. Pricing for the annual regimen is expected to range from $1,200 to $1,500. Hepalink will pay Resverlogix a royalty equal to 6% of revenues as well as milestone payments over the duration of the agreement.

To value Resverlogix, we use a discount rate of 15%, as we do with other Phase 3 candidates under our coverage and we apply a 64% probability of success in EU, Latin America and US markets, which is guided by the probability of approval observed by Phase 3 candidates at the FDA. We initially anticipate approval by the regulatory agencies in Europe in 2020, followed shortly after by approval in Latin American geographies and the United States in 2022. For China and other Hepalink markets, we assume a 2022 launch and a 50% probability of success due to the shorter history and higher degree of uncertainty related to the China Food and Drug Administration (CFDA) approval process.

We initially forecast penetration rates of 1% increasing to 10% into the indicated populations over a multi-year period in the European, Latin American or the United States markets. We assume higher penetration in Hepalink's addressable markets, which are expected to peak in the 40% to 50% range. The drug may also address orphan indications which may expand the population. We anticipate that Resverlogix will use partners to market and sell apabetalone and will pay the company a royalty (which includes milestone payments) from 15% to 20%. The agreement with Hepalink provides a lower 6% royalty payment, but also requires the payment of milestones and demands that Hepalink conduct clinical trials and secure approval from the appropriate regulatory agencies in the Asian territories under its license.

For reference, we highlight the existing market for at risk CVD patients, including approved drugs like Lipitor® ($13.7 billion peak in 2006), Crestor® ($6.6 billion peak in 2011, $5.5 billion in 2014), Lovaza ($1.1 billion peak in 2013). We are also using several estimates we found for late-stage clinical candidates such as Amgen's and Regeneron/ Sanofi's PCSK9 inhibitors, evolocumab and alirocumab, respectively. Wall Street consensus estimates, as well as independent analyst estimates from websites such as TheStreet.com, FierceBiotech, Benzinga, and Seeking-Alpha, for these drugs range between $3 billion to $10 billion. We believe apabetalone, although not nearly as well known in the investment community compared to these other compounds, has similar sales potential and we conservatively forecast a peak of over $6 billion in 2026 and 2027 for the markets we are currently considering.

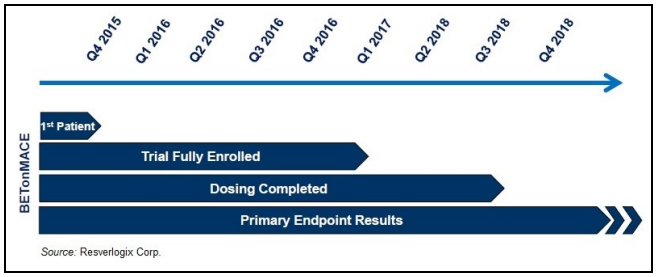
We assume that Resverlogix will refinance its $41 million in debt due August 28, 2017 on similar terms as current, which are Canadian one-year LIBOR swap rate plus 3.14%.

Based on our assumptions above our valuation target is **CAD$5.00** per share.

**Business Update**

On November 11, 2015, Resverlogix announced that the first patient was randomized and that dosing has commenced in its Phase 3 BETonMACE clinical trial with apabetalone in high-risk patients with coronary artery disease and type 2 diabetes mellitus following the October 26, 2015 announcement regarding trial commencement. Dosing commenced two weeks after the opening of the first clinical trial sites. The trial is currently recruiting participants, and further details regarding BETonMACE can be found on ClinicalTrials.gov. We recently spoke with management and patient recruitment is progressing as planned, and we believe that Resverlogix has received initial approval from the regulatory authority and ethics committee in ten countries including Belgium, Hungary and Israel. We believe that additional investigative sites are being activated and proceeding as scheduled.

**Exhibit XXII – BETonMACE Timeline**



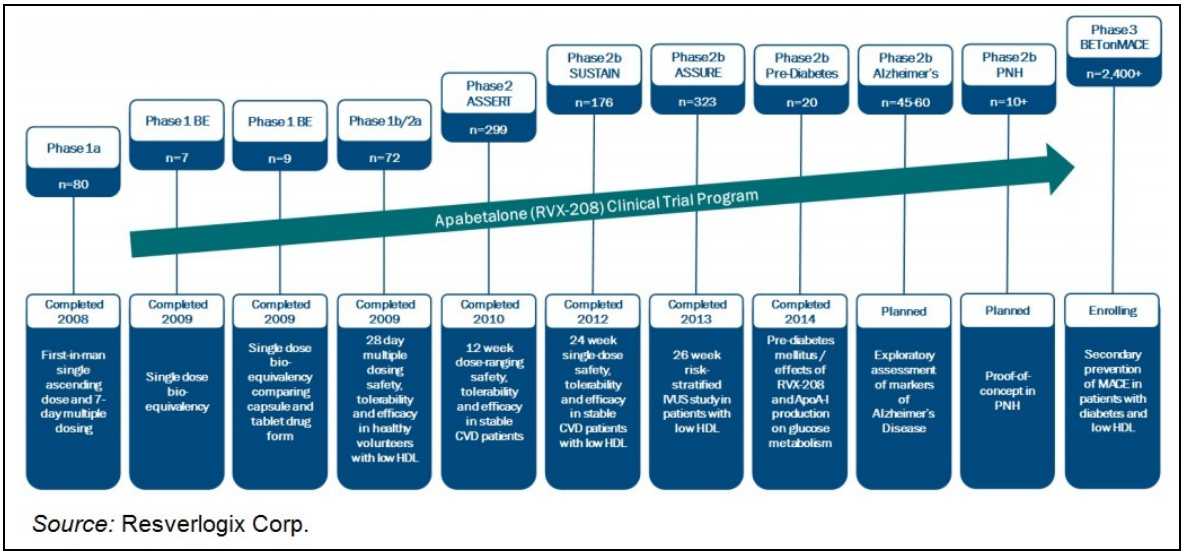

As a reminder, the primary outcome measure of the trial will assess the effect of apabetalone on time to first occurrence of Major Adverse Cardiovascular Events (MACE) in high-risk type 2 DM patients with CAD. In the primary outcome measure, MACE is narrowly defined as a single composite endpoint of cardiovascular death, or non-fatal myocardial infarction (MI), or stroke. All subjects will remain on a high-dose statin therapy (atorvastatin or rosuvastatin), with the experimental group receiving 200 mg/day of apabetalone in the form of 100 mg capsules twice daily. We believe that the company will perform an interim futility analysis, which will look at the chance of a positive result if existing trends for MACE continue, and will be formed when 50% of events are admitted in addition to an ongoing safety analysis by the Data Safety Monitoring Board (DSMB). We expect the trial to take about 3 years to complete. This puts the topline data in 2018, with the goal to file a new drug application (NDA) during the end of 2018 or early part of 2019. We believe the program will cost in the area of $30 million, but note that exact costs will depend on how many patients are ultimately enrolled since the trial is currently set up to identify 250 events before concluding.

In other company news, on September 25, 2015, Resverlogix provided a Research and Development Update on apabetalone in New York City. The presentation included analyses of diabetes and chronic kidney disease (CKD) as they relate to cardiovascular disease by BETonMACE clinical steering members. We also learned more about some recent findings from ongoing mechanistic studies focused on cardiovascular risk pathways and apabetalone's potential in reducing MACE, and have reviewed apabetalone and details from the event in our prior research report update.

***Clinical Trial History of Apabetalone***

Resverlogix has completed numerous clinical trials to date (*below*). Apabetalone has been tested in over 1,000 patients, and over the years, Resverlogix has gathered information from these studies and shifted focus to target patients with low HDL and diabetes with co-treatment of apabetalone and statin therapy either rosuvastatin (Crestor®) or atorvastatin (Lipitor®).

**Exhibit XXIII – Apabetalone Clinical Trial History**



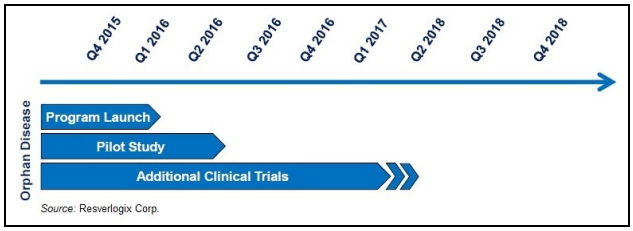

***Value Proposition***

Resverlogix hopes that successful pharmaceutical partnerships or licensing agreements for apabetalone, similar to the one with Hepalink, will help overcome the cost burden, lengthy development time, and high attrition rates, while helping to advance the drug through clinical trials and drug development stages. Management hopes that this will ultimately lead to commercialization of the drug. Through extensive modeling and ongoing outreach to key opinion leaders (KOLs), management believes that if apabetalone shows a 20-30% relative risk reduction of MACE in the Phase 3 trial, the pharmacoeconomics of apabetalone will be very compelling. The company believes it will cost around $3,000-$4,200 per year once it hits the market depending on the specific efficacy scenario (20-30% RRR). Management believes that at this price point, the drug would be in the preferred co-pay status (Tier 2, which comes right after generics in Tier 1), and if so, there is a very strong opportunity for preferred reimbursement. Greater than $5,000 would likely put the drug in Tier 3 and require prior authorization. It's also important to remember that this is a sliding scale and that numbers needed to treat (NNT) and the cost to prevent an event must also be taken into consideration. Efficient NNT are an important assessment in the accretive value added by reimbursement and payer groups. NNT is calculated as the inverse of the ARR (Absolute Risk Reduction): NNT = 1/ARR, where ARR = PER (Placebo Event Rate) – TER (Treatment Event Rate). For example, when looking at Praluent (alirocumab) and Repatha (evolocumab) with a reported $14,600 and $14,100 per year treatment cost per patient, respectively, some would argue that the cost to prevent an event could be close to or exceeding $1 million for one year as per the analysis of the NNT, in this case 63 for alirocumab and 81 for evolocumab (vs. 21 for apabetalone from pooled SUSTAIN and ASSURE trial data), based on annualized treatment therapy. Even if the costs of these drugs were lowered to around $10,000 annually per patient, the total cost to avoid such an event with the medications would be approximately $600,000 to $800,000 for one year. If apabetalone can support a greater than 20-25% relative risk reduction over standard of care medicines, pricing will be a major advantage over agents such as PCSK9 inhibitors. If approved, and if apabetalone costs mirror what management is currently predicting, we believe apabetalone has the opportunity to take a substantial market share from competing therapies.

**Orphan Disease Program**

On September 24, 2015, Resverlogix announced the commencement of an Orphan Disease Program for Complement Mediated Diseases.

**Exhibit XXIV – Orphan Disease Timeline**



Management believes that new data suggests that apabetalone downregulates different components of the complement and coagulations pathways, which are important to cardiovascular disease as well several orphan diseases. Resverlogix would like to further explore the potential of apabetalone in humans with overactive complement pathways. We believe that apabetalone will be tested in a Phase 2 proof-of-concept pilot study in a small group of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH).

We believe there is potential for Resverlogix to study other complement mediated diseases, such as atypical hemolytic uremic syndrome (aHUS), and glomerulonephritis in conjunction with apabetalone as well as other pre-clinical BET inhibitors/follow-on compounds (*below*), but we are not exactly sure the path the company wishes to pursue. Resverlogix does not currently have an orphan drug designation at this point, but based on management commentary, we believe the company is in the process of pursuing orphan indications. Management believes that the orphan drug route will allow for the drug to reach the market before that for the indications in the BETonMACE trial.

***Paroxysmal Nocturnal Hemoglobinuria***

The National Organization for Rare Disorders (NORD) states that paroxysmal nocturnal hemoglobinuria, or PNH, is a rare yet progressive and often life-threatening acquired hematopoietic stem cell disease of the blood. Hematopoietic stem cells give rise to red blood cells. In PNH, red blood cells break down or are prematurely destroyed earlier than normal (hemolysis) by an individual's own immune system (complement system), with potentially fatal consequences. It is estimated to affect between one and five million individuals. A quick search on clinicaltrials.gov shows 42 results related to PNH, with 14 being "open studies."

In healthy individuals, RBCs and other blood cell types have specific cell surface proteins that function to inhibit the complement system and ultimately protect cells against formation of the MAC (membrane attack complex). Individuals with PNH have blood cells that are missing a gene called PIG-A. This gene normally allows a substance known as glycosyl-phosphatidylinositol (GPI) to help particular proteins stick to cells. Without PIG-A, certain proteins are unable to stick to cell surfaces in order to offer protection to the cell against complement substances that are circulating in the blood. Due to the acquired mutation in their hematopoietic stem cells, patients with PNH do not express these host proteins and their red blood cells become subject to complement-mediated destruction. A direct link exists between excessive complement activation and the clinical manifestation of PNH. This process leads to early destruction of red blood cells, and leakage of hemoglobin into the blood, which can pass into the urine (hemoglobinuria) and can lead to renal failure, (U.S. National Library of Medicine, 2014) as well as repeated, potentially fatal blood clots (thromboses) that account for up to 40-67% of PNH mortality. Other symptoms of PNH include extreme fatigue, abdominal pain, and anemia. The resultant excessive red blood cell destruction often causes transfusion dependence in PNH patients.

***Treatment Options for PNH***

PNH treatment is often tailored to specific symptoms and includes many different therapeutic and supportive approaches. Treatment often involves steroids that can suppress the immune system to help slow down red blood cell destruction, as well as blood transfusions, supplemental iron and folic acid, anti-coagulation drugs to prevent clot formation, and bone marrow transplantation.

The U.S. Food and Drug Administration (FDA) approved Soliris (eculizumab), an orphan drug, in 2007 for the treatment of PNH. It was the first drug to be approved for PNH, and although it does not cure the disease, it does block the breakdown of red blood cells, and in turn, can prevent thrombosis. Soliris blocks the complement system of the body that is responsible for destroying blood cells in PNH individuals. Since it does block the immune system, the drug does increase the risk of meningococcal infections, and patients must be vaccinated with a meningococcal vaccine at least two weeks before receiving the first dose of the drug. Soliris is also approved for the treatment of aHUS. The drug was developed by Alexion Pharmaceuticals and patent expiration occurs in 2021.

Soliris has been the subject of controversy as it has been called one of the most expensive drugs in the world, and. In 2014, it had a U.S. list price of about $440,000 per patient a year. According to EvaluatePharma, worldwide sales of Soliris in 2014 were $2.2 billion, with estimated sales to be over $2.6 billion in 2015. According to a 2014 report by the International PNH Registry, close to 75% of PNH patients are not receiving Soliris treatment. Some believe it is only being used in severe cases of PNH due to the high cost of the drug. For these reasons, Resverlogix believes that if apabetalone is successful as a treatment for PNH, it could fill a large unmet medical need for patients with this severe disease.

## Conclusion

We remind investors that Resverlogix's lead product candidate, apabetalone, is the first selective BET bromodomain inhibitor in clinical trials for high-risk vascular disease. Apabetalone is targeting a very specific patient population with low HDL, type diabetes mellitus and chronic kidney disease with a high cardiovascular risk for increased MACE. The trial is progressing with patient recruitment and trial site activation in Phase 3 BETonMACE.

We believe that strong patent position and pharmacoeconomics of apabetalone, combined with a management skill set surrounding CVD and diabetes and a novel approach to addressing the residual risk in high need CVD patients, allows for Resverlogix to be in an strong position. The company secured access to approximately $37 million USD in new capital through licensing and stock purchase agreements with Hepalink and Eastern Capital, which we believe should fully fund the Phase 3 BETon MACE program. Resverlogix does face a number of both industry specific and company specific risks, some of which we have outlined above. Additionally, we are still not sure what type of cardiovascular clinical trials the FDA and EMA will require of apabetalone as the company is still waiting to discuss trial design with these agencies.

We do want to point out that data from this trial will not likely be available until mid to late-2018, but we hope to see results from the interim futility analysis which will provide a first look after 125 MACE events. The recently announced complement-mediated orphan disease program could also provide further upside to our valuation, however at this time it is too early to include in our model. Additionally, the proposed multimodal mechanism of action of Resverlogix that we have discussed in previous reports leads us to believe that Resverlogix may consider evaluating apabetalone as it relates to other conditions in more depth, such as renal disease, which would also provide additional upside to our valuation. Currently, we believe the company is undervalued. We initiate on Resverlogix with a price target of CAD$5.00 per share.

## PROJECTED FINANCIALS

### Resverlogix Corp. - Income Statement

| Resverlogix Corp. (millions of $US) | Apr. 2015 FY-15 A | Jul. 2015 Q1 A | Oct. 2015 Q2 A | Jan. 2016 Q3 A | Apr. 2016 Q4 E | Apr. 2016 FY-16 E | Apr. 2017 FY-17 E | Apr. 2018 FY-18 E |
|---|---|---|---|---|---|---|---|---|
| RVX-208 | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| Licensing & Collaborative | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *YOY Growth* | - | - | - | - | - | - | - | - |
| **Total Revenues** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** | **$0** |
| CoGS | $0 | $0 | $0 | $0 | $0 | $0 | $0 | $0 |
| *Product Gross Margin* | - | - | - | - | - | - | - | - |
| R&D Expense (net) | $4.2 | $2.2 | $3.2 | $3.9 | $3.5 | $12.9 | $15.0 | $16.0 |
| G&A Expense | $4.3 | $1.3 | $0.9 | $0.8 | $1.6 | $4.6 | $6.3 | $6.8 |
| Operating Income | ($8.5) | ($3.5) | ($4.1) | ($4.7) | ($5.1) | ($17.5) | ($21.3) | ($22.8) |
| *Operating Margin* | - | - | - | - | - | - | - | - |
| Net Finance Activities | ($9.9) | $6.1 | $0.3 | ($4.1) | ($1.5) | $0.8 | ($6.0) | ($6.0) |
| Other Gain / (Loss) | ($1.1) | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| Pre-Tax Income | ($19.4) | $2.6 | ($3.8) | ($8.9) | ($6.6) | ($16.6) | ($27.3) | ($28.8) |
| Taxes & Other | ($1.1) | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 | $0.0 |
| *Tax Rate* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* | *0%* |
| Net Income | ($18.3) | $2.6 | ($3.8) | ($8.9) | ($6.6) | ($16.6) | ($27.3) | ($28.8) |
| | | | | | | | | |
| **Reported EPS** | **($0.21)** | **$0.03** | **($0.04)** | **($0.08)** | **($0.06)** | **($0.16)** | **($0.25)** | **($0.26)** |
| *YOY Growth* | - | | | | | | - | - |
| Shares Outstanding | 85.6 | 105.1 | 105.1 | 105.2 | 105.6 | 105.2 | 108.0 | 110.0 |

*Source: Company Filing // Zacks Investment Research, Inc. Estimates*

## HISTORICAL STOCK PRICE



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