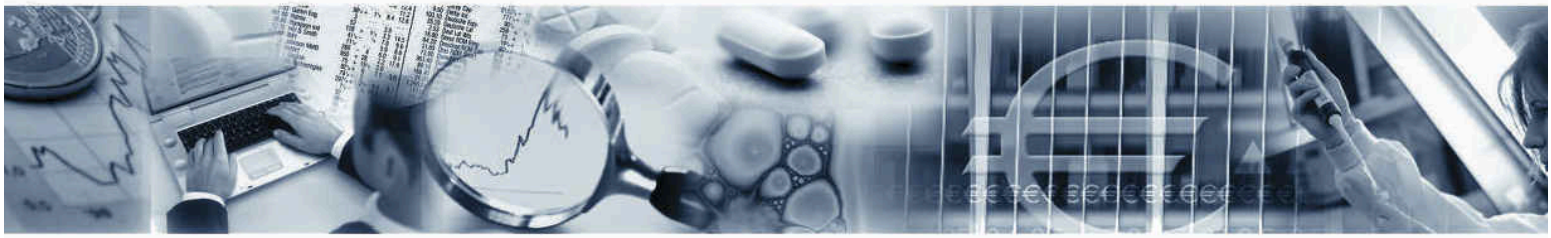

Update Report

Resverlogix

New Indications Apabetalone Justify Rerating

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Date: 1 May 2017

Name:	**Resverlogix Corp.**
Country:	**Canada**
Price:	**CAD 1.99**
ISIN Code:	**CA76128M1086**
Reuters Code:	**RVX.TO**
Market Cap (USD m):	**210.2**
EV (USD m):	**277.9**
Cash & cash eq. (USD m):	**4.9**
Shares outstanding (m):	**105.5**
Volume:	**43,862**
Free float:	**79%**
52-week Range:	**1.10-2.47**

USD m (ended 04/30)	2014/15A	2015/16A	2016/17E
Total Revenues	-	-	-
Net (Loss)/Profit	(18.323)	(19.715)	(40.000)
Net loss per share (pence)	(0.22)	(0.20)	(0.38)
R&D costs	4.185	15.681	28.000
Cash increase/(decrease)	15.621	11.898	(24.109)
Cash and marketable sec.	16.211	28.109	4.000

Contents

Executive Summary

- Resverlogix (RVX.TO) is a clinical stage cardiovascular company with an epigenetic platform technology that modulates protein production. The company is developing small molecules that selectively inhibit Bromodomain and Extra Terminal domain (BET) proteins, a new and emerging target for high risk vascular diseases. The company is the first to test the BET inhibition hypothesis as a new approach for reducing major adverse cardiovascular events (MACE) in high risk diabetes and CKD patients. A second important hypothesis the company also plans as a secondary endpoint in CKD patients in the trial is measuring a key kidney function biomarker estimated glomerular filtration (eGFR). To date the company holds a nine year lead in the field of epigenetic small molecules for vascular disease risk reduction.

- Resverlogix has a proprietary drug development platform that is based on targeting BET proteins. BET protein inhibitors have potential in many diseases including cardiovascular disease, neurodegenerative diseases and diabetes. The field of epigenetics is quickly growing and with it the understanding that both the environment and individual lifestyle can also directly interact with the genome to influence epigenetic change.

- In October 2015, Resverlogix initiated a Phase III clinical trial "BETonMACE" with apabetalone in high-risk CVD patients with type 2 diabetes mellitus and low HDL. The primary endpoint is the time to first occurrence of MACE. Secondary endpoints such as renal function (eGFR) in CKD patients are also planned. The company received regulatory approval to open clinical investigator sites in all planned countries. Resverlogix has enrolled in more than 1,400 of the planned 2,400 patients. An interim analysis is planned after 125 primary MACE events have been adjudicated. Before, Apabetalone (RVX-208) has already been successfully tested in about 1,000 patients in

various clinical studies (ASSERT, SUSTAIN and ASSURE).

- As at January 31, 2017, the company had USD 4.9 million of cash, USD 5.4 million of trade and other payables. The average monthly cash burn rate was USD 2.7 million for the nine months ended January 31, 2017. The company is expected to raise capital in order to finance the ongoing BETonMACE trial and others. Another possibility is a partnership with one or more pharma companies as was done with the out licensing of apabetalone in the Chinese Territories.

- **We have increased our valuation based on an estimated higher pricing for apabetalone and expanded markets in high risk CKD patients such as ESRD. We believe that Resverlogix remains gravely undervalued at the current share price of CAD 1.99. We feel that the company's current total value should be CAD 1,300 million, or CAD 12.50 per share. This represents a substantial upside from the current share price.**

Company Profile & Technology

Resverlogix (RVX.TO) is a clinical stage cardiovascular company with an epigenetic platform technology that modulates protein production. Resverlogix is developing apabetalone (RVX-208), a first-in-class BET inhibition small molecule called apabetalone for the treatment of and efficient reduction of MACE in high-risk vascular patient groups such as diabetes and CKD. MACE is defined as heart attack, stroke, heart failure, PCI procedures and death. Apabetalone is the first select BET bromodomain inhibitor in a Phase III clinical trial that is targeted for vascular diseases. New compounds arising from Resverlogix's epigenetic drug development platform which function by inhibiting BET bromodomains, have the potential to provide a truly novel approach to vascular diseases risk and impact disorders that drive substantial costs to health systems globally. A growing number of reported publications on BET inhibition and its potential benefits for a variety of diseases make this epigenetic drug target a novel and important new area of focus for the pharmaceutical industry.

The selective production of the proteins encoded by human genes is what leads to differences between cells, and the alteration of their levels can contribute to disease. Epigenetics, a mechanism for regulating gene activity to affect protein production, is becoming an important new field in biotechnology research and drug development. It encompasses mechanisms for regulating the production of proteins from genes without altering the genetic code. In cells, DNA is surrounded by proteins to form chromatin and ultimately human chromosomes. Epigenetics is the study of secondary modifications to DNA (without affecting the sequence) or its associated proteins, which alters their relative disposition, resulting in changes in gene transcription, the first step in producing the proteins that each gene encodes. With an increasing number of diseases being found to be associated with epigenetic factors, the epigenetics field holds a lot of promise for the development of new treatments of - often age-related - diseases ranging from

neurodegenerative diseases and cardiovascular diseases to diabetes, renal diseases, cancer and a variety of orphan diseases as well.

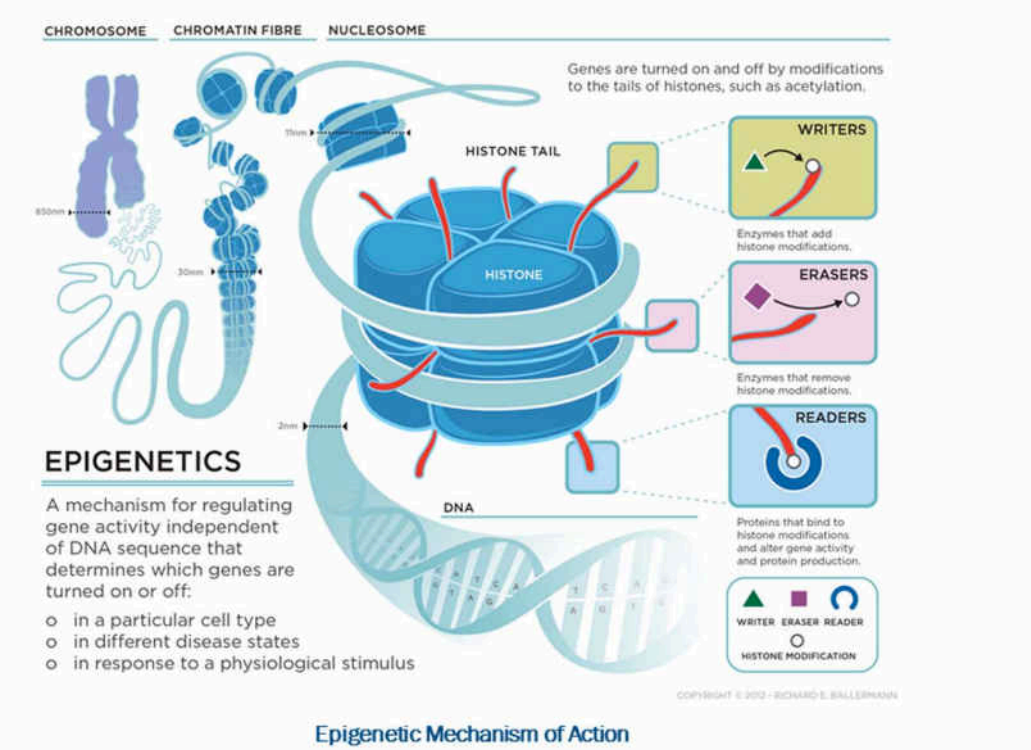
Business Strategy & Partnerships

Given the high costs, long development times and high attrition rates associated with drug development, many biotechnology companies seek the assistance of a pharmaceutical partner to advance their products through clinical trials. Resverlogix maintains active discussions with potential pharmaceutical and biotech partners for its pharmaceutical drug candidates. The Company seeks partnership

opportunities that will provide shareholders with the optimal value for their investment. New potential opportunities in high risk renal diseases as well as rare and orphan diseases, provides Resverlogix with important options for further value creation. Renal function and orphan clinical trials are usually much smaller and shorter than traditional larger CVD trials. Expansion into these high risk markets provides the company with additional value potential by commercializing the molecule more quickly and also establishing a broader indication base for its BET inhibition technology platform. We expect that Resverlogix will be able to make additional regional licensing deals that will give the company more early revenue possibilities. Deals in areas with high unmet medical need such as diabetes and CKD as well as initiation of quicker clinical trials for an orphan drug indication are likely to speed up revenue streams and value creation for the company markedly.

Epigenetics Platform Technology

Resverlogix has developed an epigenetic drug development platform that has the potential to impact multiple diseases including atherosclerosis, autoimmune diseases, cancer, neurodegenerative diseases and diabetes. This platform targets BET proteins that play a vital role in the epigenetic regulation of transcription of particular genes. BET proteins are often called 'readers' of the histone/chromatin structure.



Epigenetic Mechanism of Action

Source: Resverlogix, Richard E. Ballermann

The term epigenetics refers to heritable changes in gene expression (active versus inactive genes) that does not involve changes to the underlying DNA sequence; a change in phenotype without a change in genotype. Epigenetic change is a regular and natural occurrence but can also be influenced by several factors including age, the environment/lifestyle, and disease state.

Epigenetic modifications can manifest as commonly as the manner in which cells terminally differentiate to end up as skin cells, liver cells, brain cells, etc. Or, epigenetic change can have more damaging effects that can result in diseases like cancer. At least three systems including DNA methylation, histone modification and non-coding

RNA (ncRNA)-associated gene silencing are currently considered to initiate and sustain epigenetic change. New and ongoing research is continuously uncovering the role of epigenetics in a variety of human disorders and fatal diseases.

The Evolving Landscape of Epigenetic Research: A Brief History

What began as broad research focused on combining genetics and developmental biology by well-respected scientists including Conrad H. Waddington and Ernst Hadorn during the mid-twentieth century has evolved into the field we currently refer to as epigenetics. The term epigenetics, which was coined by Waddington in 1942, was derived from the Greek word "epigenesis" which originally described the influence of genetic processes on development. During the 1990s there became a renewed interest in genetic assimilation. This lead to elucidation of the molecular basis of Conrad Waddington's observations in which environmental stress caused genetic assimilation of certain phenotypic characteristics in *Drosophila* fruit flies. Since then, research efforts have been focused on unraveling the epigenetic mechanisms related to these types of changes. Currently, DNA methylation is one of the most broadly studied and well-characterized epigenetic modifications dating back to studies done by Griffith and Mahler in 1969 which suggested that DNA methylation may be important in long term memory function. The renewed interest in epigenetics has led to new findings about the relationship between epigenetic changes and a host of disorders including various cancers, mental retardation associated disorders, immune disorders, neuropsychiatric disorders and pediatric disorders.

The field of epigenetics is quickly growing and with it the understanding that both the environment and individual lifestyle can also directly interact with the genome to influence epigenetic change. These changes may be reflected at various stages throughout a person's life and even in later generations. For example, human epidemiological studies have provided evidence that prenatal and early postnatal environmental factors influence the adult risk of developing various chronic diseases and behavioral disorders. Studies have shown that children born during the period of the Dutch famine from 1944-1945 have increased rates of coronary heart disease and obesity after maternal exposure to famine during early pregnancy compared to those not exposed to famine. Less DNA methylation of the insulin-like growth factor II (IGF2) gene, a well-characterized epigenetic locus, was found to be associated with this exposure. Likewise, adults that were prenatally exposed to famine conditions have also been reported to have significantly higher incidence of schizophrenia.

Epigenetics and Apabetalone as first in class BET antagonist

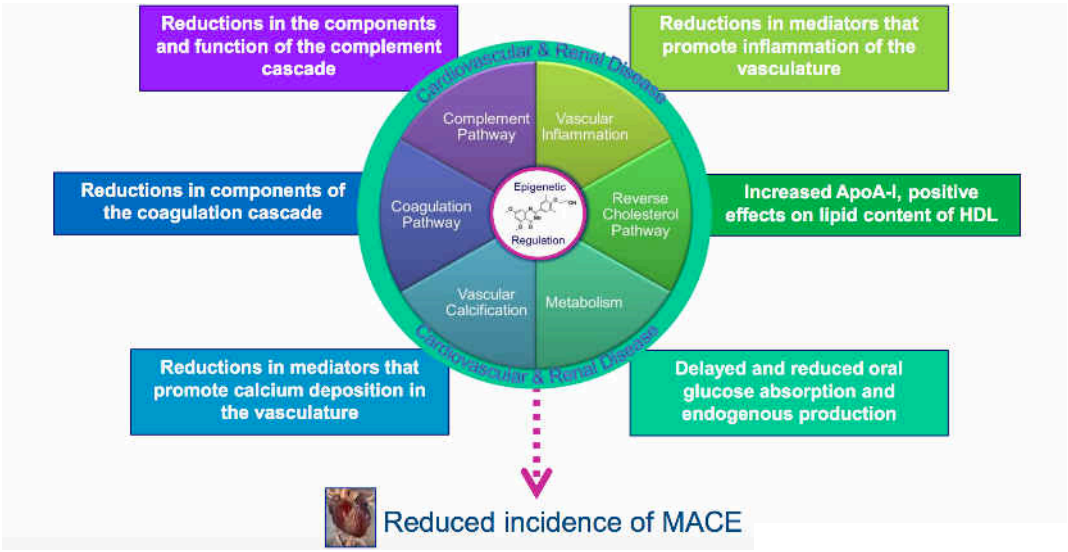
Apabetalone acts upon multiple pathways and genes that drive vascular risk such as ApoA-I (Reverse Cholesterol Transport and functional HDL), Alkaline Phosphatase (Vascular Calcification), Platelets (Thrombosis) and hsCRP (Vascular Inflammation). Apabetalone is the first small molecule to act through a novel epigenetic mechanism that regulates gene transcription to improve these biological pathways. The molecular target is select BET inhibition. Epigenetics is a new frontier in the search of treatment of human diseases. Although genes are encoded within the DNA the tight regulation of this information requires epigenetic mechanisms. To understand these mechanisms we begin by sharing that nuclear chromatin is comprised of DNA complexed with histones and other proteins.

When histone proteins coat the DNA to form chromatin, it looks like beads on a string. Chromatin is a dynamic structure that may be open or closed. But for DNA to be transcribed the chromatin must be open. The transition from the close to open confirmation is mediated by the addition or removal of modifications such as phosphorylation, methylation or acetylation at

specific amino acids within the histones. These processes are the writing and erasing part of the so-called epigenetic code.

Apabetalone does not write or erase but disrupts another component of epigenetics that reads the acetylation of specific lysines in the histones found in actively transcribed regions of DNA. When apabetalone is given orally, it enters the body before taken up by liver cells. Inside the cell, apabetalone binds to a BET protein. These proteins contain two small conserved regions called bromodomains. Each bromodomain has a pocket that combines to or read a specific acetylated lysine found at some n-terminus of some histones.

When this interaction occurs, a different region at the BET protein can recruit other components important for controlling gene transcription. Thus when a BET protein is anchored to chromatin via its chromodomain 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.

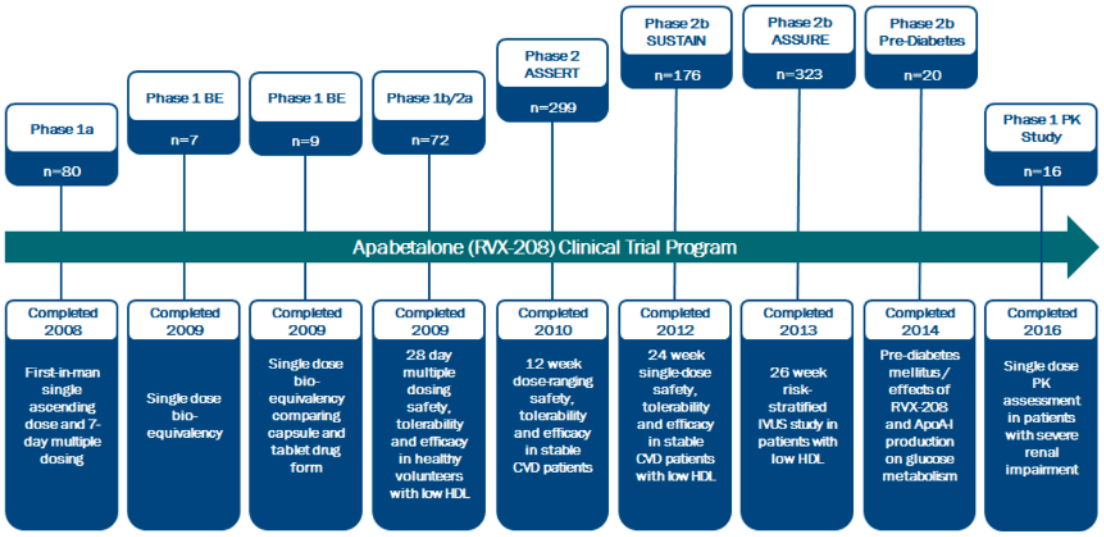


This action of apabetalone leads to an improvement of multiple pathways that play a role in vascular risk previously noted. Improvement in key risk markers such as an increase of ApoA-1 mRNA and production of ApoA-1 protein, the key building block of new functional HDL, a reduction of Alkaline Phosphatase a reported key driver for vascular calcification and reduced hsCRP a marker for vascular inflammation highlight the multiple modality approach that this new molecule has illustrated to date. Discovery at the target of RVX-208 has enabled Resverlogix to obtain a high resolution structure of RVX-208 bound to its target bromodomain and to device biochemical assays that that will hasten the discovery of additional compounds. In addition to inducing ApoA-1 production, reduced ALP, hsCRP and platelets for the treatment of atherosclerosis, potential new select BET inhibition compounds may provide attractive opportunities for treating many additional diseases including autoimmune diseases.

Pipeline: Focus on Apabetalone

Resverlogix has performed numerous clinical trials to date. It has learned from these trials to target patients with apabetalone with low HDL and diabetes. Further analysis targeting will be performed by combination with statins atorvastatin and rosuvastatin in the current Phase 3 BETonMACE trial. 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. Apabetalone is the first select BET bromodomain inhibitor in clinical trials that is targeted for vascular diseases. New compounds arising from Resverlogix's epigenetic drug development platform function by inhibiting BET bromodomains have the potential provide a truly novel approach to vascular diseases risk and impact disorders that drive substantial costs to health systems globally.

Completed Apabetalone Clinical Trials



Source: Resverlogix

A total of 1,001 subjects have participated in a number completed clinical trials, of which 722 received treatment with apabetalone and 279 received placebo. Three Phase II studies in patients with cardiovascular disease have been completed:

- 12-week ASSERT study enrolled 299 patients,
- 24-week SUSTAIN study enrolled 176 patients, and
- 26-week ASSURE study enrolled 323 patients.

A summary:

- *SUSTAIN Clinical Trial (Completed)*
  Resverlogix started enrollment and dosing of 176 patients for the SUSTAIN trial in September 2011. Enrollment was completed in November 2011 and dosing was completed in May 2012. In August 2012 the company announced that SUSTAIN met its primary and secondary endpoints.
- *ASSURE Clinical Trial (Completed)*
  In September 2011, Resverlogix began activating study sites for ASSURE and, in November 2011, it commenced enrollment and dosing of patients in ASSURE. In September 2012, Resverlogix completed enrollment in the ASSURE trial. In June 2013, the company announced that ASSURE did not meet its primary endpoint but met its secondary endpoints.
- *ASSERT Clinical Trial (Phase II completed)*
  ASSERT was a 13-week randomized, double-blind, placebo-controlled, multi-center US study with 299 patients enrolled with stable coronary artery disease. The primary endpoint of the study was increased plasma ApoA-I levels compared to placebo group after three months of dosing of RVX-208. Other objectives were to examine the safety and tolerability of RVX-208 and to compare the dose and time response relationship for ApoA-I as well as to examine key reverse cholesterol markers involved with HDL functionality. Findings drawn from ASSERT included:
    - Data illustrated that 200 mg/day of RVX-208 was the optimal dose, based on safety and efficacy;

- Data illustrated that those patients with a low level of HDL-C at baseline had a better response for HDL-C and ApoA-I increases when treated with RVX-208; and
- Data illustrated that the best response were those patients given RVX-208 in combination with non-max doses of second generation statins such as Rosuvastatin (Crestor®) or Atorvastatin (Lipitor®).

These key findings contributed to determining a therapeutics window and targeted patient group for RVX-208.

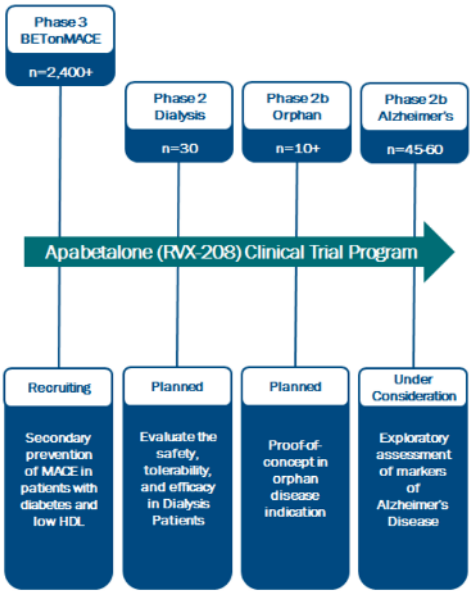
- Clinical Trial Pre-Diabetes: (completed)
  In October 2012, Resverlogix initiated an exploratory Phase 2 clinical trial in patients with pre-diabetes mellitus to examine the effects of RVX-208 and ApoA-I production on glucose metabolism. Dosing concluded in March 2014. On July 23, 2014, the company announced that the preliminary results of the trial. The investigators postulated that the RVX-208 induced rise in ApoA-I/HDL-C may impact pancreatic insulin secretion and thereby lower blood glucose (detected using an oral glucose tolerance test).

Late 2016, the company announced the collection of data from the New Zealand based Phase I PK study with apabetalone in patients with severe renal impairment. The primary objective of the Phase I study was met by demonstrating that apabetalone treated patients with severe renal impairment have the same favorable PK traits and safety profile as has been observed in previous apabetalone trials. With these positive results the company proceeded with more advanced renal impairment and dialysis trials.

Beginning of 2017, preliminary results from the Phase I PK study in late stage CKD patients were published. The data showed remarkable results in reducing acute phase proteins as well as inflammation protein biomarkers in patients with late stage CKD versus healthy control patients. It is believed that this is the first time in medical history that a direct connection of this type can be made between epigenetic regulation and its potential for positive disease impact. Protein

data was collected following a single oral administration of 100mg of apabetalone before and after multiple time points in both cohorts. Protein levels of 289 proteins were significantly different at baseline between the two groups ($p<0.05$). Initial findings from this study revealed a highly differential protein signature at baseline between CKD patients and controls. Following a single dose administration of apabetalone in the late stage CKD patients, the levels of multiple plasma proteins were changed within 12 hours after dosing, demonstrating a fast onset of drug action. Analysis of the changes in protein levels at the 12-hour time point revealed that, in the late stage CKD patients, 33 percent of proteins had statistically significant changes ($p<0.05$) compared to only 10 percent in the controls. Of these significant proteins, several established renal biomarkers such as interleukin 6 (IL6) and osteopontin, were regulated positively with respect to disease severity and progression. Ongoing expanded analysis of this exploratory data is also planned which will look at Ingenuity Pathway Analysis (IPA). The quick onset of action and improvement of reported CKD risk factors are encouraging for us in our planned expansion beyond our current cardiovascular and diabetes program.

Current and Planned Apabetalone Clinical Trials



Source: Resverlogix

Apabetalone: Ongoing Phase III BETonMACE

In October 2015, Resverlogix announced the commencement of the Phase III BETonMACE trial to confirm MACE reduction by apabetalone as shown in the Phase II trials SUSTAIN and ASSURE in high risk patients with coronary artery disease and type 2 Diabetes Mellitus. Approximately 12-15% of the patient population will also have chronic kidney disease (CKD). The primary endpoint is the time to first occurrence of MACE. Important secondary endpoints such as renal function in CKD patients will also be part of the pre-defined statistical analysis plan. 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 Phase III trial will be double-blinded, randomized, parallel group, placebo-controlled, with up to 104 weeks of dosing. MACE is defined as cardiovascular death, non-fatal myocardial infarction (MI), hospitalization for cardiovascular disease events 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. Primary outcome measures will be time to first occurrence of MACE. MACE will be adjudicated by an independent committee and the study will be monitored by a data safety monitoring board. The trial is seeking a 25-30% reduction in MACE as compared to the placebo arm, which is on best standard of care treatments such as statins, beta blockers, ACE inhibitors and dual platelet inhibition agents such as Plavix.

End of 2016 the company announced that the independent DSMB for the BETonMACE trial in high-risk CVD patients completed a second planned safety review and recommended that the study should continue as planned without any modifications. In March 2017 the DSMB has completed a third planned safety review and recommended that the study should continue as planned without any modifications. The DSMB reviewed available study data and noted that no safety or efficacy concerns were identified. The DSMB will conduct additional periodic reviews and will also perform a futility assessment once 125 adjudicated major adverse cardiac events

(MACE) have been observed. To date, more than 1,400 patients are enrolled in BETonMACE. BETonMACE will also examine in the CKD subset patients MACE as well as renal function. This subset of patients are Stage 3A and 3B CKD patients with a eGFR below 60. The company anticipates that at total of approximately 300-350 CKD patients will be in the BETonMACE trial. The rationale for examining this important organ function readout is the previous eGFR data reported at ASN and ERA EDTA presentations. Any reported delay of onset or improvement of renal function will be an important secondary readout for the molecule. 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 450 to 550 participants in the trial. This population group also represents the equivalent of conducting a large Phase IIb dementia trial within BETonMACE. Any delay or improvement of cognition, measured via MoCA within this patient group, would be an additional valuable indication for the molecule to pursue.

Apabetalone: Phase II in End Stage Renal with Dialysis

In February, Resverlogix received positive guidance from the FDA on the design of the company's proposed protocol for its Phase IIa kidney dialysis trial. The primary objective of the study will be to evaluate if treatment with apabetalone in combination with standard of care (SoC) decreases alkaline phosphatase in comparison to placebo and SoC. In light of guidance received from the FDA, the Phase IIa study design will be separated in two parts. Part A will involve a single-dose pharmacokinetic (PK) study in eight patients receiving hemodialysis. The PK results from Part A will influence the dose selection for Part B. Part B will be a double-blind, randomized, placebo-controlled, sequential cross-over study with apabetalone, and is designed to evaluate biomarker changes and safety parameters with apabetalone in up to 30 patients with end-stage renal disease treated with hemodialysis. Resverlogix intends to file an official Investigative New Drug (IND) application and proceed with the planned Phase IIa clinical trial in 2017Q2.

Advanced Chronic Kidney Disease (CKD) encompasses CKD stages 4 and 5. It can be alternatively defined as an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73m2. Reported in the 2016 United States Renal Data System (USRDS) Annual Report, approximately 1.4 million patients in the US have advanced CKD, 474,000 of which are on dialysis treatment. According to the USRDS, advanced CKD cost the US healthcare system approximately USD 17 billion in 2014, with an average cost exceeding USD 28,000 per patient. Additionally, dialysis treatment costs the US Medicare system approximately USD 28 billion with an average cost exceeding USD 80,000 per year. Currently there are no known agents that improve major adverse cardiovascular events (MACE) and renal function in CKD or dialysis patients.

Apabetalone: Phase II in End Stage Renal with Dialysis

In September 2015, the company announced the initiation of an Orphan Disease Program with initial early data on complement markers. Data generated by Resverlogix and others have demonstrated that BET inhibition and the BRD4 target has effects on multiple biological pathways that underlie several orphan diseases. Specifically, apabetalone and its target BRD4 has been shown to modulate biological pathways and markers known to play a role in a variety of orphan indications. Based on these findings, Resverlogix plans to expand proof-of-concept trial or trials in several orphan indications such as complement mediated diseases and potentially others. Apabetalone has been shown to modulate components calcification, complement and coagulation pathways both *in vitro, in vivo* and in the plasma of select patients treated with apabetalone (from the ASSURE clinical trial). The Company also has communicated that it has completed a large protein analysis where it will further reveal new pathways and proteins of interest that BET modulates. New areas of interest that may be clarified by this analysis may provide further guidance into other areas of interest such as renal orphan diseases.

Preclinical testing on other BET inhibitors in the Resverlogix library demonstrates similar effects on important markers in complement, coagulation as well as other pathways which as known to play a role in other orphan diseases. These compounds are under consideration as follow on compounds for additional orphan diseases.

Competitive Landscape in High Risk CVD

As the global population pushes past 7 billion and more people reach old age, the number of deaths from cardiovascular diseases is on the rise. Cardiovascular diseases (CVD), the leading cause of premature death in the world, include heart attacks, strokes, and other circulatory diseases.

In the United States alone, over 16 million people have existing coronary heart disease (CHD), and another 6 million have suffered strokes. According to the World Health Organization more than 17.3 million people die each year from cardiovascular disease, representing one third of all global deaths. Of these, more than 40% are due to coronary heart disease. The remaining residual risk in CVD is still far too high. What needs to be highlighted is that this risk is on top of standard of care medicines such as lipid lowering agents, anti-thrombolytic agents and blood pressure lowering medicines. As a result new approaches to lowering this risk are needed.

Of all the indicators that are used for providing prognostic predictability for CVD risk, MACE (Major Adverse Cardiovascular Events) is the most important. Patients, physicians and CVD key opinion leaders look at MACE as the most impactful marker of CVD risk. MACE includes a variety of key markers of cardiovascular risk such as worsening angina, worsening of peripheral artery pain and ischemia, prevention of percutaneous stent procedures, hospitalization for cardiac-related incidents, stroke, myocardial infarction and death. According to the 2016 AHA Statistics report, based on 2013 death rate data, more than 2,200 Americans die of CVD each day, an average of 1 death every 40 seconds. Many of these CVD patients will have some form of MACE during or after they have been diagnosed with CVD.

Reducing CVD Risk is more than addressing just lipids

Although the risk of cardiovascular disease in patients with diabetes and CKD can be partially managed through lifestyle modification and treatment with drugs to lower cholesterol, a significant unmet need still exists as 70% of cardiovascular events still occur even with optimal

LDL lowering therapy. This remaining residual risk is a major area of focus for the biopharmaceutical drug industry and specifically Resverlogix.

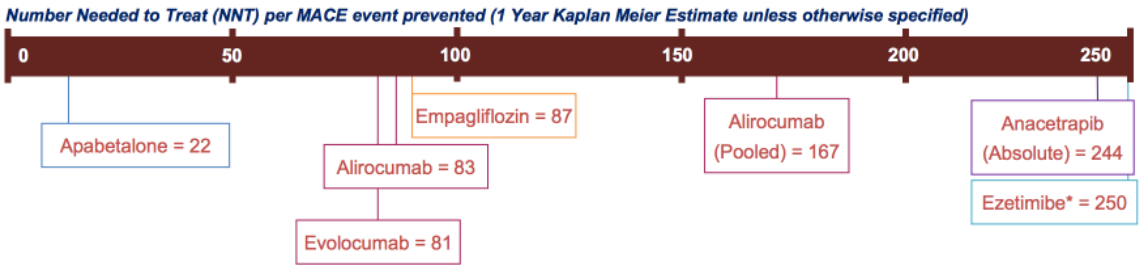
LDL Lowering

The LDL lowering hypothesis is being further tested in CVD risk with aggressive reduction of LDL to unprecedented levels such as 40-50mg/dl. Newly reported trials such ODYSSEY LONG TERM, PSCK9 LDL lowering approach via Alirocumab (ESC Barcelona 2014) and IMPROVE IT, cholesterol absorption LDL lowering approach via Ezetimibe (AHA Chicago 2014) have provided new information on the potential for very aggressive LDL lowering and its effects on efficient MACE reduction in CVD patients, on top of standard of care therapy. The following table illustrates the potential effect of additional lowering of LDL vs. BET inhibition and improvement of multiple risk pathways in high risk vascular patients:

Trial Analysis	Hypothesis	LDL Baseline	Trial Size	Treatment Duration Yr	Relative Risk Reduction	Number Needed Treat/yr
IMPROVE IT	LDL lowering 50mg/dl	60mg/dl	15000	7	6% (p<0.01)	333
ODYSSEY LONG TERM	LDL Lowering 40mg/dl	120mg/dl	2341	1.5	48% (p<0.02)	97
SUSTAIN/ ASSURE	BET Inhibition	90mg/dl	499	0.4-0.5	55% (p<0.02)	23

Although both IMPROVE IT and Odyssey Long Term were significant in lowering MACE in their respective trials, with a reported range of USD 2.5-14K a year treatment cost per patient, the cost to prevent an event could be argued to be somewhere in the area of USD 350,000 to over USD 1.3 million based on a simple analysis of NNT (number needed to treat) of annualized treatment therapy times annual treatment cost. It is critical to realize that when building a value proposition, the lower the NNT the better. If the current economic and value proposition for these LDL lowering technologies represents a standard range of NNT, reimbursement agencies could

request stronger value evidence with significantly improved pricing thresholds. This is now evident in the large outcome trials that the PCSK9 developers have had to run for payer groups. Payer groups such as NICE and US Managed Care organizations are now demanding "value for money" if any new drugs are seeking rapid reimbursement, product positioning and uptake on their respective formularies. Apabetalone's multimodal mechanism of action on numerous pathways that drive vascular risk represent a highly differentiated and potentially more efficient way to addressing the need for a value proposition.



Based on comparisons with these other therapies cardiovascular health, estimates assume a much lower cost for patients of approximately USD 7,000 per year, compared to other drugs, such as the PCSK9 inhibitors which are running at near USD 14,000 per year. When examined in terms of its potential economic benefit, the cost for apabetalone to prevent one cardiovascular event is even more striking at under USD 100,000. This level makes the implicit assumption that the potential relative risk reduction of apabetalone is greater than 25%.

Drugs, such as alirocumab (Praluent), ezetimibe (Zetia) and evolocumab (Repatha) have reported ICER scores of over USD 1 million. Recent reported news articles by both Market Insider Reuters and The Street illustrated the economic data from FOURIER did not quell the "value of drugs debate" which is taking an ever increasing role of importance in drug reimbursement today. Reported at ACC on March 17th, Amgen's (Repatha) FOURIER trial revealed an annual NNT of approx. 152. With a suggested retail price of USD 14,000 the projected ICER would be approx. over USD 2,000,000 to prevent a single MACE event in the reported population. These recent economic data on the PSCK9 class was not favorable reviewed by several key Media reports post the ACC 2017 release of FOURIER results. These results provide a very high cost comparator

relative to potential future apabetalone modeling for US Payors. ICER or the incremental cost-effectiveness ratio is a statistic used in cost-effectiveness analysis to summarize the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. Early apabetalone modeling was able to achieve attractive economic benefit due to the low number needed to treat versus competitors in their Phase II program evaluation.

Trial	Molecule	Trial Size	Treatment Duration (Years)	Absolute NNT/Yr	Kaplan Meier (KM) NNT/Yr	Tier 2 Planned Annual Medication Cost/Patient	Annual Cost per Event Prevented (KM)
SUSTAIN/ASSURE	Apabetalone	497	0.4 – 0.5	23	22	$2,400 - $4,200	**$52,800 - $92,400**
ASSERT/SUSTAIN/ ASSURE		798	0.25 – 0.5	11	22	$2,400 - $4,200	**$52,800 - $92,400**
ODYSSEY LONG-TERM	Alirocumab	2,338	1.6	97	83	$14,560	**$1,208,480**
POOLED ODYSSEY		3,459	1.6	NA	167	$14,560	**$2,431,520**
OSLER 1-2	Evolocumab	4,465	0.9	83	81	$14,100	**$1,142,104**
IMPROVE-IT	Ezetimibe	18,144	6.0	333	250*	$2,844	**~$711,000**
EMPA-REG OUTCOMES	Empagliflozin	7,042	3.1	194	87	$4,126	**$358,769**
DEFINE	Anacetrapib	1,612	1.5	244	NA	NA	NA

To further assess the potential value of apabetalone in the high risk target diabetes and CKD patients in BETonMACE, Resverlogix commissioned additional studies in 2016 from top US payers covering over 200 million lives. The focus of this analysis was to assess the cost threshold range that several of the major pharmacy benefit managers in the US market would be willing to pay to prevent one MACE event. The new analysis found that an average incremental cost efficiency ratio score (ICER) of USD 140,000 to prevent one event was seen as appropriate by US Payers for the higher risk patients targeted in BETonMACE. This score represents a substantial increase of 50% than the earlier reported KM score reported above for apabetalone in its initial US Payer assessment back in 2015. Here the molecule was modeled at a price range of USD 2200 - USD 4,400 per annum based on lower risk patient groups. Future pharmacoeconomic and health value analysis work is planned by the company for apabetalone to ensure it is well positioned to provide a strong health value proposition to key stakeholders including future pharmaceutical partners and payers alike.

SWOT Analysis

Strengths	Weaknesses
Strong patent position with its lead compound apabetalone	Operating losses cumulating year on year
Strong management and human therapy development expertise	Additional financing necessary to roll out new programs.
Novel and highly differentiated approach to impacting residual risk in diabetes and CKD	Potential delay pipeline development
Vast experience in CVD, diabetes and neurodegenerative diseases	Competition with established players
Opportunities	**Threats**
Profitable partnerships and license agreements with large pharmaceuticals	Uncertainty about the outcome of clinical trials
Blockbuster potential apabetalone	Higher level of expenditure than budgeted
Favorable pharmacoeconomics modelling with apabetalone	Failure to sign partnerships in key markets

Financials

For the first nine months till 31 January 2017, Resverlogix reported a net loss of USD 34.7 million compared to a net loss of USD 10.0 million in the same period last year. Expenses for the period totaled to USD 22.2 million (2015: USD 12.4 million) including R&D expenses of USD 21.2 million. Clinical costs totaled approximately USD 13.0 million (2016: USD 5.6 million), including USD 11.8 million on the BETonMACE clinical trial, reflecting the continued progression and expansion of the trial, and USD 0.6 million on the Renal PK clinical trial (commenced and completed within the nine month period) (2016 – USD 4.6 million on the BETonMACE clinical trial and USD 0.6 million on biomarker studies), USD 0.3 million on regulatory costs (primarily related to the BETonMACE clinical trial) (2016: USD 0.2 million) and USD 0.3 million (2016: USD 0.2 million) on other clinical costs including sample analysis, consultants and insurance.

As at January 31, 2017, the company had USD 4.9 million of cash, USD 5.4 million of trade and other payables. The average monthly cash burn rate was USD 2.7 million for the nine months ended January 31, 2017. The company is expected to raise capital in order to finance the ongoing BETonMACE trial and others. Another possibility is a partnership with one or more pharma companies as was done with the out licensing of apabetalone in the Chinese Territories.

Profit & Loss Statement (USD mln)

For nine months ended	Jan 31 2017A	Jan 31 2016A
Revenues	-	-
R&D Costs	21.225	9.384
Tax Credits	(0.048)	(0.034)
General & administrative expenses	3.198	3.035
Finance costs (income)	10.203	(2.344)
Gain on distribution	0.465	(11.681)
Loss (income) before income taxes	34.578	(2.344)
Income Taxes	0.062	(0.005)
Net Loss (Income)	*34.640*	*10.036*

Consolidated statement of cash flows

	Jan 31 2017A (9 months)	Jan 31 2016A (9 months)
Cash flow from operating activities	(19.320)	(17.438)
Cash flow from investing activities	(0.514)	(0.491)
Cash flow from financing activities	(2.324)	35.186
Cash and cash equivalents at beginning of the period	28.109	16.211
Net change in cash and cash equivalents	(23.164)	13.716
Cash and cash equivalents at the end of the period	4.945	29.927

Consolidated Balance Sheet

	Jan 31 2017A	April 30 2016A
Cash and cash equivalents	4.945	28.109
Current Assets	9.287	36.481
Non Current Assets	4.224	3.616
Total Assets	**13.511**	**40.097**
Current Liabilities	64.790	14.610
Total Liabilities	103,990	96.526
Total Equity	(90,479)	(56.429)

Valuation Apabetalone: Upward Adjustment

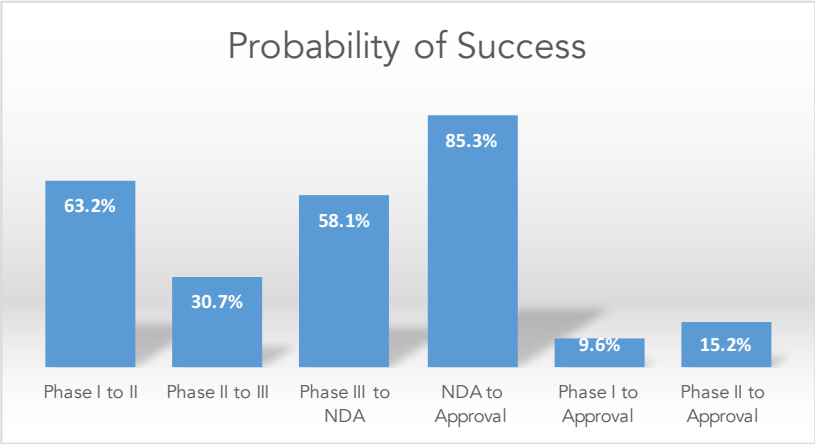
We have increased our valuation on Resverlogix to CAD 1,300 million or CAD 12.50 per share from CAD 900 million or CAD 8.50 per share due to the fact that we have increase our LOA and market potential for Resverlogix' lead product apabetalone. We also have altered our valuation model to incorporate a higher for apabetalone. At this moment we do not address value to other programs in Resverlogix's pipeline. This is a potential upside for the company.

Phase Success and Likelihood of Approval (LOA)

In estimating a value for the clinical programs with apabetalone, we made use of several studies that were done on the clinical development success rates for investigational drugs to measure success rates for investigational drugs. We analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development. These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications. Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis.

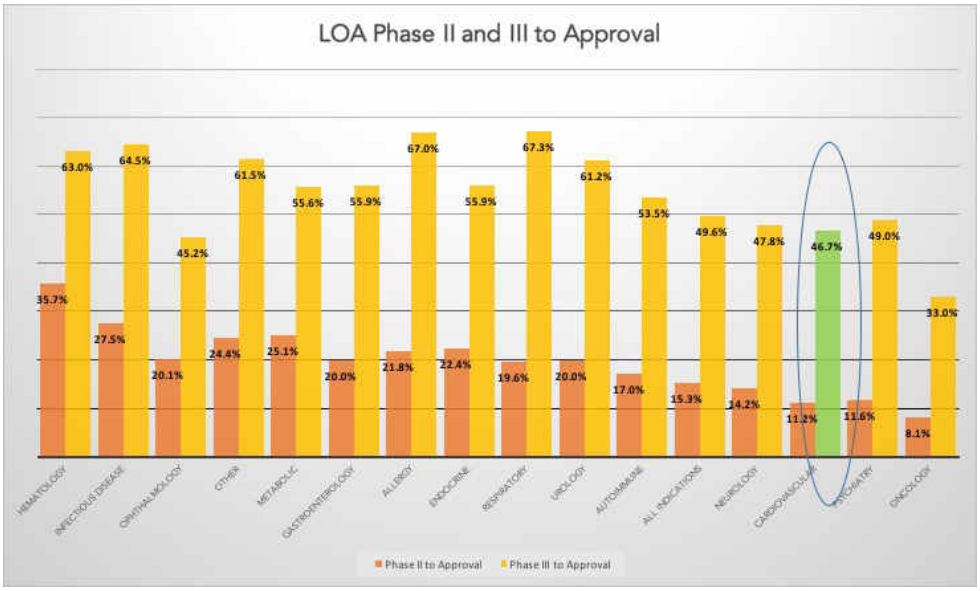
The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially

lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage where proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct. The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (see graph below)



Source: BIO Industry Analysis

Major disease areas were segmented according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. As can be seen in the graphs below, there is a wide range of Likelihood of Approval (LOA) from Phase III.

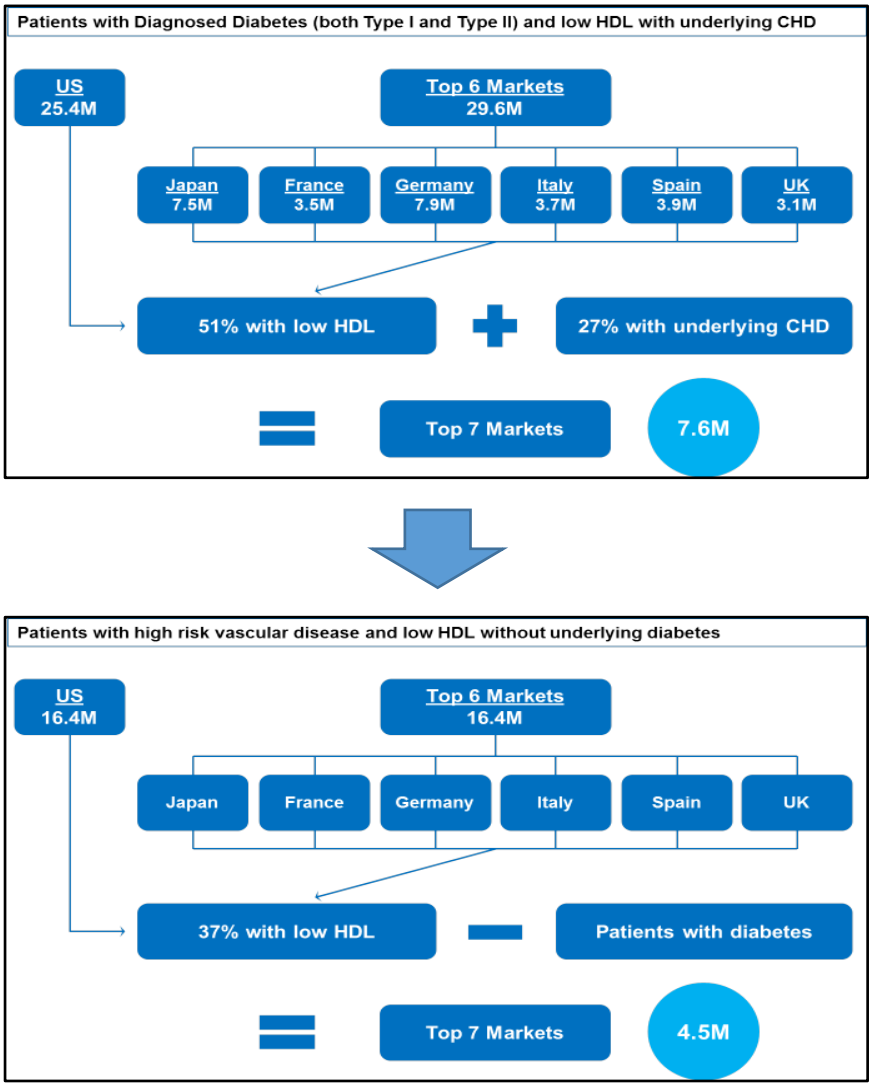


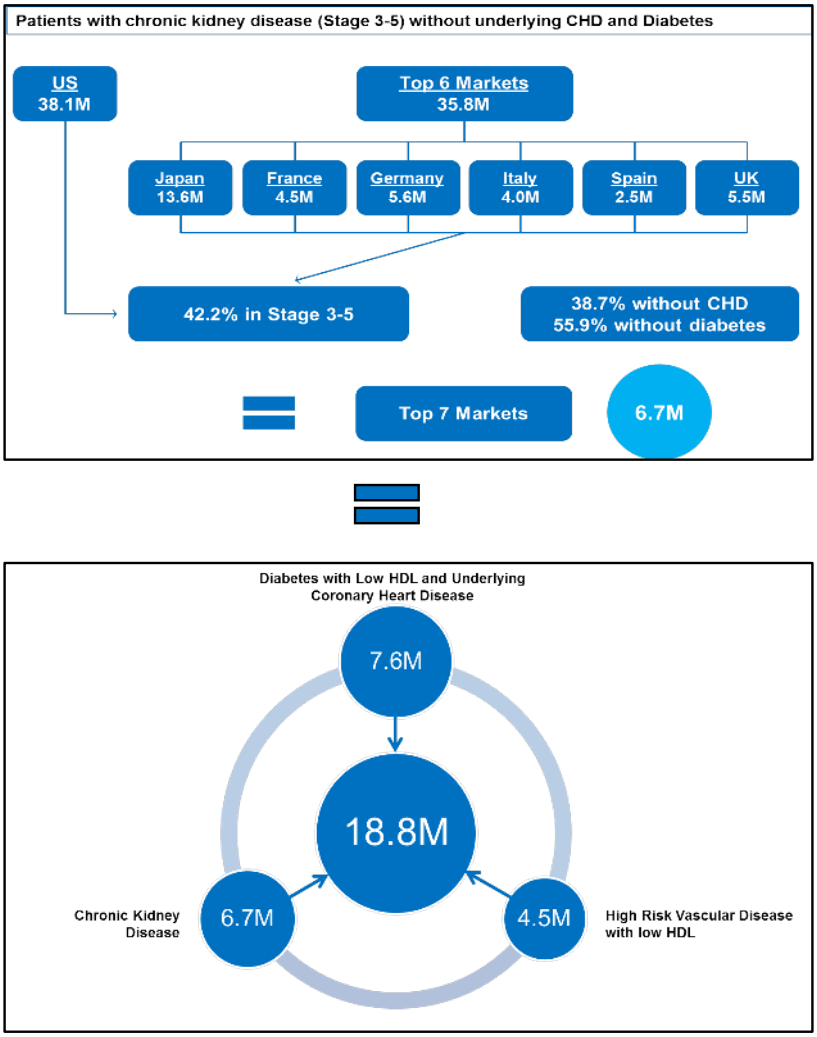
Key Value Assumptions

We have increased our value on Apabetalone, and thereby Resverlogix as a whole from CAD 900 million to CAD 1,300 million or CAD 12.50 per share. The increase in valuation is based on the ongoing successful enrolment of the Phase III trial BETonMACE as well as an increase of potential pricing for apabetalone. Apabetalone clearly has blockbuster potential. We choose not to value the company's total technology platform and potential additional indications for apabetalone. We feel that potential value of its platform and additional indications offers an additional upside potential. With the enrolment of more than half the needed patients for the Phase III clinical trial we have increased the probability of success to 46% from 35%.

We expect an approval of apabetalone in the US in 2021 as well as approval in the EU and Japan. We ascribe CAD 12.50 per share to apabetalone for high risk CVD, Diabetes mellitus and CKD based on a risk-adjusted NPV analysis of estimated its net income in the next 10 years, assuming approval and a 2021 launch. An approval of apabetalone for any Orphan Diseases expected to be up to one year earlier provided positive data.

Apabetalone is targeting specific patients with high residual risk for increased MACE: patients with low HDL and Diabetes and CKD. Expansion into ESRD and CKD will continue to add important therapeutic patients with very high CVD events and extremely poor renal function. These groups of patients represents a very significant patient populations of potentially 18 million high risk target patients in the top seven markets. Below are patient segmentation charts that outline the flow of these patients from the overall diabetes, high risk vascular and CKD patient groups.



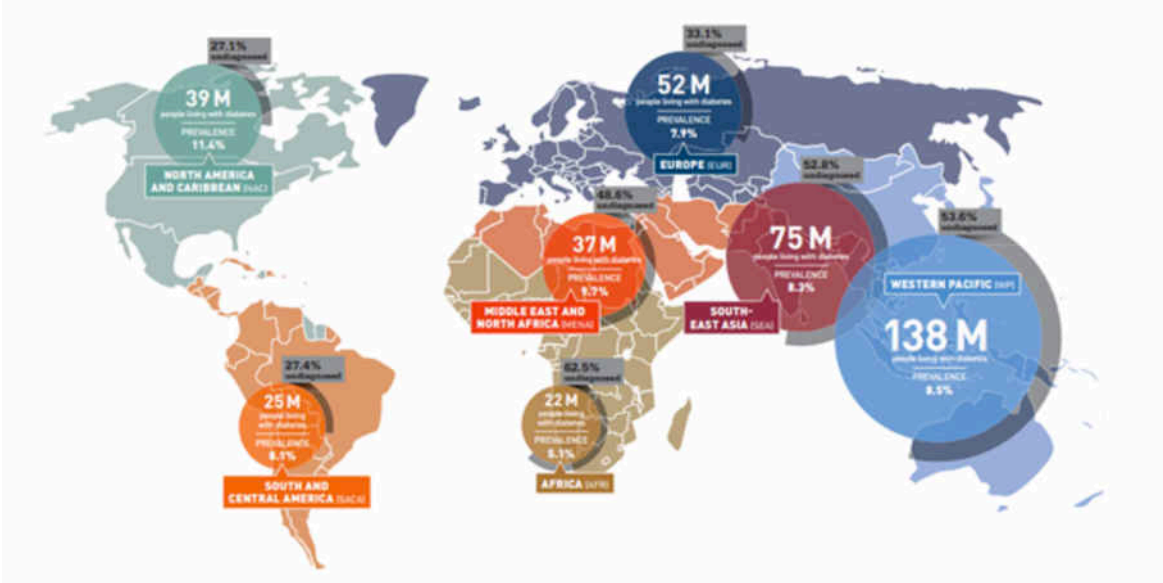


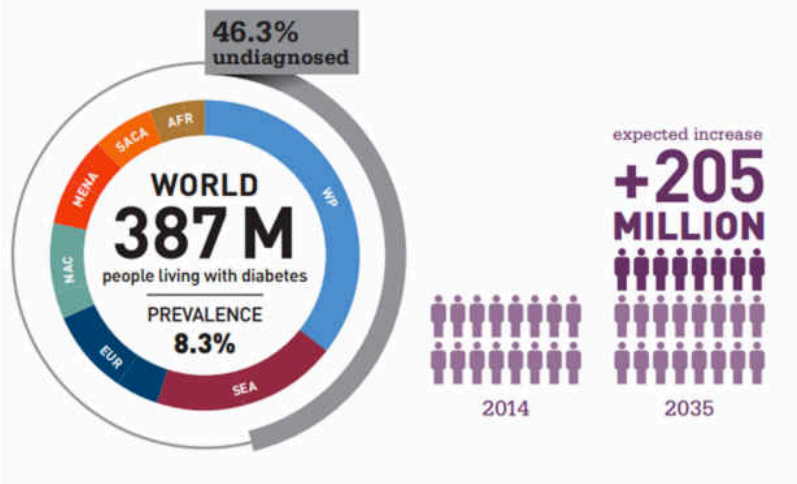
Source: RVX iInternal projections based AHA 2015 statistics, 2014 IDF Atlas, 2013 US RDS CKD Report, patient population studies

The total target patient population of **18.8** million patients eligible for apabetalone treatment represents a very significantly group of residual risk patients. Detailed notes of patient segment modeling are contained within the appendix.

Current Unmet Need in Diabetes: Apabetalone Value Proposition

Diabetes therapy for the past several decades has been developed around lowering glucose and hb1AC. Below is a detailed table highlighting this approach does little to reduce large vessel disease, namely MACE in patients with diabetes. Resverlogix intends to test this hypothesis for risk reduction in these patients coupled with CKD and other high risk vascular patients such as PAD and stroke, with apabetalone therapy.





Valuation apabetalone key markets

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	
No of eligible patients US,EU & Japan (m)	18.88										
Market penetration markets	30%										
Market share US	0.5%	1.2%	2.5%	4.0%	7.0%	10.0%	13.0%	16.0%	18.0%	20.0%	
Market Share EU	0.0%	0.5%	1.2%	2.5%	4.0%	7.0%	10.0%	13.0%	16.0%	18.0%	
Market share Japan	0.0%	0.2%	0.5%	1.2%	2.5%	4.0%	7.0%	10.0%	13.0%	16.0%	
Total Revenues (USD m)	100	300	645	1,108	1,912	2,883	3,904	4,926	5,747	6,462	
Margin 35%	35	105	226	388	669	1,009	1,366	1,724	2,011	2,262	
WACC 15%	0.57	0.50	0.43	0.38	0.33	0.28	0.25	0.21	0.19	0.16	
NPV (million)	20.1	52.3	97.7	145.7	218.8	286.8	337.8	370.6	375.9	367.6	
Total NPV (million)											**2,868**
LOA 46%											**1,319**

Glossary

Acute Coronary Syndrome ("ACS")	*a term used for any condition brought on by the sudden reduced blood flow to the heart. Acute coronary syndromes may include a heart attack, unstable angina. The first sign of acute coronary syndrome can be sudden stopping of your heart (cardiac arrest). Acute coronary syndrome is often diagnosed in an emergency room or hospital.*
Acute Phase Response Cascade	*a series of systemic events that occur within hours of an inflammatory stimulus. The most important component of this response comprises the acute phase proteins. Acute phase response takes place in response to a variety of stimuli including bacterial infection, trauma and myocardial infarction.*
Alpha1 HDL	*mature lipid-rich particles that are involved in reverse cholesterol transport whereby cholesterol is removed from cell membranes to the liver for excretion.*
Apabetalone	*generic name of RVX-208*
ApoA-I Therapeutic Field	*the prevention, treatment or mitigation of any disease via the administration of a Pharmaceutical Agent that results in therapeutic relevant elevation in the plasma levels of ApoA-I that in a predictable model of ApoA-I expression, using either a human or nonhuman primate model, the Pharmaceutical Agent is demonstrated to have at least a seven percent (7%) increase in humans and fifty percent (50%) increase in nonhuman primates in the ApoA-1 plasma level in two consecutive weeks of treatment using less than 30 milligrams – b.i.d. (60 milligrams per day) of the Pharmaceutical Agent per kilogram of the weight of the subject;*
Apolipoprotein	*the protein combined with a lipid to form a lipoprotein, a component of HDL and LDL.*
ApoA-I	*the apolipoprotein component of the HDL particle.*

Atherosclerosis	*a disease in which the deposition of lipids and plaque in arteries results in the hardening and decrease of arterial lumen size.*
Atherosclerotic Plaque	*the deposit or accumulation of lipid containing plaques in the arterial wall(also known as atheroma).*
BET proteins	***Bromodomain and ExtraTerminal domain*** *proteins that contain bromodomains, which regulate gene transcription through binding to acetylated lysines within the histones bound to DNA.*
Bioavailability	*the degree and rate at which a drug is absorbed into a living system or is made available at the site of activity after administration.*
Biopharmaceuticals	*a medical drug developed by biotechnology to improve human or animal health.*
Coagulation Cascade	*a series of events that culminate in the formation of a bloodclot and its subsequent breakdown. This process is controlled by a signaling cascade consisting of coagulation factors which interact and activate each other.*
Complement Cascade	*the complement system contains a network of tightly regulated proteins that together are a key part of the innate immune system response. The principal roles of complement include defending against invading pathogens, bridging innate and adaptive immunity, eliminating immune complexes and the products of inflammatory injury.*
Coronary artery disease ("CAD")	*the most common type of heart disease. It is the leading cause of death in the United States in both men and women. CAD occurs when arteries that supply blood to heart muscle become hardened and narrowed. This is due to the buildup of cholesterol and other material, called plaque, on their inner walls.*

Cardiovascular Disease (CVD)	*a group of diseases of the heart and blood vessels*
Cholesterol	*a fatty molecule essential for normal body functions, includingthe production of hormones and bile acids; it is also an important component of a cell membrane.*
Contract Research Organization	***"CRO"*** *an organization (commercial, academic or other), contracted by the sponsor to conduct research or development activities.*
Chromatin	*the combination of DNA and proteins that make up the contents of the nucleus of a cell. The primary functions of chromatin are: to package DNA into a smaller volume to fit in the cell, to strengthen the DNA to allow mitosis and meiosis and prevent DNA damage, and to control gene expression and DNA replication. The primary protein components of chromatin are histones that compact the DNA.*
Clinical Trial/Study	*a research study in human subjects to evaluate a new drug, medical device, biologic or other intervention under a strictly controlled scientific setting.*
Chronic Kidney Disease ("CKD")	*a progressive loss in renal function over a period of months or years, also known as chronic renal disease (CRD). Chronic kidney disease is also associated with other chronic diseases such as diabetes and or cardiovascular disease. Profession guidelines classify the severity of chronic kidney disease in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is often called end stage renal disease.*
Deoxyribonucleic Acid ("DNA")	*the material inside the nucleus of cells that carries genetic information.*

Diabetes Mellitus	*the most common metabolic disease and currently is a worldwide epidemic fueled by the wave of modernization swiping across much of the developing countries. There are two types of diabetes, Type-1 and Type-2. The difference between these two types of diabetes is that there is an absence of insulin (Type-1) or a deficiency in the amount of insulin (Type-2). While Type-1 affects less people and mostly younger individuals, Type-2 most commonly accounts for roughly 90% of the cases. The cause of Type-1 Diabetes is believed to lie in defects within the immune system. In the pathogenesis of Type-2, there is direct connection between dietary habits, sedentary life styles and obesity. One of the most feared consequences of either form DM is that it is one of many major risk factors leading to the development of CVD, the number one cause of premature death in modern societies.*
Enzyme	*a protein that acts as a catalyst in mediating and accelerating a specific chemical reaction.*
Epigenetics	*the study of heritable traits not caused by a change in the genetic code. These are typically mediated through secondary modifications to the DNA and its bound proteins, which regulate expression of genes contained within the DNA.*
Food and Drug Administration	*the United States governmental agency responsible for the approval, manufacture, usage and sale of food, human diagnostics and therapeutic products.*
Gene	*a sequence of DNA encoding a protein.*
Good Manufacturing Practice (GMP)	*the international set of regulations, codes and guidelines for the manufacture of drugs, medical devices, diagnostics and food products.*

High-density Lipoprotein (HDL)	*a complex of lipids and proteins (ApoA-I) that function in the transport of cholesterol away from the tissues to the liver and is associated with a decreased risk of atherosclerosis and coronary heart disease (also known as "good cholesterol").*
Histones	*highly alkaline proteins found in eukaryotic cell nuclei that package and order the DNA into structural units called nucleosomes. Histones are the chief protein components of chromatin. acting as spools around which DNA winds, and play role in gene regulation.*
IND-Enabling Studies	*is a toxicology package, including general acute and repeated-dose toxicity and genotoxicity studies, and safety pharmacology studies, conducted under GLP and in accordance with the International Conference of Harmonization guideline (M3(R1)) to support the filing of an IND application (21.CFR.312). Initiation of the toxicology package will occur when protocols have been written and a contract laboratory has been contracted to conduct the studies.*
Investigational New Drug (IND)	*the application submitted to the FDA prior to being tested in humans in clinical trials.*
Low-density Lipoprotein (LDL)	*a complex of lipids and proteins (ApoB) that function by transporting cholesterol to the tissues, in particular the arteries, and is associated with an increased risk of atherosclerosis and coronary heart disease (also know as "bad cholesterol").*
Lipids	*fatty substances, including cholesterol and triglycerides that are present in cell membranes and body tissues.*
Lipoproteins	*a complex of proteins and lipids that are the principal means by which fat and cholesterol is transported in the blood; major lipoproteins are low-density lipoproteins (LDL) and high-density lipoproteins (HDL).*

MACE	***Major Adverse Cardiovascular Events*** *a commonly used end point for cardiovascular research. MACE is a composite of clinical events that usually are measured in clinical trials of cardiovascular patients. It may include a variety of end points such as death, myocardial infarction (heart attack), stroke, worsening angina, hospitalization for heart disease and*
New Drug Application ("NDA")	*the documentation submitted to the FDA, Health Canada or other local regulatory authorities to obtain approval to market a new drug.*
Pharmacodynamics	*the study of the biological actions of a drug in the body, specifically the relationship between how much drug is present and its effects.*
Pharmacoeconomics	*the scientific discipline that compares the value of one pharmaceutical drug or drug therapy to another. It is a sub-discipline of Health economics. A pharmacoeconomic study evaluates the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, efficacy or enhanced quality of life) of a pharmaceutical product.*
Pharmacokinetics	*the study of how a drug is absorbed, distributed, metabolized and eliminated (ADME) by the body over time.*
Pharmacology	*the study of pharmacological agents and their origin, nature, properties and effects on living organisms.*
Phase 1 Clinical Trial	*a smaller scale trial, where a drug is first tested on a small number of healthy human volunteers to evaluate the drug's safety, schedule, dose, pharmacokinetics and pharmacodynamics (an approximate 1-2 year time trial).*
Phase 2 Clinical Trial	*a study in patients (not healthy volunteers) with the main objective to establish a safe and efficacious dose for phase 3 clinical trials.*

Phase 3 Clinical Trial	*a study or studies in a defined patient population designed to demonstrate effect to support use for a special indication, for example treatment of patients with previous coronary artery disease to prevent the occurrence of a major adverse coronary.*
Phosphorylation	*the process by which an phosphate functional group is transferred onto a molecule.*
Preclinical Studies	*the studies conducted in animals to evaluate the toxic effects, pharmacokinetics and metabolism of a drug to provide evidence for safety, efficacy and bioavailability of the drug prior to its administration to humans in clinical studies.*
PCSK9	***Proprotein convertase subtilisin/kexin type 9*** *is an enzyme that has medical significance because it functions in cholesterol homeostasis. PCSK9 binds to a domain of the LDL receptor, inducing degradation. Reduced levels of the LDL receptor result in decreased metabolism of LDL, and thus increased LDL levels, a known risk factor for CVD.*
Reader, writer, eraser	*proteins that bind to histone modifications and alter gene activity and protein production (reader); enzymes that add histone modifications (writer); enzymes that remove histone modifications (eraser).*
RVX-208	*Resverlogix' drug candidate for the treatment of atherosclerosis in patients at high risk for cardiovascular disease.*
Statin	*a class of drugs that block cholesterol production in the body by inhibiting an enzyme called HMG-CoA reductase.*
Toxicology	*the study of the harmful effects of substances in the body, including the level of toxicity, the mechanism by which toxicity occurs and how it can be controlled.*

Appendix

Diabetes with Low HDL and Underlying Coronary Heart Disease Market Assessment- Notes and Assumptions

Note 1	**Recent estimates from the International Diabetes Federation, published in the IDF Diabetes Atlas, show the prevalence of diagnosed diabetes (both Type I and Type II) in males and females aged from 20-79. These estimates do not include patients with undiagnosed diabetes and impaired glucose tolerance. The prevalence from the United States is entered as the "US Patient Population".**
Note 2	Resverlogix includes France, Germany, Italy, Japan, Spain and the United Kingdom as the Top 6 markets outside of the US. Recent estimates from the International Diabetes Federation, published in the IDF Diabetes Atlas, published in the IDF Diabetes Atlas, show the prevalence of diagnosed diabetes (both Type I and Type II) in males and females aged from 20-79. These estimates do not include patients with undiagnosed diabetes and impaired glucose tolerance. The prevalence from each country is totaled to determine the "Top 6 Markets Patient Population".
Note 3	According to the International Diabetes Federation, published in the IDF Diabetes Atlas, there were 382 million people living with diabetes worldwide in 2013. It is projected that, that number will increase to 592 million by 2035. Assuming a consistent growth rate during that time period, the prevalence of diabetes will increase by 2.01% per annum on average worldwide.
Note 4	Resverlogix estimates that the percentage of diabetes patients with low HDL is 51.3%. The following references were used to determine the percentage of diabetes patients with low HDL. In a population of patients with type 2 diabetes (n = 7,692) in 12 eastern Massachusetts outpatient practices nearly half (49.5%) of patients had low HDL cholesterol (<40 mg/dl for men, <50 mg/dl for women). In a population of patients receiving treatment for dyslipidemia under the care of specialist physicians in 11 European countries (Pan-European Survey) (n= 8,545), where 45.2% of the patients had type II diabetes, the prevalence of low HDL (<40 mg/dl for men, <50 mg/dl for women) was 33% in men and 40% in women. The average prevalence of low HDL (when taking into account the weighting of each group) is 35%. In two randomized, placebo-controlled studies, FIELD (n=9,795) and ACCORD (n=5,518), in which the inclusion criteria was type II diabetes, 59.0% had low HDL (<40 mg/dl for men, <50 mg/dl for women) and 65.2% had low HDL (≤40 mg/dL), respectively. A weighted average was used to determine the above mentioned RVX estimate of the percentage of diabetes patients with low HDL.
Note 5	Resverlogix estimates that the percentage of diabetes patients with underlying coronary heart disease (CHD) is 26.9%. The following references were used to determine the percentage of diabetes patients with underlying coronary heart disease. In a population of patients with type 2 diabetes (n = 7,692) in 12 eastern Massachusetts outpatient practices 26.7% of patients were listed as having CVD clinical characteristics. In two randomized, placebo-controlled studies, FIELD (n=9,795) and ACCORD (n=5,518), in which the inclusion criteria was type II diabetes, 21.8% had previous CVD clinical characteristics and 36.5% had experienced a previous CVD event, respectively. A weighted average was used to determine the above mentioned RVX estimate of the percentage of diabetes patients with underlying CHD.
Note 6	The projections do not include the patient populations of Brazil, Russia, India and China (BRIC) or Middle East and North Africa (MENA). The percentage of patients in these markets that can afford the therapeutic is undeterminable; however Resverlogix estimates that this number represents a small fraction of the total patient population.

High Risk Vascular Disease with low HDL- Excl. Diabetes Market Assessment- Notes and Assumptions

Note 1	**According to the Heart Disease and Stroke Statistics- 2014 Update (AHA Report), the prevalence of patients who have suffered an MI in the US is 7.6M and the prevalence of patients diagnosed with angina pectoris in the US is 7.8M. The combined prevalence of patients with CHD is 15.4M.**
Note 2	Management's internal projections extrapolate the market size for the Top 6 Markets (Japan and 5EU) to be equivalent to that of the US.
Note 3	BioMedTracker uses an annual average growth rate (AAGR) of 1.23% for the 7 major markets for the incidence of atherosclerosis. Management annual target population growth rate is 1.23%.
Note 4	RVX-208 is currently being developed for the indication of secondary prevention of major adverse cardiovascular events (MACE) in patients with high risk vascular disease (including diabetes) and low HDL. In order to determine the percentage of patients in this target market that have low levels of HDL, two populations were examined. The first was the general adult population. According to the Total and High-density Lipoprotein Cholesterol in Adults: National Health and Nutrition Examination Survey, 2009–2010, 21.3% of adults had low HDL (below 40 mg/dL). The second was patients who have previously experienced a MACE event. The following references were used to determine the percentage of coronary heart disease patients with low HDL. 55.8% of patients who presented with ACS have HDL-C below 40 mg/dL. 52.6% of NSTEMI ACS patients had HDL-C below 40 mg/dL (E). 49.7% of NSTEMI patients aged >65 years had HDL-C below 40 mg/dL. Based on these studies, the average percentage of ACS and coronary heart disease patients with low HDL-C is 52.7%. The rationale for using both the general population and patients who have experienced a MACE lies in the notion that once a patient recovers from a MACE, they will still be receiving chronic treatment of RVX-208, and thus their HDL levels may be more reflective of the general population. Using both the adherence from the general population and patients who have experienced a cardiovascular event, management calculated the average of the two patients populations. Management estimated prevalence of low HDL in high risk vascular disease patients is 37.0%.
Note 5	In the diabetes prevalence projection model, the patient prevalence of diabetes with low HDL and underlying cardiovascular disease in the US is projected. These patients are subtracted from these estimates to eliminate overlap between the patient groups.
Note 6	The projections do not include the patient populations of Brazil, Russia, India and China (BRIC) or Middle East and North Africa (MENA). The percentage of patients in these markets that can afford the therapeutic is undeterminable; however Resverlogix estimates that this number represents a small fraction of the total patient population.

Chronic Kidney Disease- Excl. CHD and Diabetes Market Assessment- Notes and Assumptions

Note 1	**Recent estimates from the National Center for Chronic Disease Prevention and Health Promotion Division of Diabetes Translation revealed that 16.0% of US adults aged 20 years and older have CKD. The U.S. Census Bureau estimated that the US population in 2013 was 316,128,839 and that 71.8% of the total population are >20 years of age. RVX estimates that the total number of patients with CKD in the US is approximately 36M patients.**
Note 2	Resverlogix includes France, Germany, Italy, Japan, Spain and the United Kingdom as the Top 6 markets outside of the US. The prevalence of chronic kidney disease in each country was reviewed in a systematic review in 2008. The prevalence of CKD in the UK was estimated in the NEOERICA Project in 2007. France and Germany did not have analyses performed in the study and thus the prevalence rate of the 3 other European countries, Italy, Spain and the UK was averaged and used as an estimated prevalence. The populations for each country were taken from the World Bank database. RVX estimate of approximately 34M CKD patients in the top 6 markets excluding the US is consistent with the notion that doubling the US patient population reflects a rough estimate of the other top 6 markets.
Note 3	According to the US Census Bureau, the growth rate of the general American population between 2010 and 2013 was 2.4%. RVX estimates a similar growth rate for the top 6 markets.
Note 4	According to the National Kidney Foundation, 39.4% of CKD patients are at stage 3, 1.83% are at stage 4 and 0.92% are at stage 5. These numbers were obtained from the NHANES III study which illustrated the prevalence of each stage of CKD in the general population. These rates were adapted to the prevalence of each stage within the CKD population by RVX.
Note 5	According to the USRDS Annual Data Report, the Atlas of Chronic Kidney Disease in the United States, 38.7% of CKD patients did not have any type of underlying cardiovascular disease (congestive heart failure, acute myocardial infarction and cerebrovascular disease). In the same report, the prevalence of various risk factors in the NHANES population is illustrated. In the CKD patients, 40.1% had diabetes, thus indicating that 59.9% did not have the underlying comorbidity. Similar rates in the top 6 markets are estimated by RVX.
Note 6	The projections do not include the patient populations of Brazil, Russia, India and China (BRIC) or Middle East and North Africa (MENA). The percentage of patients in these markets that can afford the therapeutic is undeterminable, however Resverlogix estimates that this number represents a small fraction of the total patient population.

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Marcel Wijma, Chief Research Officer and managing partner, has a longstanding history in financial biotech research. After selling Van Leeuwenhoeck Research (VLR) to SNS Securities in 2006, he established an award winning analyst team in biotech/life sciences at SNS Securities. In 2009, Marcel was awarded by Financial Times/Starmine as being one of the Top-3 biotech analysts in Europe. Later that year, Marcel purchased VLR from SNS Securities after which the company was reconstituted. At VLR, he leads the professional VLR research organisation, which is augmented by selected external financial researchers with a specialisation in Life Sciences. Mr. Wijma has a Masters degree in Financial Economics from Erasmus University in Rotterdam.