



Annual Information Form

Fiscal Year Ended December 31, 2022

March 31, 2023

Table of Contents

Advisories	4
Forward-Looking Information	4
Corporate Structure	6
Name and Incorporation	6
Inter-Corporate Relationships	6
Description of Business	6
The Drug Development Process	6
Lead Clinical Candidate Apabetalone (RVX-208)	7
Epigenetic Mechanism of Action: Single Therapeutic Target with Multiple Biological Effects	8
BET Inhibition Targets Pathways and Markers That Are Linked to Disease Progression	9
Resverlogix's Drug Development Strategy and Commercial Rationale	10
Cardiovascular Disease and Diabetes Mellitus	11
Post COVID-19 Conditions	12
Chronic Kidney Disease and End-Stage Renal Disease	13
Neurodegenerative Disease	14
Competitive Environment	14
Key Products in Development (Resverlogix and Competitors)	19
General Development of the Business	21
History of Apabetalone Development	21
Recent Clinical Developments	22
Recent Scientific Developments	25
Additional Indications and Potential Orphan Diseases	28
Apabetalone (RVX-208) Clinical Trials	30
Regulatory Affairs	30
Intellectual Property	30
Clinical and Scientific Advisory Boards	31
Financing	33
Licensing	35
Risk Factors	36
Risks Relating to Our Business	36
Risks Relating to our Intellectual Property	45
Risks Relating to Owning our Common Shares	46
Dividends	47
Description of Capital Structure	47
Common Shares	47
Preferred Shares	47
Market for Securities	48
Directors and Executive Officers	50
Name, Occupation and Security Holdings	50
Audit Committee Matters	51
Cease Trade Orders, Bankruptcies, Penalties or Sanctions	52

Conflicts of Interest.....	53
Interests of Management and Others in Material Transactions.....	53
Transfer Agent and Registrar.....	53
Material Contracts.....	53
Interests of Experts.....	54
Additional Information.....	54
Schedule “A” – Audit and Finance Committee Charter.....	55
Glossary.....	61
References.....	67

Advisories

Conventions

In this Annual Information Form (“AIF”), unless the context otherwise requires, references to “Resverlogix”, “we”, “us”, “our” or similar terms, or to the “Company” refer to Resverlogix Corp. (either alone or together with its subsidiaries).

The information contained in this AIF is presented as at December 31, 2022, except where otherwise noted.

Capitalized terms that are not otherwise defined herein have the meanings given in the Glossary at the end of this AIF.

Unless otherwise noted, all dollar amounts in this AIF are expressed in Canadian dollars.

Scientific and Industry Data

Certain independent third-party scientific research and industry data contained in this Annual Information Form is based upon information from government or other independent industry or scientific publications and reports or based on estimates derived from such publications and reports. Government and industry publications and reports generally indicate that they have obtained their information from sources believed to be reliable, but the Company has not conducted its own independent verification of such information. While the Company believes this information to be reliable, third-party information is subject to variations and cannot be verified with complete certainty due to limits on the availability and reliability of raw data, the voluntary nature of the data gathering process, and other limitations and uncertainties inherent in any statistical or scientific survey. In addition, this third-party information has been prepared as of a specific date and therefore does not contemplate changes in facts and circumstances following such date. The Company has not independently verified any of the research, findings or data from independent third-party sources referred to in this Annual Information Form or ascertained the underlying assumptions relied upon by such sources. Unless specifically stated, none of the third-party information cited in this Annual Information Form is incorporated by reference herein. All third-party information source references are provided for the reader’s convenience only and do not form a part of this Annual Information Form.

Forward-Looking Information

All statements, other than statements of historical facts, included in this Annual Information Form regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements that contain forward looking information within the meaning of Canadian securities legislation. Forward looking statements and forward-looking information are referred to collectively herein as “forward looking statements”. The words “believe”, “anticipate”, “estimate”, “plan”, “expect”, “intend”, “may”, “project”, “will”, “would” and similar expressions and the negative of such expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements.

Our statements of “belief” in respect of our drug candidate(s) are based primarily upon our results derived to date from our pre-clinical and clinical research and development and our research and development program. We also use the term “demonstrated” in this Annual Information Form to describe certain findings that we make arising from our research and development including any pre-clinical and clinical studies that we have conducted to date.

We believe that we have a reasonable scientific basis upon which we have made such statements of “belief” or arrived at such findings. It is not possible, however, to predict, based upon in vitro, animal and/or human studies whether a therapeutic agent will be proved to be safe and/or effective in humans and no conclusions should be drawn in that regard from what we state has been demonstrated by us to date. We cannot assure you that the particular results expected by us will occur.

Any forward-looking statements and statements of “belief” represent our estimates only as of the date of this Annual Information Form and should not be relied upon as representing our estimates as of any subsequent date. The forward-looking statements contained in this Annual Information Form include, but are not limited to, statements regarding our:

- aim to commercialize or license to a pharmaceutical partner our products for the treatment of unmet medical needs related to prevention of: major adverse cardiovascular events in patients with diabetes mellitus and chronic kidney disease; post COVID-19 conditions and additional indications;
- aim to carry out trials on our products for the treatment of unmet medical needs related to major adverse cardiovascular events in patients with higher risk such as acute coronary syndrome, diabetes mellitus and chronic kidney disease, post COVID-19 conditions and additional indications, and the timing of such trials;
- plans related to our post COVID-19 conditions, cardiovascular disease, and other programs and the planning and design of clinical trials as part of each of these programs;
- expectations relating to the timing of significant clinical trial milestones;
- the function and effectiveness of apabetalone, also referred to as RVX-208;

- the development of new compounds and the potential impact of these compounds on multiple diseases;
- aim to obtain regulatory approval for our products;
- expectations with respect to the cost of clinical trials and commercialization of our products;
- projected competitive conditions with respect to our products;
- anticipated sources of revenue and the estimated market for our products;
- expectations regarding the protection of our intellectual property;
- business strategy;
- intentions with respect to dividends; and
- potential milestone payments and royalties pursuant to the license agreements with Shenzhen Hepalink Pharmaceutical Co., Ltd. (“Hepalink”) and Medison Pharma Ltd.

Such forward-looking statements are based on a number of assumptions which may prove to be incorrect, including, but not limited to, assumptions about:

- general business and economic conditions;
- interest rates;
- the timing of the receipt of regulatory and governmental approvals for research and development projects;
- the availability of financing for research and development projects, or the availability of financing on reasonable terms;
- the ability to refinance existing indebtedness on reasonable terms upon maturity;
- the impact of changes in Canadian dollar-US dollar and other foreign exchange rates on our costs and results;
- market competition;
- our ability to attract and retain skilled staff; and
- ongoing relations with employees and with business partners.

Such forward-looking statements involve known and unknown risks and uncertainties, including those referred to in this Annual Information Form, which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. These risks include, but are not limited to:

- risks related to the early stage of our products;
- uncertainties related to clinical trials and product development;
- uncertainties related to current economic conditions;
- risks related to rapid technological change;
- uncertainties related to forecasts and timing of clinical trials and regulatory approval;
- competition in the market for therapeutic products to treat cardiovascular disease, post COVID-19 conditions, neurodegenerative diseases, diabetes mellitus and other high-risk vascular diseases;
- risks related to potential product liability claims;
- availability of additional financing and access to capital for research and development, clinical trials and regulatory approval;
- market acceptance and commercialization of our products;
- the availability and supply of raw materials, including supplies of sufficient active pharmaceutical ingredients for large clinical trials and future commercial production;
- risks related to the effective management of our growth;
- potential reliance on partnering agreements to provide support for discovery and development efforts, and on corporate sponsors, pharmaceutical companies, and others to successfully develop and commercialize our technology;
- the willingness of health care insurers and other organizations to pay for our products;
- risks related to our reliance on key personnel;
- risks related to the regulatory approval process for the manufacture and sale of non-therapeutic and human therapeutic products; and
- our ability to secure and protect our intellectual property, and to operate without infringing on the proprietary rights of others or having third parties circumvent the rights owned or licensed by us.

The foregoing list of important factors and assumptions is not exhaustive. Events or circumstances could cause our actual results to differ materially from those estimated or projected and expressed in, or implied by, these forward-looking statements. You should also

carefully consider the matters discussed under “Risk Factors” in this Annual Information Form. We undertake no obligation to update publicly or otherwise revise any forward-looking statements or the foregoing list of factors, whether as a result of new information or future events or otherwise, except as required by securities legislation.

Corporate Structure

Name and Incorporation

Resverlogix Corp. was incorporated under the ABCA on August 17, 2000 as Apsley Management Group Inc. and changed its name to Resverlogix Corp. on April 25, 2003. The Company amalgamated with Resverlogix Inc. to form the consolidated entity Resverlogix Corp. on February 7, 2005.

In connection with the spin-out of the Company’s former subsidiary, RVX Therapeutics Inc., to Zenith Epigenetics Corp. pursuant to a Plan of Arrangement under the ABCA completed on June 3, 2013, the Company amended its articles to authorize the issuance of royalty preferred shares which were issued to Zenith. On July 2, 2015 and December 20, 2016, the Company’s articles were amended to make certain changes to the dividend entitlement of holders of the Company’s royalty preferred shares.

Our head office is located at Suite 300, 4820 Richard Road SW, Calgary, Alberta, T3E 6L1. The registered and records office is located at Suite 600, 815 - 8th Avenue S.W., Calgary, Alberta, T2P 3P2.

As at December 31, 2022, we employed 19 full-time management, scientific and administration employees.

Inter-Corporate Relationships

The Company owns all of the voting securities of Resverlogix Inc., a corporation incorporated under the laws of the state of Delaware.

Description of Business

Since our inception, we have focused on the development of therapeutics for diseases with high unmet medical need. Our lead drug, apabetalone (“RVX-208”) is a first-in-class, small molecule inhibitor of bromodomain and extra terminal (“BET”) proteins. BET proteins play a central role in regulating the expression of disease-associated genes, and the inhibition of BET proteins can positively impact biological processes that contribute to the development and progression of disease. Apabetalone specifically affects biological processes that underlie chronic vascular diseases such as cardiovascular disease (“CVD”), diabetes mellitus (“DM”), and chronic kidney disease (“CKD”), namely: (i) vascular inflammation, (ii) acute phase response, (iii) vascular calcification, (iv) complement and coagulation, and (v) reverse cholesterol transport (“RCT”). Through inhibition of BET proteins apabetalone also limits the ability of severe acute respiratory syndrome coronavirus 2 (“SARS-CoV-2”) – the virus responsible for coronavirus disease 2019 (“COVID-19”) – to infect human cells and reduces hyperinflammatory responses to the virus. Apabetalone is in development for the secondary prevention of major adverse cardiovascular events (“MACE”) in high-risk CVD patients with a DM co-morbidity. Based on the above-mentioned effects of apabetalone, we are exploring the potential for apabetalone to modulate disease-related pathology in other indications including CKD, end-stage renal disease (late-stage CKD), vascular cognitive impairment (“VCI”), post COVID-19 conditions (“PCC”), and orphan diseases such as pulmonary arterial hypertension (“PAH”).

The Drug Development Process

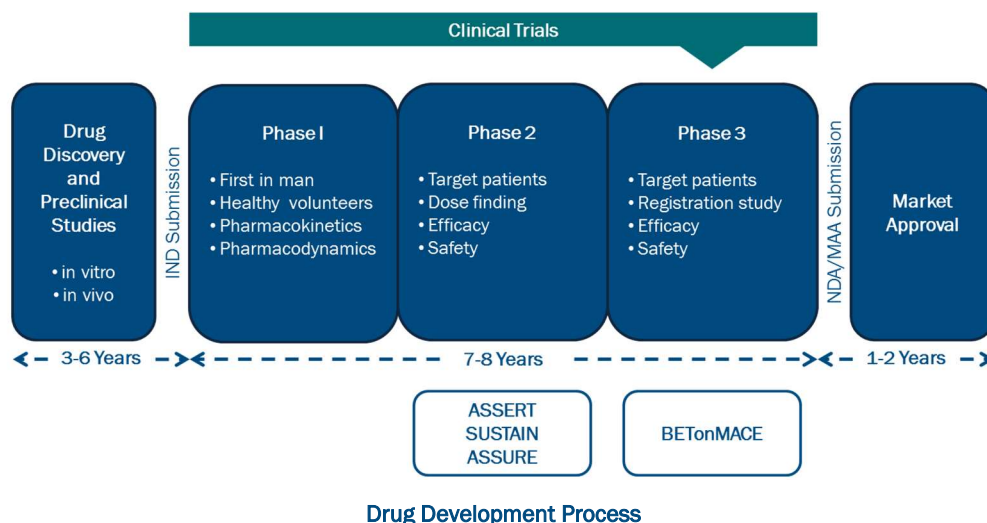
The timeline for a typical experimental drug to go from concept to approval typically ranges from 12 to 15 years as illustrated in the figure below. The production, manufacturing, research and development activities are subject to regulation for safety and efficacy by various governmental authorities around the world. In Europe and the United States, drug products are subject to regulation by the European Medicines Agency (“EMA”) and the Food and Drug Administration (“FDA”), respectively.

The FDA has outlined the following guidance for exploratory Investigational New Drug (“IND”) studies. During preclinical development, compounds are created and screened with the objective of identifying their potential for further clinical development. The potential drug candidates are studied with in vitro models (studies performed in an artificial environment outside of the living organism, including primary cells and cell lines) that examine various pharmacologic parameters. Drug candidates yielding favorable data in the early experiments are further tested with in vivo animal models (commonly performed in rodents) to evaluate efficacy and safety (toxicity). Results from animal studies provide information on the selection of a safe starting dose for humans, potential toxicity, as well as pharmacokinetic and pharmacodynamic properties of the drug. An IND containing all the data collected in the preclinical studies as well as chemical, manufacturing and control information must be submitted to applicable regulatory agencies before human clinical testing may begin.

Clinical drug development consists of four sequential phases (Phase I-IV). The steps required for drug approval in the United States, Europe and Canada are similar and follow the procedures laid out by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”). Drug development is a stepwise process through which data collected in small early studies are used to rationalize and plan larger, more definitive efficacy studies. To develop new drugs efficiently, it is essential to identify properties of the investigational medicine in the early stages of development and to plan an appropriate

development based on this profile. Phase 1 clinical trials are “first-in-man” studies with the objective of providing initial safety and tolerability information across multiple doses of the drug, pharmacokinetics data (absorption, distribution, metabolism, and excretion of the drug) and pharmacodynamics data (potential efficacy). These studies are generally conducted in healthy volunteer subjects. The main objective of Phase 2 clinical trials is to establish optimal treatment regimen for a Phase 3 trial. Phase 2 trials take approximately one to three years to complete and are carried out on a relatively small to moderate number of patients (compared to thousands required in Phase 3) suffering from the targeted condition or disease. These trials commonly include randomization of patients as well as a placebo or comparator arm. The primary aim is to determine the drug’s efficacy, optimal doses, treatment regimens, as well as pharmacokinetics, pharmacodynamics, and dose response relationships. Phase 2 trials also provide additional safety data and serve to identify possible common short-term side effects and risks in a larger group of patients and controls. Phase 3 clinical trials, if successful, provide the supporting clinical evidence to register a drug and make a drug available to patients. Phase 3 clinical trials in CVD typically take two to five years to complete and involve testing a much larger population of patients (several thousand patients) suffering from the targeted condition or disease. Phase 3 trials are usually double-blind using the dose and treatment regimen determined in Phase 2.

Upon completion of Phase 3 clinical trials, the company sponsoring the new drug then assembles and submits all preclinical and clinical data to the FDA as part of a New Drug Application (“NDA”) in the United States, a Marketing Authorization Application (“MAA”) in Europe or a New Drug Submission (“NDS”) in Canada. The NDA, MAA or NDS is then reviewed by the applicable regulatory body for approval to market the product. This process usually takes between one and two years, with the exception of evaluations of breakthrough products typically taking only 6 months. Phase 4 clinical trials are conducted after approval to identify and evaluate the long-term effects of new drugs and treatments for a greater number of patients and a more diverse patient population. Phase 4 research only takes place after the Regulatory Authorities approve the marketing of a new drug and addresses the generation of new data in the approved indication. Through Phase 4 clinical studies, new drugs can be tested continuously to uncover more information about efficacy, safety and side effects after being approved for marketing.



Lead Clinical Candidate Apabetalone (RVX-208)

Apabetalone is the first BET inhibitor in clinical trials for high-risk cardiovascular disease. A hallmark of many diseases such as cancer, inflammation, and more recently cardiovascular disease, is aberrant gene transcription. Bromodomains (“BRDs”) are a family of evolutionary conserved protein-interaction modules that play key functions in chromatin organisation and regulation of gene transcription. One recognised family of bromodomain containing proteins is the BET family. Apabetalone is the first oral agent in the BET inhibitor class that preferentially targets bromodomain 2 (“BD2”) of BET proteins. In binding to this bromodomain, apabetalone affects the expression of multiple genes with roles in a variety of cellular processes. Our lead drug, apabetalone, targets BET proteins to impact several important biological processes that are contributors to the pathophysiology of chronic vascular diseases such as CVD, DM, and CKD, namely: (i) vascular inflammation, (ii) vascular calcification, (iii) acute phase response, (iv) complement and coagulation, and (v) RCT.

Apabetalone is a first-in-class small molecule in development for the secondary prevention of a MACE in high-risk CVD patients with a DM co-morbidity. In the fall of 2015, Resverlogix initiated a Phase 3 clinical trial “BETonMACE” with apabetalone in high-risk CVD patients with type 2 DM and low levels of high-density lipoprotein (“HDL”). The primary endpoint is the time to first occurrence of MACE. On September 30, 2019, we announced the topline results of the BETonMACE study. A total of 2,425 patients were enrolled in the study (surpassing the approximately 2,400 outlined in the study’s protocol) and followed for a median study duration of 26.5 months and a total of 274 primary endpoints occurred. While the primary endpoint did not reach statistical significance, key secondary and

exploratory endpoints illustrating CVD efficacy were met with an excellent safety profile, providing rationale for the continuation of the development of apabetalone in high-risk CVD. Full results of the BETonMACE study have been published in the Journal of the American Medical Association. Based on the results of the BETonMACE study, the FDA granted Breakthrough Therapy Designation (“BTD”) for apabetalone in combination with top standard of care, including high-intensity statins, for the secondary prevention of MACE in patients with type 2 DM and recent acute coronary syndrome (“ACS”). The achievement of BTD has the potential to expedite apabetalone’s clinical development program through expedited FDA guidance.

We are also exploring the potential for apabetalone to modulate disease-related pathology in other indications including CKD, neurodegenerative disease (such as vascular cognitive impairment) and orphan diseases such as PAH. Research, published in 2020, found that the novel coronavirus, SARS-CoV-2, utilizes a cell surface receptor, angiotensin converting enzyme 2 (“ACE2”), to enter and infect human cells. BET proteins regulate the expression of ACE2, and through the inhibition of BET proteins, apabetalone is able to reduce ACE2 expression on surface of human cells and prevent infection by SARS-CoV-2. Many of the same inflammatory pathways that contribute to chronic vascular disease progression are also contributors to COVID-19 pathogenesis. The activation of inflammatory markers are predictive of COVID-19 disease severity and patient survival (Del Valle, Kim-Schulze et al. 2020).

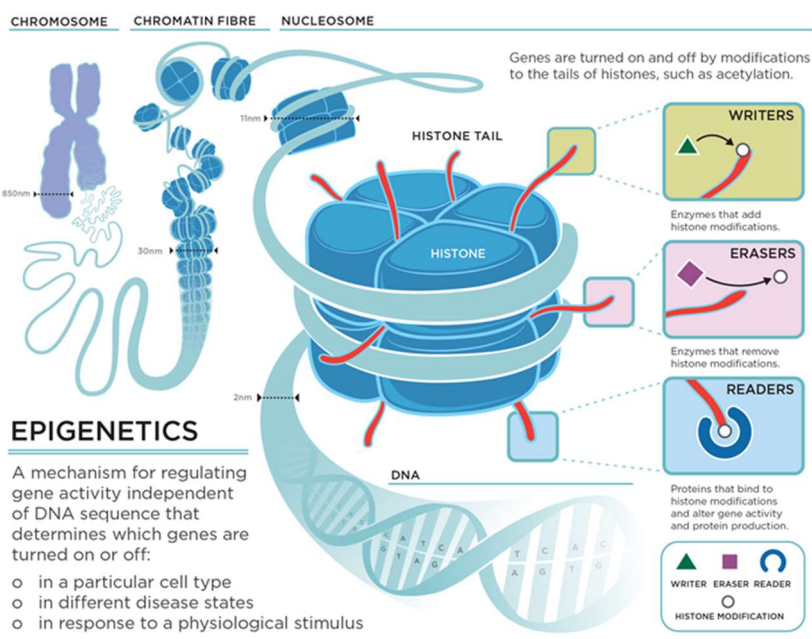
Epigenetic Mechanism of Action: Single Therapeutic Target with Multiple Biological Effects

The human body is made up of nearly two hundred different cell types that have cell-specific functions resulting from the selective production of the proteins encoded by human DNA and, more specifically, human genes. Aberrant levels of proteins can contribute to disease progression and disease states. Epigenetics describes the mechanisms by which gene activity is regulated, thereby affecting levels of transcription into messenger RNA (“mRNA”) which is then translated into protein. Epigenetics is the study of modifications to chromatin (DNA associated with proteins) that, without affecting the DNA sequence, result in regulation of gene transcription, the first step in producing the proteins that each gene encodes. Such modifications determine whether a gene is “on” or “off” or whether its activity is high or low in a particular cell type, in different disease states or in response to a physiological stimulus. Chromatin modifications are added by enzymes called “writers” and removed by enzymes called “erasers”. Other proteins, called “readers”, recognize a specific pattern of modifications.

In contrast to “writers” and “erasers” that add or remove post-translational modifications, “readers” detect the presence or absence of these modifications and serve as a scaffold for the transcriptional machinery directly responsible for gene expression. BET proteins are “readers”, proteins that recognize a specific pattern of modifications and bind to the chromatin at these sites. The BET proteins then serve as a scaffold, recruiting the necessary transcriptional machinery to the chromatin to drive gene expression and ultimately protein production.

Our compounds target one group of “reader” proteins called the Bromodomain and Extra Terminal (“BET”) proteins. BET inhibition represents an important new area of drug development, since epigenetic modification is a known hallmark of several complex pathologies, including cardiovascular disease (“CVD”), metabolic disorders, and neurological diseases. Substantial evidence has shown that alterations in the pattern of chromatin modifications underlie these multiple disease states. Epigenetic regulators are promising targets for therapeutic intervention and hold significant potential for treatment advances in important diseases of high unmet medical need.

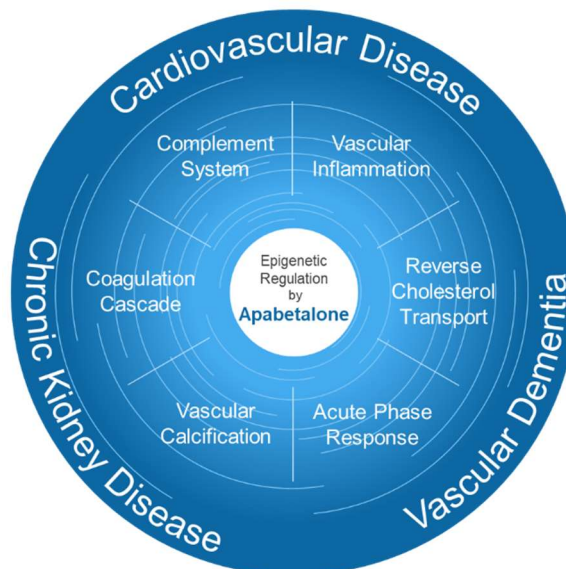
BET inhibition results in the simultaneous modulation of multiple biological pathways via a single molecular target. Studies highlighting the molecular and mechanistic functions of BET inhibitor molecules and the ongoing development of new BET inhibitors as potential therapeutics in multiple indications are initiating a shift from the current drug development paradigm. From a single molecular target for a single downstream effect, to a multimodal approach whereby multiple biological processes contributing to a disease state are concurrently modulated via a single molecular target, epigenetic modulation is a novel approach to targeting disease pathology.



Epigenetic Mechanism of Action

BET Inhibition Targets Pathways and Markers That Are Linked to Disease Progression

Numerous epidemiological and interventional studies have demonstrated that the disease pathways and biomarkers beneficially modulated by apabetalone through select BET inhibition provide biological plausibility and rationale to support the potential of apabetalone to reduce residual risk of MACE in CVD patients. Below are several key studies that highlight the potential roles these pathways and biomarkers may play in CVD and MACE reduction following apabetalone treatment. There has been considerable interest and effort within the pharmaceutical industry to identify, develop and acquire therapies that modulate the multiple risk pathways associated with the pathogenesis of CVD and MACE. These pathways include: (i) vascular inflammation, (ii) acute phase response, (iii) vascular calcification, (iv) complement and coagulation, and (v) reverse cholesterol transport (“RCT”). We have a number of pending patent applications, providing us with broad intellectual property in the area. If shown efficacious in clinical trials, our novel small molecule, apabetalone, will be well-positioned to participate in the critically important global residual risk CVD market.



Vascular Inflammation

Vascular inflammation (“VI”) is a powerful driver of atherosclerosis, coronary artery disease, hypertension, hypercholesterolemia, and diabetes mellitus (Mestas and Ley 2008). A hallmark of the VI process involves greater adhesion of white blood cells (leukocytes, including monocytes, lymphocytes and granulocytes) to the vessel wall, or vascular endothelium (Mestas and Ley 2008). The vascular endothelial cells themselves contribute to VI by promoting adhesion, where endothelial cell surface receptors (such as E-selectin, ICAM1 and VCAM1) bind to monocyte adhesion receptors (L-selectin and carbohydrate moieties) on circulating monocytes allowing for the monocytes to cross into the vessel wall and initiate and promote atherosclerotic plaque formation. VI occurs as a result of sustained high levels of harmful circulating factors (acute phase reactants such as CRP, cytokines, glucose, and Trimethylamine-N-oxide (“TMAO”)), which lead to activation of endothelial cells, upregulation of circulating cell adhesion molecules, and recruitment of circulating leukocytes. In CVD and related diseases including DM, the combination of these factors continually promote VI and contribute to atherosclerotic plaque development, growth and rupture.

Acute Phase Response

CRP is an acute phase reactant produced by hepatocytes (liver cells) in response to proinflammatory mediators (cytokines, in particular interleukin-6, interleukin-17 and interleukin-1a), that reflects different degrees of inflammation (Shrivastava, Singh et al. 2015). Multiple epidemiological, prospective and intervention studies (MRFIT, PHS, CHS/RHPP, WHS), have shown that minor CRP elevations are associated with future major CVD risk (Ridker 2001), and that CRP strongly and independently predicts adverse CVD events, including myocardial infarction, ischemic stroke, and sudden cardiac death in individuals both with and without overt CHD (Shrivastava, Singh et al. 2015). CRP is thus recognized as a major cardiovascular risk factor, and provides prognostic information beyond LDL (Ridker, Cannon et al. 2005; Ridker, MacFadyen et al. 2010). Traditionally, CRP was thought to be a bystander marker of vascular inflammation, without playing a direct role in CVD (Li and Fang 2004). However, more recent evidence suggests a direct pro-inflammatory mediating role of CRP, associated with all stages of atherosclerosis (most notably unstable plaque development and rupture), and atherogenesis (including activation of the complement pathway, lipid uptake by macrophages, release of proinflammatory cytokines, inducing the expression of tissue factors in monocytes, promoting endothelial dysfunction, and inhibiting nitric oxide production) (Shrivastava, Singh et al. 2015). Furthermore, elevated CRP is associated with increased risk of DM development (Ridker 2001). Additional acute phase response components, such as MBL2, C2, C3 and C5, and SAP (Kulikowski, Gilham et al. 2016) are pro-inflammatory, pro-atherogenic, and markers of CVD risk (Lowenstein and Matsushita 2004).

The recently completed Canakinuamb Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial has been pivotal in understanding the impact of CRP and related inflammation in CVD. CANTOS was a randomized, double-blind, placebo-controlled trial of canakinumab, an interleukin (IL)-1 β neutralizing monoclonal antibody. In 10,061 CVD patients with high “residual inflammatory risk”, history of myocardial infarction, and hsCRP \geq 2 mg/L, CANTOS results showed that directly reducing inflammation via targeting of a single inflammatory marker, interleukin (IL)-1 β , can reduce cardiovascular event rates. This trial was the first phase 3 trial validating inflammation as a viable target for CVD MACE prevention (Aday and Ridker 2018).

Vascular Calcification

Medial artery calcification is a characteristic feature of diabetes, CKD, and identifies other high risk cardiovascular patients (Chistiakov, Sobenin et al. 2014). It has been well established that higher levels of alkaline phosphatase (“ALP”) are significantly associated with the presence of vascular calcification (Lomashvili, Garg et al. 2008; Ishimura, Okuno et al. 2014), and that vascular calcification in turn is associated with increased cardiovascular morbidity and mortality (Schoppet and Shanahan 2008). ALP breaks down and inactivates inorganic pyrophosphate, a known highly potent inhibitor of vascular calcification and calcific crystal growth (Lomashvili, Garg et al. 2008). Analysis of the CARE and NHANES III study data provide insight into the epidemiological finding that ALP contributes to all-cause mortality and CVD mortality. Data from the CARE study illustrated that patients in the highest tertile of ALP levels (>99 U/L) had a 21% increased risk of coronary heart disease death, nonfatal myocardial infarction, symptomatic heart failure or stroke and a 43% increased risk of all-cause mortality. Data from the NHANES III study reveal that patients in the highest tertile of ALP levels (>87 U/L) had increased risk of all-cause and CVD mortality of 27% (Tonelli, Curhan et al. 2009). It is speculated that this epidemiological link may be a result of the role that ALP plays in the regulation of vascular calcification and that higher ALP levels represent an inflammatory calcific state (Tonelli, Curhan et al. 2009). Recently, the authors of a review elucidating the link of ALP to vascular calcification proposed that ALP is an emerging treatment target for CVD and metabolic syndrome. ALP inhibition is presented as a promising novel approach to the treatment and prevention of CVD complications in the general population, and acute inflammatory disorders associated with increased mortality in CKD and metabolic syndrome patients (Haarhaus, Brandenburg et al. 2017).

Complement and Coagulation

The complement and coagulation cascades have been shown to play a significant role in CVD risk. Overactivation of the complement pathway has been implicated in plaque development and destabilization (Seifert and Kazatchkine 1988; Hertle, Stehouwer et al. 2014). Complement activation also influences thrombosis through activation of platelets, promotion of fibrin formation, and impairment of fibrinolysis. Fibrin clotting is fundamental in the formation of thrombi and emboli. Fibrin and fibrinogen degradation products have been associated with CVD development and severity as well as cardiac events and death (Kannel, Wolf et al. 1987; Tataru, Heinrich et al. 1999; Zacharowski, Zacharowski et al. 2006; Wannamethee, Whincup et al. 2009).

Reverse Cholesterol Transport

The Framingham Heart Study illustrated the importance of HDL enhancement for CVD risk reduction. For every mg/dL increase in HDL, the 10-year risk of a heart attack fell by 2-3% (Gordon, Probstfield et al. 1989). The Veterans' Affairs Cooperative Studies Program demonstrated that men who took a lipid regulating drug for five years had a 6% increase in HDL levels, resulting in a 22% risk reduction in death due to coronary artery disease (“CAD”), heart attack or stroke (Rubins, Robins et al. 1999).

The Framingham Offspring Study (“FOS”) illustrated that certain types of HDL particles, specifically large HDL or Alpha 1 HDL particles, were even more predictive in calculating future CAD events in CVD patients (Asztalos, Cupples et al. 2004). For every mg/dl increase in Alpha 1 HDL, patients in the FOS cohort had a 26% reduction of future coronary events. These studies suggest that Alpha 1 particles were significantly better predictors of risk than HDL values.

Landmark trials such as INTERHEART (2004) and AMORIS (2005) clinically validated ApoA-I as an important target for the reduction of CVD risk. The INTERHEART trial, a landmark study of 30,000 acute myocardial infarction patients and age and sex matched controls demonstrated that the ratio of apolipoprotein B (“ApoB”) to ApoA-I was the strongest risk predictor of acute myocardial infarction (heart attack) (Yusuf, Hawken et al. 2004). In the AMORIS trial, more than 175,000 individuals (referred for clinical laboratory testing as part of a health checkup) with cardiovascular risk factors were studied for the incidence of cardiac and stroke events. AMORIS illustrated that reducing the ratio of ApoB to ApoA-I was associated with a dramatic reduction of stroke in this population (Walldius and Jungner 2005). AMORIS' key findings indicate that improvement of 'cholesterol balance', or the ApoB to ApoA-I ratio, is a robust and specific marker of virtually all ischemic events.

Resverlogix's Drug Development Strategy and Commercial Rationale

Given the high cost, long development times and high attrition rates associated with drug development, many biotechnology companies partner with or license with a pharmaceutical partner to advance their products through clinical trials. We will seek to continue to partner or license our drug candidate at the stage that will provide our shareholders with the optimal value for their investment. Should such partnering or licensing be successful, a pharmaceutical company will provide some or all of the funding and expertise to complete the latter stages of drug development and commercialization.

We believe that our approach may be considered therapeutically and commercially attractive for the following reasons:

- BET proteins all contain highly-conserved bromodomains that play a key role in epigenetic control of gene expression (in many cell types);
- Apabetalone functions via inhibition of BET bromodomain binding to chromatin, thereby modulating transcription of particular targets;

- Apabetalone preferentially binds to the second bromodomain of BET family members (BRD2, BRD3 and BRD4), with a 20-fold or higher selectivity for the second bromodomain versus the first bromodomain;
- Apabetalone is highly differentiated from other therapies that focus only on single biological targets, such as increasing HDL or decreasing low-density lipoprotein (“LDL”) in plasma, and has effects on multiple pathways and biomarkers that function in concert to reduce CVD events; and
- Apabetalone is the only selective BET inhibitor in the field of CVD with no known competitor, providing us with an estimated 7-8 year lead over competitors and significant scarcity value.

Based on the above reasons and clinical data, we believe apabetalone has illustrated potential to become an important and differentiated therapeutic for high-risk patients with post COVID-19 conditions, CVD, DM and CKD.

Cardiovascular Disease and Diabetes Mellitus

MACE is by far the most important of all clinical endpoints that are analyzed for providing future predictability for CVD risk. Health systems and payer groups study MACE carefully when considering potential reimbursement of a new CVD therapeutic agent. MACE includes a variety of key markers of cardiovascular risk such as death, myocardial infarction, stroke, worsening angina, worsening pain from peripheral arterial disease (ischemia), percutaneous stent procedures, and hospitalization for cardiac-related incidents. According to the 2020 American Heart Association Statistics report, based on 2017 death rate data, CVD claims more lives each year than cancer and chronic lower respiratory disease combined (Virani, Alonso et al. 2020). Many of these CVD patients have some form of MACE during or after they have been diagnosed with CVD. CVD related conditions include angina, heart attack, stroke, aortic aneurysms, kidney failure and severe limb ischemia; all of which are contributed to by the increasing prevalence of obesity, hypertension, diabetes and dyslipidemia. CVD research is expanding its focus from factors driving atherosclerosis (the key underlying cause of CAD and CVD) to additional vascular risk pathways. Other important areas of CVD research that are being carefully examined in high-risk patients include vascular inflammation, the innate immune response, coagulation and vascular calcification.

Although treatment of CVD includes many therapeutic agents, for example lipid lowering drugs such as statins, heart rate lowering agents such as beta blockers and blood pressure lowering drugs such as ACE inhibitors, there still remains a large residual risk of MACE in patients that take all of these current medicines. CVD and MACE remain a major cause of mortality and morbidity in North America. According to the 2020 American Heart Association Statistics report, approximately every 40 seconds, an American will have a myocardial infarction (Virani, Alonso et al. 2020). By the year 2035, the total projected economic burden and direct costs of CVD in the United States is estimated at \$749 billion annually (Virani, Alonso et al. 2020).

Statin-induced reduction of low-density lipoprotein (“LDL”) has been proven to be beneficial for people with CAD, stroke, and DM as demonstrated by a 10% and 21% reduction in all-cause mortality and major vascular events, respectively, following 1.0 mmol/L decrease in LDL levels. Despite those results, this population remains at substantial risk for cardiovascular events. Despite adequate control of LDL, statin-treated patients with clinically evident CVD maintain a 5-year elevated risk for MACE (Barter, Gotto et al. 2007).

Diabetes mellitus is the most common metabolic disease in the world. A primary defect in DM is the inability of the body to provide or efficiently utilize insulin, thus leading to increased blood glucose and numerous related health problems. CVD risk factors are also associated with insulin resistance. In fact, patients with DM have two to four times greater risk of death or serious cardiovascular morbidity compared to individuals without DM and approximately 75% of deaths in patients with DM are due to CVD (Wu and Parhofer 2014). High residual risk of MACE in DM was evident in the recent EXAMINE study of patients with DM receiving statin therapy. In a cohort of 5,380 DM patients with a history of acute coronary syndrome (“ACS”), there was no difference in incidence of MACE between alogliptin (a selective inhibitor of dipeptidyl peptidase 4 that is approved for the treatment of type 2 diabetes) treated and placebo-treated groups. The incidence of MACE remained high (both >11% during 18 months therapy) despite all patients receiving the standard of care for type 2 diabetes and ACS (White, Cannon et al. 2013). The findings in this trial add to many other preceding studies (UKPDS, ACCORD, ADVANCE AND VADT) to further underscore that, despite intensive glucose control and standard of care, the incidence of MACE remains significant in the setting of DM. Revascularization in patients with DM leads to additional increased risk of adverse outcomes. Diabetic patients are predisposed to more aggressive atherosclerosis and a higher risk for restenosis. Following percutaneous stent and coronary-artery bypass grafting procedures, the incidence of MACE in DM was 27% and 19% respectively over the subsequent five years (Farkouh, Domanski et al. 2012). Similar residual risk post ACS for patients with diabetes was demonstrated in the AleCardio Study (Lincoff, Tardif et al. 2014) (approximately 10% of individuals’ experienced cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke during the two year study period) and the ELIXA study (Pfeffer, Claggett et al. 2015) (approximately 13% of individuals’ experienced cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke during the 25 month study period).

The role of inflammation in DM has also been highlighted in recent years. It is now well-known that inflammation is one of the main reasons why people with diabetes experience heart attacks, strokes, kidney problems and other related complications. A variety of inflammatory markers have been linked to DM. Elevated circulating inflammatory markers such as CRP and interleukin-6 (IL-6) consistently predict the development of type 2 diabetes (Pickup 2004), and there is increasing evidence that an ongoing cytokine-

induced acute-phase response, sometimes called low-grade inflammation, is closely involved in the pathogenesis of DM and associated complications such as dyslipidemia and atherosclerosis. There is clearly an urgent need for new approaches to reduce MACE in patients with DM. Known effects of apabetalone on inflammation, and CRP, IL-6, and other acute phase reactants specifically, hold significant promise for reducing the risk of MACE in DM patients.

High residual cardiovascular risk persists in CVD patients treated with current evidence-based recommended care. Several pharmaceutical companies have attempted to develop therapeutics that exhibit efficacy over current standard of care therapies for this critically important therapeutic segment. According to Transparency Market Research (TMR), the global cardiovascular drugs market was valued at approximately US\$80 billion in 2016, and is anticipated to grow to over US\$91 billion by 2025, driven by the launch of proprotein convertase subtilisin/kexin type 9 (“PCSK9”) inhibitors in 2016, and the arrival of the newer oral anti-diabetic agents, sodium/glucose cotransporter 2 (“SGLT2”) and dipeptidyl peptidase-4 (“DPP-4”) inhibitors, which have demonstrated efficacy in reducing MACE in high-risk CVD and type II diabetes mellitus (“T2DM”) patients. Mordor Intelligence estimates that the global markets for SGLT2 and DPP-4 inhibitors represent approximately US\$6.6 billion and US\$10.5 billion, respectively, in 2019, with expected growth of over 16% and 4% during the 2019 to 2024 forecast period. Similarly, iHealthcareAnalyst estimates that the global market for dyslipidemia drugs is estimated to cross US\$38.9 billion by 2025, driven by an increase in overall patient numbers, sales growth for newer effective add-on therapies, and increased efforts taken by drug manufacturers to step up in the market. Dyslipidemia is a key modifiable vascular risk factor for CVD, with atherosclerotic CVD being one of the leading causes of death and major health care burdens worldwide. At the present time, the PCSK9 inhibitor programs, Alirocumab (Sanofi/Regeneron) and Evolocumab (Amgen); the SGLT2 inhibitor programs, Canagliflozin (Janssen), Dapagliflozin (AstraZeneca), Empagliflozin (Boehringer Ingelheim and Eli Lilly) and Ertugliflozin (Merck and Pfizer); the DPP-4 inhibitor programs, Sitagliptin (Merck and Pfizer), Saxagliptin (Bristol-Myers Squibb and AstraZeneca), Linagliptin (Eli Lilly and Boehringer Ingelheim) and Alogliptin (Takeda); and, the glucagon-like protein 1 (“GLP1”) receptor agonist programs, Exanatide (AstraZeneca), Liraglutide (Novo Nordisk), Albiglutide (GlaxoSmithKline), Lixisenatide (Sanofi), Dulaglutide (Eli Lilly) and Semaglutide (Novo Nordisk) are all currently targeting the CVD residual risk market, in addition to other, more alternative treatment modalities, such as Icosapent Ethyl (Amarin), Bempedoic Acid (Esperion) and Inclisiran (Novartis).

We are evaluating the potential use of apabetalone in Phase 3 clinical studies in this important therapeutic area.

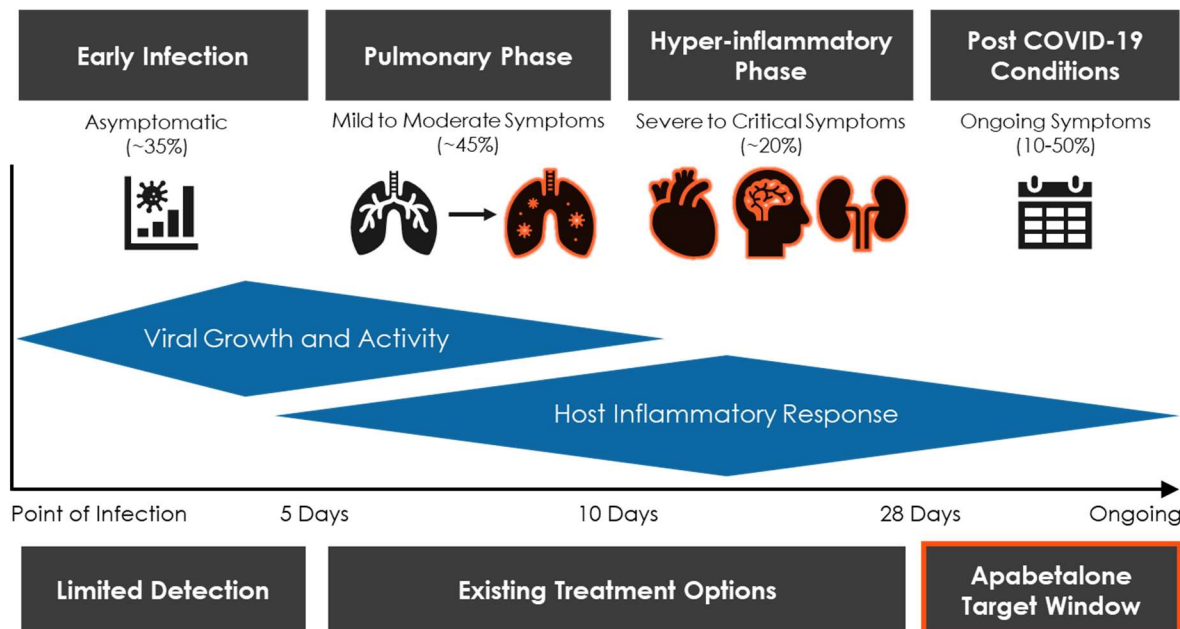
Post COVID-19 Conditions

COVID-19 is the highly contagious respiratory disease caused by SARS-CoV-2, the coronavirus that emerged in December 2019. The virus spreads mainly from person to person through respiratory droplets produced when an infected person coughs, sneezes, or talks. Some people who are infected may not have symptoms but can still transmit and spread the virus. For people who have symptoms, illness can range from mild to severe, sometimes even being fatal. Adults 65 years and older and people of any age with underlying medical conditions such as CVD, DM, or obesity are at higher risk for severe illness. According to the World Health Organization (“WHO”), globally there have been over 450 million confirmed cases of COVID-19, including more than 6 million deaths.

Treatment for COVID-19 depends on the severity of the infection. For milder illness, resting at home and taking medicine to reduce fever is often sufficient. More severe cases may require hospitalization, with treatment that might include intravenous medications, supplemental oxygen, assisted ventilation and other supportive measures. Several vaccines, including the Pfizer-BioNTech COVID-19 vaccine now called Comirnaty™, and the Moderna vaccine now called Spikevax™, have been fully approved by regulatory agencies and authorities around the world to help prevent serious disease, hospitalization, and death from COVID-19. Repurposed anti-viral medicines, including remdesivir (“Veklury™”) have been used to treat patients with severe COVID-19, or those at elevated risk of poor outcomes. Initially, the monoclonal antibodies bamlanivimab plus etesevimab, casirivimab plus imdevimab (“REGEN-COV™”), tixagevimab/cilgavimab (“Evusheld™”), and sotrovimab (“Xevudy™”) received emergency use authorizations to treat patients with confirmed acute COVID-19 infections who were at high risk for developing more serious symptoms. However, mutations in SARS-CoV-2 continues to create newer variants of concern, some of which seem to not only evade vaccine regimens, but also have markedly reduced susceptibility to monoclonal antibody treatments.

In response to these developments, newer small molecule therapeutics that have shown to markedly reduce the risk of hospitalization or death by COVID-19, such as Paxlovid™ and Molnupiravir™ have now been incorporated into the guidelines for the treatment of non-hospitalized COVID-19 patients in many countries as well. These are particularly important as the average cost of treating a single COVID-19 patient who needs intensive care in Canada according to the Canadian Institute for Health Information (“CIHI”) is estimated at more than CAD\$50,000, with average costs for patients being treated for the virus being more than CAD\$23,000. The agency estimates that COVID-19 related hospitalizations cost Canada nearly \$1 billion between January 2020 and March 2021 (the period covered by the report), with costs tripling between November 2020 and March 2022. The Global Preparedness Monitoring Board (“GPMB”) - launched by the WHO and the World Bank Group in 2018 - published a report in September 2020 estimating that the total response costs of COVID-19 globally had already exceeded \$11 trillion. Independent research estimates that the cumulative financial costs of the COVID-19 pandemic related to lost output (“GDP”) and health reductions may be as high as \$16 trillion in the US alone (Cutler and Summers 2020).

Evidence indicates that apabetalone may have a dual mechanism of action to effectively treat COVID-19 by impeding viral entry into host cells by downregulating ACE2 - the primary cell surface receptor used by SARS-CoV-2 to enter host cells - and attenuating the hyper-inflammatory responses that exacerbate the infection. This dual – anti-viral and anti-inflammatory – mechanism makes means that apabetalone’s potential therapeutic benefit is independent of SARS-CoV-2 variant (Fu, Gilham et al. 2023), and its benefit may also extend to patients with enduring symptoms, beyond the acute phase of the infection.



Apabetalone’s unique dual-mechanism gives it the potential to benefit patients at all stages COVID-19 disease progression, including those with enduring symptoms, for whom existing treatment options are limited

From the early days of the global COVID-19 pandemic, there were reports of long-term symptoms persisting for weeks and months after the initial infection, colloquially referred to as long-COVID. A growing body of literature has not only validated these reports, but quantified elevated risks of negative clinical outcomes for up to a year after SARS-CoV-2 infection (Daugherty, Guo et al. 2021). This constellation of persistent symptoms and elevated risks is referred to as Post COVID-19 Conditions (“PCC”). In particular, those with a history of COVID-19 infection are at significantly elevated and lasting risk of negative cardiovascular outcomes, including MACE and CHF (Xie, Xu et al. 2022). While more severe cases of COVID-19 appear to contribute to the greatest increases in risk, even milder cases – that those did not require hospitalization – worsen long-term outcomes when compared with people who have never contracted the disease. The exact molecular mechanism(s) contributing to PCC are not yet fully understood, but persistent inflammation, affecting in particular the cardiovascular system, is believed to play an important role (Davis, McCorkell et al. 2023). There is a strong need for effective therapies to treat and prevent PCC, providing a compelling market opportunity for apabetalone in patients with COVID-19.

Chronic Kidney Disease and End-Stage Renal Disease

CKD can result from the long-term effects of DM on blood vessels and the filtration apparatus (nephrons) of the kidneys. CKD is often referred to as a “silent killer” because it is insidious in onset, progressing slowly over many years and sometimes decades. According to the National Institute of Diabetes and Digestive and Kidney Diseases, more than 31 million people in the US (or 10% of the adult population) currently suffer from CKD. Healthy kidneys filter metabolic by-products from the blood in order for these unwanted materials to be excreted in the urine and thus eliminated from the body. One important measure of kidney function is estimated glomerular filtration rate (“eGFR”) which assesses the amount of fluid the kidney can filter over a period of time. In patients with CKD, as kidney function declines, the eGFR decreases. Unfortunately for many patients, CKD can progress to a point where the kidneys fail completely. This is called end-stage renal disease (“ESRD”) and these patients require hemodialysis, often multiple times per week, in which a machine removes the metabolic waste products from the blood. The cost of ESRD and hemodialysis to the healthcare system is large, exceeding \$34 billion each year in the U.S. The typical cost of dialysis per patient per year is nearly \$90,000.

The Company has received regulatory approval from the FDA Cardiovascular and Renal Division to further evaluate CKD and ESRD biomarkers to determine the potential use of apabetalone in this important disease area. The Company plans to assess these biomarkers and associated pathways in a phase 2a study in patients with ESRD treated with hemodialysis.

A subgroup analysis of CKD patients was included in the Phase 3 BETonMACE clinical study in this therapeutic area.

Neurodegenerative Disease

Epidemiological and mechanistic evidence indicate a link between CVD and neurodegenerative diseases such as dementia and mild cognitive impairment. A growing body of evidence now supports a strong and possibly causal relationship between the two. Both diseases are most prevalent in aged individuals, and they share many of the same risk factors including, but not limited to, smoking, hypertension, altered glucose metabolism, obesity, genetic susceptibility (i.e., ApoE allele status), inflammation, and abnormal blood lipids. Multiple studies have now demonstrated that factors affecting CVD such as moderate-to-high mid-life cholesterol values, diabetes, obesity, and smoking approximately double the risk of these neurodegenerative diseases. There are also links to cognition demonstrating an association between risk of dementia and mild cognitive impairment with a history of stroke, myocardial infarction, peripheral artery disease, and carotid plaques. Other findings demonstrate similar relationships between neurodegenerative diseases and CAD, myocardial infarction, cardiac arrest, carotid atherosclerosis, and hypercholesterolemia.

Based on its epigenetic mechanism, apabetalone has been shown to affect expression of numerous targets important for both CVD and neurodegenerative diseases such as ApoA-I/HDL, inflammatory mediators, components of the complement cascade and others. Moreover, apabetalone has been shown to repress multiple biological processes including pro-inflammatory, pro-atherosclerotic and pro-thrombotic pathways that can contribute to CVD and neurodegenerative risk. As such, apabetalone may represent a more physiologically relevant approach of treating the multiple biologies that contribute to a neurodegenerative disease state.

To evaluate the potential of BET inhibition in neurodegenerative disease, a variety of cell studies are underway to investigate the role of epigenetic modification in neurodegeneration. Moreover, ongoing preclinical studies are exploring the role of apabetalone mediated modulation of neuroinflammation and innate immunity in this important disease area. As the incidence of dementia and neurodegenerative diseases increases significantly with age, the Phase 3 BETonMACE clinical study included a subgroup analysis evaluating cognitive function in patients over the age of 70 and demonstrated a cognitive benefit of apabetalone in a subset of patients using the Montreal cognitive assessment test.

Competitive Environment

High-risk CVD

New approaches for residual MACE reduction in CVD patients are constantly being pursued by key stakeholders in the pharmaceutical marketplace. Several new hypotheses such as LDL-lowering (PCSK9 inhibitors), glucose lowering (SGLT2 inhibitors), HDL increasing/LDL-lowering (CETP inhibitors) and epigenetic regulation (BET inhibitors) are being developed in this therapeutic area.

SGLT2 inhibitors are the newest class of oral anti-hyperglycemic agents that have been approved for the treatment of diabetes mellitus. They have a unique and novel mechanism of action of reducing renal tubular glucose reabsorption in nephrons, producing a reduction in blood glucose without stimulating insulin release. These pleiotropic effects have translated into reductions in adverse cardiovascular and renal events in large cardiovascular outcome trials (“CVOT”), where SGLT2 inhibitors have shown the capacity to reduce MACE and hospitalization for heart failure and are associated with slower progression of kidney disease and with reduced rates of renal endpoints, such as progression of albuminuria, doubling of serum creatine, initiation of renal replacement therapy or death due to renal disease. These effects appear to be, at least in part, independent of glucose-lowering efficacy, and are proposed to be associated with improvements in pro- and anti-inflammatory cytokines, cardiac fibrosis, hematocrit, erythropoietin, and cardiac metabolic efficiency. Most of the beneficial effects of SGLT2 inhibitors on cardiorenal endpoints observed in CVOTs have been confirmed in large observational studies. On this basis, the FDA has approved four SGLT2i for clinical use:

Invokana® (“canagliflozin”) (Johnson & Johnson), the first SGLT2 inhibitor to be approved for use by the FDA in March 2013, was evaluated in the CANagliflozin cardioVascular Assessment Study (CANVAS) program (a combination of two sub-studies: the CANVAS and the CANVAS-Renal (CANVAS-R) study). 10,142 patients with T2D and high cardiovascular risk (34.4% of whom had no history of prior CVD) were randomly assigned to receive canagliflozin or placebo. The primary composite endpoint (MACE, cardiovascular death, nonfatal MI, and nonfatal stroke) was reduced by 14% by canagliflozin. No significant differences were found in individual components of the composite outcome. A secondary analysis of Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CRENCE) trial, showed that canagliflozin reduced the risk of MACE by 20% ($p=0.01$) with consistent reduction in both primary and secondary prevention group.

Farxiga™ (“dapagliflozin”) (Bristol-Myers Squibb and AstraZeneca) was approved for use by the FDA in January 2014. A greater proportion of patients in primary prevention were enrolled in the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58) trial, wherein 59.4% of the 17,160 patients had no established CVD. Treatment with Dapagliflozin resulted in a 17% reduction of the composite outcome of cardiovascular death or hospitalization for heart failure;

however, it failed to demonstrate significant benefit in terms of reduction of MACE (defined as cardiovascular death, nonfatal MI, and nonfatal stroke).

Jardiance® (“empagliflozin”) (Boehringer Ingelheim and Eli Lilly and Company), which was approved for use by the FDA in August 2014, was evaluated in The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) trial, which was conducted in 7,020 patients with T2D and established CVD. EMPA-REG OUTCOME showed that the primary composite outcome (MACE) of cardiovascular death, non-fatal myocardial infarction (MI), and stroke occurred 14% less frequently in patients randomized to empagliflozin versus those randomized to placebo. This difference was largely driven by significantly lower rates of cardiovascular death in the empagliflozin group. No significant differences were found in the rates of stroke and myocardial infarction.

The long-term effects of Steglatro™ (“ertugliflozin”) (Merck and Pfizer), which was approved for use by the FDA in December 2017, on cardiovascular and renal outcomes were assessed in the recently completed Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes (VERTIS-CV) trial. A total of 8,246 patients with T2DM and established CVD were recruited. Ertugliflozin failed to match its rivals in producing benefits over placebo for a composite of cardiovascular death or hospitalization for heart failure, cardiovascular death alone, and a composite of renal death and decline. Overall, the hazard ratio for the primary endpoint of MACE was 0.97.

DPP-4 inhibitors are newer oral hypoglycemic anti-diabetic agents which have shown to well maintain blood glucose level over the long-term (decent glycated hemoglobin [HbA1c]) and are not associated with hypoglycemia or weight gain in comparison to other similar drugs. There are currently four DPP4 inhibitors approved for use in adults with T2DM by the FDA; these include Januvia® (“sitagliptin”) (Merck & Co.) (October 2006), Onglyza™ (“saxagliptin”) (Bristol-Myers Squibb and AstraZeneca) (July 2009), Tradjenta™ (“linagliptin”) (Eli Lilly and Company and Boehringer Ingelheim) (May 2011), and Nesina (“alogliptin”) (Takeda Pharmaceutical Company) (January 2013). The cardioprotective effects of these DPP4 inhibitors have been studied and assessed in large CVOTs:

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus – Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53), Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care (EXAMINE), and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trials demonstrated that the addition of saxagliptin, alogliptin, and sitagliptin, respectively, had a neutral effect (i.e., did not increase or decrease the event rate versus placebo) on the primary composite endpoint (defined as cardiovascular death, non-fatal stroke or non-fatal MI) in SAVOR-TIMI 53 and EXAMINE, and as cardiovascular death, stroke, MI or hospitalization for unstable angina in TECOS in patients with high baseline risk for cardiovascular events.

Briefly, SAVOR-TIMI 53, which investigated the effects of saxagliptin versus placebo in 16,492 high-risk T2DM patients with around 78% having established atherosclerotic disease demonstrated that the addition of saxagliptin to existing therapy had a neutral effect on both the primary composite outcome, as well as the individual components (namely the risk of cardiovascular death, non-fatal MI or non-fatal ischemic stroke) versus placebo; however, saxagliptin treatment was associated with a significantly increased risk of heart failure-related hospital admissions. The EXAMINE trial showed that the addition of alogliptin to standard care in 5,380 patients with T2DM and a history of recent acute coronary syndrome was not associated with an increase in major cardiovascular events versus placebo, although a post-hoc analysis showed a non-significant 19% increased risk of hospitalization for heart failure among alogliptin-versus placebo-treated patients. In TECOS, no increases in major adverse cardiovascular events or hospitalization for heart failure were observed for sitagliptin versus placebo in 14,671 patients with T2DM and established cardiovascular disease. More recently, the Cardiovascular and Renal Microvascular Outcome Study with Linagliptin in Patients with Type 2 Diabetes Mellitus (CARMELINA) trial has demonstrated the cardiovascular and renal safety of linagliptin versus placebo when added to standard care in 6,979 patients with T2DM who were at high risk of vascular complications. Compared with placebo, the addition of linagliptin to standard care did not increase the risk of the composite cardiovascular outcome MACE (cardiovascular death, non-fatal MI, non-fatal stroke). Notably, linagliptin did not increase the risk of hospitalization for heart failure. Similarly, the Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients with Type 2 Diabetes (CAROLINA) trial concluded that linagliptin compared with glimepiride in 6,042 patients with T2DM and risk factors for or established atherosclerotic cardiovascular disease resulted in a non-inferior risk of a composite cardiovascular outcome of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

GLP-1 receptor agonists improve insulin secretion, decrease glucagon secretion, increase satiety (decrease food intake), and may have beneficial effects on β -cell function, limiting the risk for hypoglycemia (due to their glucose-dependent mechanism). Several members of this class of medications have been approved for use in the treatment of T2DM patients by the FDA, including Byetta® / Bydureon® (“exenatide”) (April 2005, January 2012) (AstraZeneca), Victoza® / Saxenda® (“liraglutide”) (Novo Nordisk) (January 2010, December 2014), Tanzeum™ (“albiglutide”) (GlaxoSmithKline) (April 2014), Adlyxin™ (“lixisenatide”) (Sanofi) (July 2016), Trulicity™ (“dulaglutide”) (Eli Lilly and Company) (September 2014), and Ozempic® (“semaglutide”) (Novo Nordisk) (December 2017). Seven CVOTs have been performed in the past 4 years using lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide and oral semaglutide. All have shown non-inferiority for cardiovascular outcomes, with liraglutide, subcutaneous semaglutide, albiglutide and dulaglutide demonstrating superiority (significant reductions in composite cardiovascular outcomes) with these drugs.

The LDL-lowering hypothesis is being further tested in CVD with aggressive reduction of LDL to unprecedented levels. PCSK9 inhibition is one such approach towards lowering LDL with potential implications for reducing MACE in high-risk vascular patients. PCSK9

inhibitors are monoclonal antibodies that inactivate the liver proprotein convertase subtilisin kexin 9 (“PCSK9”) (Seidah 2013). The function of this protein is to bind to LDL receptors on the surface of hepatocytes (liver cells) that transport LDL into the liver for metabolism and clearance. Binding results in reducing LDL clearance from the blood (Seidah, Awan et al. 2014). Therefore, targeted PCSK9 inhibition leads to more LDL receptors remaining active on liver cell surfaces to capture LDL for removal from blood, thereby promoting clearance and reducing blood LDL levels (Gouni-Berthold and Berthold 2014). This mechanism of therapeutically inhibiting PCSK9 to promote the clearance of LDL from the blood by prolonging the life span of the LDL-receptors differs greatly from statins, which inhibit the synthesis of cholesterol. The other key aspect that differentiates PCSK9 inhibitors from many of the other cardiovascular medications is that they require an IV infusion 1-2 times a month.

Praluent® (“alirocumab”) (Sanofi-Regeneron) was the first PCSK9 inhibitor approved by the FDA (July 2015) as a second line treatment to lower LDL in adults who have hereditary high cholesterol and patients who require additional LDL lowering when diet and statin treatment have been unsuccessful. Alirocumab was investigated for secondary prevention of MACE in ACS patients (ODYSSEY OUTCOMES Trial) in a large cohort of over 18,000 patients. Relative to placebo, alicumab treatment significantly reduced the risk of the primary end point (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina) with a hazard ratio of 0.85. Repatha® (“evolocumab”) (Amgen) was the second PCSK9 inhibitor to be approved by the US FDA (August 2015) for the same second line indication as Praluent. Evolocumab was investigated for secondary prevention of MACE in patients with high cholesterol and clinically evident CVD (FOURIER Outcomes trial) in a large cohort of over 27,000 patients. Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) with a hazard ratio of 0.85.

Although both therapeutics illustrated statistically significant outcome reductions from a scientific perspective, reimbursement of drug classes with potentially high cost thresholds are under ever-increasing scrutiny from a key stakeholder group, the payers. The reimbursement community has offered comments that this approach for preventing CVD events would potentially prove to be too costly. Many key US payer groups have reviewed and reported their perceptions of the data. These drugs were launched into the market with a reported annual treatment cost per patient of US\$7,000-12,000 (Staton 2015). Independent Payer groups such as the Institute for Clinical and Economic Review have determined this price to be too high and have suggested, “based on the results of the ODYSSEY Outcomes trial, [a] price benchmark, for alicumab in patients with a recent acute coronary event [of] \$2,300-\$3,400 per year,” and “given the evidence available from FOURIER, to reasonably align with clinical benefit the annual price of evolocumab would need to drop by 85-88%, to a range between \$1,725 and \$2,242” (Tice JA 2017; Tice JA 2018). This reported price threshold by a payer group represents a significant price reduction over the initial retail price of these drugs. Due to expensive antibody manufacturing procedures and other cost factors for these types of therapeutic interventions, the commercial model for this class of drugs will face increasing viability pressures in today’s ever-increasing cost containment environment.

There are several other approaches to CVD risk; however most of them have been unsuccessful in the clinical stages of development. Nicotinic acid had been widely used as a HDL-raising strategy but due to the findings of the AIM-HIGH study (Boden, Probstfield et al. 2011), this approach to HDL enhancement is now facing increased scrutiny. CETP inhibition was another approach that was being investigated by several large pharma organizations. CETP inhibition, although highly effective in raising HDL in plasma, has little target validation on clinical outcomes. The largest epidemiological study to examine CETP, COPENHAGEN, studied approximately 9,000 subjects and clearly illustrated that CETP is important for RCT biology. The study focused on subjects who naturally inhibited CETP, and noted high HDL levels but also significantly higher CVD events, particularly in women (Agerholm-Larsen, Tybjaerg-Hansen et al. 2000). These findings, along with additional data from the meta-analysis of CETP, (Thompson, Di Angelantonio et al. 2008), suggest that HDL functionality and RCT biology are potentially more important than standard HDL plasma measurements when looking for biomarker impact on MACE measurements. A third analysis of CETP also came to similar conclusions (Borggreve, Hillege et al. 2006). Anacetrapib, a CETP inhibitor being developed by Merck, was evaluated in the REVEAL study. The results of the REVEAL study illustrated a significant relative risk reduction of 11% between the anacetrapib treatment group and placebo. The primary end point was defined as the composite of coronary death, myocardial infarction, and coronary revascularization. The mechanism by which anacetrapib reduced the risk of major coronary events in this trial is currently being debated. This data was being closely scrutinized by payers to ensure compelling value when Merck announced that it would halt development of the compound, stating that “after comprehensive evaluation, [we have concluded that] the clinical profile [for anacetrapib] does not support regulatory filings”.

More recently, the use of fish oil omega-3 fatty acid derivative and eicosapentaenoic acid (EPA) based Vascepa® (“icosapent ethyl”) (Amarin Pharma) has demonstrated the potential to reduce the risk of ischemic events, including cardiovascular death, in patients with elevated triglyceride levels in the REDUCE-IT trial, which enrolled 8,179 subjects (HR of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina 0.75, 95% CI 0.68–0.83; p<0.001). It was approved for the use of reducing cardiovascular risk in patients with elevated triglyceride levels in a label expansion by the FDA in December of 2019.

Efficient numbers needed to treat (“NNT”) are also an important assessment performed by reimbursement and payer groups in the accretive value added of these technologies. There are several advantages to small molecule products and the associated research platform over potential antibody competitors such as the PCSK9 inhibitors. The key issues that need to be addressed are not only safety and efficacy but also cost efficiency and valid pharmacoeconomic modeling. Payers are now demanding cost efficiency for new therapeutics to be approved on health plans. As a result, payers will demand clear efficacy and price value model for risk reduction. If

apabetalone can illustrate a relative risk reduction of greater than 20-25% relative risk reduction over standard of care medicines, pricing will be a major competitive advantage over large molecule agents such as the PCSK9 programs.

The current landscape of drugs in development for CVD risk management is presented in the table below.

COVID-19

Following widespread recognition of the threat posed by COVID-19 in early 2020, broad efforts were initiated to develop or repurpose drugs to address the growing pandemic. Several strategies were adopted, including repurposing broad spectrum anti-viral therapeutics, developing monoclonal antibodies specific to SARS-CoV-2, small molecule inhibitors of viral proteases, and employing synthetic nucleoside derivatives to introduction of copying errors during viral RNA replication.

Veklury™ (“remdesivir”) (Gilead Sciences) is a broad-spectrum antiviral medication that received an emergency use authorization (“EUA”) in May 2020 from the FDA for use as a first-line treatment for COVID-19. It is an intravenously administered pro-drug, whose active metabolite interferes with the function of viral RNA polymerase. In the Adaptive Covid-19 Treatment Trial (“ACTT-1”), treatment with remdesivir modestly shortened median recovery time to 10 days, compared to 15 days for the placebo, a statistically significant difference (Beigel, Tomashek et al. 2020). Originally only authorized for use in severe, hospitalized cases of COVID-19, the FDA expanded the remdesivir’s EUA to include all hospitalized patients with COVID-19 in August 2020 and received approval in October 2020. Remdesivir also received EUA in jurisdictions around the world including Canada and the European Union. The high cost, intravenous administration, risk of off target effects, and limited efficacy prevent more widespread use of remdesivir.

Anti-viral monoclonal antibodies are a class of biological drugs that specifically bind to a particular antigen. A number of monoclonal antibodies have been developed to bind SARS-CoV-2 virus particles, and prevent their function, thereby neutralizing the virus. The specific target for these antibodies is a specific protein found on the surface of the virus, the spike protein. Since the spike protein is the virus’ first point of contact with human cells, these neutralizing can prevent cellular entry of the virus by binding to spike proteins. Neutralizing antibodies are sometimes given in pairs to reduce the risk that viral mutations will lessen the efficacy of the treatment. As these antibodies are highly specific to binding a particular protein sequence (in this case the SARS-CoV-2 spike protein), even minor changes to the sequence can significantly reduce binding affinity. The high cost of neutralizing antibodies, as well as the requirement for intravenous administration limits the accessibility of this class of treatments.

Bamlanivimab/etesevimab (Eli Lilly and Company) was the first neutralizing monoclonal antibody, targeting SARS-CoV-2 spike protein, to receive a EUA from the FDA in February 2021. The authorization was based on data from the Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (“BLAZE-1”) clinical trial, in which a total 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group, as compared with 36 of 517 patients (7.0%) in the placebo group, had a Covid-19–related hospitalization (defined as acute care for ≥ 24 hours) or death from any cause by day 29 (absolute risk difference, -4.8% ; $P < 0.001$) (Dougan, Nirula et al. 2021). In February 2022, following evidence of reduced efficacy in the Omicron variant of concern, the FDA revoked its EUA for bamlanivimab/etesevimab, limiting their future use to only COVID-19 variants in which their benefit has been demonstrated.

Xevudy™ (sotrovimab) (GlaxoSmithKline) received EUA from the FDA in May 2021, based on interim results from the Covid-19 Monoclonal Antibody Efficacy Trial–Intent to Care Early (“COMET-ICE”) clinical trial. , All-cause hospitalization lasting longer than 24 hours or death was significantly reduced with sotrovimab (6/528 [1%]) vs placebo (30/529 [6%]) (absolute risk difference, -4.53% ; $P < .001$) (Gupta, Gonzalez-Rojas et al. 2022).

REGEN-COV™ (casirivimab/imdevimab) (Regeneron Pharmaceuticals) received EUA from the FDA in November 2021, following results of their phase 3 clinical trial conducted throughout 2020 and 2021. The trial found that Covid-19–related hospitalization or death from any cause were reduced in both the REGEN-COV 1200-mg group and the 2400-mg group compared to the placebo groups (relative risk reductions of 70.4% and 71.3% respectively; $P < 0.001$ and $P = 0.002$) (Weinreich, Sivapalasingam et al. 2021). In February 2022, following evidence of reduced efficacy in the Omicron variant of concern, the FDA revoked its EUA for casirivimab/imdevimab, limiting their future use to only COVID-19 variants in which their benefit has been demonstrated.

Evusheld™ (tixagevimab/cilgavimab) (AstraZeneca) is the only neutralizing monoclonal antibody treatment issued a EUA by the FDA for the pre-exposure prophylaxis of COVID-19. The Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult (“PROVENT”) found that symptomatic COVID-19, the primary endpoint, occurred in 8 patients (0.2%) who received the antibodies and in 17 (1.0%) who received placebo (HR 0.23 [95% CI 0.10-0.54]) (Letter 2022).

Paxlovid™ (nirmatrelvir/ritonavir) (Pfizer) is a co-packaged combination of two anti-viral drugs, which was granted an EUA by the FDA for the treatment of COVID-19 in December 2021. The first drug nirmatrelvir is a 3C-like protease inhibitor, which interferes with the SARS-CoV-2 virus’ ability to reproduce its proteins and thereby its replication. The second drug, ritonavir, is a repurposed antiretroviral protease inhibitor, previously approved for the treatment of HIV/AIDS. Co-administration with ritonavir increases the availability of nirmatrelvir. Unlike remdesivir and neutralizing monoclonal antibody treatment, Paxlovid™ is taken orally. In 2021, Pfizer completed the Phase 3 Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (“EPIC-HR”) clinical trial establishing the safety and efficacy of Paxlovid™ in the treatment of COVID-19 in patients with high-risk of disease progression. In the planned interim analysis of patients treated within 3 days after symptom onset, significantly fewer recipients of nirmatrelvir plus ritonavir had COVID-19–related

hospitalization or death by day 28 (3 of 389 [0.77%]) than placebo recipients (27 of 385 [7.01%]), an absolute risk difference of -6.32% (P<0.001) (Hammond, Leister-Tebbe et al. 2022). Anti-viral drugs, including Paxlovid™, are only effective within a narrow window of time following infection, while the virus is actively replicating. It is recommended that Paxlovid™ administration be initiated within 5 days of symptom onset. The use of Paxlovid™ is limited by extensive drug interactions, including with commonly used classes of drugs such as HMG-CoA reductase inhibitors (“statins”). The high cost of Paxlovid™ treatment courses also limits the accessibility of the drug.

Molnupiravir (Merck & Co.) is an orally-available anti-viral medication, granted a limited EUA from the FDA in December 2021. A pro-drug, whose active metabolite is a synthetic nucleoside derivative, molnupiravir inhibits viral replication by incorporating into viral RNA during copying, resulting in inactive copies of the genetic material. In the Phase 3 MOVE-OUT clinical trial, the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (absolute risk difference -6.8%; P=0.001) (Jayk Bernal, Gomes da Silva et al. 2022). Due to concerns of limited efficacy, and off-target effects, molnupiravir’s EUA was only granted for use in certain populations where other treatments are not feasible.

While several therapeutics have been applied to treating acute COVID-19, none have been approved specifically for the treatment of PCC. The current landscape of drugs in development for the treatment of COVID-19 is presented in the Key Products in Development table.

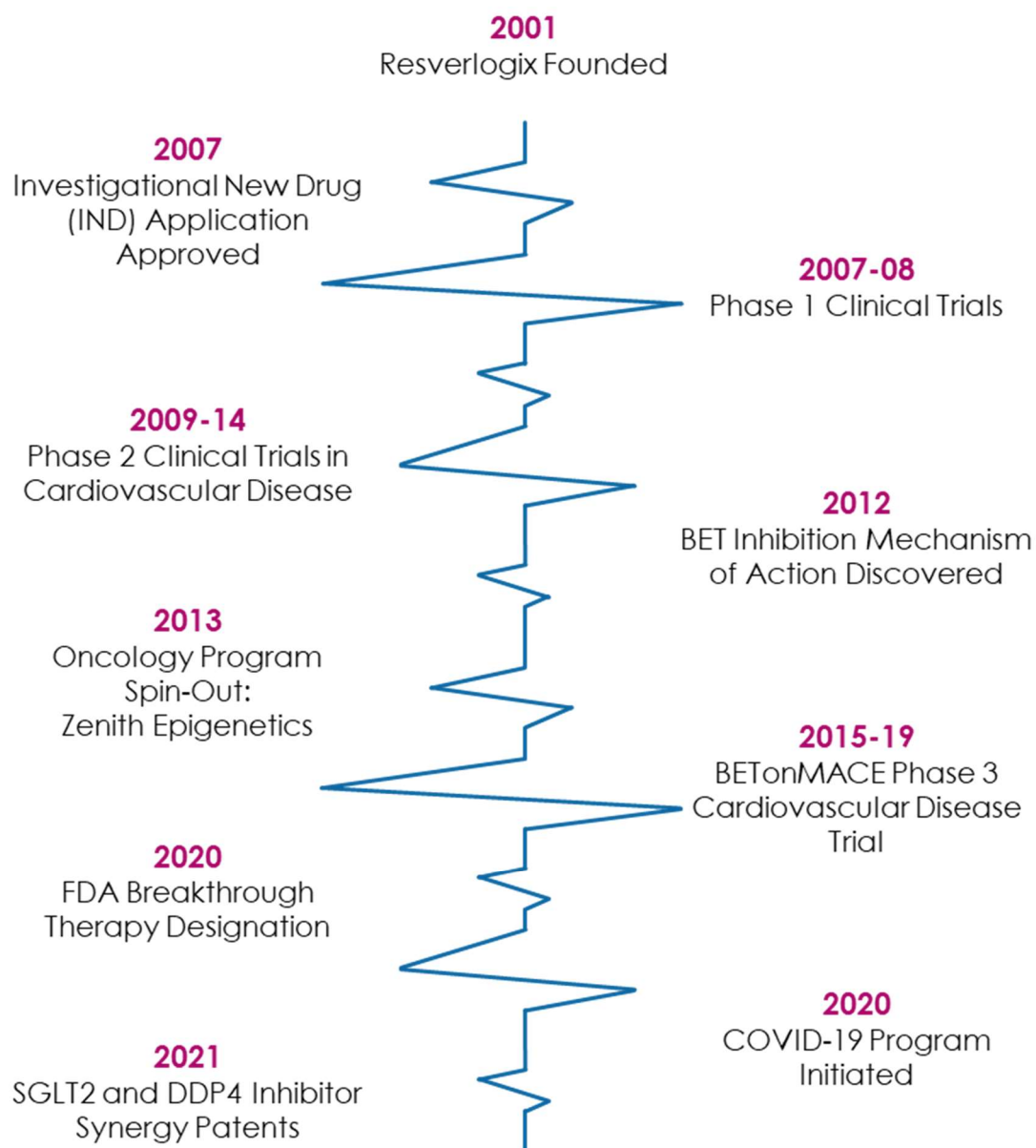
Key Products in Development (Resverlogix and Competitors)

Product	Mechanism of Action	Market Status
Apabetalone/ RVX-208 (Resverlogix)	BET Inhibition	Phase 3
Cardiovascular Disease		
Invokana® / Sulisent® (Canagliflozin) (Johnson and Johnson)	SGLT2 Inhibition	On Market (2013)
Farxiga™ (Dapagliflozin) (Bristol-Myers Squibb and AstraZeneca)	SGLT2 Inhibition	On Market (2014)
Jardiance® (Empagliflozin) (Boehringer Ingelheim and Eli Lilly and Company)	SGLT2 Inhibition	On Market (2014)
Steglatro™ (Ertugliflozin) (Merck and Pfizer)	SGLT2 Inhibition	On Market (2017)
Praluent® (Alirocumab) (Sanofi / Regeneron)	PCSK9 Inhibition	On Market (2015)
Repatha® (Evolocumab) (Amgen)	PCSK9 Inhibition	On Market (2015)
Januvia® (Sitagliptin) (Merck & Co.)	DPP-4 Inhibition	On Market (2006)
Onglyza™ (Saxagliptin) (Bristol-Myers Squibb and AstraZeneca)	DPP-4 Inhibition	On Market (2009)
Tradjenta™ (Linagliptin) (Eli Lilly and Company and Boehringer Ingelheim)	DPP-4 Inhibition	On Market (2011)
Nesina (Alogliptin) (Takeda)	DPP-4 Inhibition	On Market (2013)
Byetta®, Bydureon® (Exenatide) (AstraZeneca)	GLP-1 Receptor Agonism	On Market (2005 and 2012)
Victoza®, Saxenda® (Liraglutide) (Novo Nordisk)	GLP-1 Receptor Agonism	On Market (2010 and 2014)
Tanzeum™ (Abiglutide) (GlaxoSmithKline)	GLP-1 Receptor Agonism	On Market (2014)

Adlyxin™ (Lixisenatide) (Sanofi)	GLP-1 Receptor Agonism	On Market (2016)
Trulicity™ (Dulaglutide) (Eli Lilly and Company)	GLP-1 Receptor Agonism	On Market (2014)
Ozempic® (Semaglutide) (Novo Nordisk)	GLP-1 Receptor Agonism	On Market (2017)
Actos® (Pioglitazone) (Takeda and Eli Lilly and Company)	Thiazolidinediones	On Market (1999)
Zetia® / Vytorin® (Ezetimibe) (Merck & Co.)	Cholesterol Absorption Inhibitor	On Market (2002 and 2004)
Vascepa® (Icosapent Ethyl) (Amarin)	VLDL-TG Reduction Multiple Atherosclerotic Processes	On Market (2012)
Nexleto™ (Bempedoic Acid) (Esperion)	ATP Citrate Lyase inhibitor	On Market (2020)
Inclisiran (Novartis)	LDL-C lowering siRNA therapy	On Market (2021)
COVID-19		
Paxlovid™ (Nirmatrelvir/ritonavir) (Pfizer)	Viral protease inhibitor	EAU (2021)
Molnupiravir (Merck & Co.)	Synthetic nucleoside derivative	EUA (2021)
Bamlanivimab/etesevimab (Eli Lilly and Company)	Anti-viral monoclonal antibody	EUA (2021) Revoked (2022)
Evusheld™ (Tixagevimab/cilgavimab) (AstraZeneca)	Anti-viral monoclonal antibody	EUA (2021)
Xevudy™ (Sotrovimab) (GlaxoSmithKline)	Anti-viral monoclonal antibody	EUA (2021)
Veklury™ (Remdesivir) (Gilead Sciences)	RNA polymerase inhibitor	EUA (2020) On Market (2020)
REGEN-COV™ (Casirivimab/imdevimab) (Regeneron Pharmaceuticals)	Anti-viral monoclonal antibody	EUA (2021) Revoked (2022)

General Development of the Business

History of Apabetalone Development



Recent Clinical Developments

The following principal events have influenced the general development of our business during the most recent three fiscal years. Detailed findings and highlights from the clinical development of apabetalone are highlighted below.

Cardiovascular Disease

Based on the Company's completed clinical trials, a broader and more integrated view of the effects of treatment with apabetalone has been developed across the CVD spectrum with safety and efficacy results for up to 3.5 years of treatment. Analysis of the Company's CVD program data continues to not only strengthen the Company's understanding but also provides a more targeted pathway for future clinical trials with apabetalone. We have completed one Phase 3 study and three Phase 2 studies in patients with varying degrees of CVD severity. In these four foundational CVD trials - ASSERT, SUSTAIN, ASSURE and BETonMACE - a total of 1,771 patients have been dosed with apabetalone and 1,452 with placebo.

The following key findings contributed to determining a therapeutic window and targeted patient group for apabetalone.

- 1) The Phase 2 ASSERT study enrolled 299 patients (225 treated with apabetalone and 74 with placebo). Findings demonstrated by ASSERT included:
 - 200 mg/day of apabetalone was the optimal dose, based on safety and efficacy;
 - Patients with a low level of HDL-C at baseline had a better response for HDL-C and ApoA-I increases when treated with apabetalone; and
 - Best responses were observed in those patients given apabetalone in combination with second generation statins such as Rosuvastatin (Crestor®) or Atorvastatin (Lipitor®).
- 2) The Phase 2b SUSTAIN study enrolled 176 patients (88 treated with apabetalone and 88 with placebo). Findings demonstrated by SUSTAIN included:
 - Low baseline HDL and low baseline ApoA-I were the best responders; and
 - There was one MACE event in subjects treated with apabetalone compared to six in subjects treated with placebo.
- 3) The Phase 2b ASSURE study enrolled 323 patients (243 with apabetalone and 80 with placebo). Findings demonstrated by ASSURE included:
 - Low baseline HDL were the best responders;
 - Elevated baseline hsCRP were strong responders; and
 - A decrease in percent atheroma volume (-0.4 in apabetalone treatment group) from baseline to 26 weeks ($p=0.08$)
 - Significant reductions in atherosclerotic plaque ("AP") length and AP index compared to baseline (pre-treatment) measures and favourable modulation of ultrasonic measures of plaque vulnerability (Shishikura et al. 2018); and
 - There were fewer MACE events in subjects treated with apabetalone (7.4%) vs. subjects treated with placebo (13.8%).
- 4) The combined data from ASSERT, SUSTAIN and ASSURE represented 798 patients (556 treated with apabetalone and 242 with placebo). This data was published in the American Journal of Cardiovascular Drugs by Nicholls et al. 2017. Findings demonstrated by this analysis included:
 - Treatment with apabetalone led to a significant reduction in MACE. Patients treated with apabetalone had a lower cumulative MACE rate of 5.9% vs. 10.4% in the placebo treated group ($p=0.02$);
 - In exploratory subgroups, the benefit of apabetalone treatment appeared more striking with MACE occurring less frequently in association with apabetalone than with placebo among patients with DM (5.4% vs. 12.7%; $p=0.02$); and
 - Similarly, MACE occurred less frequently in association with apabetalone than with placebo in patients with baseline HDL-C < 39 mg/dL (5.5 vs. 12.8%; $p=0.01$) or with baseline hsCRP levels > 2 mg/L (5.4 vs. 14.2%; $p=0.02$).

Based on these findings, the Company's intention with the BETonMACE trial was to reconfirm in a larger prospective setting, in patients with modifiable vascular disease (i.e. low HDL and DM), the reduction of MACE coupled with favourable effects on markers of CVD risk.

BETonMACE

The BETonMACE study, "Effect of RVX-208 on Time to Major Adverse Cardiovascular Events in High-Risk Type 2 Diabetes Mellitus Subjects with Coronary Artery Disease", was 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 increased the time to MACE compared to treatment with rosuvastatin or atorvastatin alone. The study was conducted at 195 sites in 13 countries worldwide. The primary endpoint of the BETonMACE trial was designed to show a relative risk reduction ("RRR") of MACE, narrowly

defined as a single composite endpoint of cardiovascular (“CV”) death, non-fatal myocardial infarction (“MI”) and stroke. Secondary endpoints included: 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-I (“ApoA-I”)), changes in diabetes mellitus variables (glucose and glycated hemoglobin), change in alkaline phosphatase (“ALP”), changes in kidney function as well as additional safety and tolerability of apabetalone (RVX-208). In order to be eligible to participate in the study, patients had 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 low levels of HDL (<40 mg/dL for males and <45 mg/dL for females). Standard of care high potency statin therapy was maintained throughout the study, consisting 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 were treated with standard of care statin therapy, subjects were then randomized to either apabetalone (RVX-208) 100 mg b.i.d. (twice daily) or matching placebo with continued statin treatment. This combination treatment period continued for the duration of the study. A full detailed protocol for the BETonMACE study can be viewed on www.clinicaltrials.gov with the following NCT ID, NCT02586155.

The dosing of the first patient occurred on November 11, 2015, the topline results were announced on September 30, 2019 and presented November 16, 2019 at a Late Breaking Science Session during the American Heart Association’s (“AHA”) annual conference. BETonMACE’s primary endpoint did not reach statistical significance. Additional Important milestones are highlighted below.

In BETonMACE, a total of 274 primary endpoints occurred, 125 (10.9%) in the apabetalone group and 149 (12.4%) in the placebo group. The reduction in the primary endpoint of CV death or non-fatal MI or stroke by apabetalone did not reach statistical significance (hazard ratio 0.82, 95% confidence interval [CI] 0.65-1.04, $p=0.11$). The prespecified sensitivity analysis excluding the 21 deaths adjudicated as undetermined narrowly missed statistical significance with 113 primary endpoints in the apabetalone group (9.3%) and 140 in the placebo group (11.6%) (hazard ratio 0.79, 95% CI 0.62-1.01, $p=0.06$). These types of sensitivity analyses are included for regulatory agencies because the cause of death cannot always be conclusively adjudicated for reasons including unavailable documentation and the patient’s family consent. Apabetalone was well tolerated with similar rates of adverse events and serious adverse events compared to placebo. Full results of the BETonMACE study have been published in the *Journal of the American Medical Association*¹.

Consistent trending MACE improvements were observed for all the secondary endpoints including in CV death, non-fatal MI, and hospitalization for congestive heart failure (“CHF”) except for stroke which demonstrated neutral efficacy. These trends are clinically relevant for these MACE endpoint components with a hazard ratio range of 0.79-0.81 for CV death and MI, the combination of the two and recurrent events. The results for time to first hospitalization for CHF illustrated a statistically significant hazard ratio of 0.59 (95% CI 0.38-0.94, $p=0.03$). This hazard ratio widened to 0.47 (95% CI 0.23-0.83) when recurrent adjudicated events of hospitalization for CHF were considered. Full results of the prespecified hospitalization for congestive heart failure analysis have been published in the *Cardiovascular Diabetology* journal². Analysis of an alternative primary endpoint defined as the composite of CV death, non-fatal MI or hospitalization for CHF illustrated a significant hazard ratio of 0.76 (95% CI 0.60-0.95, $p=0.02$). This finding will be considered for future study design.

Evaluation of the prespecified subgroups illustrated a significant reduction in the primary endpoint for patients with an estimated glomerular filtration rate (“eGFR”) below 60 mL/min/1.73m².

Exploratory analysis of patients who were concomitantly administered sodium-glucose cotransporter-2 (“SGLT2”) inhibitors, a new class of anti-diabetic therapy, illustrated potential synergy with apabetalone. Analysis of the primary endpoint in patients taking apabetalone with empagliflozin (Jardiance™) for at least 30 days illustrated a hazard ratio of 0.34 (95% CI 0.12-1.01, $p=0.05$). Further analysis of this synergistic finding and evaluation of additional classes of anti-diabetic therapies is ongoing and appropriate intellectual property was filed in January 2020.

The addition of apabetalone to standard of care therapy after ACS in patients with type II DM and low HDL cholesterol, although not reaching statistical significance, showed a strong trend towards a reduction in MACE. Although BETonMACE did not have a sufficiently large sample size to detect a statistically significant relative risk reduction between apabetalone and placebo, it represents provisional clinical evidence that epigenetic modulation of pathologic gene expression by BET protein inhibition may be a potential therapeutic approach to the prevention of MACE and CHF. The results of BETonMACE study validates the need to continue the clinical development of apabetalone in patients with high-risk CVD, an area of critical unmet need.

¹ jamanetwork.com/journals/jama/fullarticle/2763951

² cardiab.biomedcentral.com/articles/10.1186/s12933-020-01199-x

Breakthrough Therapy Designation

On February 3, 2020, we announced that the FDA has granted BTB for apabetalone in combination with top standard of care, including high-intensity statins, for the secondary prevention of MACE in patients with type 2 DM and recent ACS.

According to the FDA, BTB is intended to expedite the development and review of new drugs to address the unmet medical need in the treatment of serious or life-threatening conditions. The criteria for BTB require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy. Expedited FDA programs, including BTB, help ensure that therapies for serious conditions are available as soon as it can be concluded that the therapies' benefits justify their risks, considering the seriousness of the condition and the availability of alternative treatment.

A drug that receives BTB is eligible for intensive guidance to ensure a time-efficient drug development program with FDA organizational commitment involving senior managers throughout the development program. Such guidance includes the expedited review of clinical trial design and protocols along with planning to accelerate the manufacturing development strategy of the drug. In the case of apabetalone, BTB will potentially allow for an interim efficacy analysis in a subsequent clinical trial to support regulatory approval thus shortening the overall development time.

Chronic Kidney Disease

Further elucidation from the SUSTAIN and ASSURE clinical trials included a subset of patients with CKD stage 3 or worse, defined as an eGFR below 60 mL/min/1.73m². A total of 48 patients (35 treated with apabetalone and 13 with placebo) were identified in this analysis. This data was published in *Kidney and Blood Pressure by Kulikowski et al. 2018*. Findings demonstrated by this analysis included:

- Treatment with apabetalone led to a significant reduction in ALP of -14.0% compared to -6.3% in the placebo group (p=0.02); and
- Treatment with apabetalone led to an increase in eGFR of 3.4% (p=0.04 versus baseline) compared to a decrease of 5.8% in the placebo group (p=0.6 versus baseline); and

Based on these findings, a phase I pharmacokinetic ("PK") trial was initiated and designed in accordance with the Company's strategy to expand into new indications including kidney disease. The phase I PK study was designed to determine if patients with severe kidney impairment treated with apabetalone had the same favourable PK traits and safety profile as has been illustrated in previous apabetalone trials. Dosing commenced on July 21, 2016 and on November 17, 2016, the Company announced that the primary endpoint had been met. As expected, results showed no significant difference in PK between renal failure patients and age and sex matched controls. These results allowed the Company to proceed with more advanced renal impairment and dialysis trials.

The study also explored acute changes in biomarkers relevant to BET inhibition in subjects with severe renal impairment. This data was published in *Kidney International Reports by Wasiak et al. 2018*. The data showed remarkable results in reducing inflammatory protein biomarkers in patients with late-stage CKD versus healthy control patients. 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 288 proteins were significantly different at baseline between the two groups (p<0.05), revealing a highly differential protein signature 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 significantly 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 positively regulated with respect to disease severity and progression. The quick onset of action and improvement of reported CKD risk factors are encouraging for the Company in the planned expansion beyond its cardiovascular program.

On February 23, 2017, we announced the receipt of the final minutes of an in-person Type B meeting with the Cardiovascular and Renal Products Division of the FDA. The purpose of the meeting was to request written comments, recommendations, and feedback on the proposed protocol for a Phase 2a 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 2a 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 (the final stage of chronic kidney disease) treated with hemodialysis. On May 15, 2017, we announced the acceptance by the Cardiovascular and Renal Products Division of the FDA, of the Company's Investigational New Drug ("IND") application to commence a Phase 2a kidney dialysis trial. The details of the study are described above. We intend to proceed with the Phase 2a clinical trial once we raise the required capital.

The BETonMACE trial included a prespecified subgroup of patients with CKD stage 3 or worse (eGFR below 60 mL/min/1.73m²). In participants with CKD, apabetalone treatment was associated with fewer MACE events (13 events in 124 patients [11%] in the apabetalone group compared to 35 events in 164 patients [21%] in the placebo group). The hazard ratio was 0.50 (95% CI 0.26 – 0.96). In addition, fewer heart failure-related hospitalizations were observed in the apabetalone group (3 events versus 14) with a hazard ratio of 0.48 (95% CI 0.26 – 0.86). Full results of this prespecified analysis of the BETonMACE study have been published in the Clinical Journal of the American Society of Nephrology. The proportion of CKD patients was 11%, lower than anticipated (possibly because of competing trials) which compares to 25-29% from similar DM post-ACS populations.

The effect of BET inhibition with apabetalone in patients with impaired renal function and the results of BETonMACE CKD subgroup validates the need to continue the clinical development of apabetalone in patients with high-risk CVD and a CKD comorbidity, an area of critical unmet need. With leading experts on our renal clinical and scientific advisory board providing input and guidance, we continue to consider conducting additional clinical trials in this therapeutic area.

Neurodegenerative Disease

Epidemiological and mechanistic evidence indicate a link between low ApoA-I/HDL, complement overactivation, peripheral inflammation and neurodegenerative diseases such as vascular cognitive dementia. Based on apabetalone's ability to raise plasma ApoA-I/HDL by ApoA-I production and modulate the complement cascade and other factors important for vascular inflammation, we believe apabetalone has the potential to beneficially impact various neurodegenerative diseases. Additionally, DM is known to increase the risk of developing dementia by two-fold while coronary heart disease and congestive heart failure are associated with a 27% to a 60% increased risk of cognitive decline, cognitive impairment or dementia (Rosano, Simonsick et al. 2005; Ravona-Springer and Schnaider-Beeri 2011; Umegaki 2014; Baumgart, Snyder et al. 2015; Saedi, Gheini et al. 2016; Zilliox, Chadrasekaran et al. 2016; Deckers, Schievink et al. 2017; Munshi 2017; Wolters, Segufa et al. 2018). It has been hypothesized that this increased risk of cognitive impairment is caused by transcriptional disturbances at the epigenetic level.

The BETonMACE trial included an exploratory assessment of cognition in patients over the age of 70 years (n=469). The results from this prespecified cognition assessment were announced on December 2, 2019 and presented on December 5, 2019 at the Clinical Trials on Alzheimer's Disease ("CtAD") Congress 2019. Cognition was assessed in BETonMACE using the Montreal Cognitive Assessment ("MoCA") which was designed as a rapid screening instrument for mild cognitive dysfunction. The test assesses eight different cognitive domains including attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Given that BETonMACE patients are recent ACS, DM patients with low HDL, the assumption is that dementia in this population is largely due to vascular cognitive impairment. In patients with a baseline MoCA below 22 (defined as mild to severe cognitive impairment), apabetalone treatment was associated with significant improvements versus placebo (mean change from baseline of 3.0 units in the apabetalone treatment group compared to 1.2 units in placebo group, p=0.02).

Further exploratory analysis of archived plasma samples planned for additional cognitive dysfunction markers including amyloid burden with plasma AB42/40 ratio, ApoE isoform, YKL40 and Neurofilament light are planned. Early observations on BET inhibition to modulate cognitive function in elderly patients with high-risk cardiovascular disease and DM warrant more research to address this critical unmet need. Preclinical analyses of brain-derived cell lines and animal models of neuroinflammation is ongoing and, with leading experts on our neurodegenerative clinical and scientific advisory board providing input and guidance, we continue to consider conducting additional clinical trials in this therapeutic area.

Recent Scientific Developments

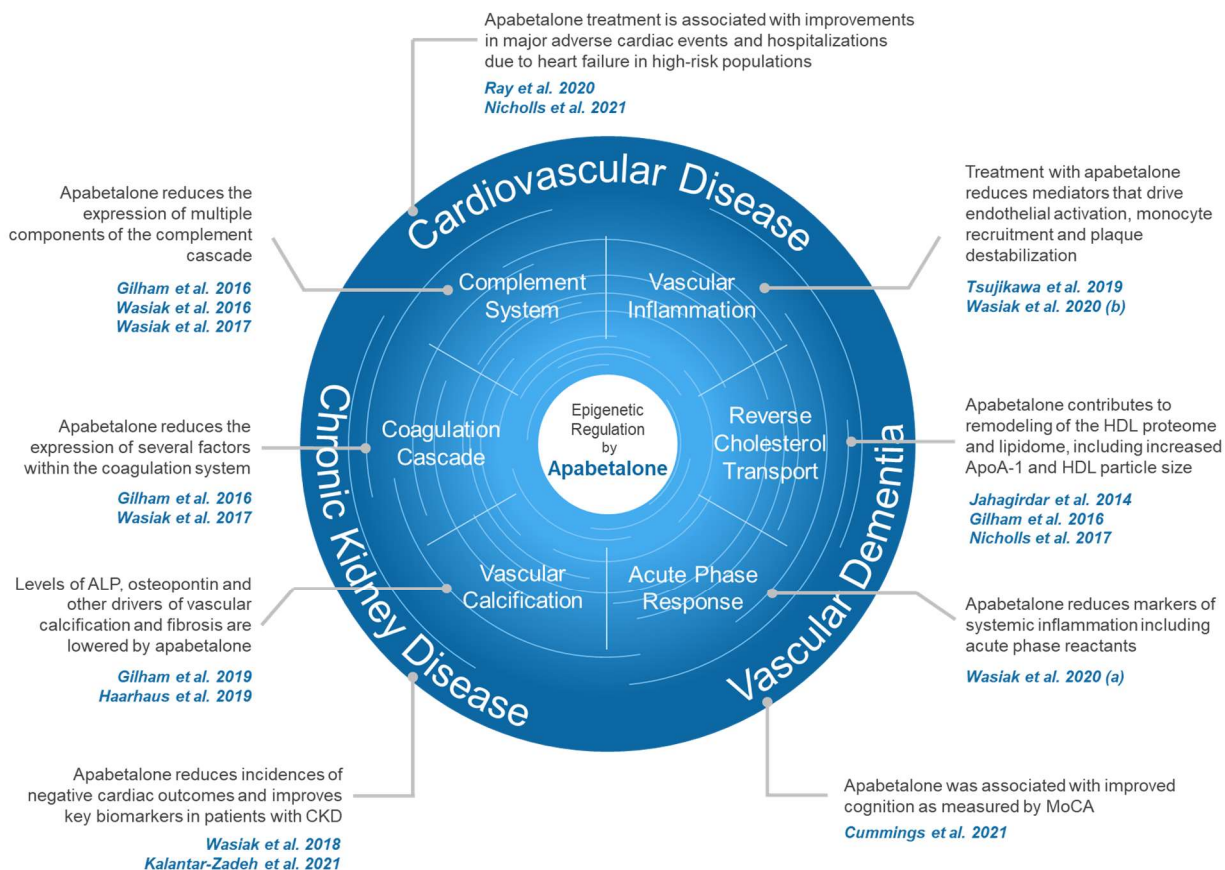
Based on our observed MACE reduction data from the pooled post-hoc analysis of the ASSERT, SUSTAIN and ASSURE clinical trials, a number of hypotheses were generated to help investigate the driving factors responsible for the MACE reductions observed. Based on our research and in-depth analysis of the activity of apabetalone in multiple cell types, a combination of BET responsive activities were identified as probable underlying contributors to the MACE reductions observed in the clinic, including, reverse cholesterol transport, acute phase response, vascular inflammation, vascular calcification, complement and coagulation. Downregulation of these pathways by apabetalone may avoid catastrophic vascular events leading to occlusion and death.

We performed microarray-based gene expression analysis on multiple cell types including human hepatocytes, human hepatocarcinoma cells, as well as whole blood treated with apabetalone. Results were verified by real-time PCR, a more sensitive and robust method of measuring mRNA expression, as well as using enzyme-linked immunosorbent assay ("ELISAs") to measure protein levels. In addition, protein levels from patients' plasma from the ASSERT, SUSTAIN and ASSURE clinical trials were analyzed. Further analysis of this nature is in progress.

Apabetalone-mediated BET inhibition affects multiple processes important for CVD, CKD and DM. Based on mechanistic data, we believe that apabetalone treatment, or select BET inhibition, attenuates the inflammatory process that contributes to disease initiation and progression. We have recently published data in cell models of vascular inflammation which support the anti-inflammatory effect of apabetalone treatment in endothelial cell lines, and prevention of cellular adhesion that occurs between endothelial cells and monocytes that initiate and promote plaque formation. In addition, the reduction in vascular calcification seen in osteogenic vascular

smooth muscle cells treated with apabetalone supports apabetalone’s potential in treating CKD and related complications. We have recently published results on the effects of ex vivo treated DM patient blood, with particular focus on the effects of apabetalone on the immune response in relevant cell types. Data collected to date has also supported investigation of apabetalone effects in models of neurodegenerative diseases, due to apabetalone’s peripheral anti-inflammatory effects and the known links between CVD, DM and cognitive deficits.

The abovementioned analyses show consistent regulation of markers and pathways known to contribute to CVD, DM, and CKD and are highlighted in the publications below.



BET Responsive Activity	Author	Publication
Acute Phase Response	Wasiak 2020 (a)	Epigenetic Modulation by Apabetalone Counters Cytokine-Driven Acute Phase Response In Vitro, in Mice and in Patients with Cardiovascular Disease
	Tsujikawa 2019	Apabetalone (RVX-208) reduces vascular inflammation in vitro and in CVD patients by a BET-dependent epigenetic mechanism
Vascular Inflammation	Wasiak 2020 (b)	BET protein inhibitor apabetalone (RVX-208) suppresses pro-inflammatory hyper-activation of monocytes from patients with cardiovascular disease and type 2 diabetes
	Wasiak 2023	Epigenetic BET reader inhibitor apabetalone (RVX-208) counters proinflammatory aortic gene expression in a diet induced obesity mouse model and in human endothelial cells
Vascular Calcification	Gilham 2019	Apabetalone downregulates factors and pathways associated with vascular calcification
	Haarhaus 2019	Apabetalone lowers serum alkaline phosphatase and improves cardiovascular risk in patients with cardiovascular disease
Reverse Cholesterol Transport	Jahagirdar 2014	A novel BET bromodomain inhibitor, RVX-208, shows reduction of atherosclerosis in hyperlipidemic ApoE deficient mice

	Gilham 2016	RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease
	Nicholls 2017	Selective BET Protein Inhibition with Apabetalone and Cardiovascular Events: A Pooled Analysis of Trials in Patients with Coronary Artery Disease
Cardiovascular Disease	Ray 2020	Effect of Apabetalone Added to Standard Therapy on Major Adverse Cardiovascular Events in Patients With Recent Acute Coronary Syndrome and Type 2 Diabetes
	Nicholls 2021	Apabetalone and hospitalization for heart failure in patients following an acute coronary syndrome: a prespecified analysis of the BETonMACE study
	Schwartz 2021	Relation of insulin treatment for type 2 diabetes to the risk of major adverse cardiovascular events after acute coronary syndrome: an analysis of the BETonMACE randomized clinical trial
Chronic Kidney Disease	Wasiak 2018	Benefit of Apabetalone on Plasma Proteins in Renal Disease
	Kalantar-Zadeh 2021	Effect of Apabetalone on Cardiovascular Events in Diabetes, CKD, and Recent Acute Coronary Syndrome
Vascular Dementia	Cummings 2021	Cognitive Effects of the BET Protein Inhibitor Apabetalone: A Prespecified Montreal Cognitive Assessment Analysis Nested in the BETonMACE Randomized Controlled Trial
Non-alcoholic Fatty Liver Disease	Toth 2022	Reduction in the risk of major adverse cardiovascular events with the BET protein inhibitor apabetalone in patients with recent acute coronary syndrome, type 2 diabetes, and moderate to high likelihood of non-alcoholic fatty liver disease
Coagulation Cascade	Gilham 2016	RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease
	Wasiak 2017	Downregulation of the Complement Cascade In Vitro, in Mice and in Patients with Cardiovascular Disease by the BET Protein Inhibitor Apabetalone (RVX-208)
Complement System	Wasiak 2016	Data on Gene and Protein Expression Changes Induced by Apabetalone (RVX-208) in ex vivo Treated Human Whole Blood and Primary Hepatocytes
	Gilham 2016	RVX-208, a BET-inhibitor for treating atherosclerotic cardiovascular disease, raises ApoA-I/HDL and represses pathways that contribute to cardiovascular disease
	Wasiak 2017	Downregulation of the Complement Cascade In Vitro, in Mice and in Patients with Cardiovascular Disease by the BET Protein Inhibitor Apabetalone (RVX-208)

Recent participation at leading, international scientific conferences included:

- 58th European Renal Association - European Dialysis and Transplant Association Congress 2021 (virtual conference): “Apabetalone Downregulates Fibrotic, Inflammatory and Calcific Processes in Renal Mesangial Cells Which May Contribute to Reduced Cardiac Events Observed in CKD Patients” poster presentation
- American Association of Immunologists – Immunology 2021 (virtual conference): “Inhibition of Epigenetic Reader BET Proteins by Apabetalone Counters Inflammation in Activated Innate Immune Cells from Fabry Disease Patients Receiving ERT” poster presentation
- European Society of Cardiology Congress 2021 (virtual conference): “Bromodomain and Extraterminal (BET) Protein Inhibitor, Apabetalone, Reduces ACE2 Expression and Attenuates SARS-CoV-2 Infection In Vitro” poster presentation
- American College of Cardiology’s Scientific Session 2021 (virtual congress): “Epigenetic BET Reader Inhibitor Apabetalone (RVX-208) Counters Proinflammatory Aortic Gene Expression In a Diet-Induced Obesity Mouse Model” poster presentation and “Apabetalone (RVX-208) Reduces ACE2 Protein Abundance And Prevents SARS-CoV-2 Spike Protein Binding To Human Lung Cells, A MOA That Could Attenuate Viral Entry” poster presentation
- FSHD International Research Congress 2021 (virtual conference): “Apabetalone, a Clinical-stage Cardiovascular Disease Drug, Inhibits DUX4 Expression in FSHD Cells” poster presentation
- American Society of Nephrology, Kidney Week 2021 (virtual conference) “Apabetalone Downregulates Fibrotic, Inflammatory and Calcific Processes in Renal Mesangial Cells: Mechanism for Reduced Cardiac Events in CKD Patients” poster presentation
- Alzheimer’s Association International Conference (AAIC) 2021: “Favorable Cognitive Effects of the BET Protein Inhibitor Apabetalone in Patients 70 and Older” poster presentation
- American Heart Association Scientific Sessions 2021 (virtual conference): “Epigenetic BET Reader Inhibitor Apabetalone (RVX-208) Counters Proinflammatory Aortic Gene Expression In A Diet Induced Obesity Mouse Model” poster presentation
- Clinical Trials on Alzheimer’s Disease (CTAD) Congress 2021: “BET-Inhibition by Apabetalone and Cognitive Effects: A Pre-Specified MoCA Analysis Nested in the BETonMACE Randomized Controlled Trial” poster presentation and “The Epigenetic Modulator Apabetalone Decreases Neuroinflammation in Blood Brain Barrier Cell Models and LPS-Treated Mice” oral presentation

- 16th International Conference on Alzheimer’s & Parkinson’s Diseases (AD/PD) 2022: “Apabetalone BET-Inhibition and Cognition: A MOCA Assessment in the Phase 3 CVD-Outcomes Trial BETonMACE” oral presentation
- European Society of Cardiology Congress 2022: “Apabetalone, a BET Inhibitor, Attenuates Inflammation Induced by Viral RNA Mimetic and Reduces SARS-CoV-2 Spike Protein Binding Regardless of Variants” poster presentation
- American College of Cardiology’s Scientific Session 2022: “The Epigenetic BET-Inhibitor Apabetalone Reduces Cardiovascular Events in Patients with Type 2 Diabetes, Acute Coronary Syndrome and an Elevated Angulo Nonalcoholic Fatty Liver Disease Fibrosis Score Exploratory Analysis of the BETonMACE Trial” poster presentation
- American Heart Association Scientific Sessions 2022: “Apabetalone Downregulates Pathways Associated with Nephropathy in Renal Mesangial Cells, which May Contribute to Reduced Cardiac Events Observed in CKD Patients” poster presentation
- American Heart Association Scientific Sessions 2022: “New Cardiovascular Events After COVID-19 Infection: Role of Long COVID” poster presentation
- Clinical Trials on Alzheimer’s Disease (CTAD) Congress 2022: “The Bromodomain and Extraterminal Domain Protein Inhibitor Apabetalone Inhibits the Neurotoxic Kynurenine Pathway in Monocytes and Brain Endothelial Cells” poster presentation

Through participation at major conferences and events, we continue to highlight apabetalone’s ability to regulate multiple biological pathways that underlie and contribute to CVD, diabetes, and neurodegenerative diseases.

Additional Indications and Potential Orphan Diseases

Post COVID-19 Conditions

The severe acute respiratory syndrome coronavirus 2 (COVID-19) emerged in late 2019 and spread globally, prompting an international effort to accelerate not only the development of a vaccine but also the search for potential treatment options. The scientific understanding of how SARS-CoV-2, the virus responsible for COVID-19, enters host cells and replicates, has increased drastically in recent months and research targeting how to impede this mechanism continues to expand at an accelerated rate. Recent evidence indicates that apabetalone may have a dual mechanism of action to effectively treat COVID-19 by impeding viral entry into host cells and hyper-inflammatory responses that exacerbate the infection. Angiotensin converting enzyme 2 (ACE2), the primary cell surface receptor used by SARS-CoV-2 to enter host cells, is transcriptionally downregulated by apabetalone by 40-90% in various cell lines (Gilham, Smith et al. 2021). Decreasing ACE2 transcripts lowers the total and surface abundance of ACE2 protein in vitro by 60%; circulating ACE2 protein in the blood of phase 2 CVD clinical trial patients treated with apabetalone also declines. This reduction in ACE2 receptor abundance inhibits the binding of recombinant SARS-CoV-2 spike protein to the host cell surface by 60% and prevents live viral infection by up to 90%. Apabetalone also decreases transcripts and protein abundance of DPP4, a potential co-factor that facilitates SARS-CoV-2 infection of host cells.

COVID-19 hyper-inflammatory viral responses can compromise the function of multiple organs; apabetalone may stifle this cytokine storm and long-term COVID. Indeed, ex vivo treatment of monocytes isolated from diabetic CVD patients with apabetalone diminishes their pro-inflammatory phenotype and hyper responsiveness to IFN γ stimulation. Apabetalone also counters cytokine driven acute phase response in cells and in treated mice (Wasiak, Gilham et al. 2020) as well as reduces the levels and activity of the complement cascade. These preclinical results bear out in the clinic, where apabetalone treatment lowers the abundance of multiple inflammatory markers in patient plasma. Accordingly, apabetalone is a novel, safe, clinical trial ready candidate for the prevention and treatment of COVID-19 based on its capacity to lower SARS-CoV-2 infection and combat hyper-inflammatory responses. This preclinical research has been published in various high-impact peer-reviewed journals including *Cell* (Mills, Humphrey et al. 2021).

The evolving COVID-19 pandemic has produced numerous SARS-CoV-2 variants of concern including the Delta and Omicron variants that were responsible for deadly waves of the disease in 2022. These, and other variants, derive from mutations of the SARS-CoV-2 virus, as it adapts to the changing pandemic environment. In particular, mutations in the viruses spike protein have proven effective in increasing its virulence and improving its ability to evade immunity. Vaccines first developed based on the virus’ ancestral strain, have proven less effective at preventing the spread of new variants. Likewise, some treatment options have demonstrated declining efficacy in managing infections with new SARS-CoV-2 variants. Though new emergent variants have undergone mutations in their spike protein, all variants to date remain dependent on ACE2 to complete their replication cycle. Apabetalone’s dual anti-viral/anti-inflammatory mechanism may allow the treatment to benefit COVID-19 patient regardless of variant (Fu, Gilham et al. 2023).

BET Responsive Activity	Author	Publication
COVID-19	Mills 2021	BET inhibition blocks inflammation-induced cardiac dysfunction and SARS-CoV-2 infection
	Gilham 2021	Bromodomain and Extraterminal Protein Inhibitor, Apabetalone (RVX-208), Reduces ACE2 Expression and Attenuates SARS-Cov-2 Infection In Vitro
	Fu 2023	Dual mechanism: Epigenetic inhibitor apabetalone reduces SARS-CoV-2 Delta and Omicron variant spike binding and attenuates SARS-CoV-2 RNA induced inflammation

Potential Orphan Disease Indications

Based on the literature and knowledge of epigenetics and BET inhibition, our analysis of apabetalone-treated human plasma and our recent proteomics assessment, new pathways, genes and biomarkers known to play a role in orphan diseases have been investigated. New data generated in our research laboratory has demonstrated that BET inhibition by apabetalone has effects on multiple biological pathways that underlie disease pathology. Based on these recent advancements and scientific knowledge gained, we intend to continue to expand our research and development to explore orphan diseases such as PAH. We will perform detailed commercial and scientific analysis in all these opportunities to build the best possible rationale for advancing any of these opportunities forward. In addition to apabetalone, preclinical testing with other BET inhibitors from within our compound library has demonstrated similar effects on important markers known to play a role in orphan diseases. These compounds are under consideration as follow-on compounds.

Pulmonary Arterial Hypertension

On March 18, 2019, we announced the advancement of a project led by academic collaborators at Quebec Heart and Lung Institute, Laval University, to research the clinical potential of apabetalone as a potential therapy for PAH. An article titled: “Multicenter Preclinical Validation of BET Inhibition for the Treatment of Pulmonary Arterial Hypertension” was published in the high-impact, peer-reviewed medical journal, *American Journal of Respiratory and Critical Care Medicine*, published by the American Thoracic Society (Van der Feen, Kurakula et al. 2019). This article presented our collaborative work with top research groups in Canada and the Netherlands and illustrated the beneficial effects of apabetalone treatment in several animal and cell models of PAH. A clinical pilot study, APPRoACH-p, commenced in September 2019 to evaluate the potential use of apabetalone, assessing patient safety and effects on key biomarkers of PAH. The study was completed in late 2021, finding that apabetalone was well tolerated by study participants and observing improvements in key hemodynamic outcome measures, including pulmonary vascular resistance, cardiac output, and stroke volume. These findings were also published in the *American Journal of Respiratory and Critical Care Medicine* (Provencher, Potus et al. 2022).

Fabry Disease

Fabry Disease is an inherited genetic disorder that is classified as a lysosomal storage disease. It results from a mutation leading to a deficiency of the enzyme alpha galactosidase-A, which is responsible for the breakdown of the glycolipid globotriaosylceramide (“Gb3”). This deficiency causes an accumulation of Gb3 within blood vessels, tissues, and organs. Patients with Fabry disease experience various heart, kidney, and dermatological complications with stroke, heart disease and kidney complications being the top causes of mortality. The first-line treatment for Fabry is enzyme replacement therapy (“ERT”), which involves the intravenous administration of alpha galactosidase to compensate for the deficiency. Adjunctive medications include acetylsalicylic acid, angiotensin converting enzyme (“ACE”) inhibitors or angiotensin II receptor blockers (“ARB”), statins, and pain medications. Current medications approved for Fabry disease are not sufficient and there remains a large unmet need. We intend to proceed with the planned Phase 2a clinical trial once we raise the required capital.

The Company’s clinical program in Fabry Disease is supported from in-house research and development. A preclinical, ex vivo study, examining the effect of apabetalone on primary blood cells taken directly from Fabry Disease patients was completed and the findings recently published (Fu, Wasiak et al. 2022). Expression of inflammatory cytokines, which is heightened in Fabry Disease patients, was dose-dependently downregulated with apabetalone treatment. Production of reactive oxygen species, which can damage cells, was reduced by 80% following apabetalone treatment. These findings overall suggest that apabetalone has the potential to alleviate the inflammation and oxidative stress that are characteristic of Fabry Disease, and which contribute to its progression.

Orphan Disease Fact Sheet

- Defined as rare diseases and disorders.
- Affect fewer than 200,000 people in the US.
- An estimated 7,000 rare diseases have been identified affecting over 30 million patients in the US.
- 400 drugs and biologics have been FDA approved.
- Due to the difficulty in recovering the therapeutic development costs associated with small patient segments, the Orphan Drug Act (ODA) was introduced in 1983 to foster research into rare diseases.
- The ODA provides for granting special status to a drug or biological product to treat a rare disease. This status is referred to as orphan designation.
- Orphan designation allows the drug sponsor to benefit from incentives for the development of these products.
- Incentives include tax credits on clinical research, technical assistance during new drug application (NDA) filing and exclusivity of 7 years after the marketing approval is granted.

Source: NIH Rare Diseases Clinical Research Network Fact Sheet

Apabetalone (RVX-208) Clinical Trials

Indication	Phase 1	Phase 2	Phase 3
High-Risk CVD <i>Type 2 Diabetes Mellitus, Low HDL-C, and Recent ACS</i>		ASSERT [2b] SUSTAIN [2b] ASSURE [2b]	BETonMACE <i>(Completed)</i> BETonMACE2 <i>(Ready)</i>
High-Risk CKD <i>Type 2 Diabetes Mellitus, CVD, and CKD</i>			BETonCKD <i>(Ready)</i>
Post COVID-19 Conditions			Phase 2/3 <i>(Planned)</i>
PAH	APPRoACH-p <i>(Completed)</i>	APPRoACH-2 <i>(Planned)</i>	
Vascular Dementia			BETonMACE <i>(Subgroup)</i>
Combined Patient-years of Safety			4,200

Regulatory Affairs

Apabetalone is being investigated for the secondary prevention of MACE including emergency/urgent revascularization in coronary artery disease patients with type 2 DM, and low HDL. An IND was filed and accepted by the FDA in 2007 to commence clinical testing in humans. Subsequently, clinical trial applications were submitted and accepted by national, central and local health authorities in Poland, Belgium, Spain, Netherlands, Russia, Brazil, Argentina, South Africa and Australia in connection with Phase 2 clinical trials. To support the IND and ex-US applications, we submitted manufacturing, nonclinical study and clinical study information (data, protocols, processes, reports, etc.) to the FDA and the ex-US health authorities. We have also submitted safety data and other pertinent information in the form of annual reports to the FDA and applicable ex-US health authorities. We continue to provide all applicable health authorities with the required nonclinical, manufacturing and clinical information as outlined in country specific regulations.

Meetings with health authorities in 2015 in Germany, Sweden and UK provided scientific insight useful in the design of a Phase 3 study to support filing a Marketing Authorisation Application (“MAA”) within Europe; the learnings were incorporated into the Phase 3 BETonMACE clinical study which commenced recruitment in the fall of 2015. The BETonMACE study received clinical trial approval from regulatory authorities in 14 countries.

Future product development activities related to apabetalone and/or related products will be subject to extensive regulation by various government authorities, including the FDA and comparable regulatory authorities in other countries, which regulate the design, research, clinical and non-clinical development, testing, manufacturing, storage, distribution, import, export, labeling, advertising and marketing of pharmaceutical products and devices.

Intellectual Property

We devote significant resources to ensure protection of the ideas and inventions related to core areas of our business. Our intellectual property portfolio covers compositions, methods and treatments for cardiovascular, inflammatory, autoimmune disease, cancers and fibrotic indications.

As of December 31, 2022, we own and/or have rights to twenty patent families, comprising 145 allowed/issued patents (including twenty-one issued US patents). Our intellectual property portfolio includes a number of pending US applications and world-wide equivalents. Our patent portfolio covers compositions, methods of use, manufacturing and formulation claims to apabetalone.

In fiscal 2012, we were issued five patents within four patent families in two jurisdictions, including a United States Patent covering composition of matter claims to apabetalone, and a United States Patent covering the manufacturing of apabetalone. In fiscal 2013, we were issued eight patents within four patent families in six jurisdictions, including a United States Patent related to inflammatory diseases. In fiscal 2014, we were issued fourteen patents within five patent families in nine jurisdictions, including a patent in Europe containing composition of matter claims to apabetalone. In fiscal 2015, we were issued eighteen patents within seven patent families in eleven jurisdictions, including United States patents related to use claims for apabetalone and manufacturing of apabetalone. In fiscal 2016, we were issued seventeen patents within eight patent families in twelve jurisdictions, including United States patents related to use claims for apabetalone. In fiscal 2017, we were issued twenty patents within six patent families in thirteen jurisdictions,

including a United States patent related to formulation of apabetalone. In fiscal 2018, we were issued fifteen patents within five patent families in twelve jurisdictions, including a United States patent related to apabetalone for treating anti-inflammatory diseases. In fiscal 2019, we were issued ten patents within five patent families in six jurisdictions, including a United States patent related to apabetalone for treating complement-associated diseases. In the year ended April 30, 2020, we were issued eight patents within four patent families in six jurisdictions, including five patents related to formulation of apabetalone. In the eight months ended December 31, 2020, we were issued eight patents within five patent families in six jurisdictions, including two patents related to apabetalone for treating complement-associated diseases. During the year ended December 31, 2021, we were issued thirteen patents within five patent families, including two patents related to apabetalone for treating complement-associated diseases. During the year ended December 31, 2022, we were issued six patents within two patent families, including a European patent related to apabetalone for treating complement-associated diseases. One US patent was abandoned in 2022.

Our patents and patent applications have been filed in numerous jurisdictions, including the USA, Europe, China, Japan, South Korea, Canada and India; the details for each patent vary depending on the nature of the claims and importance to the Company. The patent containing compound claims to apabetalone has been granted in all jurisdictions in which we applied (the USA, Australia, Canada, China, Europe, Hong Kong, India, Japan, South Korea, Macau, Mexico, and New Zealand). One of the core patents around apabetalone, titled “Novel Compounds Useful in the Synthesis of Benzamide Compounds” has been granted in all jurisdictions in which we applied (the USA, Australia, Brazil, Canada, China, Europe, Hong Kong, Israel, India, Japan, South Korea, Macau, Mexico, and New Zealand, Saudi Arabia, and Russia). Another core patent related to the use of apabetalone, titled “Methods of Treatment and/or Prevention of Major Adverse Cardiovascular Events (MACE) with a Combination of a BET Bromodomain Inhibitor and a SGLT2 Inhibitor” has been filed in 17 jurisdictions.

Our intellectual property strategy is to build a strong patent portfolio around core technology that is important to development of leading-edge medicines. Our strategies include being the first to identify, isolate, and patent therapeutic agents with commercial importance, to seek out and license intellectual property believed to be useful in connection with potential products, and to control disclosure of proprietary knowledge.

We also believe that our proprietary know-how will provide a significant competitive advantage; we intend to continue to develop and protect our proprietary tools, methods and trade secrets. Our policy is to require employees, consultants, members of our advisory boards and collaborators to execute confidentiality agreements. Employees, consultants and contract research organizations specify that all inventions resulting from work performed utilizing our property, business strategies, and work completed pursuant to their employment/services performed remains our exclusive property to the fullest extent permitted by law.

Clinical and Scientific Advisory Boards

BETonMACE Clinical Steering Committee

Our Clinical Steering Committee (“CSC”) for the BETonMACE trial provided overall supervision of the clinical trial and ensured that the trial was conducted in accordance with the principles of Good Clinical Practice and applicable regulations. The CSC established the trial protocols, any protocol amendments and provided advice to the investigators on various aspects of the trial. The members of the CSC are as follows:

Professor Kausik Ray is Professor of Public Health, Department of Primary Care and Public Health, School of Public Health at Imperial College London. A clinical cardiologist by training, Professor Ray received his medical education (MB ChB, 1991) at the University of Birmingham, his MD (2004) from the University of Sheffield, a postdoctoral fellowship at Harvard Medical School (2004-2005) an MPhil in epidemiology (2007) from the University of Cambridge and was Chair in Preventive Cardiology at St Georges University of London from 2010. Professor Ray’s research interests focus on the prevention of CVD using observational methods and intervention studies including large clinical trials. Professor Ray established the first global registry of Familial Hypercholesterolaemia in conjunction with the European Atherosclerosis Society (“EAS”) named the FH studies collaboration (“FHSC”) and is the Principal Investigator for the TOGETHER study investigating cardiometabolic risk factors and clinical outcomes in approximately 250,000 people using electronic health records in London, England. He is president elect of the European Atherosclerosis Society.

Gregory G. Schwartz is Professor of Medicine in the Division of Cardiology of the University of Colorado Denver. He earned MD and PhD degrees at Duke University School of Medicine, and served as resident and Chief Resident in Internal Medicine at the University of Colorado and fellow in Cardiology at the University of California San Francisco. His research interests include clinical trials investigating new lipid and metabolic treatments to improve outcomes after heart attacks. Dr. Schwartz has been the lead investigator in large global CVD trials such as MIRACL and dal-OUTCOMES, and is co-Chair of the recently completed Odyssey Outcomes trial. Dr. Schwartz serves as Section Editor for Clinical Trials on the Editorial Board of the Journal of the American College of Cardiology. He is a fellow of the American Heart Association and the American College of Cardiology.

Peter P. Toth, MD, PhD is director of preventive cardiology, CGH Medical Center, Sterling, Ill., and professor of clinical family and community medicine at University of Illinois, Peoria. Dr. Toth has authored and coauthored over 220 publications in medical and scientific journals and textbooks. He is Editor-in-Chief of the *Year in Lipid Disorders* and an Associate Editor for the *Year Book of*

Endocrinology. He is coeditor with Antonio Gotto of the textbook, *Comprehensive Management of High Risk Cardiovascular Patients* with Michael Davidson of *Therapeutic Lipidology*, with Dominic Sica of *Current Controversies in Dyslipidemia Management*, with Kevin Maki of *Practical Lipid Management*, with Christopher Cannon of *Comprehensive Cardiovascular Care in the Primary Care Setting*, and Domenic Sica of *Clinical Challenges in Hypertension* vols I and II. He has lectured on many topics in cardiovascular medicine throughout the United States.

Dr. Stephen J. Nicholls, MBBS, PhD is Director of MonashHeart, Monash Health and Professor of Cardiology, Monash University, Melbourne Australia. Dr. Nicholls was previously Professor of Cardiology at the University of Adelaide. He has authored more than 350 original manuscripts, meeting abstracts and book chapters. His current research interests include the functional properties of HDL, the role of inflammation and oxidative stress in atherogenesis and the development of new imaging modalities to assess factors that influence the natural history of atherosclerosis. He plays a lead role in clinical trials that employ IVUS to investigate the impact of novel anti-atherosclerotic therapies.

Henry N. Ginsberg, MD is the Irving Professor of Medicine at Columbia University College of Physicians and Surgeons, Associate Dean for Clinical and Translational Research, and Director of the Irving Institute for Clinical and Translational Research at Columbia University Medical Center in New York, New York. He is the Principal Investigator of one of the first 12 National Institute of Health (“NIH”) funded Clinical Translational Science Awards. Dr. Ginsberg is also Principal Investigator on two R01 research grants from the NIH, National Heart, Lung, and Blood Institute. He is also the Co-Principal Investigator at Columbia on the ACCORD Trial. His research interests have focused on the regulation of plasma cholesterol and triglyceride blood levels, particularly the metabolism of apolipoprotein B-containing lipoproteins in cells, mice, and humans. He has authored or coauthored more than 200 articles, reviews, and chapters related to lipids, diabetes, and heart disease.

Renal Clinical Advisory Board

Our Renal Clinical Advisory Board (“RCAB”) was established for the future development of apabetalone into renal indications. The members of the RCAB are as follows:

Dr. Kamyar Kalantar-Zadeh (Chair) is Professor and Chief, Division of Nephrology and Hypertension at University of California, Irvine. Dr. Kalantar-Zadeh is the founder and director of the Harold Simmons Center for Kidney Disease Research and Epidemiology. Among his numerous appointments in the renal field, Dr. Kalantar-Zadeh is Associate Editor of several peer-reviewed journals including *Nephrology Dialysis Transplantation*, *American Journal of Kidney Diseases*, *Cardiorenal Medicine*, *Seminars in Dialysis*, *Sarcopenia and Muscle*, and a member of the editorial board of *Journal of Kidney International*, *Journal of American Society Nephrology*, *Nature Reviews Nephrology*, *American Journal of Nephrology*. Dr. Kalantar-Zadeh has authored 3 textbooks and over 500 peer-reviewed publications.

Dr. Carmine Zoccali is a specialist in Renal Diseases (Pisa University) and Hypertension. Dr. Zoccali's appointments include: Director, Division of Nephrology, Hypertension and Renal Transplantation, Ospedali Riuniti, Reggio Cal, Italy; Chief, CNR-IBIM Clinical Epidemiology and Pathophysiology of Renal Diseases and Hypertension; Professor, Postgraduate Schools of Nephrology, Palermo, Catania and Messina Universities. Dr. Zoccali's current editorial positions include: Editor in Chief, *Nephrology Dialysis and Transplantation*, Academic Editor, (Nephrology) *PlosOne*, and Editorial Board member, *Journal of the American Society of Nephrology*. Editorial Board member, *Clinical Journal of the American Society of Nephrology* and Editorial Board member, *Kidney International*. Dr. Zoccali has over 402 international peer-reviewed publications. Dr Zoccali was president (2017-2020) of the European Dialysis and Transplant Association and Renal Association (EDTA-ERA).

Dr. Marcello Tonelli is Associate Vice-President (Research) at the University of Calgary. Dr. Tonelli was the recipient of the 2013 United States National Kidney Foundation Medal for Distinguished Service and the Kidney Foundation of Canada's 2013 Medal for Research Excellence for changing nephrology practice in Canada and beyond. Along with the two other team co-leads, he received a Top Canadian Achievements in Health Research Award from the CIHR-CMAJ in 2013 for his work with the Interdisciplinary Chronic Disease Collaboration. He was elected a fellow of the Canadian Academy of Health Sciences in 2012 and a member of the American Society for Clinical Investigation in 2014. He has been named a "Highly Cited" researcher in 2015, 2016 and 2017 by Clarivate Analytics, representing a ranking in the top 1% by citations of all researchers worldwide for field and publication year.

Dr. Vincent Brandenburg is Nephrologist, Associate Professor and Senior Consultant at the Department of Cardiology, Intensive Care Medicine and Vascular Medicine, University Hospital of the RWTH Aachen, Germany. Dr. Brandenburg has been leader of the German Calciphylaxis registry since 2007. He is a board member of the ERA-EDTA scientific working group Chronic Kidney Disease – Mineral and Bone Disorder (“CKD-MBD”). Dr. Brandenburg has authored or co-authored over 140 articles in peer-reviewed journals. The primary focus of these articles has been chronic kidney disease – mineral and bone disorder, cardiorenal syndrome, and calciphylaxis. Dr. Brandenburg is also a member of the German and European Societies of Nephrology and the Societies of Cardiology.

Dr. Srinivasan Beddhu is a tenured Professor of Medicine at the University of Utah School of Medicine. He is Board Certified in Internal Medicine and Nephrology. Dr. Beddhu received his medical degree from Stanley Medical College, Chennai, India. His clinical and research interests include hypertension, CKD progression and complications and end-stage renal disease. Dr. Beddhu's research is funded primarily by NIH grants. He has served in several national committees including NIH panels, American Society of Nephrology

Research Committee and National Kidney Foundation clinical practice guidelines committee. Dr. Beddhu has published approximately 100 articles including peer-reviewed publications, editorials and book chapters.

Dr. Mathias Haarhaus is a Consultant Nephrologist at the Department of Nephrology, Karolinska University Hospital, Stockholm, Sweden, where he is Head of the Bone and Mineral Program. His research at the Division of Renal Medicine, Karolinska Institutet focuses primarily on the link between skeletal disorders and cardiovascular complications in CKD, with a special focus on ALP. He is an active member of the CKD-MBD working group of the ERA-EDTA and a member of the Guidelines Committee of the Swedish Society of Nephrology.

Neurodegenerative Clinical and Scientific Advisory Board

Our Neurodegenerative Clinical and Scientific Advisory Board provides insight and guidance on all aspects of the development program. Appointed members of the clinical and scientific advisory board are:

Dr. Bengt Winblad, MD, PhD, Chairman, is professor emeritus of geriatric medicine and former chief physician at the Karolinska University Hospital, Huddinge and the Karolinska Institute in Stockholm, Sweden. Professor Winblad is co-chair of the European Alzheimer Disease Consortium and chairs the Medical Scientific Advisory Panel of the Alzheimer Disease International and was closely involved in the development and registration of memantine (Axura, Ebixa, Namenda) and other Alzheimer's disease programs. In 2009, Dr. Winblad was ranked the world's most prolific researcher in the Alzheimer's disease field and he has published more than 1,200 peer-review papers.

Dr. Jeffrey Cummings, MD, ScD is Founding Director, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Nevada and Cleveland, Ohio. Dr. Cummings is Professor of Medicine (Neurology) at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and he is Principal Investigator/Director of the NIH/NIGMS-funded Center for Neurodegeneration and Translational Neuroscience. In 2008, Dr. Cummings received the Ronald and Nancy Reagan Research Award from the National Alzheimer's Association. Dr. Cummings has published more than 500 peer-review articles.

Dr. Henrik Zetterberg, MD, PhD is Professor of Neurochemistry at the University of Gothenburg, Sweden, and at University College London, UK, as well as the Head of the Department of Psychiatry and Neurochemistry at the Sahlgrenska Academy at the University of Gothenburg, Sweden. Dr. Zetterberg was a Fulbright Scholar and research fellow in neurology at the Harvard Institutes of Medicine, Boston between 2004 and 2005. He has published more than 1,000 peer-reviewed articles with focus on the central nervous system and Alzheimer's disease. Dr. Zetterberg provides expert knowledge on blood and cerebrospinal fluid biomarkers. Dr. Zetterberg is an established leader in the field of neurochemistry, biomarkers and diagnostics.

Radosveta P Koldamova, MD, PhD, is Professor, Environmental and Occupational Health at the School of Public Health, University of Pittsburgh's. The Koldamova and Lefterov laboratory is focused on translational neuroscience. Using animal models of Alzheimer's disease such as mice expressing human APOE3 or APOE4 isoforms Dr. Koldamova explores the role of genes associated with Late Onset Alzheimer's disease such as APOE, TREM2, ABCA7 and others.

Financing

Private Placements and Prospectus Offering

In March 2020, we issued 134,100 equity units at CAD\$1.30 per unit pursuant to a private placement for gross proceeds of CAD\$0.2 million (US\$0.1 million). Each equity unit consisted of one common share and one-half of a common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.75 per underlying common share for a period of one year from the closing of the private placement.

In March 2020, we also issued 724,638 equity units at CAD\$1.00 per unit pursuant to a private placement for gross proceeds of CAD\$0.7 million (US\$0.5 million). Each equity unit consisted of one common share and one-half of a common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.25 per underlying common share for a period of two years from the closing of the private placement.

In May 2020, we issued 490,410 equity units at CAD\$0.85 per unit pursuant to a private placement for gross proceeds of CAD\$0.4 million (US\$0.3 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of two years from the closing of the private placement. We also issued 87,222 shares at CAD\$0.72 per share pursuant to a private placement for gross proceeds of CAD\$0.1 million (US\$0.05 million).

In August 2020, we issued 3,573,333 equity units at CAD\$0.75 per unit pursuant to a private placement to Shenzhen Hepalink Pharmaceutical Co., Ltd. ("Hepalink") for gross proceeds of CAD\$2.7 million (US\$2.0 million). Each equity unit consisted of one common share and one-half common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of one year from the closing of the private placement.

In September 2020, we issued 982,000 equity units at CAD\$0.80 per unit pursuant to a private placement for gross proceeds of CAD\$0.8 million (US\$0.6 million). Each equity unit consisted of one common share and one-half common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of one year from the closing of the private placement. We also issued 134,000 shares at CAD\$1.00 per share for settlement of a CAD\$0.1 million debt (US\$0.1 million).

In November 2020, we issued 663,062 equity units at a price of CAD\$1.20 per unit for gross proceeds of CAD\$0.8 million (US\$0.6 million). Each equity unit consisted of one common share and one-half common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.35 per underlying common share for a period of one year from the closing of the private placement.

In January 2021, we issued 51,634 equity units at CAD\$1.00 per unit pursuant to a private placement for gross proceeds of CAD\$0.05 million (US\$0.04 million). Each equity unit consisted of one common share and one-half common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.15 per underlying common share for a period of one year from the closing of the private placement.

In February and March 2021, we issued 330,388 equity units at CAD\$0.94 per unit pursuant to a private placement for gross proceeds of CAD\$0.3 million (US\$0.2 million). Each equity unit consisted of one common share and one-half common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.15 per underlying common share for a period of one year from the closing of the private placement.

In April 2021, we issued 145,000 equity units at CAD\$1.00 per unit pursuant to a private placement for gross proceeds of CAD\$0.1 million (US\$0.1 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.15 per underlying common share for a period of one year from the closing of the private placement.

In April and May 2021, we issued a total of 5,048,587 equity units at CAD\$0.85 per unit pursuant to private placements for gross proceeds of CAD\$4.3 million (US\$3.5 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of three years from the closing of the private placements.

In December 2021, we issued 148,000 equity units at CAD\$0.85 per unit pursuant to a private placement for gross proceeds of CAD\$0.1 million (US\$0.1 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of three years from the closing of the private placement.

In March 2022, we issued 4,727,192 equity units at CAD\$0.48 per unit pursuant to a private placement for gross proceeds of \$1.8 million (CAD\$2.3 million). Each equity unit consists of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$0.50 per underlying common share for a period of either three or five years from the closing of the private placement.

In April 2022, we issued 400,000 equity units at CAD\$0.48 per unit pursuant to a private placement for gross proceeds of \$0.2 million (CAD\$0.2 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$0.50 per underlying common share for a period of three years from the closing of the private placement.

In June 2022, we issued 2,090,454 equity units (including 1,923,787 equity units issued to a relative of the Chief Executive Officer / Chairman of the Company) at CAD\$0.30 per unit pursuant to a private placement for gross proceeds of \$0.5 million (CAD\$0.6 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$0.30 per underlying common share for a period of three years from the closing of the private placement.

In August and September 2022, we issued 11,494,256 equity units (including 666,667 equity units issued to an officer of the Company to settle CAD\$0.2 million of promissory notes) at CAD\$0.24 per unit pursuant to a private placement for gross proceeds of \$2.1 million (CAD\$2.8 million). Each equity unit consisted of one common share and one common share purchase warrant. Each warrant is exercisable at a price of CAD\$0.30 per underlying common share for a period of five years from the closing of the private placement.

Vision Leader Limited Convertible Debenture

On September 26, 2019, we closed a US\$12.0 million secured convertible debenture with Vision Leader Limited (“Vision Leader”), a wholly-owned subsidiary of ORI Star Fund LP (“ORI”). The debenture bore interest at 10% per annum, and initially matured on September 26, 2020. In July 2020, the maturity date of the debenture, and the corresponding payment date of interest thereon, were both extended by one year from September 26, 2020 to September 26, 2021. In connection with the extension of the maturity date of the debenture, Vision Leader was issued an additional 600,000 warrants, exercisable until December 31, 2024 at a price of CAD\$0.74 per underlying common share. Prior to conversion, as described below, ORI was able to elect to convert the debenture into common shares of the Company at a conversion price equal to the lesser of CAD\$2.54 per share and the 5-day volume weighted average trading price of the common shares on the date of conversion. We granted Vision Leader a security interest in all of our assets, including our patents and other intellectual property, as security for our obligations under the debenture. In connection with the

debenture, ORI was entitled to nominate a director to the Company's Board of Directors for so long as any amount remained outstanding pursuant to the debenture; on December 19, 2019, a nominee of ORI was appointed to the Board of Directors and remains on the Board of Directors notwithstanding full repayment of the debenture.

On October 13, 2020, the full principal amount of the US\$12.0 million debenture and US\$1.2 million of accrued interest was converted into common shares; the conversion price was CAD\$1.08 per share. Accordingly, Vision Leader's security interest in the Company's assets was released and discharged. The carrying value of the debenture and the fair value of the derivative liability related to the conversion feature of the debenture were reclassified to equity on the date of conversion.

Hepalink Convertible Debenture

On May 13, 2021, we closed a US\$6.0 million secured convertible debenture (the "Debenture") with a subsidiary of Hepalink. The Debenture bears interest at 10% per annum and matures on May 13, 2024. During the year ended December 31, 2022, the maturity date of the Debenture, and the corresponding payment date of interest thereon, were both extended by one year from May 13, 2022 to May 13, 2023. Furthermore, subsequent to December 31, 2022, the Debenture was further amended to extend the maturity date to May 13, 2024, and to increase the interest rate to 12% per annum effective May 14, 2023. Hepalink may elect to convert the principal amount of the Debentures and accrued and unpaid interest thereon into common shares of the Company at a conversion price equal to the lesser of CAD\$0.93 per share and the 5-day volume weighted average trading price of the common shares on the date of conversion. The Company granted Hepalink a security interest in all of its assets, including its patents and other intellectual property, as security for its obligations under the Debenture. In addition, Hepalink received 300,000 common share purchase warrants exercisable for a period of four years from the grant date at a price of CAD\$0.93 per share.

Board of Directors Changes

Norma Biln resigned as a director of the Company effective June 21, 2022.

Licensing

Licensing Agreements

On July 8, 2015, we entered into a licensing agreement with Hepalink. Under the terms of the agreement, Hepalink has the exclusive rights to distribute and market apabetalone in China, Hong Kong, Taiwan and Macau (the "Territories"), for all indications.

The license between us and Hepalink provides for certain milestone payments based on net sales of RVX-208 in the Territories. The annual sales milestones range from 500 million renminbi ("RMB") to 10 billion RMB (US\$72 million to US\$1.4 billion, incorporating the period end spot exchange rate), with Resverlogix being eligible to receive sales-based milestone payments from Hepalink ranging from US\$5 million to US\$90 million. In addition, Hepalink shall pay a royalty of 6% of annual net sales of RVX-208 in the Territories. The royalty is subject to an adjustment mechanism that may reduce the royalty rate to a minimum of 4% in the event that certain annual sales milestones are achieved and applicable regulatory authorities in the Territories reduce the approved selling price of RVX-208. Hepalink will be responsible for all clinical and development costs in the Territories, including a patient population that is expected to be included in the Company's Phase 3 BETonMACE trial. We are contractually obligated to pay a fee to the financial advisor involved with the transaction equal to 3.5% on the first \$10.0 million of payments, if any, received from Hepalink pursuant to the license, and 2.5% on amounts above \$10.0 million, up to a maximum of \$1.0 million of fees. As at December 31, 2022, these potential payments do not satisfy the criteria for recognition as a liability.

The aforementioned license agreement between us and Hepalink was amended effective June 17, 2022 such that we agreed to pay up to CAD\$8.0 million of clinical development costs associated with apabetalone, including a global Phase 3 clinical trial (which we intend to perform in any event), in the Territories and if the costs incurred by Resverlogix after May 1, 2020 and up to December 31, 2023 total less than CAD\$8 million, then Resverlogix and Hepalink shall negotiate a mutually-agreeable timeframe regarding any difference, in principle by not later than June 30, 2024.

Under the terms of a licensing agreement between us and Medison Pharma Ltd., Medison has the exclusive rights to distribute and market apabetalone in Israel. Resverlogix is eligible to receive from Medison, ascending double digit royalties based on future net sales of the product in the licensed territory. Medison will be responsible for all regulatory, sales and marketing costs for apabetalone in the Israel licensed territory.

Services and Licensing Agreements with Zenith Capital Corp.

In 2013, we reorganized into two companies and spun off research and development activities related to the epigenetics platform technology with the potential to impact multiple diseases, including cancer and autoimmune diseases, to Zenith, a newly-formed company. We retained research and development activities related to the development of compounds for applications with indications involving a therapeutic increase in ApoA-I, including our CVD and DM clinical programs and our neurodegenerative diseases program. RVX Therapeutics Inc. ("RVX Therapeutics"), which was a wholly-owned subsidiary of Resverlogix prior to the reorganization, held all of the assets spun off and was acquired by Zenith as part of the reorganization.

Services Agreements

Pursuant to an Assignment and Services Agreement dated June 3, 2013 and effective May 1, 2012 between us and RVX Therapeutics, which was subsequently assumed by Zenith, we perform research and related administrative and support services requested by Zenith from time to time. The agreement was for an initial term of three (3) years and automatically renews for successive one (1) year periods unless a party provides the other party with written notice of non-renewal at least sixty (60) days prior to the expiration of the then-current term. During the year ended December 31, 2022, we did not perform any research for Zenith.

Pursuant to a Management Services Agreement dated June 3, 2013 between us and Zenith, we provide management and administrative services pertaining to Zenith as required. We receive a management fee from Zenith based on the cost of our personnel and the proportionate time worked on behalf of Zenith. We are also reimbursed for general and administrative costs. The purpose of the agreement is to enable each party to achieve greater utilization of their respective resources.

On January 1, 2015, we entered into a Services Agreement with Zenith whereby Zenith performs research services on our behalf on an ongoing basis. The purpose of the agreement is to enable us to obtain access to specialized research services on a more cost-effective basis than other alternatives.

Risk Factors

An investment in the Company should be considered highly speculative due to the nature of its activities and the stage of its development. Biotechnology research and development involves a significant degree of risk. The risks and uncertainties set forth below are not the only ones we will face. Additional risks and uncertainties not presently known to us or that we currently consider immaterial may also impair our business and operations and cause the price of the Common Shares to decline. If any of the following risks actually occur, our business may be harmed, and our financial condition and results of operations may suffer significantly. In that event, the value of the Common Shares could decline and purchasers of the Common Shares or securities convertible into Common Shares may lose all or part of their investment. Readers should carefully consider the following risk factors in addition to the other information contained herein before investing in the Company.

Risks Relating to Our Business

We have a history of net losses and negative cash flow. We expect to continue to incur substantial net losses for the foreseeable future, and we may never achieve or maintain positive cash flow.

To date, we have not recorded any revenues from the sale of biopharmaceutical products and have incurred significant negative cash flows in many periods since our inception. As at December 31, 2022, we had a deficit of US\$445.7 million. We expect to incur substantial net losses and negative cash flow for the foreseeable future. Such losses and negative cash flow have had, and will continue to have, an adverse effect on our shareholders' equity and working capital.

The process of developing and commercializing our products requires significant preclinical testing and clinical trials as well as regulatory approvals for commercialization and marketing before we could begin product sales. In addition, commercialization of our products would require us to establish a sales and marketing organization or contractual relationships to enable product manufacturing and other related activities. Because of the numerous risks and uncertainties associated with pharmaceutical product development and commercialization, we are unable to accurately predict the timing or amount of future expenses or when, or if, we will be able to achieve or maintain positive cash flow. Currently, we have no products approved for commercial sale, and to date we have not generated any product revenue. We have financed our operations primarily through the sale of equity securities and advances pursuant to credit facilities. The size of our future negative cash flow will depend, in part, on the rate of growth or contraction of our expenses and the level and rate of growth, if any, of our revenues. We expect to report net losses and negative cash flow unless and until such time as payments, if any, from corporate collaborations, product sales and/or royalty payments generate sufficient revenues to fund our continuing operations. Quarter to quarter fluctuations in revenues, expenses, net losses, and cash flow are also expected. Even if we do achieve profitability, we may not be able to sustain positive cash flow on an ongoing basis.

We will need to raise additional capital in the future to fund our operations. If we cannot raise additional capital, we will have to delay, reduce, or cease operations.

We will need to raise additional capital to fund our operations and to develop our products. We expect to raise additional funds through equity or debt financing and/or from other sources. Our future capital requirements will be substantial and will depend on many factors, such as the following:

- the scope, rate of progress, results, and costs of any clinical and nonclinical programs;
- timing, costs, and outcomes of regulatory proceedings;
- the cost and timing of developing sales and marketing operations or partnerships;
- payments received under any future partnerships;

- prosecution or defense of patent claims;
- the cost and timing of developing manufacturing capacity;
- costs associated with commercialization of our products; and
- competing technological and market developments, including the introduction by others of new therapies in our market.

Our cash as at December 31, 2022 is not sufficient to fund our contractual commitments or our planned business operations over the next year. We will have to raise additional capital. If we are not able to raise sufficient capital to fund our operations, we may be forced to cease operations. These conditions result in a material uncertainty which casts significant doubt on our ability to continue as a going concern.

The Company has not complied fully with the payment terms associated with certain amounts owing to certain vendors. Until the Company fully satisfies its obligations, it is possible that the vendors could assert that the Company is in default and could pursue any remedies available to them.

We will also require additional capital to fund research, development, and corporate activities beyond the next year. We will continue to explore alternatives to generate additional cash including raising additional equity and product licensing; however, there is no assurance that these initiatives will be successful. We intend to raise capital from equity and/or debt offering and/or partnering in the future.

Further, changing circumstances may cause us to consume capital significantly faster or slower than we currently anticipate. We have based these estimates on assumptions that may prove to be wrong, and we could utilize our available financial resources sooner than we currently expect.

There can be no guarantee that we will be able to access capital markets in the future to fund our ongoing operations. If we cannot access capital markets in the future, we may be forced to cease operations. Any financing transaction may contain unfavourable terms. If we raise additional funds by issuing equity securities, our stockholders' equity will be diluted. If we raise additional funds through strategic partnerships, we may be required to relinquish rights to our products, or to grant licenses on terms that are not favourable to us.

There is no certainty that insiders will make further investments in the Company.

In recent years, we have often raised additional capital to fund repayment of indebtedness and operating activities through private placements of equity and debt securities to insiders of the Company. However, there is no certainty that insiders will continue to make further investments in the Company or that any further investments will be sufficient to fund the Company's existing obligations or ongoing research and development activities. In addition, there are restrictions relating to the amount that insiders may invest in the Company pursuant to stock exchange policies and applicable securities laws, without the Company obtaining the prior approval of shareholders. There is no certainty that all necessary approvals could be obtained to enable insiders to make further investments in the Company or that the Company will be able to obtain such approvals in a timely manner.

We are a development stage company. If we do not develop commercially successful products, we may be forced to cease operations.

We are a development stage company, which may require significant additional investment for research and development, manufacturing, clinical testing, and regulatory submissions prior to commercialization. Investors must evaluate our business considering the uncertainties and complexities affecting a development stage biotechnology company and there can be no assurance that any such product will eventually be developed. Any product would be unsuccessful if it:

- does not demonstrate acceptable safety and efficacy in preclinical studies and clinical trials or otherwise does not meet applicable regulatory standards for approval;
- does not offer therapeutic or other improvements over existing drugs used to treat the same or similar conditions;
- is not capable of being produced in commercial quantities at an acceptable cost, or at all; or
- is not accepted by patients, the medical community or third-party payors.

A commitment of substantial time and resources is required to conduct research and clinical trials if we are to complete the development of any product. We have not proven our ability to develop and commercialize products. It is not known whether any of these products will meet applicable health regulatory standards and obtain required regulatory approvals, or (i) whether such products can be produced in commercial quantities at reasonable costs and be successfully marketed, (ii) whether our products will achieve market acceptance, or (iii) if our investment in any such products will be recovered through sales or royalties. Problems frequently encountered in connection with the development and utilization of new and unproven technologies and the competitive environment in which we operate might limit our ability to develop commercially successful products.

Results of early research and development may not be indicative of the results that will be obtained in later stages of research and development. If regulatory authorities do not approve the products or if regulatory compliance is not maintained, we would have limited ability to commercialize our products, and our business and results of operations would be harmed. We may fail to develop any products, to obtain regulatory approvals, to enter clinical trials, or to commercialize any products. If we are unable to make our product candidates commercially available, we will not generate product revenues, and we may be forced to cease operations.

We have been advanced funds under a secured convertible debenture and failure to pay all amounts when they become due could result in a loss of all of our assets.

In May 2021, we obtained a US\$6 million Debenture from Hepalink. The Debenture bears interest at a rate of 10% per annum. During the year ended December 31, 2022, the maturity date of the Debenture, and the corresponding payment date of interest thereon, were both extended by one year from May 13, 2022 to May 13, 2023. Furthermore, subsequent to December 31, 2022, the Debenture was further amended to extend the maturity date to May 13, 2024, and to increase the interest rate to 12% per annum effective May 14, 2023. The loan is secured by all of our assets.

We do not currently have sufficient cash available to repay the principal amount of the Debenture when it becomes due. Unless the Debenture is converted in full into equity or the maturity date is extended, we will have to raise additional capital to repay the Debenture on the maturity date of May 13, 2024.

If an event of default under the Debenture occurs, the lender could elect to declare all principal amounts outstanding under the loan at such time, together with accrued interest and applicable fees, to be immediately due and payable. If we are unable to repay amounts owing under the loan, the lender could proceed to foreclose or otherwise realize upon all of our assets, including our intellectual property, that is security for the indebtedness.

Unstable market conditions may have serious adverse consequences on our business.

The economic downturn and market instability made the business climate more volatile and more costly. Our business strategy may be adversely affected by unpredictable and unstable market conditions. If the current equity and credit markets deteriorate it may make any necessary equity or debt financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favourable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. There is a risk that one or more of our current or future strategic partners may encounter difficulties during challenging economic times, which would directly affect our ability to attain our operating goals on schedule and on budget.

If our clinical trials fail to establish the safety and efficacy of our products, including apabetalone, we will not be able to commercialize our products.

Drug discovery and development has inherent risk, and the historical failure rate is high. Failures in the HDL cholesterol market by some pharmaceutical companies have highlighted the risk of these types of therapies.

To obtain regulatory approval to market and sell any of our products, we must satisfy the FDA, the TPD, and other regulatory authorities, through extensive clinical trials and preclinical studies, that our products are safe and efficacious. The BETonMACE trial did not meet its primary endpoint and if we cannot demonstrate that our drugs, including apabetalone, are safe and effective for human use, we may need to abandon one or more of our drug development programs.

We may not have conducted or may not conduct in the future the types of testing ultimately required by regulatory authorities, or future tests may indicate that our products are not safe for use in humans. Preclinical testing and clinical trials are expensive, can take many years and have an uncertain outcome. In addition, success in initial preclinical testing does not ensure that later preclinical testing or clinical trials will be successful. There are a number of factors that could cause a clinical trial to fail or be delayed including:

- the clinical trials may produce negative or inconclusive results, which may require us to conduct additional preclinical testing or to abandon product candidates that we believed to be promising;
- the regulators may require that we hold, suspend, or terminate clinical research for noncompliance with regulatory requirements;
- we, our potential partners, the FDA, the TPD or foreign regulatory authorities could suspend or terminate a clinical trial due to adverse side effect of a drug on subjects or patients in the trial;
- we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials;
- enrollment in our clinical trials may be slower than anticipated;
- the cost of our clinical trials may be greater than anticipated;
- our product candidates may have unfavourable pharmacology, toxicology, or carcinogenicity;
- our product candidates may cause undesirable side effects; and

- the supply or quality of our drugs or other materials necessary to conduct clinical trials may be insufficient, inadequate, or delayed.

If any of our product candidates in clinical studies, including apabetalone, do not show sufficient efficacy in patients with the targeted indication, it could negatively impact our development and commercialization or goals for this and other product candidates and, as a result, materially adversely affect our business, financial condition, and results of operations.

We may be required to conduct additional clinical trials to address concerns that the use of our leading product, apabetalone, might increase the risk of liver injury. This may materially adversely affect our business, financial condition, and results of operations.

In our 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 fewer occurrences between weeks ten and thirteen. In our subsequent Phase 2b clinical trials, SUSTAIN and ASSURE, increases in ALTs were observed in a small group of patients. Those who had ALT elevations of 3X ULN all dosed through the trial which potentially illustrated adaptability to the drug. Those who had elevation greater than 5XULN, 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. We 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. With these learnings, we believe 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 us 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. Adverse results in these trials could delay or prevent commercialization of apabetalone or could jeopardize existing development in other indications.

If our testing assumptions are incorrect our products may not be approved for marketing.

The design of our clinical trials is based on many assumptions about the expected effect of our product candidates. If those assumptions prove incorrect, the clinical trials may not produce statistically significant results. We cannot assure you that the design of, or data collected from, the clinical trials of our product candidates will be sufficient to support the FDA and foreign regulatory approvals.

We are dependent on third parties to conduct our clinical trials and to provide services for certain important aspects of our business. If these third parties do not perform as contractually required or expected, we may not be able to obtain regulatory approval for our products, or we may be delayed in doing so.

We rely on third parties, such as contract research organizations, medical institutions, academic institutions, independent clinical investigators, and contract laboratories, to conduct our clinical trials and preclinical studies, and we expect to continue to do so in the future. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. As a result, many important aspects of our product development are outside our direct control. We are responsible for confirming that our preclinical studies are conducted in accordance with applicable regulations and that each of our clinical trials is conducted in accordance with its general investigational plan and protocol. The FDA requires us to comply with regulations and standards, commonly referred to as good laboratory practices, or GLP, for conducting and recording the results of our preclinical studies and good clinical practices for conducting, monitoring, recording, and reporting the results of clinical trials, to assure that data and reported results are accurate and that the clinical trial participants are adequately protected. Our reliance on third parties does not relieve us of these responsibilities. If the third parties conducting our clinical trials do not perform their contractual duties or obligations, do not meet expected recruitment or other deadlines, fail to comply with the FDA's good clinical practice regulations, do not adhere to our clinical trial protocols or otherwise fail to generate reliable clinical data, development, approval and commercialization of our products, including apabetalone, may be extended, delayed or terminated or may need to be repeated, and we may not be able to obtain regulatory approval.

We do not currently own or operate manufacturing facilities for clinical or commercial production of the active pharmaceutical ingredient, or API, used in apabetalone. As a result, we rely on third parties to supply the API. We expect to continue to depend on third parties to supply the API for our lead product candidate and any additional product candidates we develop in the foreseeable future. An API manufacturer must meet high precision and quality standards for that API to meet regulatory specifications and comply with regulatory requirements. A contract manufacturer's failure to comply with applicable regulations and requirements could result in refusal to approve or a delay in approval of apabetalone or other product candidates. We are ultimately responsible for confirming that the APIs used in our product candidates are manufactured in accordance with applicable regulations. Furthermore, if our third-party drug suppliers fail to achieve and maintain high manufacturing standards in compliance with applicable regulations, we could be subject to certain product liability claims in the event such failure to comply resulted in defective products that caused injury or harm.

Natural disasters, public health crises, political crises, and other catastrophic events or other events outside of our control may damage the facilities or disrupt the operations of our strategic partners, third-party manufacturers, suppliers or other third parties upon which we rely, and could delay or impair our ability to initiate or complete our clinical trials or commercialize approved products.

Our strategic partners, third-party manufacturers, suppliers and other third parties upon which we rely have operations around the world and are exposed to a number of global and regional risks outside of our control. These include, but are not limited to: natural disasters, such as earthquakes, tsunamis, power shortages or outages, floods, or monsoons; public health crises, such as pandemics and epidemics; political crises, such as terrorism, war, political instability or other conflict; or other events outside of our control.

We cannot presently predict the scope and severity of any potential business shutdowns or disruptions, but if we or any of the third parties with whom we engage, including the suppliers, regulators and other third parties with whom we conduct business, were to experience shutdowns or other business disruptions, our ability to conduct our business in the manner and on the timelines presently planned could be materially and negatively impacted.

We rely on partnerships and strategic relationships for our success. The failure to successfully collaborate with third parties may delay, prevent, or otherwise impair the development or commercialization of our products or revenue expectations.

In June 2021, we entered into a partnership with EVERSANA. EVERSANA supported the planned commercialization of apabetalone for the treatment of COVID-19 in the United States, Canada and any other countries agreed upon in the future as Emergency Use Authorization and/or a New Drug Application or equivalent if issued or approved in said countries. In the April 2022 Amendment, the Company and EVERSANA expanded its partnership to include cardiovascular and pulmonary arterial hypertension indications. EVERSANA provides fully integrated commercialization services including market access, agency services, clinical and commercial field teams, medical science liaisons, channel management, patient services, health economics and outcomes research, and compliance. The partnership may be expanded to include additional global markets, should additional approvals be issued. There can be no assurance that commercialization of apabetalone for the treatment of any indication will be successful. The Company and EVERSANA have mutually agreed to temporarily pause services until additional capital is raised.

As a result of the costs associated with commercializing a product candidate, we seek strategic partnerships with corporate and academic collaborators, licensors, licensees and others for the research, development, clinical testing, manufacturing, marketing, and commercialization of our products, and we intend to attract corporate partners and enter into additional research collaborations. Our goal is to partner apabetalone so that it may be developed for clinical conditions. There can be no assurance, however, that such collaborations will be established, that such collaborations will be established on favourable terms, if at all, or that future collaborations will be successful. In particular, failures in HDL cholesterol therapies may negatively impact our potential partners' willingness to enter into partnering agreements due to the potential risks in the cholesterol market and the high clinical costs to bring such drugs to market. Failure to attract commercial partners for our products may result in our incurring substantial clinical testing, manufacturing, and commercialization costs prior to realizing any revenue from product sales or result in delays or program discontinuance if funds are not available in sufficient quantities, and this may materially adversely affect our business, financial condition, and results of operations.

Should a collaborative partner fail to develop, manufacture, or successfully commercialize any product to which it has rights, or any partner's product to which we have rights, the business may be adversely affected. Failure of a collaborative partner to continue to participate in any particular program could delay or halt the development or commercialization of products generated from such program. In addition, there can be no assurance that the collaborative partners will not pursue other technologies or develop alternative products either alone or in collaboration with others, including our competitors, as a means for developing treatments for the diseases targeted by our programs.

Furthermore, we may hold licenses for certain technologies and there can be no assurance that these licenses will not be terminated, or that they will be renewed on conditions acceptable to us. We may negotiate additional licenses in respect of technologies developed by other companies and academic institutions. Terms of license agreements to be negotiated may include, inter alia, a requirement to make milestone payments, which may be substantial. We may also be obligated to make royalty payments on the sales, if any, of products resulting from licensed technology and, in some instances, are responsible for the costs of filing and prosecuting patent applications.

We face significant competition in seeking appropriate strategic partners, and these strategic partnerships can be intricate, and time consuming to negotiate and document. We may not be able to negotiate additional strategic partnerships on acceptable terms, or at all. We are unable to predict when or if we will enter into any additional strategic partnerships because of the numerous risks and uncertainties associated with establishing strategic partnerships. If we are unable to negotiate additional strategic partnerships for our products, we may be forced to delay or terminate development or commercialization of one or more of our products. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us.

If we enter into partnerships or other strategic relationships, we may lose important rights to and control over the development of our products.

As a result of the costs and risks associated with commercializing a product candidate, we will seek strategic partnerships in order to continue to develop and, if approved, market our products. Such strategic partnerships may require us to relinquish control over the timing and manner of clinical trials and commercialization of our product candidates. Strategic partners may experience financial difficulties or choose to terminate the arrangement or independently work on a competing product resulting in the delay or discontinuation of development or commercialization of our product candidates. Furthermore, disputes may arise between us and our strategic partners that result in the delay or termination of the research, development, or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management's attention and consumes resources. Strategic partners may not properly maintain or defend our intellectual property rights or may use our proprietary information in a manner that could jeopardize or invalidate our proprietary information or expose us to potential litigation.

We may not receive the full payment of all milestone or royalty payments pursuant to partnerships or strategic relationships.

We may enter into license agreements and other forms of agreements with third parties regarding the development and commercialization of our product candidates. These agreements generally require that the third party pays us certain amounts upon the attainment of various milestones and possibly include royalties on the sale of the developed product. There can be no guarantee that we will receive the payments described in those agreements since the development of the products may be cancelled if clinical trials do not yield positive results. Under such circumstances, we would not receive royalties as well. Even if the development of a product yields positive results, all of the risks described herein with respect to the obtaining of regulatory approval and market acceptance of the product are applicable. Finally, if there occurs a disagreement between us and the third party, the payment relating to the attainment of milestones or of royalties may be delayed. The occurrence of any of these circumstances could have a material adverse effect on our financial condition and operating results.

If our products fail to achieve market acceptance for any reason, such failure may materially adversely affect our business, financial condition, and results of operations.

There can be no assurance that any of our product candidates, if approved for marketing, will achieve market acceptance. If our product candidates, once approved, do not receive market acceptance for any reason, it will adversely affect our business, financial condition, and results of operations. The degree of market acceptance of any products we develop will depend on a number of factors, including:

- the clinical efficacy and safety of our product candidates;
- our product candidates' potential advantages over existing and future treatment methods;
- the price of our products; and
- reimbursement policies of government and third-party payers, including hospitals and insurance companies.

If after we obtain regulatory approval to sell our products, physicians, and healthcare payors fail to adopt our products or conclude that our products are not safe and effective, physicians could choose not to use them to treat patients. Our competitors may also develop new technologies or products which are more effective or less costly, or that seem more cost-effective than our products.

In addition, regulations affecting the pricing of pharmaceutical products may change in ways adverse to us. While we cannot predict the likelihood of any regulatory proposals, if a government agency were to adopt proposals limiting market or third-party payor pricing for pharmaceutical products, it could materially adversely affect our business, financial condition, and results of operations.

We cannot be certain that we will ever obtain regulatory approvals in European countries, the United States, Canada, China, or any other jurisdictions. The failure to obtain such approvals may materially adversely affect our business, financial condition, and results of operations.

Biotechnology, medical device, and pharmaceutical companies operate in a high-risk regulatory environment. The study, manufacture and sale of products are governed by countries' numerous statutes and regulations. We are required to obtain various regulatory approvals prior to being able to study, commercialize and distribute our product candidates. The regulatory review and approval process required to perform a clinical study in any country includes evaluation of preclinical studies and clinical studies, as well as the evaluation of our manufacturing process. This process is complex, lengthy, expensive, resource intensive and uncertain. Securing regulatory approval to market our products also requires the submission of extensive preclinical and clinical data, manufacturing information regarding the process and facility, scientific data characterizing our product and other supporting data to the regulatory authorities in order to establish its safety and effectiveness. We, or our collaborators, may fail to obtain the necessary approvals to commence or continue preclinical or clinical testing of our product candidates, including apabetalone, or to manufacture or market our products in reasonable time frames, if at all.

Governmental authorities in any country may enact regulatory reforms or restrictions on the development of new therapies that could adversely affect our ability to develop our products. Many of the products and processes that are being currently developed by us

require significant development, testing and the investment of significant funds prior to their commercialization. There can be no assurance that apabetalone or any other drugs we attempt to develop will actually be developed to a commercial level. Completing clinical testing through late-stage trials and obtaining required approvals is expected to take several years and to require the expenditure of substantial resources. There can be no assurance that clinical trials will be completed successfully within any specified period of time, if at all. Furthermore, clinical trials may be delayed or suspended at any time by us or by the FDA, the TPD or foreign regulatory authorities if it is determined that the subjects or patients are being exposed to unacceptable risks. We may encounter delays or rejections based on varying regulatory interpretations or changes in regulatory agency policies, during the period in which we develop a product.

No assurance can be given that apabetalone or any other product candidate will prove to be safe and effective in clinical trials or that we will receive the requisite regulatory approval. Moreover, any regulatory approval of a drug which is eventually obtained may be granted with specific limitations on the indicated uses for which that drug may be marketed or may be withdrawn if complications occur following initial marketing or if compliance with regulatory standards is not maintained. We have limited experience in filing and pursuing applications necessary to gain these regulatory approvals.

The approval procedures vary among countries and can involve additional product testing and administrative review periods. The time required to obtain approval in various countries vary from one another. Approval in one country does not ensure approval by the regulatory authorities of other countries. The failure to obtain such approvals may materially adversely affect our business, financial condition, and results of operations.

Regulatory authorities may not approve our products even if they meet safety and efficacy endpoints in clinical trials.

The FDA, the TPD and other foreign regulatory agencies can delay, limit, or deny marketing approval for many reasons, including finding a product may not be considered safe and effective; the manufacturing processes or facilities may not meet applicable requirements; or changes in approval policies or regulations. Our product candidates may not be approved even if they achieve their endpoints in clinical trials. Regulatory agencies, including the FDA, or their advisors may disagree with our trial design and our interpretations of data from preclinical studies and clinical trials. Regulatory agencies may change requirements for approval even after a clinical trial design has been approved. Regulatory agencies also may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates.

Our products will remain subject to ongoing regulatory review even if they receive marketing approval. If we fail to comply with continuing regulations, we could lose these approvals, and the sale of any future products could be suspended.

In the event we receive regulatory approval to market a particular product candidate, United States, Canadian or other foreign regulatory authority could condition approval on conducting additional costly post-approval studies or could limit the scope of approved uses. In addition, the product may later cause adverse effects that limit or prevent its widespread use, force us to withdraw it from the market or prevent or delay our ability to obtain regulatory approvals in additional countries. In addition, we will continue to be subject to regulatory review and periodic inspections to ensure adherence to applicable regulations. After receiving marketing approval, the FDA imposes extensive regulatory requirements on the manufacturing, labeling, packaging, adverse event reporting, storage, advertising, promotion, and record keeping related to the product. Failure to comply with the regulatory requirements could result in:

- civil or criminal penalties or fines;
- injunctions;
- product seizures, detentions or import bans;
- voluntary or mandatory product recalls and publicity requirements;
- suspension or withdrawal of regulatory approvals; and
- refusal to approve pending applications for marketing approval of new drugs or supplements to approved applications.

We may be subject to product liability claims if our products harm people, and we do not have product liability insurance.

The manufacture and sale of pharmaceutical products involve an inherent risk of product liability claims and associated adverse publicity. We have entered into human clinical trials that involve inherent risks in the testing of unproven products. We currently have only clinical trial liability insurance for our products; we do not have product liability insurance. We do not know if we will be able to maintain existing or obtain additional clinical trial liability insurance or obtain product liability insurance on acceptable terms or with adequate coverage against potential liabilities. This type of insurance is expensive and may not be available on acceptable terms. If we are unable to obtain or maintain sufficient insurance coverage on reasonable terms or to otherwise protect against potential clinical trial and product liability claims, we may be unable to commercialize our products. A successful clinical trial liability or product liability claim brought against us in excess of our insurance coverage, if any, may require us to pay substantial amounts. This could have a material adverse effect on our business, financial condition, and results of operations.

The pharmaceutical industry is extremely competitive. If our competitors develop and market products that are more effective, safer, or less costly than any future products that we may develop, our commercial opportunity will be reduced or eliminated.

The technological competition we face from new and established pharmaceutical companies, biopharmaceutical companies and universities is intense and is expected to increase, in particular in the market for therapeutic products to treat, mitigate or prevent cardiovascular disease. Competitors may develop products more quickly and obtain regulatory approval for such products more rapidly or develop products which are more effective than those which we intend to develop. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects or are less expensive than any future products that we may develop and commercialize. In addition, significant delays in the development of our product candidates could allow our competitors to bring products to market before us and impair our ability to commercialize our product candidates. Research and development by others may render our technology or products obsolete or noncompetitive or produce treatments or cures superior to any therapy developed or to be developed by us.

We anticipate that, if approved for the reduction of MACE in cardiovascular / atherosclerotic disease, apabetalone would be positioned to be used in conjunction with leading standard of care statin treatments such as Lipitor and Crestor to further reduce major adverse cardiac events such as myocardial infarction, stroke and death and potentially compete with other therapeutic programs in development, such as, the LDL reduction programs (“PCSK9”), sodium-glucose cotransporter-2 inhibitor (“SGLT2”) programs, dipeptidyl peptidase inhibitor (“DPP-4”) programs, peptide programs, ApoA-I infusion treatments, delipidated HDL programs and cholesteryl transfer protein (“CETP”) inhibitors.

We anticipate that, if apabetalone is approved for reduction of CVD risk and MACE and it improves other biomarkers such as eGFR, Albumin and ALP, apabetalone would potentially compete with, or be added to, novel and existing CKD products in clinical development.

We anticipate that, if approved for neurodegenerative disorders, apabetalone would potentially be used in conjunction with standard of care therapies such as Aricept to improve therapeutic outcomes and/or compete with other agents and novel approaches to this disease such as small molecules, Namenda and PBT2, and monoclonal antibody technologies (“MOABs”) such as Bapineuzumab.

We anticipate that, if approved for reduction of CVD risk and MACE in diabetes mellitus patients, apabetalone would potentially be a complimentary agent added to standard of care diabetes mellitus agents in clinical development.

We anticipate that, if approved for the treatment of COVID-19, apabetalone would be used alongside current standard of care therapies to potentially reduce the severity and duration of the disease, shorten related hospitalizations, and limit the need for more serious interventions, such as mechanical ventilation.

Many of our competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Established pharmaceutical companies may invest heavily to discover quickly and develop novel compounds or drug delivery technology that could make our product candidates obsolete. Smaller or early-stage companies may also prove to be significant competitors, particularly through strategic partnerships with large and established companies. In addition, these third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies and technology licenses complementary to our programs or advantageous to our business. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval or discovering, developing and commercializing products before we do. If we are not able to compete effectively against our current and future competitors, our business will not grow, and our financial condition will suffer.

We are dependent upon retaining and attracting key personnel and others, the loss of which could materially adversely affect our business, financial condition, and results of operations.

We depend on certain members of our management and scientific staff, the loss of whose services might significantly delay or prevent the achievement of research, development or business objectives and would materially adversely affect our business, financial condition, and results of operations. We do not have employment agreements with any of our senior management that would prevent them from leaving us. In addition, our success depends, in large part, on our ability to improve our management systems and attract and retain qualified management, scientific and medical personnel, and on our ability to develop and maintain important relationships with commercial partners, leading research institutions and key distributors. We face intense competition for such personnel and relationships. We cannot assure that we will attract and retain such persons or maintain such relationships. In addition, failure to succeed in clinical trials may make it more challenging for us to recruit and retain qualified scientific personnel.

We may not be able to attract, train and retain a sufficient number of qualified employees to maintain and grow our business.

We expect that our potential expansion into areas and activities requiring additional expertise, such as further clinical trials, governmental approvals, manufacturing, sales, marketing, and distribution will place additional requirements on our management, operational and financial resources. We expect these demands will require an increase in management and scientific personnel and

the development of additional expertise by existing management personnel. There is currently aggressive competition for employees who have experience in technology and engineering. The failure to attract and retain such personnel or to develop such expertise could materially adversely affect our business, financial condition, and results of operations.

Confidentiality agreements with employees and others may not adequately prevent disclosure of trade secrets and other proprietary information. Disclosure of this information may materially adversely affect our business, financial condition, and results of operations.

We rely on trade secrets, which we seek to protect, in part, through confidentiality and non-disclosure agreements with our employees, collaborators, suppliers, and other parties. There can be no assurance that these agreements will not be breached, that we would have adequate remedies for any such breach or that our trade secrets will not otherwise become known to or independently developed by our competitors. We might be involved from time to time in litigation to determine the enforceability, scope, and validity of our proprietary rights. Any such litigation could result in substantial cost and divert management's attention from our operations.

We may need to implement additional finance and accounting systems, procedures and controls in the future as we grow and to satisfy new reporting requirements.

As we grow, we may access capital markets more broadly which could require us to implement additional finance and accounting systems along with enhanced internal control systems. This will result in increased costs to us as we continue to undertake efforts to comply with best practices and applicable rules and requirements applicable to public companies. These rules may make it more difficult and costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage as compared to the policies previously available to public companies. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors or our board committees or as executive officers. In addition, we may need to hire additional legal and accounting staff with appropriate experience and technical knowledge, and we cannot assure that if additional staffing is necessary that we will be able to do so in a timely fashion.

Our products may not be eligible for reimbursement from government or private third-party payors, or may be eligible for reimbursement at lower prices than we currently anticipate, which could materially adversely affect our business, financial condition, and results of operations.

Our ability to successfully market therapeutic products depends in part on the extent to which reimbursement for the cost of such products and related treatments will be available from government health administration authorities, private health insurers and other healthcare organizations. Significant uncertainty exists as to whether newly approved pharmaceutical products will qualify for reimbursement from these organizations. Furthermore, challenges to the price of medical products continue to grow in frequency due to increased focus on cost containment and pharmacoeconomic issues. These recent changes will become more pronounced as leading therapeutics in the atherosclerosis market such as statins continue to come off patent. Health authorities will continue to increase their scrutiny and pharmacoeconomic diligence on new products in all disease areas including those for the cardiovascular market. These rapid changes in the healthcare reimbursement marketplace will potentially have a significant impact on the future marketability of new drugs in development and could materially adversely affect our business, financial condition, and results of operations. It is expected that new drug entrants will not only have to be effective and safe but also have to provide a clear value proposal to health systems, such as risk reduction in MACE, over the current standard of care therapy, statin therapy.

In light of these market changes in drug development, pricing of drug therapies has come under significant pressure with government authorities and private health insurers around the world. The top current leading reimbursed markets; USA, Japan, Germany, UK, France, Spain, Italy, and Canada have implemented healthcare reforms that focus specifically on value and reimbursement. Reforms such as reference-based pricing, pharmacoeconomics, and numbers needed to treat are a few of the many instruments that healthcare organizations utilize to ensure maximum value for reimbursed therapeutics. Healthcare reform is underway in these top global markets and there is additional uncertainty about the viability of current pricing methodologies for reimbursement. There can be no assurance that adequate third-party coverage will be available to establish price levels which would allow us to realize an acceptable return on our investment in product development. If we cannot realize an acceptable return on our investment in product development, we may need to delay or cease our product development.

It may be difficult or impossible for U.S. investors to enforce judgments against us, our directors, or our officers in Canada.

We were formed under the laws of the Province of Alberta. Some of the members of our board of directors and our officers are residents of countries other than the United States. As a result, it may be impossible for U.S. investors to affect service of process within the United States upon us or these persons or to enforce against us or these persons any judgments in civil and commercial matters, including judgments under U.S. federal or state securities laws. In addition, a Canadian court may not permit U.S. investors to bring an original action in Canada or to enforce in Canada a judgment of a state or federal court in the United States.

Risks Relating to our Intellectual Property

We may not accurately predict the protection afforded by our patents and proprietary technology and if our predictions are wrong, this may materially adversely affect our business, financial condition, and results of operations.

Our success will depend in part on our ability to obtain, maintain, and enforce patent rights, maintain trade secret protection, and operate without infringing the proprietary rights of third parties, both domestically and internationally.

Our patent positions are highly uncertain, and any future patents we receive for our potential products will be subject to this uncertainty, which may adversely affect our business, financial condition, and results of operations. There can be no assurance that pending patent applications will be allowed and that we will develop additional proprietary products that are patentable, that issued patents will provide any competitive advantage or will not be challenged by any third parties, or that patents of others will not have an adverse effect on the ability to do business. Furthermore, there can be no assurance that others will not independently develop similar products, duplicate any of the products, or design around the products patented by us. In addition, we may be required to obtain licenses under patents or other proprietary rights of third parties. No assurance can be given that any licenses required under such patents or proprietary rights will be available on terms acceptable to us. If such licenses are not obtained, we could encounter delays in introducing one or more of our products to the market, while we attempt to design around such patents, or could find that the development, manufacturing, or sale of products requiring such licenses could be foreclosed. In addition, we could incur substantial costs in defending suits brought against us on such patents or in suits in which we attempt to enforce our own patents against other parties. Such disputes could involve arbitration, litigation or proceedings declared by the U.S. Patent and Trademark Office or International Trade Commission or other foreign patent authorities. Intellectual property litigation can be extremely expensive, and this expense, as well as other consequences should we not prevail, could seriously harm our business. With respect to any infringement claim asserted by a third party, we can give no assurances that we will be successful in the litigation or that such litigation would not have a material adverse effect on our business, financial condition, and results of operation.

Until such time, if ever, that patent applications are filed and/or approved, our ability to maintain the confidentiality of the described technology may be crucial to our ultimate possible commercial success. While procedures have been adopted to protect the confidentiality of our technology through signed invention and service agreements, no assurance can be given that such arrangements will be effective, that third parties will not gain access to trade secrets or disclose the technology, or that we can meaningfully protect our rights to our trade secrets.

Even if valid and enforceable patents cover our products and technologies, such patents will provide protection only for a limited amount of time.

Even if patents are issued regarding our product candidates or methods of using them, those patents can be challenged by our competitors who can argue that our patents are invalid and/or unenforceable. Third parties may challenge our rights to, or the scope or validity of, our patents. Patents also may not protect our products if competitors devise ways of making these or similar product candidates without legally infringing our patents. The Federal Food, Drug and Cosmetic Act and the FDA regulations and policies provide incentives to manufacturers to challenge patent validity or create modified, non-infringing versions of a drug or device in order to facilitate the approval of generic substitutes. These same types of incentives encourage manufacturers to submit new drug applications that rely on literature and clinical data not prepared for or by the drug sponsor.

We also rely on trade secrets to protect our technology, especially where we do not believe that patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. The employees, consultants, contractors, outside scientific collaborators and other advisors of our company and our strategic partners may unintentionally or willfully disclose our confidential information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming and the outcome is unpredictable. Failure to protect or maintain trade secret protection could adversely affect our competitive business position.

Our research and development collaborators may have rights to publish data and other information in which we have rights. In addition, we sometimes engage individuals or entities to conduct research that may be relevant to our business. The ability of these individuals or entities to publish or otherwise publicly disclose data and other information generated during the course of their research is subject to certain contractual limitations. These contractual provisions may be insufficient or inadequate to protect our trade secrets and may impair our patent rights. If we do not apply for patent protection prior to such publication or if we cannot otherwise maintain the confidentiality of our technology and other confidential information, then our ability to receive patent protection or protect our proprietary information may be jeopardized.

Litigation or other proceedings or third-party claims of intellectual property infringement could require us to spend time and money and could shut down some of our operations.

Our commercial success depends in part on not infringing patents and proprietary rights of third parties. Others have filed, and in the future are likely to file, patent applications covering products that are similar to our product candidates, as well as methods of making

or using similar or identical products. If these patent applications result in issued patents and we wish to use the claimed technology, we would need to obtain a license from the third party. We may not be able to obtain these licenses at a reasonable cost, if at all.

In addition, administrative proceedings, such as interferences and reexaminations before the U.S. Patent and Trademark Office, could limit the scope of our patent rights. We may incur substantial costs and diversion of management and technical personnel as a result of our involvement in such proceedings. In particular, our patents and patent applications may be subject to interferences in which the priority of invention may be awarded to a third party. We do not know whether our patents and patent applications would be entitled to priority over patents or patent applications held by such a third party. Our issued patents may also be subject to reexamination proceedings. We do not know whether our patents would survive reexamination in light of new questions of patentability that may be raised following their issuance.

We may be subject to claims for intellectual property infringement from former employers of our key employees, which could result in loss of intellectual property, our key employees or both.

Many of our employees were previously employed at universities or other biotechnology or pharmaceutical companies, including competitors or potential competitors. We could be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. In many cases, litigation may be necessary to defend against these claims.

Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could hamper or prevent the ability to commercialize certain product candidates, which could severely harm our business, financial condition, and results of operations.

Risks Relating to Owning our Common Shares

Our share price has been and may continue to be extremely volatile. It may be difficult to resell our common shares.

The market price of our common shares has fluctuated substantially in the past and could fluctuate substantially in the future. During the twelve months preceding December 31, 2022, the closing market price of our common shares ranged from CAD\$0.14 to CAD\$0.75 per share. In addition, the trading prices of life science and biotechnology company stocks in general have experienced extreme price fluctuations in recent years. The valuations of many life science companies without consistent product revenues and earnings are high based on conventional valuation standards, such as price-to-revenue ratios. These trading prices and valuations may not be sustained. Any negative change in the public's perception of the prospects of life science or biotechnology companies could depress our stock price regardless of our results of operations. In addition our stock may fluctuate based on a variety of factors, including actual or anticipated regulatory approvals or disapprovals of our products or competing products, actual or anticipated results and timing of our clinical trials, changes in the expected or actual timing of our development programs, changes in our operating results, conditions or trends in the life science and biotechnology industries, announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments, additions or departures of key personnel, sales and distributions of our common shares by us or our shareholders, changes in general conditions in the economy or other developments affecting us, our clients, or our competitors, some of which may be unrelated to our performance.

Among other things, volatility in our share price could mean that investors will not be able to sell their shares at or above prices at which they were acquired. The volatility also could impair our ability in the future to offer common stock as a source of additional capital. In addition, in the past, stockholders have often instituted securities class action litigation after periods of volatility in the market price of a company's securities. If a stockholder files a securities class action suit against us, we would incur substantial legal fees, and our management's attention and resources would be diverted from operating our business in order to respond to the litigation.

If we sell common shares in the future, existing common shareholders will experience immediate dilution and our stock price may decrease.

We will need to raise additional capital to fund our operations and to develop our products. We will likely raise such additional capital through the sale of our common shares and/or warrants from time to time. Any such financing transaction will result in our existing common shareholders experiencing immediate dilution.

If our estimates regarding timing of milestones are incorrect our share price may decrease.

For planning purposes, we estimate and may disclose timing of a variety of clinical, regulatory, and other milestones. We base our estimates on present facts and a variety of assumptions. Many underlying assumptions are outside our control such as the ability to recruit patients, obtain access to clinical sites as expected or obtain approval from regulatory bodies such as the FDA to enter into trials. If we do not achieve milestones consistent with investors' expectations, the price of our shares would likely decline.

We do not currently intend to pay dividends on our common shares and, consequently, investors' ability to achieve a return on investment will depend on appreciation in the price of our common shares.

We have not to date paid any dividends on our Common Shares. We currently intend to invest our future earnings, if any, to fund the development and growth of our business. The payment of dividends will be at the discretion of our board of directors and will depend on our results of operations, capital requirements, financial condition, future prospects, contractual arrangements, restrictions imposed by applicable law, any limitations on payments of dividends present in any debt agreements we may enter into, the dividends that we may be required to be pay to holders of the royalty preferred shares in accordance with the terms of such securities and other factors our board of directors may deem relevant. If we do not pay dividends, your ability to achieve a return on your investment in the Company will depend on any future appreciation in the market price of our common shares. There is no guarantee that our Common Shares will appreciate in value or even maintain the price at which our holders have purchased their Common Shares.

Dividends

We have not declared or paid any dividends on our Common Shares in our past fiscal years or current financial year.

The ABCA does not permit a corporation to pay dividends if the corporation is, or would after the payment, be unable to pay its liabilities as they become due or the realizable value of the corporation's assets would thereby be less than the aggregate of its liabilities and stated capital of all classes. Our directors may issue preferred shares that have preference over the Common Shares with respect to the payment of dividends, in which case such preference may prevent us from paying dividends on the Common Shares. There are 75,202,620 royalty preferred shares outstanding as at the date hereof. There are no other restrictions on our ability to pay dividends.

We intend to retain any earnings to finance growth and do not expect to pay dividends on our Common Shares in the near future. The Board will review this policy from time to time having regard for our financial condition, financing requirements and other factors considered relevant.

Description of Capital Structure

We are authorized to issue an unlimited number of Common Shares, an unlimited number of Preferred Shares issuable in series and 75,202,620 Royalty Preferred Shares. As at December 31, 2022, we had 265,673,607 Common Shares, 75,202,620 Royalty Preferred Shares, and no preferred shares are issued and outstanding.

The following is a summary of the rights, privileges, restrictions and conditions attaching to our Common Shares, Preferred Shares, and Royalty Preferred Shares.

Common Shares

The holders of Common Shares are entitled, subject to the rights of holders of any class of preferred shares, to dividends declared by the Board, to one vote per share at meetings of the shareholders and, upon liquidation, dissolution or winding up, to receive pro rata our remaining assets, subject to the rights of any class of preferred shares.

Preferred Shares

We may issue preferred shares from time to time in one or more series. The terms of each series of preferred shares, including the number of shares, the designation, rights, privileges, restrictions and conditions, will be determined at the time of creation of each such series by our Board. Preferred shares shall rank senior to Common Shares and the shares of any other class ranking junior to the preferred shares with respect to the payment of dividends or distribution of capital of the Company in the event of a dissolution, liquidation or winding up of the Company.

Royalty Preferred Shares

The Royalty Preferred Shares were issued to Zenith on June 3, 2013 as part of the spin-off transaction that resulted in the Company's epigenetic platform technology (excluding apabetalone) being transferred to Zenith and shareholders of the Company at the time of that transaction receiving common shares of Zenith.

The terms of the Royalty Preferred Shares were amended on July 2, 2015 to limit the dividends payable to holders of Royalty Preferred Shares in a particular period to amounts received by the Company during that period and to include certain additional deductions in the calculation of net revenue subject to the royalty. These amendments were necessary to align the terms of the Royalty Preferred Shares with the terms of the royalties to which the Company would be entitled pursuant to a license agreement entered into with Hepalink on July 8, 2015.

The terms of the Royalty Preferred Shares were further amended on December 20, 2016 to provide that the holder of the Royalty Preferred Shares is entitled to a dividend calculated based on a percentage of net revenue earned from the sale or licensing of any pharmaceutical product in which the Company holds an intellectual property right and remove the requirement that the pharmaceutical product elevate plasma levels of a certain lipoprotein associated with a decreased risk of atherosclerosis and coronary heart disease.

The Company determined that this amendment was necessary and appropriate based on detailed analysis of the results of the Company's phase 2 clinical program.

The Royalty Preferred Shares, after giving effect to the foregoing amendments, entitle Zenith to cumulative preferential dividends in an amount ranging from 6% to 12% of Net Revenue during any year, subject to an adjustment for tax payable on the dividend. The dividend amount is calculated based on 6% of the aggregate Net Revenue of up to US\$1 billion, 8% of the aggregate Net Revenue of between US\$1 billion and US\$2 billion, 10% of the aggregate Net Revenue between US\$2 billion and US\$5 billion and 12% of the aggregate Net Revenue in excess of US\$5 billion. The dividend amount in a prescribed dividend payment period may not exceed the aggregate of all amounts received by us or our affiliates in respect of and including Net Revenue in such period.

Net Revenue is defined as the aggregate of the following amounts: (i) amounts received by us or our affiliates from any person who is not us or our affiliate (a "third party") in consideration for granting a license or other rights to the third party which entitle the third party to research, develop, make, manufacture, modify, administer, offer to sell, sell or distribute one or more of products and/or intellectual property rights or amounts received under the terms of such license or other right that are granted to the third party; (ii) the gross consideration received from a third party by us, any licensee or their respective affiliates from the sale of any product (other than consideration received by us, any licensee or their respective affiliates from a licensee of such product or its affiliate); less (A) credits or allowances, if any, actually granted; (B) discounts actually allowed; (C) freight, postage, and insurance charges and additional special packaging charges; (D) customs duties, and excise sales taxes, duties or other taxes imposed upon and paid with respect to such sales (excluding what is commonly known as income taxes); (E) rebates and chargebacks or retroactive price reductions made to federal, state or local governments (or their agencies), or any third party payor, administrator or contractor, including managed health organizations; and (F) commissions related to import, distribution or promotion of any product paid to third parties (specifically excluding any commissions paid to sales personnel, sales representatives and sales agents who are employees or consultants of, or members of a contract sales force engaged by or on behalf of us, any licensee or their respective affiliates); and (iii) amounts received from a third party by us or an affiliate in consideration for the sale of any intellectual property right.

In the event we do not declare and pay the dividend on the applicable payment date, holders of Royalty Preferred Shares are entitled to receive additional cumulative preferential dividends in an amount equal to twenty percent (20%) per annum of the dividend payable on such payment date, subject to a tax adjustment, calculated daily and compounded monthly.

Subject to the ABCA, holders of Royalty Preferred Shares are not entitled to receive notice of or attend meetings of the shareholders of the Company and are not entitled to vote at any such meetings other than in respect of separate meetings of the holders of the Royalty Preferred Shares.

In the event of the liquidation, dissolution or winding-up of the Company, whether voluntary or involuntary, or any other return of capital or distribution of our assets among shareholders for the purpose of winding up its affairs, the holders of the Royalty Preferred Shares are entitled to receive in respect of each such share, before any distribution of any part of our assets among the holders of Common Shares or other shares of the Company ranking junior to the Royalty Preferred Shares, an amount equal to the greater of \$1.00 divided by the number of outstanding Royalty Preferred Shares and the amount of any accrued, but unpaid dividends.

Market for Securities

Our Common Shares are listed and posted for trading on the TSX under the symbol "RVX". Our securities are not listed on any stock exchange in the United States and there is no established trading market for our securities in the United States.

Trading Prices and Volume by Month for Year Ended December 31, 2022

Date	High (\$)	Low (\$)	Volume
12/30/2022	0.19	0.12	1,570,000
11/30/2022	0.22	0.16	720,700
10/31/2022	0.20	0.15	1,161,800
9/30/2022	0.30	0.19	632,500
8/31/2022	0.38	0.24	679,400
7/29/2022	0.33	0.21	1,126,100
6/30/2022	0.31	0.22	2,227,300
5/31/2022	0.40	0.25	1,214,200
4/29/2022	0.53	0.39	937,200
3/31/2022	0.63	0.42	1,129,100
2/28/2022	0.75	0.54	1,213,200
1/31/2022	0.82	0.49	1,794,500

In addition, on June 7, 2019 we issued 3,789,936 warrants expiring June 7, 2023, each exercisable for one Common Share at an exercise price of \$4.60 (the “June 2019 Warrants”). The June 2019 warrants are listed for trading on the TSX under the symbol “RVX.WT.A”. The following table shows the high and low trading prices and the volume of June 2019 Warrants traded on the TSX during the year ended December 31, 2022 (as reported by the TSX).

Date	High (\$)	Low (\$)	Volume
12/30/2022	0.02	0.02	775
11/30/2022	0.03	0.02	1,000
10/31/2022	0.04	0.03	1,000
9/30/2022	N/A	N/A	N/A
8/31/2022	N/A	N/A	N/A
7/29/2022	N/A	N/A	N/A
6/30/2022	0.07	0.04	4,000
5/31/2022	0.11	0.07	5,500
4/29/2022	0.19	0.10	6,100
3/31/2022	0.22	0.19	4,000
2/28/2022	0.48	0.21	61,050
1/31/2022	0.28	0.15	7,600

Prior Sales

We issued the following securities that are not listed or quoted in the marketplace at the prices set out below during the year ended December 31, 2022:

Date	Type of Security	Issue Price or Exercise Price of Securities	Number of Securities	Type of Issuance
December 2022	DSUs	N/A	405,384	Pursuant to deferred share unit plan
December 2022	RSUs	N/A	200,000	Pursuant to long term incentive plan
November 2022	RSUs	N/A	500,000	Pursuant to long term incentive plan
October 2022	RSUs	N/A	800,000	Pursuant to long term incentive plan
October 2022	Stock Options	\$0.17	440,000	Pursuant to stock option plan
September 2022	Warrants	\$0.30	78,750	Pursuant to private placement
September 2022	DSUs	N/A	267,512	Pursuant to deferred share unit plan
August 2022	Warrants	\$0.30	11,415,506	Pursuant to private placement
August 2022	RSUs	N/A	2,650,754	Pursuant to long term incentive plan
June 2022	Warrants	\$0.30	2,090,454	Pursuant to private placement
June 2022	DSUs	N/A	238,149	Pursuant to deferred share unit plan
April 2022	Warrants	\$0.50	400,000	Pursuant to private placement
April 2022	DSUs	N/A	169,206	Pursuant to deferred share unit plan
April 2022	RSUs	N/A	120,000	Pursuant to long term incentive plan
March 2022	Warrants	\$0.50	4,727,192	Pursuant to private placement

Date	Type of Security	Issue Price or Exercise Price of Securities	Number of Securities	Type of Issuance
February 2022	RSUs	N/A	2,667,700	Pursuant to long term incentive plan
February 2022	Stock Options	\$0.72	240,000	Pursuant to stock option plan
January 2022	RSUs	N/A	100,000	Pursuant to long term incentive plan
January 2022	Stock Options	\$0.52	500,000	Pursuant to stock option plan

Directors and Executive Officers

Name, Occupation and Security Holdings

The following table sets forth the name, municipality of residence, year of appointment as a director or executive officer of the Company, and position held with us and principal occupation of each of the directors or executive officers of the Company.

The Board is comprised of five directors. The directors are elected annually by the shareholders and serve until the next annual meeting of shareholders unless their successors are duly elected or appointed prior thereto.

Name and Municipality of Residence	Position	Principal Occupation During Past 5 Years	Director Since
Donald J. McCaffrey Calgary, Alberta, Canada	Chairman of the Board, President, CEO and Secretary	President, Chief Executive Officer and Secretary of Resverlogix since 2003. Chairman of Resverlogix since April 2016. President, Chief Executive Officer and Secretary of Zenith Capital Corp. since 2013.	2003
Kenneth Zuerblis, CPA ^{(1), (3)} Sarasota, Florida, U.S.A.	Director and Chair of the Audit and Finance Committee	Currently a director of the Corporation and Zenith Capital Corp.	2010
Kelly McNeill, CPA, CA ^{(1), (2), (3)} Winnipeg, Manitoba, Canada	Director and Chair of the Compensation and HR Committee and Chair of the Corporate Governance and Nominating Committee	Chief Executive Officer of RTDS Technologies Inc. since 2018. Currently a director of the Corporation and Zenith Capital Corp.	2009
Shawn Lu ^{(1), (2)} Toronto, Ontario Canada	Director	Chief Financial Officer of Hepalink USA Inc. (a subsidiary of Hepalink) since 2014.	2016
Siu Lun (Dicky) To ^{(2), (3)} Hong Kong	Director	Partner, ORI Capital since 2019. From 2005 to 2019, Mr. To served as Partner with RSM Hong Kong.	2019
A. Brad Cann, CPA, CA, CBV Calgary, Alberta, Canada	Chief Financial Officer	Chief Financial Officer of Resverlogix since 2009. Chief Financial Officer of Zenith Capital Corp. since 2013.	N/A
Dr. Michael Sweeney, MD Menlo Park, California, U.S.A.	Senior Vice President of Clinical Development	Senior Vice President of Clinical Development of Resverlogix since 2014.	N/A
Dr. Ewelina Kulikowski, PhD Calgary, Alberta, Canada	Senior Vice President Scientific Development Chief Scientific Officer	Chief Scientific Officer of Resverlogix since 2022. Senior Vice President Scientific Development of Resverlogix from 2016 to 2022. From 2005 to 2016, Dr. Kulikowski held various positions at Resverlogix of increasing responsibility.	N/A

Name and Municipality of Residence	Position	Principal Occupation During Past 5 Years	Director Since
Dr. Jan Johansson, MD, PhD San Ramon, California, U.S.A.	Senior Vice President Medical Affairs	Senior Vice President Medical Affairs of Resverlogix since 2004.	N/A

Notes:

- (1) Member of the Audit and Finance Committee
- (2) Member of the Corporate Governance and Nominating Committee
- (3) Member of the Compensation and HR Committee

The directors and executive officers, in the aggregate, beneficially own, directly or indirectly, or exercise control or direction over 6,200,306, or 2.3%, of issued and outstanding Common Shares as of March 31, 2023.

Audit Committee Matters

Audit and Finance Committee Charter

The Audit and Finance Committee Charter is attached hereto as Schedule “A”.

Composition of the Audit and Finance Committee

The Audit and Finance Committee is comprised of three directors – Mr. Zuerblis as Chair, Mr. McNeill and Mr. Lu. All three members of the Committee are considered financially literate. Each of the members have held board and executive positions on behalf of several companies, and have a wealth of experience in leading and managing companies.

The Board has determined that Messrs. Zuerblis and McNeill are both independent within the meaning of National Instrument 52-110 - Audit Committees and that Mr. Lu, although not independent due to his role as an executive officer of a subsidiary of a major shareholder, is exempt from the requirement to be independent under NI 52-110 pursuant to Section 3.3(2) of that instrument. The Corporation has relied on this exemption in order that Mr. Lu may be a member of the Audit and Finance Committee in accordance with NI 52-110. The Board has determined in its reasonable judgment that Mr. Lu is able to exercise the impartial judgment necessary to fulfill his responsibilities as an Audit and Finance Committee member and that his appointment is required in the best interests of the Corporation and its shareholders.

Relevant Education & Experience

Kenneth Zuerblis

Mr. Zuerblis received a BS in Accounting and is a Certified Public Accountant with approximately 30 years of experience, has held senior financial positions with three publicly-traded companies and has held directorships with numerous organizations. Mr. Zuerblis served as Executive Vice President and Chief Financial Officer of Savient Pharmaceuticals, Inc. from 2011 to 2012. Prior to joining Savient, Mr. Zuerblis served as Chief Financial Officer and Senior Vice President at ImClone Systems from 2008 through 2009. From 1994 through 2005, Mr. Zuerblis served as Chief Financial Officer of Enzon Pharmaceuticals Inc. and held the position of Corporate Controller from 1991 through 1994. Mr. Zuerblis began his career at KPMG, LLP in 1982 where he held management positions of increasing responsibility over a 10-year period. Mr. Zuerblis also serves on the board of directors of Zenith Capital Corp. (since 2013).

Kelly McNeill

Mr. McNeill holds a Masters of Accountancy and a Bachelor of Commerce (Honours), and is a Chartered Professional Accountant with over 20 years of experience. Mr. McNeill has served as Chief Financial Officer of RTDS Technologies Inc. since 2014 as well as the Chief Executive Officer since May 2018. Mr. McNeill served as Executive Vice President, Finance and Administration, Chief Financial Officer and Secretary of IMRIS Inc. between 2009 and 2014. From 2006 to 2009, Mr. McNeill was Resverlogix's Chief Financial Officer. Prior thereto, Mr. McNeill held senior financial positions with two multinational companies. Mr. McNeill also serves on the board of directors of Zenith Capital Corp. (since 2013).

Shawn Lu

Mr. Lu has extensive experience in the areas of corporate finance, capital markets and investment financing spanning over 25 years. Prior positions include: Area Manager for BMO Bank of Montreal; TD Bank Residential Mortgage Manager; TD Bank Senior Financial Advisor; Chief Financial Officer and Vice President of Corporate Finance, Hepalink USA Inc.; Vice President of Investment and Corporate Finance, Shenzhen FuTianXin Investment Co.; General Manager of Corporate Finance Department and Manager of Investment & Finance Department, China Merchant Shekou Port Co. Ltd. Mr. Lu holds the following designations: Canadian Investment Manager (CIM) and a Certified Accountant and Certified Corporate Economist in China. He has Master of Finance Management and a Master of

Corporate Economics and Business Administration. Mr. Lu currently also serves on the board of directors (since 2015) of Quest PharmaTech Inc.

Pre-approval of Audit Fees

We will not engage external auditors to carry out any Prohibited Service as defined in the CICA revised Rules of Professional Conduct.

The Board, upon recommendation from the Audit and Finance Committee, will consider the pre-approval of permitted services to be performed by the external auditors in each of the following broad categories:

- Audit Services
- Audit Related Services
- Tax Services

Engagements of external auditors will only commence subsequent to Board pre-approval of audit services, and only a member of the Audit and Finance Committee, or the President and CEO or Chief Financial Officer shall be authorized to request services of external auditors.

External Auditor Service Fees

The following table sets out the aggregate fees billed by our external auditor in each of the last two financial years for services provided to us:

Year	Audit Fees ⁽¹⁾	Audit-Related Fees	Tax Fees ⁽²⁾	Other Fees
2022	\$193,000	\$Nil	\$5,992	\$Nil
2021	\$257,335	\$Nil	\$5,885	\$Nil

Notes:

- (1) Audit fees were for professional services for the audit of our annual financial statements and reviews of our unaudited interim financial statements.
- (2) Tax Fees were for professional services for compliance services paid to KPMG LLP.

Cease Trade Orders, Bankruptcies, Penalties or Sanctions

Other than as set out below, no director or executive officer is as at the date hereof, or has been within ten years before the date hereof, a director or chief executive officer or chief financial officer of any company (including the Company) that, while he was acting in such capacity: (i) was the subject of a cease trade or similar order, or an order that denied the relevant company access to any exemption under securities legislation for a period of more than 30 consecutive days; (ii) was subject to an event that resulted, after the director or executive officer ceased to be a director or chief executive officer or chief financial officer, in the company being the subject of a cease trade or similar order or an order that denied the relevant company access to any exemption under securities legislation, for a period of more than 30 consecutive days.

In addition, other than set out below, no director or executive officer or shareholder holding a sufficient number of securities of the Company to affect materially the control of the Company is as at the date hereof, or has been within ten years before the date hereof, a director or executive officer of any company (including the Company) that, while that person was acting in that capacity or within a year of that person ceasing to act in that capacity, became bankrupt, made a proposal under any legislation relating to bankruptcy or insolvency or was subject to or instituted any proceedings, arrangement or compromise with creditors or had a receiver, receiver manager, or trustee appointed to hold its assets.

Mr. McNeill was the Chief Financial Officer of IMRIS Inc. ("IMRIS") from 2009 until his resignation on September 5, 2014. IMRIS is a biomedical company that is a reporting issuer in all provinces of Canada and at the time of Mr. McNeill's resignation was listed on TSX and NASDAQ. On May 26, 2015, IMRIS and certain of its subsidiaries filed voluntary petitions under Chapter 11 of the United States Bankruptcy Code in the United States Bankruptcy Court for the District of Delaware which granted a stay of proceedings against IMRIS. On June 3, 2015, the Manitoba Court of Queen's Bench granted an initial recognition order under the Companies' Creditors Arrangement Act (Canada) recognizing the Chapter 11 proceedings and granting a stay of proceedings against IMRIS.

No director, executive officer or shareholder holding a sufficient number of our securities to affect materially the control of the Company has, within the past ten years, become bankrupt, made a proposal under any legislation relating to bankruptcy or insolvency, or became subject to or instituted any proceedings, arrangement or compromise with creditors, or had a receiver, receiver manager or trustee appointed to hold the assets of such person.

No director, executive officer or shareholder holding a sufficient number of our securities to affect materially the control of the Company has been subject to any penalties or sanctions imposed by a court relating to Canadian securities legislation or by a Canadian securities regulatory authority or has entered into a settlement agreement with a Canadian securities regulatory authority or been subject to any

other penalties or sanctions imposed by a court or regulatory body that would likely be considered important to a reasonable investor in making an investment decision.

Conflicts of Interest

Certain directors and officers of the Company and our subsidiary are associated with other reporting issuers or other corporations which may give rise to conflicts of interest. In accordance with the ABCA directors who have a material interest or any person who is a party to a material contract or a proposed material contract with us are required, subject to certain exceptions, to disclose that interest and abstain from voting on any resolution to approve the contract.

Interests of Management and Others in Material Transactions

Other than as described below, there are no material interests, direct or indirect of directors, executive officers, any shareholders that beneficially own, directly or indirectly, more than 10% of our outstanding Common Shares, or any known associates or affiliates of such persons, in any transaction within the last three years or in any proposed transaction which has materially affected or is reasonably expected to materially affect us.

In August 2020, we completed a private placement of 3,573,333 equity units to Hepalink for aggregate proceeds of CAD\$2.7 million (US\$2.0 million), or CAD\$0.75 per unit. Each unit consisted of one common share and one-half of a common share purchase warrant. Each warrant is exercisable at a price of CAD\$1.00 per underlying common share for a period of one year from the closing of the private placement.

On May 13, 2021, we closed a US\$6.0 million Debenture with a subsidiary of Hepalink. The Debenture bears interest at 10% per annum and matures on May 13, 2024. Hepalink may elect to convert the principal amount of the Debentures and accrued and unpaid interest thereon into common shares of the Company at a conversion price equal to the lesser of CAD\$0.93 per share and the 5-day volume weighted average trading price of the common shares on the date of conversion. The Company granted Hepalink a security interest in all of its assets, including its patents and other intellectual property, as security for its obligations under the Debenture. In addition, Hepalink received 300,000 common share purchase warrants exercisable for a period of four years from the grant date at a price of CAD\$0.93 per share. During the year ended December 31, 2022, the maturity date of the Debenture, and the corresponding payment date of interest thereon, were both extended by one year from May 13, 2022 to May 13, 2023. Furthermore, subsequent to December 31, 2022, the Debenture was further amended to extend the maturity date to May 13, 2024, and to increase the interest rate to 12% per annum effective May 14, 2023.

Transfer Agent and Registrar

The transfer agent and registrar for our Common Shares is Computershare at its transfer offices in Calgary and Toronto.

Material Contracts

Material contracts which we entered into within the most recently completed financial year, subsequent to the most recently completed financial year and prior to the date of this AIF, or before the most recently completed financial year which remain in effect, other than contracts entered into in the ordinary course of business are as follows:

1. Investor Rights Agreement (“IRA”) dated April 15, 2009 and amended April 30, 2013 among us, NGN BioMed Opportunity II, L.P. (“NGN”) and certain other investors and each of Donald McCaffrey, Wayne Chiu and Norman Wong. The IRA provides that we shall not issue any new securities without offering a proportionate share to NGN and the other investors. The IRA also provides NGN with certain approval rights including, any offering of securities that rank senior to the Common Shares, any increase or decreases from the intended composition of seven Board members, any amendment to our constating documents and any related party transactions.
2. Secured Convertible Debenture Investment Agreement dated May 5, 2021 among us and a subsidiary of Hepalink. The Debenture bears interest at 10% per annum and matures on May 13, 2024. During the year ended December 31, 2022, the maturity date of the Debenture, and the corresponding payment date of interest thereon, were both extended by one year from May 13, 2022 to May 13, 2023. Furthermore, subsequent to December 31, 2022, the Debenture was further amended to extend the maturity date to May 13, 2024, and to increase the interest rate to 12% per annum effective May 14, 2023. Hepalink may elect to convert the principal amount of the Debentures and accrued and unpaid interest thereon into common shares of the Company at a conversion price equal to the lesser of CAD\$0.93 per share and the 5-day volume weighted average trading price of the common shares on the date of conversion. The Company granted Hepalink a security interest in all of its assets, including its patents and other intellectual property, as security for its obligations under the Debenture. In addition, Hepalink received 300,000 common share purchase warrants exercisable for a period of four years from the grant date at a price of CAD\$0.93 per share.

Interests of Experts

RSM Canada LLP are the auditors of the Company and have confirmed with respect to the Company, that they are independent within the meaning of the relevant rules and related interpretations prescribed by the relevant professional bodies in Canada and any applicable legislation or regulations.

Additional Information

Additional information, including directors' and executive officers' remuneration and indebtedness, principal holders of our securities and securities authorized for issuance under equity compensation plans is contained in the Management Information Circular with respect to the most recent annual meeting of shareholders. Additional financial information is provided in our audited financial statements and MD&A for the year ended December 31, 2022.

Additional information relating to us may be found on SEDAR at www.sedar.com. In addition, we maintain updated information on our website at www.resverlogix.com.

Schedule "A" – Audit and Finance Committee Charter

RESVERLOGIX CORP.

AUDIT & FINANCE COMMITTEE CHARTER

PART I ESTABLISHMENT OF COMMITTEE

1. Committee Purpose

The Audit and Finance Committee (the "**Committee**") is established by the board of directors (the "**Board of Directors**") of Resverlogix Corp. ("Resverlogix") primarily for the purpose of overseeing the accounting and financial reporting processes of Resverlogix and the reviews and audits of the financial statements of Resverlogix.

The Committee shall assist the Board of Directors in fulfilling its oversight responsibilities by monitoring, among other things:

- (a) the quality and integrity of the financial statements and related disclosure of Resverlogix;
- (b) compliance by Resverlogix with legal and regulatory requirements that could have a material effect upon the financial position of Resverlogix which are not subject to the oversight of another committee of the Board of Directors or the Board of Directors as a whole;
- (c) the independent auditor's qualifications and independence; and
- (d) performance of Resverlogix's independent auditor.

2. Composition of Committee

The Committee shall consist of as many members as the Board shall determine, but in any event not fewer than three directors, provided that all members of the Committee shall be determined by the Board to be independent within the meaning of National Instrument 52-110 (Audit Committees), Rule 10A-3(b)(1) under the United States Securities Exchange Act of 1934 and the rules of any stock exchange or market on which Resverlogix's shares are listed or posted for trading (collectively, "**Applicable Governance Rules**"). In this Charter, the term "independent" includes the meanings given to similar terms by Applicable Governance Rules, including the terms "non-executive", "outside" and "unrelated" to the extent such terms are applicable under Applicable Governance Rules. No member of the Audit Committee shall have participated in the preparation of the financial statements of the Corporation or any current subsidiary of the Corporation at any time during the past three (3) years.

All members of the Audit Committee must be able to read and understand fundamental financial statements (including a balance sheet, income statement and cash flow statement) and read and understand a set of financial statements that present a breadth and level of complexity of accounting issues that are generally comparable to the breadth and level of complexity of the issues that can reasonably be expected to be raised by the Corporation's financial statements. In addition: (i) at least one member of the Audit Committee must have past employment experience in finance or accounting, requisite professional certification in accounting or any other comparable experience or background that results in the individual's financial sophistication, including service as a chief executive officer, chief financial officer, or other senior officer with financial oversight responsibilities or otherwise satisfy standards for financial expertise required for audit committees of companies listed on the Toronto Stock Exchange and/or NASDAQ Stock Market, and (ii) at least one member of the Audit Committee must be an "audit committee financial expert" as defined by the Applicable Governance Rules.

3. Appointment of Committee Members

The members of the Committee shall be appointed by the Board of Directors on the recommendation of the Corporate Governance and Nominating Committee. The members of the Committee shall be appointed at the time of each annual meeting of shareholders and shall hold office until the next annual meeting, until they are removed by the Board of Directors or until their successors are earlier appointed, or until they cease to be directors of Resverlogix.

PART II COMMITTEE PROCEDURE

4. Vacancies

Where a vacancy occurs at any time in the membership of the Committee, it may be filled by the Board of Directors on the recommendation of the Corporate Governance and Nominating Committee and shall be filled by the Board of Directors if the membership of the Committee is fewer than three directors. The Board of Directors may remove and replace any member of the Committee.

5. Committee Chair

The Board of Directors shall appoint a chair (the "**Chair**") for the Committee. The Chair may be removed and replaced by the Board of Directors.

6. Absence of Chair

If the Chair is not present at any meeting of the Committee, one of the other members of the Committee present at the meeting shall be chosen by the Committee to preside at the meeting.

7. Secretary of Committee

The Committee shall appoint a Secretary who need not be a director of Resverlogix.

8. Regular Meetings

The Chair, in consultation with the Committee members, shall determine the schedule and frequency of the Committee meetings, provided that the Committee shall meet at least quarterly. The Committee at any time may, and at each regularly scheduled Committee meeting shall, meet without management present and shall meet periodically with management and the independent auditor. The Committee shall also meet separately with the independent auditor at every regularly scheduled meeting of the Committee at which the independent auditor is present. The Committee shall record and maintain minutes of meetings.

9. Special Meetings

The Chair, any two members of the Committee, the independent auditor or the Chief Executive Officer of Resverlogix may call a special meeting of the Committee.

10. Quorum

A majority of the members of the Committee, present in person or by telephone or other telecommunication device that permits all persons participating in the meeting to speak to each other, shall constitute a quorum.

11. Notice of Meetings

Notice of the time and place of every meeting shall be given in writing or by e-mail or facsimile communication to each member of the Committee at least 48 hours prior to the time fixed for such meeting; provided, however, that a member may, in any manner, waive notice of a meeting and attendance of a member at a meeting is a waiver of notice of the meeting, except where a member attends a meeting for the express purpose of objecting to the transaction of any business on the grounds that the meeting is not lawfully called.

12. Agenda

The Chair shall develop and set the Committee's agenda, in consultation with other members of the Committee, the Board of Directors and management of Resverlogix. The agenda and information concerning the business to be conducted at each Committee meeting shall, to the extent practicable, be communicated to the members of the Committee sufficiently in advance of each meeting to permit meaningful review.

13. Delegation

Subject to subsection PART III19(e), the Committee shall have the power to delegate its authority and duties to subcommittees or individual members of the Committee as it deems appropriate.

14. Access

In discharging its oversight role, the Committee shall have full access to all books, records, facilities and personnel of Resverlogix.

15. Attendance of Others at a Meeting

At the invitation of the Chair, one or more officers, directors or employees of Resverlogix may, and if required by the Committee shall, attend a meeting of the Committee.

16. Procedure, Records and Reporting

The Committee shall fix its own procedure at meetings, keep records of its proceedings and report to the Board of Directors when the Committee may deem appropriate (but not later than the next meeting of the Board of Directors).

17. Outside Consultants or Advisors

The Committee, when it considers it necessary or advisable, may retain, at Resverlogix's expense, outside consultants or advisors (including independent counsel) to assist or advise the Committee independently on any matter within its mandate. The Committee shall have the sole authority to retain or terminate such consultants or advisors, including the sole authority to approve the fees and other retention terms for such persons.

PART III MANDATE OF COMMITTEE

18. Appointment of Resverlogix's Independent Auditor

Subject to confirmation by the independent auditor of its compliance with Canadian regulatory registration requirements, the Committee shall recommend to the Board of Directors the appointment of the independent auditor for the purpose of preparing or issuing any audit report or performing other audit, review or attest services for Resverlogix, such appointment to be confirmed by Resverlogix's shareholders at each annual meeting. The Committee shall also recommend to the Board of Directors the engagement letter with the independent auditor, the approval of fees to be paid to the independent auditor for audit services and shall pre-approve the retention of the independent auditor for any permitted non-audit service. The Committee shall also be directly responsible for overseeing the work of the independent auditor (including resolution of disagreements between management of Resverlogix and the independent auditor regarding financial reporting) for the purpose of preparing or issuing an audit report or performing other audit, review or attest services for Resverlogix. The Committee shall communicate directly with the independent auditor. The independent auditor shall report directly to the Committee.

The Committee shall review the independence of the independent auditor including a written report from the independent auditor delineating all relationships between the auditor and Resverlogix, considering whether the advisory services performed by the independent auditor during the course of the year have affected its independence, and ensuring that no relationship or service between the independent auditor and Resverlogix is in existence that may affect the objectivity and independence of the auditor, or recommending appropriate action to ensure the independence of the independent auditor.

19. Specific Mandates

The Committee, to the extent required by applicable laws or rules, or otherwise considered by the Committee to be necessary or appropriate, shall:

(a) Oversight in Respect of Financial Disclosure

- (i) review, discuss with management of Resverlogix and the independent auditor, and recommend to the Board of Directors for approval:
 - A. the annual and interim financial statements;
 - B. the annual information form;
 - C. the annual and interim management's discussion and analysis;
 - D. the portions of the management proxy circular, for any annual or special meeting of shareholders, containing significant financial information respecting Resverlogix;
 - E. all financial statements included in prospectuses or other offering documents;

- F. any significant financial information contained in all prospectuses and all documents which may be incorporated by reference in a prospectus;
- G. any significant financial information respecting Resverlogix contained in a material change report or a business acquisition report;
- (ii) review and discuss with management of Resverlogix:
 - A. each press release which contains significant financial information respecting Resverlogix (including, without limitation, annual and interim earnings press releases) or contains earnings guidance, prior to public dissemination thereof;
 - B. the use of "pro forma" or "adjusted" non-IFRS information;
 - C. financial information and earnings guidance provided to analysts and rating agencies; provided, however, that such discussion may be done generally (consisting of discussing the types of information to be disclosed and the types of presentations to be made), and the Committee need not discuss in advance each instance in which Resverlogix may provide earnings guidance or presentations to rating agencies;
- (iii) review with management and the independent auditor the scope of the audit, in particular the independent auditor's view of Resverlogix's accounting principles as applied in the financial statements in terms of disclosure quality and evaluation methods, inclusive of the clarity of Resverlogix's financial disclosure and reporting, degree of conservatism or aggressiveness of Resverlogix's accounting principles and underlying estimates, and other significant decisions made by management in preparing the financial disclosure and reviewed by the independent auditor;
- (iv) review with management of Resverlogix and the independent auditor major issues regarding accounting and auditing principles and practices as well as the adequacy of internal controls and procedures for financial reporting and management information systems and inquire of management and the independent auditor about significant risks and exposures to the Corporation that could significantly affect Resverlogix's financial statements;
- (v) review with management of Resverlogix and the independent auditor, and satisfy itself as to the adequacy of the procedures that are in place for the review of Resverlogix's disclosure of financial information extracted or derived from Resverlogix's financial statements, and periodically assess the adequacy of those procedures;
- (vi) review with management of Resverlogix and the independent auditor (including those of the following that are contained in any report of the independent auditor): (a) all critical accounting policies and practices to be used by Resverlogix in preparing its financial statements; (b) all alternative treatments of financial information within IFRS that have been discussed with management, ramifications of the use of these alternative treatments, and the independent auditor's assessment of the alternatives; and (c) other material communications between the independent auditor and management of Resverlogix, such as any management letter or schedule of unadjusted differences;
- (vii) review with management of Resverlogix and the independent auditor the effect of regulatory and accounting initiatives as well as off-balance sheet transactions on Resverlogix's financial statements;
- (viii) review the plans of management of Resverlogix and the independent auditor regarding any significant changes in accounting practices or policies and the financial and accounting impact thereof;
- (ix) review with management of Resverlogix, the independent auditor and, if necessary, legal counsel, any litigation, claim or contingency, including tax assessments, that could have a material effect upon the financial position of Resverlogix, and the manner in which these matters have been disclosed in the financial statements;
- (x) review disclosures by Resverlogix's Chief Executive Officer and Chief Financial Officer with respect to any required certification for Resverlogix's financial statements by such individuals; and
- (xi) discuss with management Resverlogix's material financial risk exposures and the steps management of Resverlogix has taken to monitor and control such exposures, including Resverlogix's financial risk assessment and financial risk management policies.
- (b) **Oversight in Respect of Legal and Regulatory Matters**
 - (i) review, if necessary, with legal counsel, Resverlogix's compliance policies, legal matters and any material reports or inquiries received from regulators or governmental agencies that could have a material effect upon the financial position of Resverlogix and which are not subject to the oversight of another committee of the Board of Directors or the Board of Directors as a whole.

(c) **Oversight in Respect of the Chief Financial Officer**

- (i) consult with management on management's appointment, replacement, reassignment or dismissal of the Chief Financial Officer of Resverlogix; and
- (ii) ensure the Chief Financial Officer of Resverlogix has access to the Chair, the Chairman of the Board of Directors and the Chief Executive Officer of Resverlogix, and shall meet separately with the Chief Financial Officer of Resverlogix to review any problems or difficulties he or she may have encountered in the performance of his or her responsibilities and report to the Board of Directors on such meetings.

(d) **Oversight in Respect of the Independent Auditor**

- (i) meet with the independent auditor prior to the annual audit to review the planning and staffing of the audit;
- (ii) review annually the independent auditor's formal written statement of independence delineating all relationships between itself and Resverlogix and review all such relationships;
- (iii) receive confirmation from the independent auditor as to its standing as a "participating audit firm" and its compliance with any restrictions or sanctions imposed by the Canadian Public Accountability Board as those concepts are set forth in National Instrument 52-108 of the Canadian Securities Administrators;
- (iv) review and evaluate the independent auditor, including the lead partner of the independent auditor team and shall confirm compliance by the independent auditors with laws and regulations relating to audit partner rotation;
- (v) meet separately with the independent auditor to review with them any problems or difficulties they may have encountered and specifically:
 - A. any difficulties which were encountered in the course of the audit work, including any restrictions on the scope of activities or access to required information, and any disagreements with management of Resverlogix; and
 - B. any changes required in the planned scope of the audit; and report to the Board of Directors on such meetings;
- (vi) review the engagement reports of the independent auditor on unaudited financial statements of Resverlogix; and
- (vii) review and approve Resverlogix's hiring policies regarding partners, employees, former partners and former employees of Resverlogix's present and former independent auditor.

(e) **Oversight in Respect of Audit and Non-Audit Services**

- (i) have the sole authority to pre-approve all audit services (which may entail providing comfort letters in connection with securities underwritings) and all permitted non-audit services, other than non-audit services where:
 - A. the aggregate amount of all such non-audit services provided to Resverlogix or its subsidiaries constitutes not more than 5% of the total amount of fees paid by Resverlogix (and its subsidiaries) to the independent auditor during the fiscal year in which the non-audit services are provided;
 - B. such services were not recognized by Resverlogix (or any subsidiary) at the time of the engagement to be non-audit services; and
 - C. such services are promptly brought to the attention of the Committee and approved, prior to the completion of the audit, by the Committee or by one or more members of the Committee to whom authority to grant such approvals has been delegated by the Committee; and
- (ii) delegate to one or more designated members of the Committee the authority to grant pre-approvals required by this section; provided that the decision of any member to whom authority is delegated to pre-approve an activity shall be presented to the Committee at the first scheduled meeting following such decision, and provided further that, if the Committee approves an audit service within the scope of the engagement of the independent auditor, such audit service shall be deemed to have been pre-approved for purposes of this section

(f) **Oversight in Respect of Certain Policies**

- (i) establish procedures for: (a) the receipt, retention and treatment of complaints received by Resverlogix regarding accounting, internal accounting controls or auditing matters; and (b) the confidential, anonymous submission by employees of Resverlogix of concerns regarding questionable accounting or auditing matters; and
- (ii) periodically review Resverlogix's public disclosure policy.

20. Non-Exhaustive List

The foregoing list of duties is not exhaustive, and the Committee may, in addition, perform such other functions as may be necessary or appropriate for the performance of its oversight responsibilities.

21. Review of Committee's Charter

The Committee shall assess the adequacy of this Charter on an annual basis and recommend any changes to the Board of Directors.

22. Oversight Function

While the Committee has the responsibilities and powers set forth in this Charter, it is not the duty of the Committee to plan or conduct audits or to determine that Resverlogix's financial statements are complete and accurate or are in accordance with IFRS. These are the responsibilities of management of Resverlogix and the independent auditor. The Committee and its Chair are members of the Board of Directors, appointed to the Committee to provide broad oversight of the financial risk and control related activities of Resverlogix, and are specifically not accountable nor responsible for the day to day operation or performance of such activities. The role of all Committee members is to oversee the process, not to certify or guarantee the accuracy or completeness of the external audit of Resverlogix's financial information or public disclosure.

Glossary

The following terms shall have the following meanings, unless otherwise defined elsewhere in this Annual Information Form:

ABCA	means the Business Corporations Act (Alberta).
Acetylated Lysine	an acetyl-derivative of the amino acid lysine (also known as Acetyllysine). In proteins, the acetylation of lysine residues is an important mechanism of epigenetics. It plays a role in regulating the transcription of genes through recruitment of additional proteins to histones associated with DNA.
Acetylation	the process by which an acetyl functional group is transferred onto a molecule.
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.
Alkaline Phosphatase (“ALP”)	a hydrolase enzyme responsible for removing phosphate groups from many types of molecules, including proteins. Data suggests that elevated serum alkaline phosphatase levels are associated with increased mortality and morbidity in diseases such as diabetes, chronic kidney disease, heart failure and Alzheimer’s disease.
ALTs	Alanine transaminase, also called serum glutamic pyruvic transaminase (“SGPT”) or alanine aminotransferase (“ALAT”), is found in serum and most commonly associated with the liver, measurements are used as a part of a diagnostic evaluation of hepatocellular injury.
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.
Angiography	a medical imaging technique used to visualize the inside (lumen) of blood vessels and organs of the body, with particular interest in the arteries, veins and the heart chambers.
Angiotensin-converting enzyme 2 (“ACE2”)	an enzyme that is found on the surface of cells in tissues and organs throughout the body, including the lungs, heart, kidneys and intestines. ACE2 plays an important role in the renin–angiotensin–aldosterone system which serves to control blood pressure. It also serves as the touchpoint for some coronaviruses, including SARS-CoV-2, allowing them to gain entry into cells.
apabetalone	generic name of RVX-208
Apolipoprotein	the protein combined with a lipid to form a lipoprotein, a component of HDL and LDL.
ApoA-I	is one of the apolipoprotein components of the HDL particle.
ApoB	is one of the apolipoprotein components of the LDL particle.
Atherosclerosis	a disease in which the deposition of lipids and inflammatory cells in the arterial wall creates a plaque resulting in the hardening and decrease of arterial lumen size.
Atherosclerotic Plaque	the deposit or accumulation of lipid and lipid-containing cells (plaque) in the arterial wall (<i>also known as atheroma</i>).
BET proteins	BET proteins (Bromodomain and ExtraTerminal domain) are proteins that contain bromodomains, which regulate gene transcription through binding to acetylated lysines within the histones bound to DNA.
b.i.d.	“bis in die” (Latin) refers to twice a day dosing.
Bilirubin	the yellow breakdown product of normal heme catabolism, that is excreted in bile and urine; elevated levels may indicate a disease state.

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.
Bromodomain (“BRD”)	(see BET proteins)
Cancer	a disease characterized by abnormal and uncontrolled cell growth.
Cardiac Output	the total volume of blood pumped from the heart per unit time (often expressed in litres/minute). Cardiac output is the product of the stroke volume (volume per beat) and the heart rate (beats per minute), and an important measure of heart function.
Coagulation Cascade	a series of events that culminate in the formation of a blood clot 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.
Coronavirus disease 2019 (“COVID-19”)	a contagious respiratory illness caused by infection of SARS-CoV-2, a coronavirus. COVID-19 is responsible for a global pandemic that began in late 2019.
C-Reactive Protein (“CRP”)	a biomarker of cardiovascular inflammation
Cardiovascular disease (“CVD”)	a group of diseases of the heart and blood vessels.
Cholesterol	a fatty molecule essential for normal body functions, including the production of hormones and bile acids; it is also an important component of a cell membrane.
Common Shares	common shares in the capital of Resverlogix Corp.
Compound	a chemical substance formed from two or more elements (<i>also see drug</i>).
Contract Research Organization	an organization (commercial, academic or other), contracted by the sponsor to conduct (“CRO”) 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. Professional 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 (“DM”)	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.

Drug	is any substance that can be used to modify a chemical process or processes in the body to mitigate, treat or prevent a medical condition.
Dyslipidemia	a disorder associated with abnormal levels of blood lipids and lipoproteins.
Emergency Use Authorization (“EUA”)	is a mechanism to facilitate the availability and use of medical countermeasures on a limited basis, during a medical emergency. Under an EUA, regulators such as the FDA may allow the use of unapproved medical products when alternatives are not available, as they did for several unapproved treatments and vaccines during the COVID-19 pandemic. Other regulators, including the EMA and Health Canada, have also employed EUAs.
End Stage Renal Disease (“ESRD”)	the last stage of chronic kidney disease. The stage at which the kidneys have incurred permanent damage and lost nearly all function and the treatments include dialysis or a transplant.
European Medicines Agency (“EMA”)	is the European governmental agency responsible for the approval for manufacture, usage and sale of food, human diagnostics and therapeutic products within the European Union.
Endogenous	is a process whereby a molecule is produced within the body.
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.
Estimated Glomerular Filtration Rate (“eGFR”)	a rate calculated using the results of a blood creatinine test, age and gender. The result indicates the severity and stage of chronic kidney disease. An eGFR below 60 for three months or more indicates CKD.
Food and Drug Administration (“FDA”)	is the United States governmental agency responsible for the approval for manufacture, usage and sale of food, human diagnostics and therapeutic products within the US.
Gene	a sequence of DNA encoding a protein.
Good Clinical Practice (“GCP”)	is the international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human subjects.
Good Laboratory Practice (“GLP”)	is the international regulation which embodies a set of principles which provide a framework for laboratory studies, ensuring high quality experimental standards and reliable data.
Good Manufacturing Practice (“GMP”)	is 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 a role in gene regulation.
Health Canada	is the governmental agency which regulates the manufacture, use and sale of human diagnostics and therapeutic products in Canada, and oversees safety of foods.
Hepatic Transaminases	are variables analyzed in plasma that describe liver function and liver cell integrity. They include, for example, Alanine Transaminase (“ALT”) and Aspartate Transaminase (“AST”).
IND-Enabling Studies	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 to permit a drug to be tested in humans in clinical trials in the US.
Intravascular Ultrasound (“IVUS”)	an invasive procedure, performed along with cardiac catheterization; a miniature sound probe (transducer) on the tip of a coronary catheter is threaded through the coronary arteries and, using high-frequency sound waves, produces detailed images of the interior walls of the arteries. Where angiography shows a two-dimensional silhouette of the interior of the coronary arteries, IVUS shows a cross-section of both the interior, and the layers of the artery wall itself.
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 (<i>also known as “bad cholesterol”</i>).
Lipids	are 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 LDL and HDL.
Major Adverse Cardiovascular (“MACE”)	a commonly used end point for cardiovascular research. MACE is a composite of clinical Events 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, angina, hospitalization for heart disease and operative treatments for heart
worsening disease.	
Medical Device	a diagnostic or therapeutic article that does not work by chemical action.
Metabolism	is the biochemical modification or degradation of a drug, often readily removing the drug from the body.
Net Revenue	the aggregate of the following amounts: (i) amounts received by us or our affiliates from any person who is not us or our affiliate (a “third party”) in consideration for granting a license or other rights to the third party which entitle the third party to research, develop, make, manufacture, modify, administer, offer to sell, sell or distribute one or more of the products and/or intellectual property rights or amounts received under the terms of such license or other right that are granted to the third party; (ii) the gross consideration received from a third party by us, any licensee or their respective affiliates from the sale of any product (other than consideration received by us, any licensee or their respective affiliates from a licensee of such product or its affiliate); less (A) credits or allowances, if any, actually granted; (B) discounts actually allowed; (C) freight, postage, and insurance charges and additional special packaging charges; (D) customs duties, and excise sales taxes, duties or other taxes imposed upon and paid with respect to such sales (excluding what is commonly known as income taxes); (E) rebates and chargebacks or retroactive price reductions made to federal, state or local governments (or their agencies), or any third party payor, administrator or contractor, including managed health organizations; and (F) commissions related to import, distribution or promotion of any product paid to third parties (specifically excluding any commissions paid to sales personnel, sales representatives and sales agents who are employees or consultants of, or members of a contract sales force engaged by or on behalf of, us, any licensee or their respective affiliates); and (iii) amounts received from a third party by us or its affiliates in consideration for the sale of any intellectual property right.
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.
New Drug Submission (“NDS”)	(see “New Drug Application”)
Pharmacological Agent	(see “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 monetary 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 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 event.
Polymerase Chain Reaction (“PCR”)	the technique uses thermocycling to amplify a region of DNA. Resverlogix uses real-time PCR as a method to assess gene expression.
Preclinical Studies	the studies conducted in animals to evaluate the pharmacology, 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.
Proprotein convertase subtilisin/kexin type 9 (“PCSK9”)	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
Protease	a class of enzymes that support proteolysis, the process of breaking down proteins into smaller components to allow for new protein synthesis. Viruses use various proteases to reproduce their protein components as part of their replication process
Pulmonary Vascular Resistance	the resistance to blood flowing through the pulmonary circulation loop (from the heart through the lungs, and back to the heart). Elevated pulmonary vascular resistance is a characteristic of PAH, and requires increased work by the heart to overcome.
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).
Reverse Cholesterol Transport (“RCT”)	the term that signifies the process whereby cholesterol, an insoluble molecule, is packaged and transported by special particles in the plasma called lipoproteins for movement from peripheral tissues through the blood and back to the liver for excretion from the body. Cholesterol that moves from peripheral tissues to the liver is considered to be moving reverse direction.
in the	
Ribonucleic Acid (“RNA”)	is a biological macromolecule that plays a critical role in the coding, regulation, and expression of genes. Like DNA, RNA consists of a chain of nucleotides, but RNA typically takes the form of a single stranded helix, while DNA forms a paired double strand. Many viruses, including SARS-CoV-2 utilize RNA exclusively to store genetic information.
RNA Polymerase	is an enzyme that catalyzes the replication of RNA. Viruses require RNA polymerase to copy their genetic material (stored in RNA) during their replication process.
RVX-208	our drug candidate for the treatment of atherosclerosis in patients at high risk for cardiovascular disease.
Severe acute respiratory syndrome coronavirus 2 (“SARS-CoV-2”)	a strain of coronavirus that causes COVID-19, a respiratory disease that resulted in a global pandemic beginning in late 2019.
SGLT2	Sodium-glucose Cotransporter-2 (SGLT2). SGLT2 is a glucose transporter located in the kidneys and it is responsible for 90% of glucose reabsorption. Inhibition of SGLT2 leads to the decrease in blood glucose due to the increase in renal glucose excretion. SGLT2 inhibitors are a class of

	prescription medicines that are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. Medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, and empagliflozin.
Statin	a class of drugs that block cholesterol production in the body by inhibiting an enzyme called HMG-CoA reductase.
Stroke Volume	the volume of blood pumped from the left ventricle with each heartbeat (typically expressed in milliliters). Stroke volume is an important measure of cardiac function and is a key prognostic measure for PAH
Therapeutic	a biopharmaceutical useful for treating a disease.
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.
Therapeutic Products Directorate (“TPD”)	the Canadian governmental agency that is responsible for the regulation and approval of the sale of drugs and diagnostics in Canada.
Triglycerides	a type of fat found in the blood and other parts of the body.
Type II Diabetes	(see “ <i>Diabetes Mellitus</i> ”)
Zenith	Zenith Capital Corp. (formerly Zenith Epigenetics Corp.), a corporation incorporated under the ABCA, and its subsidiaries.

References

- Aday, A. W. and P. M. Ridker (2018). "Antiinflammatory Therapy in Clinical Care: The CANTOS Trial and Beyond." Front Cardiovasc Med **5**: 62.
- Agerholm-Larsen, B., A. Tybjaerg-Hansen, et al. (2000). "Common cholesteryl ester transfer protein mutations, decreased HDL cholesterol, and possible decreased risk of ischemic heart disease: The Copenhagen City Heart Study." Circulation **102**(18): 2197-2203.
- Asztalos, B. F., L. A. Cupples, et al. (2004). "High-density lipoprotein subpopulation profile and coronary heart disease prevalence in male participants of the Framingham Offspring Study." Arteriosclerosis, thrombosis, and vascular biology **24**(11): 2181-2187.
- Barter, P., A. M. Gotto, et al. (2007). "HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events." The New England journal of medicine **357**(13): 1301-1310.
- Baumgart, M., H. M. Snyder, et al. (2015). "Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective." Alzheimers Dement **11**(6): 718-726.
- Beigel, J. H., K. M. Tomashek, et al. (2020). "Remdesivir for the Treatment of Covid-19 - Final Report." The New England journal of medicine **383**(19): 1813-1826.
- Boden, W. E., J. L. Probstfield, et al. (2011). "Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy." The New England journal of medicine **365**(24): 2255-2267.
- Borggreve, S. E., H. L. Hillege, et al. (2006). "An increased coronary risk is paradoxically associated with common cholesteryl ester transfer protein gene variations that relate to higher high-density lipoprotein cholesterol: a population-based study." The Journal of clinical endocrinology and metabolism **91**(9): 3382-3388.
- Chistiakov, D. A., I. A. Sobenin, et al. (2014). "Mechanisms of medial arterial calcification in diabetes." Current pharmaceutical design **20**(37): 5870-5883.
- Cutler, D. M. and L. H. Summers (2020). "The COVID-19 Pandemic and the \$16 Trillion Virus." JAMA **324**(15): 1495-1496.
- Daugherty, S. E., Y. Guo, et al. (2021). "Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study." BMJ **373**: n1098.
- Davis, H. E., L. McCorkell, et al. (2023). "Long COVID: major findings, mechanisms and recommendations." Nature reviews. Microbiology **21**(3): 133-146.
- Deckers, K., S. H. J. Schievink, et al. (2017). "Coronary heart disease and risk for cognitive impairment or dementia: Systematic review and meta-analysis." PloS one **12**(9): e0184244.
- Del Valle, D. M., S. Kim-Schulze, et al. (2020). "An inflammatory cytokine signature predicts COVID-19 severity and survival." Nature medicine **26**(10): 1636-1643.
- Dougan, M., A. Nirula, et al. (2021). "Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19." The New England journal of medicine **385**(15): 1382-1392.
- Farkouh, M. E., M. Domanski, et al. (2012). "Strategies for multivessel revascularization in patients with diabetes." The New England journal of medicine **367**(25): 2375-2384.
- Fu, L., D. Gilham, et al. (2023). "Dual mechanism: Epigenetic inhibitor apabetalone reduces SARS-CoV-2 Delta and Omicron variant spike binding and attenuates SARS-CoV-2 RNA induced inflammation." International immunopharmacology **117**: 109929.
- Fu, L., S. Wasiaik, et al. (2022). "Inhibition of epigenetic reader proteins by apabetalone counters inflammation in activated innate immune cells from Fabry disease patients receiving enzyme replacement therapy." Pharmacology research & perspectives **10**(3): e00949.
- Gilham, D., A. L. Smith, et al. (2021). "Bromodomain and Extraterminal Protein Inhibitor, Apabetalone (RVX-208), Reduces ACE2 Expression and Attenuates SARS-Cov-2 Infection In Vitro." Biomedicines **9**(4).
- Gordon, D. J., J. L. Probstfield, et al. (1989). "High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies." Circulation **79**(1): 8-15.
- Gouni-Berthold, I. and H. K. Berthold (2014). "PCSK9 antibodies for the treatment of hypercholesterolemia." Nutrients **6**(12): 5517-5533.
- Gupta, A., Y. Gonzalez-Rojas, et al. (2022). "Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial." JAMA.
- Haarhaus, M., V. Brandenburg, et al. (2017). "Alkaline phosphatase: a novel treatment target for cardiovascular disease in CKD." Nature reviews. Nephrology **13**(7): 429-442.
- Hammond, J., H. Leister-Tebbe, et al. (2022). "Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19." The New England journal of medicine.
- Hertle, E., C. D. Stehouwer, et al. (2014). "The complement system in human cardiometabolic disease." Molecular immunology **61**(2): 135-148.
- Ishimura, E., S. Okuno, et al. (2014). "Relationship between serum sclerostin, bone metabolism markers, and bone mineral density in maintenance hemodialysis patients." The Journal of clinical endocrinology and metabolism **99**(11): 4315-4320.
- Jayk Bernal, A., M. M. Gomes da Silva, et al. (2022). "Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients." The New England journal of medicine **386**(6): 509-520.
- Kannel, W. B., P. A. Wolf, et al. (1987). "Fibrinogen and risk of cardiovascular disease. The Framingham Study." JAMA **258**(9): 1183-1186.
- Kulikowski, E., D. Gilham, et al. (2016). "Apabetalone Reduces Levels of Key Markers Involved in Vascular Calcification." Journal of the American Society of Nephrology : JASN **27**(Abstract Edition).

- Letter, T. M. (2022). "Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19." *JAMA* **327**(4): 384-385.
- Li, J. J. and C. H. Fang (2004). "C-reactive protein is not only an inflammatory marker but also a direct cause of cardiovascular diseases." *Medical hypotheses* **62**(4): 499-506.
- Lincoff, A. M., J. C. Tardif, et al. (2014). "Effect of aleglitazar on cardiovascular outcomes after acute coronary syndrome in patients with type 2 diabetes mellitus: the AleCardio randomized clinical trial." *JAMA* **311**(15): 1515-1525.
- Lomashvili, K. A., P. Garg, et al. (2008). "Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification." *Kidney Int* **73**(9): 1024-1030.
- Lomashvili, K. A., P. Garg, et al. (2008). "Upregulation of alkaline phosphatase and pyrophosphate hydrolysis: potential mechanism for uremic vascular calcification." *Kidney international* **73**(9): 1024-1030.
- Lowenstein, C. and K. Matsushita (2004). "The acute phase response and atherosclerosis." *Drug Discovery Today: Disease Mechanisms* **1**(1): 17-22.
- Mestas, J. and K. Ley (2008). "Monocyte-endothelial cell interactions in the development of atherosclerosis." *Trends in cardiovascular medicine* **18**(6): 228-232.
- Mills, R. J., S. J. Humphrey, et al. (2021). "BET inhibition blocks inflammation-induced cardiac dysfunction and SARS-CoV-2 infection." *Cell* **184**(8): 2167-2182 e2122.
- Munshi, M. N. (2017). "Cognitive Dysfunction in Older Adults With Diabetes: What a Clinician Needs to Know." *Diabetes Care* **40**(4): 461-467.
- Pfeffer, M. A., B. Claggett, et al. (2015). "Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome." *The New England journal of medicine* **373**(23): 2247-2257.
- Pickup, J. C. (2004). "Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes." *Diabetes Care* **27**(3): 813-823.
- Provencher, S., F. Potus, et al. (2022). "BET Protein Inhibition for Pulmonary Arterial Hypertension: A Pilot Study." *American journal of respiratory and critical care medicine*.
- Ravona-Springer, R. and M. Schnaider-Beerli (2011). "The association of diabetes and dementia and possible implications for nondiabetic populations." *Expert Rev Neurother* **11**(11): 1609-1617.
- Ridker, P. M. (2001). "Role of inflammatory biomarkers in prediction of coronary heart disease." *Lancet* **358**(9286): 946-948.
- Ridker, P. M., C. P. Cannon, et al. (2005). "C-reactive protein levels and outcomes after statin therapy." *The New England journal of medicine* **352**(1): 20-28.
- Ridker, P. M., J. MacFadyen, et al. (2010). "Relation of baseline high-sensitivity C-reactive protein level to cardiovascular outcomes with rosuvastatin in the Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)." *The American journal of cardiology* **106**(2): 204-209.
- Rosano, C., E. M. Simonsick, et al. (2005). "Association between physical and cognitive function in healthy elderly: the health, aging and body composition study." *Neuroepidemiology* **24**(1-2): 8-14.
- Rubins, H. B., S. J. Robins, et al. (1999). "Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group." *The New England journal of medicine* **341**(6): 410-418.
- Saedi, E., M. R. Gheini, et al. (2016). "Diabetes mellitus and cognitive impairments." *World J Diabetes* **7**(17): 412-422.
- Schoppet, M. and C. M. Shanahan (2008). "Role for alkaline phosphatase as an inducer of vascular calcification in renal failure?" *Kidney international* **73**(9): 989-991.
- Seidah, N. G. (2013). "Proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors in the treatment of hypercholesterolemia and other pathologies." *Current pharmaceutical design* **19**(17): 3161-3172.
- Seidah, N. G., Z. Awan, et al. (2014). "PCSK9: a key modulator of cardiovascular health." *Circulation research* **114**(6): 1022-1036.
- Seifert, P. S. and M. D. Kazatchkine (1988). "The complement system in atherosclerosis." *Atherosclerosis* **73**(2-3): 91-104.
- Shrivastava, A. K., H. V. Singh, et al. (2015). "Serial measurement of lipid profile and inflammatory markers in patients with acute myocardial infarction." *EXCLI journal* **14**: 517-526.
- Staton, T. (2015) "Say what? CVS Health execs figure PCSK9 meds to cost up to \$150B."
- Tataru, M. C., J. Heinrich, et al. (1999). "D-dimers in relation to the severity of arteriosclerosis in patients with stable angina pectoris after myocardial infarction." *European heart journal* **20**(20): 1493-1502.
- Thompson, A., E. Di Angelantonio, et al. (2008). "Association of cholesteryl ester transfer protein genotypes with CETP mass and activity, lipid levels, and coronary risk." *JAMA* **299**(23): 2777-2788.
- Tice JA, O. D., Chapman R, Kumar V, Seidner M, Rind DM, Pearson SD (2017). "Evolocumab for Treatment of High Cholesterol: Effectiveness and Value New Evidence Update." *Institute for Clinical and Economic Review*.
- Tice JA, O. D., Chapman R, Rind DM, Pearson SD, Kazi DS, Coxson PG, Penko J, Bibbins-Domingo K (2018). "Alirocumab for Treatment of High Cholesterol: Effectiveness and Value Preliminary New Evidence Update." *Institute for Clinical and Economic Review*.
- Tonelli, M., G. Curhan, et al. (2009). "Relation between alkaline phosphatase, serum phosphate, and all-cause or cardiovascular mortality." *Circulation* **120**(18): 1784-1792.
- Umegaki, H. (2014). "Type 2 diabetes as a risk factor for cognitive impairment: current insights." *Clin Interv Aging* **9**: 1011-1019.
- Van der Feen, D. E., K. Kurakula, et al. (2019). "Multicenter Preclinical Validation of BET Inhibition for the Treatment of Pulmonary Arterial Hypertension." *American journal of respiratory and critical care medicine* **200**(7): 910-920.
- Virani, S. S., A. Alonso, et al. (2020). "Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association." *Circulation* **141**(9): e139-e596.
- Walldius, G. and I. Jungner (2005). "Rationale for using apolipoprotein B and apolipoprotein A-I as indicators of cardiac risk and as targets for lipid-lowering therapy." *European heart journal* **26**(3): 210-212.

-
- Wannamethee, S. G., P. H. Whincup, et al. (2009). "Circulating inflammatory and hemostatic biomarkers are associated with risk of myocardial infarction and coronary death, but not angina pectoris, in older men." Journal of thrombosis and haemostasis : JTH **7**(10): 1605-1611.
- Wasiak, S., D. Gilham, et al. (2020). "Epigenetic Modulation by Apabetalone Counters Cytokine-Driven Acute Phase Response In Vitro, in Mice and in Patients with Cardiovascular Disease." Cardiovascular therapeutics **2020**: 9397109.
- Weinreich, D. M., S. Sivapalasingam, et al. (2021). "REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19." The New England journal of medicine **385**(23): e81.
- White, W. B., C. P. Cannon, et al. (2013). "Alogliptin after acute coronary syndrome in patients with type 2 diabetes." The New England journal of medicine **369**(14): 1327-1335.
- Wolters, F. J., R. A. Segufa, et al. (2018). "Coronary heart disease, heart failure, and the risk of dementia: A systematic review and meta-analysis." Alzheimers Dement **14**(11): 1493-1504.
- Wu, L. and K. G. Parhofer (2014). "Diabetic dyslipidemia." Metabolism: clinical and experimental **63**(12): 1469-1479.
- Xie, Y., E. Xu, et al. (2022). "Long-term cardiovascular outcomes of COVID-19." Nature medicine **28**(3): 583-590.
- Yusuf, S., S. Hawken, et al. (2004). "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study." Lancet **364**(9438): 937-952.
- Zacharowski, K., P. Zacharowski, et al. (2006). "Fibrin(ogen) and its fragments in the pathophysiology and treatment of myocardial infarction." Journal of molecular medicine **84**(6): 469-477.
- Zilliox, L. A., K. Chadrasekaran, et al. (2016). "Diabetes and Cognitive Impairment." Curr Diab Rep **16**(9): 87.