NephroGenex, Inc.
Form 10-K
March 31, 2014

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

ý **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2013

OR

o **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to
Commission file number: 001-36303

NephroGenex, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**20-1295171**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
79 T.W. Alexander Drive 4401 Research Commons Building Suite 290 P.O. Box 14188 Research Triangle Park, NC	**27709** (Zip Code)
(Address of principal executive offices)	

(609) 986-1780
Registrant's telephone number, including area code

Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.001 Par Value Per Share	NASDAQ Capital Market

Securities registered pursuant to Section 12(g) of the Exchange Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No ý

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes o No ý

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ý No o

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. o

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o	Accelerated filer o	Non-accelerated filer o [Do not check if a smaller reporting company]	Smaller reporting company ý

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No ý

The aggregate market value of the registrant's voting and non-voting common stock held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the common stock was last sold as of March 17, 2014 was $25,182,571. The registrant has provided this information as of March 17, 2014 because its common stock was not publicly traded as of the last business day of its most recently completed second fiscal quarter.

As of March 17, 2014, the registrant had 8,855,114 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The following documents (or parts thereof) are incorporated by reference into the following parts of this Form 10-K: Certain information required in Part III of this Annual Report on Form 10-K is incorporated from the Registrant's Proxy Statement for the Annual Meeting of Stockholders to be held on May 15, 2014.

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Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements. All statements other than statements of historical facts contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, objectives of management and expected market growth are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The words "anticipate," "believe," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements include, among other things, statements about:

- our ability to obtain additional financing;
- our use of net proceeds from our recently completed initial public offering;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- the success and timing of our preclinical studies and clinical trials;
- our ability to obtain and maintain regulatory approval of Pyridorin and any other product candidates we may develop, and the labeling under any approval we may obtain;
- regulatory developments in the United States and other countries;
- the performance of third-party manufacturers;
- our plans to develop and commercialize our product candidates;
- our ability to obtain and maintain intellectual property protection for our product candidates;
- the successful development of our sales and marketing capabilities;
- the potential markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of any future products;
- the success of competing drugs that are or become available; and
- the loss of key scientific or management personnel.

These forward-looking statements are only predictions and we may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, so you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our business, financial condition and operating results. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Item 1.A. Risk Factors, that could cause actual future results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

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You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to the Annual Report on Form 10-K with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements whether as a result of new information, future events or otherwise, except as required by applicable law.

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PART I

All brand names or trademarks appearing in this report are the property of their respective holders. Unless the context requires otherwise, references in this report to "NephroGenex," the "Company," "we," "us," and "our" refer to NephroGenex, Inc.

Item 1. BUSINESS

Overview

We are a pharmaceutical company focused on the development of therapeutics to treat kidney disease, an area of significant unmet medical need. Since our inception, we have collaborated with the world's leading experts in kidney disease and leveraged our knowledge of pathogenic oxidative chemistries to build a strong portfolio of intellectual property and to advance the development of our drug candidates. We believe that our comprehensive effort to develop a new generation of therapeutics that target kidney disease provides us with a leadership position in this large and attractive market.

Pathogenic oxidative chemistries are collectively a group of oxygen-based chemical reactions that occur in the body during stress, injury, or disease, to form compounds that can induce pathological changes in tissues that effect normal physiological function. These include (i) advanced glycation end-products (AGE's), which are oxidative end products of glucose-modified biomolecules which adversely affect their function; (ii) reactive oxygen species (ROS), which are chemically reactive molecules containing oxygen such as oxygen ions and peroxides that when elevated in the body can induce pathology; and (iii) toxic carbonyls which are reactive compounds that can modify biomolecules and affect their function. These chemistries are generally agreed to be involved in the etiology of diabetic nephropathy, a common complication of diabetes. We are developing Pyridorin ("Pyridorin"), a small molecule drug that is a unique and broadly acting inhibitor of the pathogenic oxidative chemistries which are elevated in diabetic patients.

We licensed patents covering methods of use and synthesis of Pyridorin from BioStratum, Inc. in May of 2006. We subsequently acquired Pyridorin-related patents from BioStratum through a Series A financing completed in May of 2007. At the time of acquisition, BioStratum, through its contracted investigators, contract research organizations, and collaborators had completed 5 preclinical efficacy studies, 36 preclinical safety studies, 4 Phase 1 studies and 5 Phase 2 studies with Pyridorin. After the acquisition, we conducted a multi-center, randomized, placebo-controlled Phase 2b study, namely PYR-210. In addition, we worked with the FDA to establish a new regulatory pathway for Pyridorin approval.

Pyridorin has demonstrated preliminary evidence of efficacy in slowing the progression of diabetic nephropathy in relevant patient populations in three Phase 2 clinical studies. Based on these results, Pyridorin will be further developed in a Phase 3 program agreed to by the U.S. Food and Drug Administration (FDA) under a Special Protocol Assessment (SPA). This Phase 3 program will use a novel endpoint based on a novel, events-based endpoint based on end stage renal disease (ESRD) or a 50% increase in serum creatinine (SCr). We believe this change will significantly reduce the cost and time for completion of the Phase 3 program compared to the traditional endpoint used in previous pivotal trials for diabetic nephropathy. The traditional renal endpoint used in previous pivotal trials for diabetic nephropathy is a 100% increase in SCr from baseline or ESRD. Based on an analysis of the Irbesartan Type II Diabetic Nephropathy Trial (IDNT) used for the approval of the drug irbesartan, the follow-up time required to reach the new endpoint of a 50% SCr increase would be approximately 50% less than the follow-up time required to reach the traditional endpoint in a similar patient population. We believe that we will be the first company to use this novel endpoint in a Phase 3 trial.

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We are also studying the application of an intravenous formulation of Pyridorin to specific types of acute kidney injury (AKI) where pathogenic oxidative chemistries have been identified as a possible contributing factor to the severity of this condition.

Corporate Objectives

There is a large medical need and market opportunity for treatments that can (1) slow the progression of renal disease and thus delay or avoid the onset of end stage renal disease (ESRD); or (2) reduce the severity of acute kidney injury and its associated potential treatment costs and long term complications.

Our principal corporate objective is the maximization of shareholder value by advancing Pyridorin through Phase 3 development and approval. In order to maximize the market potential of Pyridorin, we intend to consider entering into a partnership for the launch and marketing of the product at the end of Phase 3 or possibly earlier, based on interim clinical data. We also intend to consider acquisitions and the development of other clinical candidates as we see appropriate.

We acquired commercial rights to Pyridorin in 2007 and, since then, have been investigating the safety and efficacy of Pyridorin therapy for diseases in which pathogenic oxidative chemistries are an established and/or causative and contributing factor in kidney disease. These include diabetic nephropathy and acute kidney injury.

We anticipate seeking corporate partners to aid us in commercialization and market entry.

Our Strategy

There is a large medical need and market opportunity for treatments that can (1) slow the progression of renal disease and thus delay or prevent the onset of end stage renal disease (ESRD); or (2) reduce the severity of acute kidney injury and potentially its associated treatment costs and long term complications.

We are committed to applying our leadership position in the field of kidney disease to transform the lives of patients with debilitating, costly diseases or conditions. Each of our ongoing and planned development projects addresses kidney diseases or conditions with high unmet medical need that presents a significant market opportunity. The core elements of our strategy include:

- advancing Pyridorin through Phase 3 development for the treatment of diabetic nephropathy in patients with type 2 diabetes;
- submission and approval of a new drug application (NDA) in the United States and a Market Authorization Application (MAA) in Europe;
- commercializing Pyridorin using a highly-targeted sales force in the United States and the rest of the world;
- maximizing the value of our Pyridorin franchise by expanding into additional indications; and
- deploying capital strategically to develop our portfolio of product candidates and create shareholder value.

Rationale for Development of Pyridorin

Diabetic microvascular complications arise in tissues that are not under direct insulin control and are thus exposed to elevated levels of glucose in hyperglycemic conditions. This exposure leads to a perturbation or deviation of many metabolic pathways and the emergence of non-enzymatic oxidative chemistries that form pathogenic reactive compounds including: (1) reactive oxygen species; (2) reactive carbonyl intermediates (which are reactive compounds containing a carbonyl function group that can

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react with biomolecules and modify their function, a process collectively referred to as carbonyl stress); and (3) glycated protein amino groups and their subsequent advanced glycation end-products (AGEs).

One pathway of particular interest is the post-Amadori pathway of AGE formation. The study of this pathway led to the discovery of Pyridorin as a promising drug candidate for diabetic nephropathy. Our founding scientists first isolated protein-Amadori intermediates and utilized them to search for compounds that could specifically block the degradation of protein-Amadori intermediates into AGEs. They examined many previously studied AGE inhibitors in this screening assay, including aminoguanidine (pimagedine). The majority of such AGE inhibitors, including aminoguanidine (Graph 2), did not exhibit inhibitory activity towards formation of the AGE carboxymethlylysine (CML) under these conditions. However, Pyridorin uniquely exhibited potent post-Amadori inhibitory activity (Graph 1). Due to the possible importance of this AGE pathway, this inhibitory activity may form the basis for the activity of Pyridorin in inhibiting the progression of diabetic nephropathy, as evidenced in nonclinical studies and as summarized below.

Chronic hyperglycemia is directly associated with end-organ damage in patients with diabetes. The major target organs affected, namely the kidney, peripheral nerves, retina, and the vasculature, are all exposed to glucose fluctuations since they are not under insulin regulation. This hyperglycemia damage may be initiated by direct chemical reaction of glucose (an aldehyde) with protein amino groups, leading to the formation of harmful products collectively designated as AGEs. It has been established that circulating and tissue levels of AGEs are elevated in patients with poorly controlled diabetes and

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increase dramatically when the glomerular filtration rate (GFR) declines. GFR is the calculation of the flow rate of filtered fluid through the glomerulus that determines how well the kidney is filtering the blood.

In extensive in-vitro studies, Pyridorin has been shown to inhibit AGE formation and scavenge ROS and toxic carbonyl compounds. For example, Pyridorin has been shown to:

- inhibit the degradation of glycated proteins to AGEs;
- inhibit lipoxidation (lipid oxidation) by trapping lipoxidation intermediates, (reactive lipid compounds that form during the oxidation of lipids that normally proceed to lipid oxidation end-products), particularly 1,4-dicarbonyls;
- scavenge glycoaldehyde and dicarbonyls intermediates of carbonyl stress such as glyoxal and methylglyoxal;
- trap the hydroxyl radical (which is a highly reactive and short-lived neutral form of the hydroxide ion (HO-); and
- bind redox transition metal ions (such as Cu2+, Mn2+, and Fe 2+),which interfere with their catalytic role in oxidative reactions (redox chemical reactions are common physiological chemical reactions involving the transfer of electrons).

All of the above processes and reactive compounds have been implicated directly or indirectly in the development of diabetic microvascular disease, the basis of diabetic complications.

Pyridorin Targets Specific
Pathogenic Oxidative Chemistries

The above graphic is for illustrative purposes only.

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Preclinical Efficacy Results

The ability of Pyridorin to slow the progression of diabetic nephropathy in animals has been examined in several preventative and interventional preclinical studies. These include a "proof-of-principle" rat model of AGE-albumin induced nephropathy (Khalifah, et al, J. Am. Soc. Nephrol. 1997 Sep; 8:641A), an STZ-treated rat classical model of type 1 diabetic nephropathy (Degenhardt, et al, Kidney Int. 2002; 61:939-950), a db/db mouse spontaneous model of type 2 diabetic nephropathy Zheng, et al, Kidney Int. 2006; 70: 507-514), the Zucker fa/fa rat model of non-diabetic, hyperlipidemic nephropathy (Alderson, et al, Kidney Int. 2003; 63:2123-2133), and the type 2 diabetic KK-Ay/Ta mouse (Tanimoto, et al, Metabolism. 56:160-7, 2007).

In the first model, AGE-modified rat serum albumin (RSA), which is the most abundant protein in rat blood plasma, was injected daily for 6 weeks into normoglycemic rats to mimic damage from circulating AGE-modified plasma proteins. These normoglycemic rats were given daily tail vein injections of AGE-modified RSA at 50 mg/kg/day with and without concomitant treatment with 25 mg/kg/day Pyridorin in the drinking water. Another AGE inhibitor, aminoguanidine (pimagedine) was also evaluated in this model for comparative purposes. At the time of this study, aminoguanidine was being developed by Alteon for the treatment of diabetic nephropathy. Previous studies have demonstrated that such daily injections of AGE-modified RSA induce pathological changes in the kidney consistent with the onset of diabetic nephropathy. As expected, overt nephropathy did not develop during this short-term study. However, statistically significant early diabetic-like morphological changes were observed in the glomerulus, such as an increase in glomerular volume, an increase in albumin deposition (Graph 3), and a decrease in heparin sulfate, a component of the kidney anionic filtration barrier (Graph 4).

Treatment with Pyridorin protected the animals from the damaging effects of AGE-albumin with regard to all three parameters mentioned above. All of the results were statistically significant when compared to untreated animals. Treatment with similar amounts of aminoguanidine did not lead to significant amelioration except for a partial reduction in albumin deposition.

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Results from an STZ-treated rat model of type 1 diabetic nephropathy are shown in Graphs 5 and 6 below. Pyridorin inhibited the development of albuminuria compared to untreated animals ($p = 0.0001$ at 27 weeks). It also inhibited the increase in plasma creatinine levels compared to untreated animals ($p = 0.0001$ at 28 weeks). Increases in albuminuria and plasma creatinine levels are indications of decreasing kidney function. Additionally, at equal doses, Pyridorin exhibited an improvement over aminoguanidine in preventing increases in plasma creatinine ($p = 0.021$ at 28 weeks) and albuminuria.

In addition to these results on kidney function, this study demonstrated that Pyridorin significantly inhibited AGE formation in skin collagen, as measured by standard methods of quantifying AGE levels (i.e. pepsin digestibility, AGE fluorescence, and carboxymethyllysine AGE content).

In a second STZ study similar in design to the above, treatment with Pyridorin at 1 g/L drinking water was compared to treatment with the ACE inhibitor enalapril (the standard of care treatment for diabetic nephropathy) dosed at 50 mg/L drinking water (Alderson, et al, Diabetologia 2004; 47:1385-1395). At 28 weeks, Pyridorin significantly inhibited the development of albuminuria relative to both untreated diabetic controls (43 mg/24 hr versus 12mg/24 hr) and diabetic animals treated with enalapril (26 mg/24 hr versus 12 mg/24 hr). The differences were statistically significant. Pyridorin also significantly reduced the increases in plasma creatinine relative to both untreated diabetic controls (110 µmol/L versus 45 µmol/L) and diabetic animals treated with enalapril (70 µmol/L versus 45 µmol/L). The differences were statistically significant.

Pyridorin has also been evaluated in a standard model of type 2 diabetic nephropathy. The db/db mouse is a commonly used mouse model of type 2 diabetes and develops histologic changes in the kidney which are very similar to those observed in humans with diabetic nephropathy. The study was designed to evaluate the effects of Pyridorin in established diabetic nephropathy. In mice with biopsy-proven diabetic nephropathy, Pyridorin orally administered at 250 mg/kg/day for 2 months resulted in a 43% reduction in the urinary albumin/creatinine ratio. In contrast, the placebo group albumin/creatinine ratio increased 215% ($p<0.05$). The ACE inhibitor treated group increased 40%.

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Microscopic lesions of glomerulosclerosis in the kidney were also reduced in the Pyridorin group when compared with control animals ($p<0.05$).

A second db/db mouse study of 16-week treatment duration was conducted to assess the combination of Pyridorin plus the ACE inhibitor enalapril versus enalapril alone. As in the initial study, there were significant effects on urinary albumin/creatinine ratio. In the placebo group albumin/creatinine ratio increased approximately 350% over 16 weeks. The enalapril treated group increased approximately 220%. The Pyridorin plus enalapril group increased approximately 50% ($p<0.05$ compared to control). There was also a reduction in glomerular lesions in the Pyridorin plus ACE inhibitor group ($p<0.05$ compared to control). In addition, Pyridorin plus enalapril significantly improved survival versus the control or enalapril alone ($p<0.05$).

Pyridorin has also been studied in a non-diabetic, "syndrome X-like" model to assess its effects on the development of nephropathy in the absence of diabetes. In this study, the development of nephropathy and dyslipidemia in treated and untreated obese fa/fa rats was compared to those in lean Fa/fa littermates. Pyridorin, administered at 1 g/L in the drinking water, markedly inhibited the development of dyslipidemia and nephropathy in the fa/fa rats. A 10-fold increase in albuminurea was observed in the untreated obese fa/fa rats over 32 weeks as well as an increase in plasma creatinine from 0.9 mg/dL to 1.5 mg/dL. Pyridorin provided nearly complete protection against increases in both of these parameters ($p<0.0001$). Pyridorin also inhibited the thickening of the aortic and coronary vasculature observed in the untreated obese fa/fa rats by approximately 90% ($p<0.05$). Furthermore, Pyridorin significantly reduced AGE levels in the rat skin collagen when compared to the untreated fa/fa group ($p<0.05$).

Pyridorin was also studied in the type 2 diabetic KK-Ay/Ta mouse. KK-Ay/Ta mice were given Pyridorin (200 or 400 mg/kg per day) starting at 8 weeks of age for 12 weeks. Pyridorin therapy, especially at 400 mg/kg per day, prevented an increase in albuminuria relative to untreated controls (increase of 6.4 mg/L versus 43.5 mg/L, $p<0.05$). Accumulations or Carboxymethyllysine (an AGE) and nitrotyrosine in the kidney were also decreased ($p<0.05$). TGF-β1 and laminin-β1 messenger RNA expressions in kidneys were significantly lower than those in the controls ($p<0.05$).

Preclinical Safety Summary

Pyridorin was studied in acute and chronic rat, rabbit and dog studies for up to one year. Acute and chronic toxicology studies were conducted by Quintiles Preclinical Services. Developmental & reproductive toxicology studies were conducted by Charles River Laboratories Inc. All of these studies were sponsored by BioStratum, Inc. There were no observable side effects seen at blood levels as high 100x over therapeutic blood levels in humans. In a full battery of genotoxicity tests, no mutagenicity or clastogenicity was observed. These studies were conducted by Bioreliance Labs, Quintiles Toxicology/Pathology Services, and Sequani Ltd and sponsored by BioStratum, Inc. Human hepatic cytochrome P450 enzymes are involved in the metabolism and elimination of many widely used drugs. Any induction or inhibition of these enzymes can potentially lead to drug-drug interactions. In human hepatic cell assays, Pyridorin had no effect on cytochrome P450 enzymes. Thus, the potential for Pyridorin to interact with the metabolism of other drugs in-vivo is unlikely. The P450 enzyme studies were conducted by RTI International and sponsored by BioStratum, Inc.

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Clinical Safety Summary

An investigational new drug application (IND) was filed for Pyridorin by BioStratum, Inc. on July 30, 1999. The sponsorship of the IND was transferred to NephroGenex on July 10, 2007.

The safety, tolerability, and pharmacokinetics of Pyridorin was investigated in four Phase 1 studies conducted in healthy male volunteers. A summary of these studies is provided in the table below:

Protocol #	**440-01 (PO)**	**440-01 (IV)**	**440-02**	**PYR-103**
Conducted	Sep 99 - Nov 99	Sep 99 - Nov 99	Nov 99 - Dec 99	Mar 2001
CRO/Sponsor	MDS Harris/BioStratum	MDS Harris/BioStratum	MDS Harris/BioStratum	PPD Development/BioStratum
Location(s)	Lincoln, NE	Lincoln, NE	N. Ireland	Morrisville, NC
Active/Placebo	16/8	4/2	18/6	6/0
Type of Subject M/F	Healthy 24/0	Healthy 6/0	Healthy 24/0	Healthy 6/0
Age range	19 - 41 yrs	19 - 41 yrs	18 - 45 yrs	19 - 50 yrs
Study Design	Ascending Single dose Randomized Double Blind Placebo control	Single dose Randomized Double Blind	Ascending Multiple dose Randomized Double Blind Placebo control	Single dose High fat meal vs fasted 2-way crossover
Route of admin.	Oral	I.V.	Oral	Oral
Dose	3 mg/kg 10 mg/kg 30 mg/kg 50 mg/kg	10 mg/kg	5mg/kg BID 15 mg/kg BID 25 mg/kg BID	500 mg
Duration	Single dose	Single dose	7 days	Single dose
Results	No safety signal	No safety signal	No safety signal	No safety signal

In all four of these studies, Pyridorin was well tolerated with no drug-related toxicity observed in any patients. Based on its benign profile in healthy patients, the decision was made by BioStratum to advance Pyridorin into Phase 2 testing in patients with diabetic nephropathy. The safety, tolerability, and pharmacokinetics of Pyridorin was investigated by BioStratum in a Phase 2 study conducted in patients with Type 1 diabetic nephropathy. In addition, the safety, tolerability and biological activity of Pyridorin was investigated in another Phase 2 study conducted in Type 2 diabetic patients with microalbuminuria (ACR≤ 300 mg/g). This study was conducted in Japan under the sponsorship and management of Kowa Company Ltd.

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A summary of these two studies is provided in the table below:

Protocol #	PYR-202	K-163-04
Conducted	Nov 2000 - Mar 2001	2005 - 2006
CRO/Sponsor	PPD Development/BioStratum	Kowa
Location(s)	USA (5 sites)	Japan
Active/Placebo	9/3	68/67
Type of Subject M/F	Type 1 Diabetic nephropathy 8/4	Type 2 Diabetes w/microalbuminurea 107/28
Age range	28 - 54 yrs	20 - 70 yrs
Study Design	Multiple dose Randomized Escalating dose Double Blind Placebo control	Multiple dose Randomized Double Blind Placebo control
Route of admin.	Oral	Oral
Dose	50 mg BID for 7 days then 250 mg BID for 7 days then 500 mg BID for 28 days	300 mg BID
Duration	6 weeks	26 weeks
Results	No safety signal	No safety signal No effect on microalbuminuria

In both of these studies, Pyridorin was well tolerated with no drug-related toxicity observed in any patients. Based on its benign profile in diabetic nephropathy patients, the decision was made by BioStratum to continue evaluation of the safety, tolerability and biological activity of Pyridorin in type 1 and type 2 diabetic nephropathy patients with macroalbuminuria (ACR >300 mg/g).

In two randomized, placebo-controlled, Phase 2 studies of 24-week treatment duration, patients with nephropathy due to either type 1 or type 2 diabetes showed no consistent across-study differences between Pyridorin and placebo groups in the type or incidence of adverse event reporting or in vital signs, weight, blood pressure, electrocardiograms (ECGs), general chemistry, urinalysis, hematology or special laboratories (coagulation and thyroid function tests). In the first study, the adverse events defined as definitely, probably, or possibly related to the study drug as determined by the investigator, were reported in 26.2% and 33.3% Pyridorin and Placebo patients respectively. In the second study, the adverse events defined as definitely, probably, or possibly related to the study drug as determined by the investigator, were reported in 35.1% and 44.4% Pyridorin and Placebo patients respectively. The types of serious adverse events (SAEs) observed were quite varied and very similar to what is typically observed in diabetic nephropathy patients. Cardiac related events were the most common followed by infections. While a numerical imbalance in SAE reporting was seen, the lack of a specific type of SAE reported in patients receiving Pyridorin, the similarity to the types of SAEs reported in other diabetic nephropathy studies, and the significant baseline medical conditions in these patients suggest that the SAEs were related to the underlying medical conditions, not an effect attributable to Pyridorin. In a retrospective ECG analysis using pooled data from the two 24-week studies, there was no evidence for an effect of Pyridorin on the QT/QTc interval, either at the group level or at the individual patient

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level (using Fridericia's and Bazett's formulae). The QT/QTc interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. In general, the QT interval represents electrical depolarization and repolarization of the left and right ventricles. A lengthened QT interval is a biomarker for ventricular tachyarrhythmias and a risk factor for sudden death. Fridericia's and Bazett's formulae are two different correction methods commonly used to correct for heart rate differences when calculating the QT interval.

In a 12-month Phase 2 study treatment with Pyridorin, up to 300 mg twice daily (BID) was generally well tolerated. Most of the AEs were mild or moderate in severity and there was a slight increase in the incidence of diarrhea and constipation in the 300 mg BID group relative to placebo. The pattern and occurrence of AEs were consistent with the patient population under study. The overall incidence of AEs and AEs deemed drug-related was similar among the treatment groups. The types of serious adverse events (SAEs) observed were quite varied and very similar to what is observed in diabetic nephropathy patients. Cardiac related events were the most common followed by infections. There were no meaningful differences in SAEs between the placebo group and the Pyridorin group. The observed SAEs were attributed to underlying baseline medical conditions in these patients and not attributed to Pyridorin therapy.

Phase 2 Efficacy Results

PYR-206

PYR-206 was a Phase 2, multi-center, placebo-controlled, randomized, double-blind study which evaluated the safety and tolerability of Pyridorin administered orally via 50 mg capsules BID for 24 weeks to patients with nephropathy due to type 1 or type 2 diabetes.This study was conducted by BioStratum Inc. which utilized the services of the contract research organization Pharmaceutical Product Development (PPD). The study was conducted from October 2001 to January 2003 in the United States.

Although PYR-206 was designed as a safety and tolerability study, post-hoc analyses were performed on various efficacy parameters, including serum creatinine (SCr), urinary creatinine clearance, and TGF-β1. Creatinine is a breakdown product of creatine. Its level in serum reflects the efficiency of the kidney to remove waste products from the blood. Serum creatinine is the most commonly used indicator of renal function. The SCr change from baseline was analyzed for all patients and for the patient subgroups listed in Table 1 below using a repeated measures mixed model with baseline SCr as a fixed covariate.

Treatment with Pyridorin reduced the change in SCr concentration from baseline by 27% for all patients (65 Pyridorin and 63 placebo). While the treatment was not statistically significant in the Intent to Treat (ITT) patient population, which included all patients that received at least one dose of study drug, this effect was statistically significant for a subgroup of patients with type 2 diabetes and a starting baseline SCr ≥ 1.3 mg/dL (Table 1 and Figure 1).

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Table 1: PYR-206 Serum Creatinine Change from Baseline Analysis

Patient Population	Treatment Group	N	Baseline SCr(1)	SCr Change from Baseline(2)	Treatment Effect(3)
All Patients	Pyridorin	65	1.27 ± 0.34	0.12 ± 0.40	-27%
	Placebo	63	1.33 ± 0.38	0.16 ± 0.28	
Type 2 Diabetes	Pyridorin	40	1.28 ± 0.34	0.08 ± 0.29	-53%
	Placebo	40	1.30 ± 0.36	0.17 ± 0.30	
Baseline SCr ≥ 1.3 mg/dL	Pyridorin	34	1.54 ± 0.21	0.13 ± 0.53	-50%
	Placebo	30	1.65 ± 0.28	0.26 ± 0.33	
Type 2, Baseline SCr ≥ 1.3 mg/dL	Pyridorin	22	1.53 ± 0.20	0.06 ± 0.37	-79%**
	Placebo	19	1.59 ± 0.73	0.29 ± 0.35	

(1) Mean ± SD in mg/dL

(2) Unadjusted mean within group change from baseline in mg/dL

(3) Difference relative to placebo in unadjusted mean change from baseline where a negative value indicates a lesser change from baseline in Pyridorin patients (*i.e.* reno-protection)

** Statistically significant, p<0.01

Figure 1. PYR-206 Serum Creatinine Change from Baseline Analysis in Patients with Type 2 Diabetes and a Baseline SCr ≥ 1.3 mg/dL

(1) Mean ± SEM; P= 0.0074 (Repeated measures mixed model analysis with baseline serum creatinine as a fixed covariate)

In the total patient population, Pyridorin also reduced the rate of rise in SCr levels by 23% relative to placebo. The rise in SCr was 0.161 mg/dL/yr and 0.210 mg/dL/yr in the Pyridorin (n=65) and placebo (n=63) groups, respectively. In the sub-population of patients with more substantial renal impairment as evidenced by a baseline SCr level of ≥ 1.3 mg/dL, the ability of Pyridorin to preserve renal function was more pronounced with a 59% reduction in the rate of rise in SCr relative to placebo. In this sub-population of patients, the rise in SCr was 0.183 mg/dL/yr and 0.445 mg/dL/yr in the Pyridorin (n=34) and placebo (n=31) groups, respectively. This result suggests Pyridorin therapy may be slowing the progression of kidney disease in diabetic patients with more substantial renal

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impairment exhibiting a larger increase in SCr over the treatment period. However, it is part of a post-hoc analysis, and this effect may not be observed in a subsequent study.

Urinary creatinine clearance findings were consistent with the beneficial effects of Pyridorin on slowing the decline of renal function with an 18% reduction in the decline of creatinine clearance in the Pyridorin group relative to patients treated with placebo in the total patient population.

Urinary excretion of TGF-β1, a factor implicated in the pathogenesis of chronic renal failure in diabetic nephropathy, was also assessed. The mean change from baseline to endpoint in urinary TGF-β1 levels was -9.34 and 14.38 pg/mg creatinine in the Pyridorin and placebo patients respectively, with a relative change from baseline of -24.7% and 41.8%, respectively, in the total patient population. As in the case of the observed changes in SCr and urinary creatinine clearance, these results on urinary TGF-β1 are part of a post-hoc analysis, and they may not repeat in a subsequent clinical study.

PYR-205/207

PYR-205 and PYR-207 were identical in design, with the exception of the patient entrance criteria for SCr (≤ 2.0 mg/dL and > 2.0 mg/dL but ≤ 3.5 mg/dL, respectively). The data were merged, as prespecified in the Statistical Analysis Plan, and analyzed as a single study. PYR-205 and 207 were Phase 2, international, multi-center, randomized, double-blind, placebo-controlled, escalating dose studies to evaluate the safety, tolerability, and biologic activity of Pyridorin given orally in a sequential fashion to patients with diabetic nephropathy due to type 1 or type 2 diabetes at:

50 mg BID for two weeks,

100 mg BID for two weeks, and

250 mg BID for 20 weeks.

This study was conducted by BioStratum Inc. which utilized the services of the contract research organizations Pharmaceutical Product Development (PPD), Cato Research, and PharmaNet. The study was conducted from July 2002 to September 2003 in the United States, Belgium, the United Kingdom, Canada and South Africa.

In PYR-205/207, baseline renal function was more impaired than patients studied in PYR-206. In PYR-205/207, Pyridorin reduced the change from baseline SCr in either a statistically significant fashion or trending toward a significant p-value close to 0.05 in all prospectively defined patient sub-groups. The reno-protective effect of Pyridorin as compared to placebo was seen to an equal degree across all patient groups with an approximate 70% reduction relative to placebo in the increase of baseline SCr (Table 2 and Figure 2).

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Table 2: PYR-205/207 Serum Creatinine Change from Baseline Analysis

Patient Population	Treatment Group	N	Baseline SCr(1)	SCr Change from Baseline(2)	Treatment Effect(3)
All Patients	Pyridorin	57	1.75 ± 0.64	0.11 ± 0.26	-68%*
	Placebo	27	1.96 ± 0.86	0.34 ± 0.92	
Type 2 Diabetes	Pyridorin	45	1.74 ± 0.67	0.12 ± 0.27	-68%*
	Placebo	22	1.94 ± 0.92	0.38 ± 1.02	
Baseline SCr ≥ 1.3 mg/dL	Pyridorin	42	2.00 ± 0.55	0.12 ± 0.30	-74%*
	Placebo	19	2.37 ± 0.67	0.47 ± 1.09	
Type 2, Baseline SCr ≥ 1.3 mg/dL	Pyridorin	33	2.00 ± 0.58	0.14 ± 0.31	-75%
	Placebo	15	2.40 ± 0.73	0.55 ± 1.22	

(1) Mean ± SD in mg/dL

(2) Unadjusted mean within group change from baseline in mg/dL

(3) Difference relative to placebo in unadjusted mean change from baseline, where a negative value indicates a lesser change from baseline in Pyridorin patients (*i.e.*, reno-protection)

(4) Determined using repeated measures mixed model analysis with baseline SCr as a fixed covariate and treatment effect being the difference relative to placebo in change from baseline measured in mg/dL.

* Statistically significant, $p<0.05$

Figure 2. PYR-206 Serum Creatinine Change from Baseline Analysis in Patients with Type 2 Diabetes and a Baseline SCr ≥ 1.3 mg/dL

(1)

Mean ± SEM; P= 0.058 (Repeated measures mixed model analysis with baseline serum creatinine as a fixed covariate)

Relative to placebo, Pyridorin treatment also slowed the rate of SCr increase (slope analysis) by approximately 70% in all populations analyzed. The rise in SCr was 0.177 mg/dL/yr in Pyridorin group (n=57) and 0.629 mg/dL/yr in the placebo group (n=27), with a P value of 0.062.

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No significant between-group differences were observed in urinary albumin excretion. Short term effects on proteinuria are usually only seen with anti-hypertensive drugs that improve renal hemodynamics. Pyridorin treatment did not affect blood pressure.

AGE measurements were performed in plasma of patients with more advanced renal disease (all PYR-207 patients) using gas chromatography-mass spectrometry. Whereas carboxymethyllysine (CML) and carboxyethyllysine (CEL) levels increased from baseline by 0.02 and 0.015 mmol/mol Lys, respectively, in the placebo group, CML and CEL levels were decreased from baseline by 0.04 and 0.01 mmol/mol Lys in the Pyridorin-treated group. These data suggest that Pyridorin-induced inhibition of AGE formation occurs concomitantly with the beneficial effects of Pyridorin on renal function, thus lending support to the hypothesis that Pyridorin exerts beneficial effects on renal function via an AGE-dependent mechanism.

The mean change from baseline to endpoint in urinary TGF-β1 levels was -9.7 pg/mg creatinine in Pyridorin patients and +14.2 pg/mg creatinine in placebo patients with a relative change from baseline of -13.1% and 55.7% in the Pyridorin and placebo groups, respectively. These relative differences in TGF-β1 levels could represent one of the mechanisms by which Pyridorin could potentially slow the progressive decline in renal function.

PYR-210

PYR-210 was a randomized, double-blind, placebo-controlled study of Pyridorin at doses of 150 mg BID, 300 mg twice daily (BID) or placebo for 12 months. PYR-210 was designed to further study the efficacy and safety of Pyridorin in patients with overt nephropathy due to type 2 diabetes and to identify the appropriate dose and patient population for Phase 3 pivotal trials.

We conducted the study and utilized the services of the contract research organization Medpace. The study was conducted from August 2008 to August 2010 in the United States, Australia and Israel.

The population selected had macroalbuminuria and impaired renal function. Although previous pivotal trials for diabetic nephropathy (notably, the IDNT study of the drug Irbesartan and the RENAAL study of the drug Losartan) have excluded patients with baseline SCr values ≥ 3.0 mg/dL, patients with higher bSCr values (up to 3.7 mg/dL) were included in the PYR-210 study in order to evaluate Pyridorin safety in more advanced renal disease patients. Pre-specified efficacy analyses according to starting baseline SCr levels were included in the statistical analysis plan. Patients were required to be on an established diabetic nephropathy standard of care (SOC) at screening. Specifically, patients must have received a renin-aldosterone-angiotensin-system (RAAS) inhibitor (ACE-I) or an ARB for at least 3 months prior to screening where the dose of the ACE-I or the ARB was considered appropriate for that patient and had been stable for at least 2 months. Patients were also required to be on stable blood pressure medications (other than an ACE-I or ARB) for 2 months prior to screening.

Patients not on an established, stable regimen of SOC were allowed to enter a screening phase (designated the "run-in period") during which ACE-I/ARB or blood pressure dosing was initiated or adjusted to establish SOC. This was followed by a run-in period of at least 2 months at these same doses before patients could be randomized. These patients were required to meet the other entry criteria at the screening visit. Because changes in ACE-I/ARB or blood pressure medications are known to affect baseline SCr values, a pre-specified analysis of patients on an established standard of care at screening, excluding run-in patients, was included in the statistical analysis plan.

Eligible patients also had:

- a history of overt diabetic nephropathy defined by a SCr measurement of 1.3 mg/dl to 3.3 mg/dl (women) or 1.5 mg/dl to 3.5 mg/dl (men), inclusive, and

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a 24-hour urine collection Protein to Creatinine Ratio (PCR) > 1200 mg/g.

The trial did not reach its primary endpoint on the intent to treat (ITT) population. In the overall patient population, Pyridorin did not demonstrate a significant treatment effect on the progressive increase in serum creatinine concentration that these patients experienced over one year. However, results from the pre-specified analysis of patients on established SOC at screening showed a treatment effect of 45% for Pyridorin 300 mg BID and 21% for Pyridorin 150 mg BID treatment as compared to placebo treatment. This analysis included patients with a baseline SCr ≥ 3.0 mg/dL, which is higher than the baseline SCr used in the precedent IDNT and RENAAL clinical studies and represents patients who are not appropriate for a pivotal trial in diabetic nephropathy due to their baseline instability and advanced stage of renal insufficiency. Nonetheless, these patients were included in PYR-210 for the purposes of a broad safety assessment. When patients with a baseline SCr < 3.0 mg/dL (the patient population studied in the RENAAL trial of Losartan) that were on established SOC at screening were analyzed, a statistically significant treatment effect of 57% for the Pyridorin 300 mg dose (p=0.0094) and 45% for the Pyridorin 150 mg dose (p=0.0414) was observed. The more robust treatment effect observed in the Pyridorin 300 mg BID group over the Pyridorin 150 mg BID group suggests a potential dose response in this patient population. This subgroup is the patient population that will be studied in the Phase 3 trial. Our subgroup analysis carries the inherent risk that the results may not be repeatable in a subsequent trial. It is possible that the treatment effect observed in this subgroup of PYR-210 may not be repeated in the Phase 3 trials.

A summary of these results is shown in Table 3.

Table 3: Change in Serum Creatinine (mg/dl) From Baseline to Endpoint in Various Subgroups from PYR-210

Patient Population	Treatment Group	N	Baseline SCr	SCr Change from Baseline	Treatment Effect
ITT Population	Pyridorin 300mg	105	2.17 ± 0.57	0.36 ± 0.57	N/A
	Pyridorin 150mg	99	2.22 ± 0.55	0.42 ± 0.72	N/A
	Placebo	103	2.20 ± 0.56	0.36 ± 0.70	
Patients requiring a run-in period(1)	Pyridorin 300mg	36	2.32 ± 0.59	0.62 ± 0.75	N/A
	Pyridorin 150mg	30	2.33 ± 0.56	0.73 ± 0.90	N/A
	Placebo	34	2.34 ± 0.67	0.31 ± 0.68	
Patients on SOC @ screening in the RENAAL population (bSCr < 3.0)(1) *(FDA approved patient population for Phase 3)*	Pyridorin 300mg	64	2.01 ± 0.49	0.18 ± 0.34	-57%**
	Pyridorin 150mg	60	2.03 ± 0.40	0.23 ± 0.45	-45%*
	Placebo	63	2.04 ± 0.40	0.42 ± 0.70	

(1) A separate analysis of this group was pre-specified in the statistical analysis plan.

(2) The patient population used in the RENAAL clinical trial of Losartan is considered to be the established population used for pivotal trials in diabetic nephropathy.

* Statistically significant, p<0.05

** Statistically significant, p<0.01

Patients who were not on a stable regimen of SOC at screening, and required a run-in period, are also shown in Table 3. These patients did not show a Pyridorin treatment effect. The analysis of the ITT patient population also showed no Pyridorin treatment effect. Since the patients on SOC did show a Pyridorin treatment effect, it is possible that inclusion of patients requiring a run-in period

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confounded the analysis of the ITT population. It is generally accepted that the initiation or change in ACEi/ARB or blood pressure medication dosing in overt diabetic nephropathy patients with established renal insufficiency can result in an increase in SCr levels (or a decrease in GFR). A recently published post-hoc analysis of the RENAAL study showed that patients assigned to Losartan (an ARB marketed by Merck & Co. Inc.) had a greater acute fall in eGFR during the first three months compared to patients assigned to placebo. A post-hoc analysis of the database of the IDNT study indicates that this effect of a blood pressure medication can persist for up to 6 months. Since the run-in period in PYR-210 only required stable doses of ACEi/ARB or blood pressure medications for 2 months prior to randomization, it is likely that some run-in patients had not reached a stable SCr baseline value prior to randomization. In addition, there was an increased number of post-randomization blood pressure medication changes in the run-in patients as compared to patients on established SOC at screening. For future Pyridorin studies, the FDA has agreed that all patients will need to be on stable SOC for at least 6 months prior to screening.

When the subgroup of patients that will be studied in the Phase 3 trials was examined (the RENAAL patient population with bSCr < 3.0 mg/dL on stable SOC @ screening) a dose dependent statistically significant treatment effect of 57% at 300 mg BID was observed.

In addition to the primary efficacy endpoint of change from baseline in SCr, the changes in serum cystatin C were also measured based on the demonstration of a 50% reduction in serum cystatin C by Pyridorin relative to placebo in all patients in Study PYR-205/207. The cystatin C results in PYR-210 followed similar trends to what was observed in the subgroups analyzed for SCr changes. A 26% treatment effect was observed in both treated arms (300 mg BID and 150 mg BID) of patients on SOC at screening in the RENAAL population (bSCr < 3.0 mg/dL).

Changes in urinary TGF-β1 were measured based on the demonstration of a reduction in TGF-β1 in PYR 206 and PYR 205/207. The mean change from baseline to endpoint in urinary TGF-β1 levels was -5.8 pg/mg for the Pyridorin 300 mg BID group, +21.4 pg/mg for the Pyridorin 150 mg BID group and +264 pg/mg for the placebo group. Although a dose dependent trend of decreasing TGF-β1 was observed in treated patients, the differences did not reach statistical significance.

Changes in 24 hour urinary protein creatinine ratio (PCR) were also measured. The mean change from baseline to endpoint in urinary PCR was -118 mg/g for the Pyridorin 300 mg BID group, +182 mg/g for the Pyridorin 150 mg BID group and +179 mg/g for the placebo group. Although there was evidence of a possible reduction in the 300 mg BID group relative to the placebo group, the difference was not statistically significant. The average baseline PCR was extremely high in this patient population (~3000 mg/gm) making the likelihood of observing significant effects within one year very low. It is possible that Pyridorin would further reduce urinary PCR with exposures longer than those in the PYR-210 study. Shorter term effects on proteinuria are usually only seen with anti-hypertensive drugs that improve renal hemodynamics. Pyridorin treatment did not affect blood pressure.

In summary, treatment with Pyridorin up to 300 mg BID was well tolerated. No safety signals were observed in this study. Treatment with Pyridorin for 1 year demonstrated a statistically significant treatment effect of 57% for the Pyridorin 300 mg dose (p=0.0094) and 45% for the Pyridorin 150 mg dose (p=0.0414) in the subgroup of patients with a baseline SCr < 3.0 that were on established SOC at screening. The more robust treatment effect observed in the Pyridorin 300 mg BID group over the Pyridorin 150 mg BID group indicates evidence for a dose response in this patient population. Pyridorin also demonstrated evidence of a reduction in serum cystatin C and urinary TGF-β1.

The efficacy data from PYR-210 was consistent with the previous Phase 2 trials PYR-206 and PYR-205/207. These results support the use of the 300 mg BID dose for pivotal studies, as all doses were well tolerated and there was a suggestion of a better treatment effect with the highest dose.

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We have reached agreement with the FDA in a Special Protocol Assessment (SPA) on the patient population to be studied in the pivotal Phase 3 studies: type 2 diabetic patients with overt nephropathy and a bSCr < 3.0 mg/dL that are on an established and stable SOC regimen at screening. In this specific patient population, Pyridorin dosed at 300 mg BID demonstrated a 57% treatment effect in PYR-210 in the endpoint of SCr change from baseline relative to placebo.

Clinical Development Strategy

The clinical development path for a drug to treat diabetic nephropathy has traditionally been very long and associated with significant risk. In the past few years there have been four drug candidates that failed in Phase 3 clinical trials: Pimagedine, Sulonex, Avosantan and Bardoxalone. These drug candidates all looked promising in their respective Phase 2 studies, but all four failed in pivotal trials. A close examination of these clinical development programs reveals that in each case the Phase 3 studies were conducted in a different patient population using a different endpoint than was studied in their respective Phase 2 programs. This unusual circumstance arose because of the very challenging regulatory pathway that previously existed in this field. The long term endpoint that the FDA previously required in Phase 3 (time to SCr doubling or ESRD) made it nearly impossible to evaluate the drug against a similar endpoint in a Phase 2 trial. For example, the recruitment and patient follow-up time for the IDNT study totaled 60 months or 5 years. Bearing in mind trial costs and patent lifetime, this is very long and expensive for a Phase 2 study. Companies chose to use Phase 2 trials to study surrogate endpoints. They also chose patient populations where a treatment effect on the surrogate endpoint would be the most pronounced. Since the FDA did not accept these surrogate endpoints and narrow patient populations for the Phase 3 program, the transition to a Phase 3 trial was quite risky. All four companies ended up evaluating a significant number of types of patients in Phase 3 that they had never evaluated before, using an endpoint for which they had relatively little data.

We took a different approach in our clinical development strategy for Pyridorin. Specifically, during the Phase 2 program, working closely with the FDA, we examined broader patient populations under different conditions of standard of care to identify those patients most appropriate for the Phase 3 program. The pre-specified subgroup analyses of the Phase 2b study indicate that the appropriate diabetic nephropathy patient population to study in Phase 3 is patients on long term establish standard of care at screening with a baseline SCr >1.3 and < 3.0 mg/dL. In this patient population, Pyridorin therapy produced a greater than a 50% treatment effect that was statistically significant (P = 0.009) at the 300 mg bid dose. The Phase 2b study also indicated that patients that would not be appropriate to include in the Phase 3 pivotal study are those not on a stable regimen of standard of care at screening. These patients did not demonstrate a Pyridorin treatment effect and very likely did not reach a stable blood pressure and stable SCr baseline prior to the start of the study which would confound the treatment effect analysis.

We also used a SCr increase-based endpoint that would correlate with a potentially approvable endpoint. Simultaneously, we provided the FDA with analyses from previously completed Phase 3 clinical studies in diabetic nephropathy that supported a new, lower SCr increase-based endpoint. As a result, we potentially significantly reduced the cost of the Phase 3 trials and made our Phase 2b endpoint even closer to the Phase 3 endpoint.

As agreed to in the SPA, the Pyridorin Phase 3 study will be conducted in the specific patient population where Pyridorin has previously shown greater than a 50% treatment effect on a year-1 SCr endpoint (PYR-210).

Phase 3 Development Plan

Based on these clinical results and the SPA agreement with the FDA, we intend to commence the first of two Pyridorin Phase 3 diabetic nephropathy clinical trials (PYR-311) in the first half of 2014.

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We intend to commence the second of the Phase 3 trials (PYR-312) during the first half of 2016. These two clinical trials (PYR-311 and PYR-312), if successful, will serve as the basis for the product registration application.

PYR-311 and PYR-312 are identical Phase 3 randomized, double-blind, placebo-controlled, international multi-center studies to evaluate the efficacy of Pyridorin 300 mg twice daily (BID) compared to placebo in reducing the rate of progression of renal disease due to type 2 diabetes. Each study will provide approximately 90% power to detect a 28% treatment effect. This progression rate will be estimated by the time to the composite endpoint consisting of the earliest event amongst:

A SCr increase of ≥ 50% from baseline that occurs during follow-up; or

End Stage Renal Disease (ESRD).

The FDA has agreed to the SCr increase of ≥ 50% from baseline endpoint as indicated in our SPA agreement with the FDA which covers the design of the Pyridorin Phase 3 program and the endpoint to be used for drug approval. This endpoint was previously validated by an FDA-NKF (National Kidney Foundation) Workshop held in December of 2012 that included leading nephrology clinical investigators and extensive analyses of completed kidney disease clinical studies demonstrating a highly significant correlation between time to a 50% SCr increase and time to ESRD.

The key secondary objective of the studies is to determine the safety of Pyridorin compared to placebo, as assessed by adverse events, 12-lead ECGs, vital signs, physical examination, clinical chemistries, glycosylated hemoglobin (HbA1c), and hematology.

Each study will enroll approximately 600 patients with a history of overt diabetic nephropathy defined by a SCr measurement of ≥ 1.3 mg/dL for female patients or ≥ 1.5 mg/dL for male patients, < 3.0 mg/dL for all patients, and a urine PCR ≥ 1200 mg/g at screening. Patients must be on stable standard of care (SOC) regimen which is defined as an ACE-I or ARB at a constant dose for at least 26 weeks prior to randomization.

PYR-311 will include one interim analysis that will be conducted approximately 18 months following study initiation. At that time, an independent Data and Safety Monitoring Board (DSMB) will assess the general safety of Pyridorin and will perform an analysis of its effect on the rate of SCr progression. If the DSMB determines that Pyridorin is not safe or that it is futile to continue the trial because of lack of efficacy, the trial will be terminated. On the other hand, if the DSMB determines Pyridorin is safe and it is not futile to continue the study, the study will be continued until the necessary number of events have accrued per the study design.

We have had extensive discussions with the FDA regarding this new clinical endpoint as well as the protocol design, inclusion-exclusion criteria, and the trial population. These discussions culminated in an agreement with the FDA on a SPA. The new primary endpoint for this study has the potential to provide for a significantly shorter clinical development path at a substantially reduced cost as compared to the previous clinical endpoint of SCr doubling or ESRD. We believe that we will be the first company to conduct a Phase 3 clinical trial for diabetic nephropathy using this new endpoint.

Acute Kidney Injury (AKI)

Pyridorin targets specific pathogenic oxidative chemistries that emerge in diabetes. These same pathogenic oxidative chemistries emerge with the onset of AKI and are believed to contribute to the severity of the AKI. An intravenous formulation of Pyridorin could provide significant benefit in this acute setting. Because of its benign safety profile, Pyridorin could also be used as preventative therapy in patients at high risk.

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AKI constitutes a very significant market opportunity for Pyridorin. Since this would be an intravenous product used in an acute setting, it would not compete with an oral Pyridorin product used for the chronic treatment of diabetic nephropathy.

AKI is characterized by a rapid reduction in kidney function resulting in a failure to maintain fluid, electrolyte and acid-base homoeostasis. It covers a wide spectrum of disease ranging from less severe forms of injury to more advanced injury when acute kidney failure may require renal replacement therapy (RRT). The incidence of AKI varies from 20% to 40% in critical care patients. In the U.S., it is estimated that up to 7% of all patients who visit the hospital will experience AKI. Patients with uncomplicated AKI have a mortality rate of up to 10%. If RRT is required, the mortality rate rises to as high as 80%.

The most common causes of AKI include:

- Sepsis
- Cardiovascular surgery
- Ischemic reperfusion injury
- Contrast dye induced AKI
- Chemotherapy induced AKI
- Trauma
- Serious Burns

Severe AKI is characterized by surge in pathogenic oxidative chemistries. These oxidative chemistries can lead to further damage to the kidneys and ultimately result in acute renal failure (ARF). Even if ARF does not occur, there is evidence that patients who experience AKI have a much higher incidence of subsequent chronic kidney disease.

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New biomarkers have been identified that allow for earlier detection of AKI. One such biomarker is neutrophil gelatinase-associated lipocalin (NGAL). Early detection of AKI would allow therapeutic intervention with an agent like Pyridorin that could inhibit these pathogenic oxidative chemistries and prevent further damage to the kidneys. Because of its benign safety profile, Pyridorin is an attractive candidate for early intervention (e.g. elevated NGAL). Pyridorin may also have application as a preventative therapy in patients at high risk such as those patient undergoing cardiovascular surgery, receiving contrast dye or undergoing chemotherapy.

We will conduct additional preclinical studies to identify those indications where Pyridorin would be most effective. This will form the basis for our clinical development plan.

Commercialization

Given our stage of development, we have not yet established a commercial organization or distribution capabilities. Pyridorin, if approved, is intended to be prescribed to patients with diabetic nephropathy. These patients are normally under the care of a nephrologist, an endocrinologist, and/or a primary care physician (PCP). All of these specialties prescribe therapy for diabetic nephropathy, with the endocrinologist or the PCP typically treating patients in the earlier stage of the disease and the nephrologist typically treating patients in the later stages of the disease (overt diabetic nephropathy). Our current plan is to evaluate a possible partnership to commercialize Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes in the United States and Europe if it is approved. We may also build our own commercial infrastructure or utilize contract reimbursement specialists, sales people and medical education specialists, and take other steps to establish the necessary commercial infrastructure at such time as we believe that Pyridorin is approaching marketing approval. Outside of the United States and Europe, subject to obtaining necessary marketing approvals, we will likely seek to commercialize Pyridorin through distribution or other collaboration arrangements for kidney disease in patients with type 2 diabetes. As a result of our ongoing clinical work, we have been engaged in dialogue with specialists who treat patients with kidney disease. We believe that these activities have provided us with a growing knowledge of the physicians we plan to target for commercial launch of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, subject to marketing approval in the United States and Europe.

Competition

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Although we believe that Pyridorin is one of the few drug candidates in advanced clinical trials for diabetic kidney disease, our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price and reimbursement.

Diabetic Nephropathy

As of 2010, the Center for Disease Control and U.S. Census data estimate the prevalence of diabetic nephropathy across all stages of disease to be approximately 6 million patients in the U.S. and this population is expected to grow. According to a 2010 study commissioned by us, approximately 2.8 million diabetic patients have overt nephropathy, approximately 3.5 million patients have early stage diabetic nephropathy and approximately 3.6 million patients are at high risk of progressing to diabetic nephropathy.

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While the market opportunity for drugs to treat diabetic nephropathy is large and growing, the availability of drugs to treat this condition is very limited. There are two classes of drugs currently approved to slow the progression of diabetic nephropathy: ACE-Inhibitors and ARBs. These agents target the renin-angiotensin system. Approved initially as anti-hypertension drugs, these agents are now considered standard of care (SOC) for patients with diabetic nephropathy. Pyridorin is intended to be given in conjunction with these therapies; therefore, actual competition will not come from drugs targeting the renin-angiotensin system. Instead, it may come from companies seeking to treat diabetic nephropathy through some other mechanism of action. The table below summarizes the competitive landscape.

COMPANIES WITH CLINICAL PROGRAMS IN DIABETIC NEPHROPATHY

Company	Agent	Phase	Program Status
AbbVie	Endothelin receptor antagonist	3	Active
Bayer Healthcare	Mineralcorticoid Receptor Antagonist	2	Active
Pfizer	Chemokine CCR2/5 Receptor Antagonist	2	Active
	Phosphodiesterase type 5 inhibitor	2	Active
ChemoCentryx	Chemokine CCR2 Receptor Antagonist	2	Active
Eli Lilly	Transforming Growth Factor B Monoclonal Antibody (IV)	2	Active
	MR Antagonist	2	Active
Mitsubishi Tanabe Pharma	Unknown	1	Active

Competition for Phase 3 Recruitment

AbbVie's Phase 3 trial is actively recruiting over 4,100 patients worldwide. While the eligible patient population is not identical, it is similar enough to potentially affect enrollment goals set by our Pyridorin Phase 3 program.

Acute Kidney Injury

In the U.S., the incidence of AKI varies from 20% to 40% in critical care patients. It is estimated that up to 7% of all patients who visit the hospital will experience AKI. Patients with uncomplicated AKI have a mortality rate of up to 10%. If RRT is required, the mortality rate rises to as high as 80%.

The current treatment for AKI is mainly supportive in nature; no therapeutic modalities to date have shown efficacy in treating the condition.

The market opportunity for effective treatments for AKI is large. There are a small number of industry drug trials in later stage development. Companies with an active AKI agent or program include AbbVie, Novartis, Thrasos Innovation, and AlloCure.

Sales of Pyridoxamine as a Dietary Supplement

Following the publication of the initial Phase 2 studies that evaluated pyridoxamine therapy in diabetic nephropathy patients, a number of dietary supplement companies began selling pyridoxamine over the internet.

In January 2009, the FDA ruled that pyridoxamine is an investigational drug candidate not eligible for sale as a dietary supplement. A significant decline in product availability occurred after the issuance of the above mentioned FDA ruling. We believe this decline was in response to the FDA ruling, and not a result of subsequent specific FDA letters to these vendors.

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In the case of Pyridorin, we believe that illegal sales of pyridoxamine will have little if any effect on Pyridorin sales for the following reasons:

1. The FDA has a track record of enforcing the regulations against dietary supplement companies that attempt to sell the active ingredient of an FDA approved drug. Since pyridoxamine will be approved for diabetic patients with substantial kidney disease, it is likely the FDA will continue this policy for pyridoxamine.

2. NephroGenex has issued patents covering pyridoxamine as an agent to treat diabetic nephropathy patients and other diabetic complications, and also as an agent to inhibit pathogenic oxidative chemistries that emerge in diabetes. This intellectual property makes it difficult to effectively market pyridoxamine as a dietary supplement without infringing on these issued patents.

3. A significant investment in pyridoxamine production capacity would be required by the dietary supplement industry just to impact a small percentage of Pyridorin drug sales. Furthermore, a non-oxidative method of pyridoxamine production would have to be developed, since the commonly used oxidative method cannot be scaled up due to safety and environmental concerns. We have already developed and patented a non-oxidative method of pyridoxamine production (used in the Phase 2b study), thus making the task of developing a new, non-infringing, non-oxidative method of pyridoxamine production that much more difficult and expensive.

Food and dietary supplements in Europe are regulated by Directive 2002/46/EC, European Commission, Health and Consumers Directorate-General. Those approved are listed in Annex I and II of this directive. Pyridoxamine is not included on either list, and therefore the sale of pyridoxamine in foods and supplements in Europe is not permitted. We have kept the European Commission Health and Consumers Protection Directorate-General up to date on the clinical status of Pyridorin, and plans for Phase 3 trials.

This office has indicated to NephroGenex as recently as April of this year, that no applications for pyridoxamine have been received and that any new product intended for preventing, curing or treating diseases, would fall under the scope of medicinal products and not dietary supplements products.

Intellectual Property

The proprietary nature of, and protection for, our product candidates and our discovery programs, processes and know-how are important to our business. We have sought patent protection in the United States and internationally for Pyridorin and our discovery programs, and any other inventions to which we have rights, where available and when appropriate. Our policy is to pursue, maintain and defend patent rights, whether developed internally or licensed from third parties, and to protect the technology, inventions and improvements that are commercially important to the development of our business. We also rely on trade secrets that may be important to the development of our business. However, we do not have composition of matter patent protection for Pyridorin which may result in competitors being able to offer and sell products including pyridoxamine so long as these competitors do not infringe any other patents that we or third parties hold, including synthesis and method of use patents.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection of our current and future product candidates and the methods used to develop and manufacture them, as well as successfully defending these patents against third-party challenges. Our ability to stop third parties from making, using, selling, offering to sell or importing our products depends on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will

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be commercially useful in protecting our product candidates, discovery programs and processes. For this and more comprehensive risks related to our intellectual property, please see "Risk Factors Risks Relating to Our Intellectual Property."

Patents and Proprietary Rights Covering Our Drug Candidates

We strive to protect our product candidates and exclusivity rights, as well as both maintain and fortify our position in the field of kidney disease therapeutics. We believe our intellectual property portfolio consists of early and broad filings in the area. We have focused on patents and patent applications covering, where possible, use of our products in disease treatment. We have sought and continue to seek the strongest possible intellectual property protection available to us in order to prevent others from directly competing with us, as well as to exclude competition around our products where possible, their manufacture, and methods for use of the products in disease treatment. Our intellectual property portfolio contains 28 issued patents and at least 8 pending patent applications in the U.S. and worldwide of both in-licensed and NephroGenex-owned inventions. This portfolio includes patents and proprietary rights around:

(i) Methods for using Pyridorin (pyridoxamine dihydrochoride) as a therapeutic agent to treat diabetic nephropathy;

(ii) Methods for manufacture of Pyridorin;

(iii) Methods for using Pyridorin as a therapeutic agent to treat a variety of other kidney diseases and other disorders; and

(iv) Pyridorin analog drug candidates, and their use for treating kidney disease.

We own patents covering methods for using Pyridorin to treat diabetic nephropathy in patients with type 2 diabetes and elevated levels of SCr, and thus closely track the anticipated drug label for an approved Pyridorin drug. These patents consist of an issued U.S. patent (U.S. Patent 8067444) and corresponding issued patents in Canada and Europe, which will expire in 2024 absent any extension to the patent term. As discussed in more detail herein, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

We also have a worldwide, exclusive license from Kansas University Medical Center to an earlier set of patents covering methods for using Pyridorin to treat diabetic nephropathy. These patents include an issued patent in the U.S. (US Patent 5985857) and corresponding patents in Europe and Japan, which will expire in 2016 absent any extension to the patent term. We expect that expiration in 2016 of some of our method-of-use patents, or their foreign equivalents, covering use of Pyridorin for treating diabetic nephropathy will have a limited impact on our ability to protect our intellectual property in the United States, Europe, and Canada, where we have additional issued patents covering this use that extend until 2024. In other countries, our patent protection covering use of Pyridorin for treating diabetic nephropathy will expire in 2016. We will attempt to mitigate the effect of patent expiration by seeking data exclusivity, or the foreign equivalent thereof, in conjunction with product approval, as well as by filing additional patent applications covering improvements in our intellectual property.

We also own patents covering Methods for manufacture of Pyridorin; these patents consist of two issued U.S. patents (U.S. Patents 7214799 and 8431712), which will expire in 2025.

We also have worldwide, exclusive licenses from Kansas University Medical Center, the University of South Carolina, and Vanderbilt University to patents covering methods for using Pyridorin to treat a variety of other disorders. These patents include patents for treating urinary stone disease (US Patent 6521645), proteinuria (U.S. Patent 6472400), retinopathy (U.S. Patent 6750209), neuropathy (U.S. Patents 6750209 and 7030146), oxidative protein modification (U.S. Patent No. 6730686),

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oxidative stress-related disorders (U.S. Patent No. 6716858), hypercholesterolemia (U.S. Patent No. 6740668), and some corresponding foreign patents. The term of these patents will expire at various times, but all would expire by 2021. These patents further include pending applications in the United States for treating symptoms of kidney disorders, and inflammatory disorders. If granted, patents issuing from these patent applications would expire at different times, but all would expire by 2032.

We own pending patent applications in the United States and Europe covering Pyridorin analogs, and uses of such analogs as therapeutics to treat a variety of disorders, including kidney disorders such as nephropathy. Patent protection, to the extent it issues, would be expected to extend to 2027.

Intellectual Property Strategy

We continually assess our intellectual property strategy in order to fortify our position in our market space. To that end, we are prepared to file additional patent applications in any of the above families should our intellectual property strategy require such filings and/or where we seek to adapt to competition or seize business opportunities. Further, we are prepared to file patent applications relating to the other products in our pipeline soon after the experimental data necessary for a strong application become available and our cost-benefit analyses justify filing such applications. In addition to filing and prosecuting patent applications in the United States, we typically file counterpart patent applications in Europe and additional countries where we think such foreign filing is likely to be beneficial.

We do not know if patents will be issued for all of the patent applications in our portfolio. Furthermore, for patent claims now issued and for claims to be issued in the future, we do not know if such claims will provide significant proprietary protection to our drug candidates and proprietary technologies or if they will be challenged, circumvented, or invalidated. Our success will in part depend on our ability to obtain and maintain patents protecting our drug candidates, technologies and inventions, to operate without infringing the proprietary rights of third parties, and to enforce and defend our patents and ensure others do not infringe on our proprietary rights.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent's term may be shortened if a patent is terminally disclaimed over another patent or as a result of delays in patent prosecution by the patentee, and a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent.

The patent term of a patent that covers an FDA-approved drug or biologic may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug or biologic is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug or biologic may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug or biologic. In the future, if and when our pharmaceutical products receive FDA approval we expect to apply for patent term extensions on patents covering those products. We anticipate that some of our issued patents may be eligible for patent term extensions. For more information regarding U.S. patent laws, see "Business Government Regulation."

In addition to the patent term extension rights described above, any of our product candidates that receive FDA approval may also be eligible for market exclusivity protection under the Federal Food,

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Drug and Cosmetic Act or the Biologics Price Competition and Innovation Act of 2009. For more information regarding market exclusivity laws, see "Business Government Regulation."

Many pharmaceutical companies, biotechnology companies and academic institutions are competing with us in the field of diabetic nephropathy and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third party intellectual property conflicts, from time to time, we review and assess the third-party intellectual property landscape for competitive and other developments that may inform or impact our intellectual property development and commercialization strategies. From time to time, we may find it necessary or prudent to obtain licenses from third party intellectual property holders. Where licenses are readily available at reasonable cost, such licenses are considered a normal cost of doing business. In other instances, however, where a third party holds relevant intellectual property and is a direct competitor, a license might not be available on commercially reasonable terms or available at all. Accordingly, we attempt to manage the risk that such third party intellectual property may pose by conducting, among other measures, freedom-to-operate studies to guide our early-stage research away from areas where we are likely to encounter obstacles in the form of third party intellectual property. As our programs advance, we continue to monitor the intellectual property landscape in an effort to assess the advisability of licensing third party intellectual property or taking other appropriate steps to address such freedom-to-operate or development issues in the manner we deem in the best interests of the Company.

With respect to third party intellectual property, it is impossible to establish with certainty that our product candidates will be free of claims by third party intellectual property holders or whether we will require licenses from such third parties. Even with modern databases and on-line search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third party patent is identified, we may conclude upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third party patent owner disagrees with our conclusion and we continue with the business activity in question, we might have patent litigation thrust upon us. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third party patent invalid or not infringed by our activity. In either scenario, patent litigation typically is costly and time-consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our discovery platform as a result of patent infringement claims asserted against us. This could have a material adverse effect on our business.

To protect our competitive position, it may be necessary to enforce our patent rights through litigation against infringing third parties. Litigation to enforce our own patent rights is subject to the same uncertainties discussed above. In addition, however, litigation involving our patents carries the risk that one or more of our patents will be held invalid (in whole or in part, on a claim-by-claim basis) or held unenforceable. Such an adverse court ruling could allow third parties to commercialize our products, and then compete directly with us, without payment to us.

Trade Secrets

In addition to patents, we rely on trade secrets and know-how to develop and maintain our competitive position. Trade secrets and know-how can be difficult to protect. We seek to protect our proprietary processes, in part, by confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and commercial partners. These agreements are designed to protect our proprietary information. We also seek to preserve the integrity and confidentiality of our data, trade secrets and know-how by maintaining physical security of our premises and physical and electronic security of our information technology systems.

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License Agreements

Licensing Payments

Set forth below is a summary chart outlining various potential license payments due under our license agreements referenced below:

Indication	Diabetic Nephropathy *Phase III*	Acute Kidney Injury, Chemotherapy Protection, or Radiation Damage *Pre-clinical AKI*	Diabetic Neuropathy or Hyperlipedemia *Not in current pipeline*
Institution	Kansas University Medical Center	Vanderbilt University	South Carolina Research Foundation
FDA Approval of SPA	$25,000		
Filing of IND		$75,000	
Commencement of first Phase 1		$100,000	
Commencement of first Phase 2		$150,000	$325,000
Commencement of first Phase 3		$250,000	$500,000
File NDA or foreign equivalent			$750,000
FDA Approval of NDA	$200,000	$500,000 ($250,000 credited against royalty)	$2,000,000
First commercial sale			$2,500,000
Royalty on Net Sales	None	5% (minus $250,000 credit)	None
Licensing Fee	None	None	$112,000 due 3/31/14 $30,000 per quarter thereafter (credited against milestone payments & upfront sublicense fees)
Upon execution of a sublicense		25% of any sublicense fees or milestone payments	$35,000 plus 25% of upfront sublicense fees

License Agreements

Kansas University Medical Center (KUMC) Exclusive License Agreement

In May 2007, we entered into an amended license agreement with KUMC. Under the agreement, KUMC grants us an exclusive, royalty-free, worldwide license, with a right to grant sublicenses, to make, have made, use, distribute, sell, have sold, have distributed, offer to sell, market, import, have imported or otherwise dispose of licensed products for diagnostic testing and palliative, prophylactic and therapeutic treatments which incorporate the use of the technology relating to the licensed patents and improvements. The patents licensed from KUMC include claims reciting methods for using Pyridorin to: (a) treat diabetic nephropathy (expires by 2016 absent any extension); (b) treat proteinuria or albuminuria associated with elevated blood sugar levels (expires by 2016 absent any extension); (c) treat retinopathy or neurodegenerative disease (expires by 2016 absent any extension); (d) inhibiting oxidative modification of proteins or treating atherosclerosis in a non-hyperglycemic mammal (expires by 2016 in the U.S. and 2019 outside the U.S. absent any extension); (e) treat a condition associated with oxidative stress in a hyperglycemic mammal (expires by 2016 absent any extension); (f) treat diabetes-associated increases in hypercholesterolemia or hypertriglyceridemia in a diabetic mammal; (expires by 2016 in the U.S. and 2019 outside the U.S. absent any extension);

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(g) treat diabetic neuropathy (expires by 2016 absent any extension); (h) decrease dialysis-related amyloidosis or dialysis-related increases in permeability of the peritoneal membrane in a dialysis patient (expires by 2016 absent any extension); and (i) urinary stone disease (expires by 2021 absent any extension).

The patents licensed from KUMC also include patents with claims reciting novel Pyridorin analogues, and methods for using them to treat AGE-related pathologies, diabetic nephropathy, proteinuria, albuminuria; diabetes-associated increases in hypercholesterolemia or hypertriglyceridemia in a diabetic mammal; and for inhibiting oxidative modification of proteins or treating atherosclerosis in a non-hyperglycemic mammal (expire by 2016 in the U.S. and 2019 outside the U.S. absent any extension). The granted license is subject to certain rights and license granted to the United States and to foreign governments pursuant to U.S. government patent laws and regulations.

We must pay KUMC milestone payments related to milestones met in the FDA regulatory approval process. These milestone payments include $25,000 upon receipt of FDA approval of our SPA for our first licensed product and $200,000 upon receipt of FDA approval of our submitted NDA for our first licensed product in respect to the first primary indication. We must exercise commercially reasonable efforts to seek regulatory approval for the marketing of a licensed product for at least one primary indication, effect the introduction of a licensed product for at least one primary indication into the commercial market and to maximize these sales. Primary indications are the diagnosis, treatment, palliation or prophylaxis of diabetic nephropathy, diabetic retinopathy and diabetic neuropathy.

The agreement survives until expiration of the last to expire licensed patent, or in November 2018, whichever occurs last. We may terminate the license for any reason upon 90 days written notice. If either we or KUMC breach a material obligation under the agreement the non-breaching party may terminate the agreement upon an additional written notice.

The South Carolina Research Foundation (SCRF) Exclusive License Agreement

In April 2012, we entered into an amended license agreement with SCRF. Under the agreement, SCRF grants us an exclusive, royalty-free, worldwide license, under certain patent rights and related technology (including know-how) with a right to sub-license to utilize the patent rights and the technology during the term of the agreement and to practice under the patent rights to make, have made, use, sell, have sold, offer to sell, market, import, lease, or otherwise dispose of licensed products for all uses covered under the patent rights. The licensed product is Pyridorin or any other pharmaceutical compound labeled for an FDA-approved indication that would infringe a valid claim of the patent rights in the absence of the license.

The patents licensed from SCRF include claims reciting methods for using Pyridorin to: (a) inhibit oxidative modification of proteins or treating atherosclerosis in a non-hyperglycemic mammal (expires by 2016 in the U.S. and 2019 outside the U.S. absent any extension); (b) treat diabetes-associated increases in hypercholesterolemia or hypertriglyceridemia in a diabetic mammal; (expires by 2016 in the U.S. and 2019 outside the U.S. absent any extension); and (c) treat diabetic neuropathy (expires by 2016 in the U.S. and 2019 outside the U.S. absent any extension). The patents licensed from SCRF also include patents with claims reciting novel Pyridorin analogues, and methods for using them to treat diabetes-associated increases in hypercholesterolemia or hypertriglyceridemia in a diabetic mammal, and for inhibiting oxidative modification of proteins or treating atherosclerosis in a non-hyperglycemic mammal; (expire in 2016 in the U.S. and 2019 outside the U.S. absent any extension).

Under the license, SCRF retains the right to practice under the patents in the field solely for non-profit, educational, research, and academic purposes. The license also is subject to any U.S. government rights in the patent rights, if the technology or patent rights were developed with the support of the U.S. government or an agency thereof.

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We must exercise commercially reasonable efforts to develop and commercialize one or more licensed products. If we fail to comply with our diligence obligations with respect to at least one licensed product, then SCRF may terminate the license. If we develop Pyridorin for the treatment of hyperlipidemia or diabetic *neuro*pathy, we must pay SCRF milestone payments related to milestones met in the FDA regulatory approval process in the aggregate amount of $6,075,000. We must pay SCRF an annual license fee each year that we are actively marketing Pyridorin or have an active sublicense for Pyridorin for the treatment of hyperlipidemia or diabetic *neuro*pathy, which are creditable only against Licensed Product Sublicense upfront fees and milestone payments earned and payable in the same calendar year. We must pay SCRF an annual fee of $122,000 for 2013 and $120,000 for 2014 and the years thereafter. We must pay SCRF a one-time fee of $35,000 upon execution of a sub-license between NephroGenex and a third party, and must pay to SCRF 25% of any non-royalty sublicense payments made by such sub-licensee to NephroGenex. The planned phase 3 program for Pyridorin is for the treatment of diabetic nephropathy. Hyperlipidemia and diabetic neuropathy are not being evaluated in the current trial.

The agreement survives until the expiration or other disposition of the licensed patent rights. We may terminate the license at any time on three months prior written notice to SCRF. If we breach a material obligation under the agreement, and such obligation is not cured within 90 days after we receive written notice of the breach, then SCRF may terminate the agreement upon an additional written notice. SCRF may also terminate the license if (i) we cease operations and have not assigned the license to a third party; (ii) we become insolvent or make a general assignment of substantially all of our assets for the benefit of creditors, or if a petition of bankruptcy or any reorganization shall be commenced by, against, or in respect of us; or (iii) we fail to make a payment due under the license and the default is not cured within 30 days after written notice of such default, and SCRF has provided additional written notice.

Vanderbilt University (VU) Exclusive License Agreement

In connection with our additional pipeline opportunities for specific types of acute kidney injury, in July 2012, we entered into a license agreement with VU, which was amended on November 6, 2013. Under the agreement, VU grants us an exclusive, royalty-bearing, worldwide license, under certain patent rights, and a corresponding nonexclusive license under related know-how, with a right to sub-license, to make, have made, use, offer to sell, sell, and import licensed products incorporating the technology embodied in the licensed VU patent rights for use of pyridoxamine in the field of use, which is defined as treatment of acute renal failure or acute renal injury, use for radiation protection, and use for chemotherapy protection. The patent applications licensed from VU include claims reciting methods for using Pyridorin to: (a) ameliorate at least one symptom of a kidney disorder associated with oxidative stress, carbonyl stress, or combinations thereof (if issued, would expire by 2026); (b) treat or prevent acute renal injury or acute renal failure (if issued, would expire by 2026); and (c) treat an inflammatory disorder (if issued, would expire by 2032).

The patent applications licensed from VU also include claims reciting intravenous formulations of Pyridorin (if issued, would expire by 2026). Federal government rights in the licensed patents are reserved, as are VU's right to use the subject matter of the licensed patents for academic research or other not-for-profit scholarly purposes, and to grant to other academic, governmental, or not-for-profit organizations a non-exclusive right, non-transferable, non-sublicensable right to practice the licensed patent rights for academic research or other not-for-profit scholarly research purposes, expressly excluding any human use.

We must pay VU milestone payments related to milestones met in the FDA regulatory approval process in the aggregate amount of $1,075,000. We must also pay VU a 5% royalty on net sales of licensed products in the field of use. We must also pay VU 25% of non-royalty sublicense payments to us such as milestone payments we recoup from sub licensees. We must exercise commercially

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reasonable efforts to develop and commercialize a licensed product for at least one indication. Our diligence obligations include a series of patent prosecution and clinical trial milestones. If we fail to comply with our diligence obligations with respect to at least one licensed product, then VU may terminate the license.

The agreement survives until the last to expire of the licensed patent rights. We may terminate the agreement upon 60 days written notice to VU. If either we or VU breach a material obligation under the agreement, and such obligation, then the non-breaching party may terminate the agreement upon an additional written notice. VU may also terminate the license if we become insolvent or suspend business, or file a voluntary petition or an answer admitting the jurisdiction of the court, or consent to an involuntary petition pursuant to any reorganization or insolvency law of any jurisdiction, or make an assignment for the benefit of creditors, or apply for or consent to the appointment of a receiver or trustee of a substantial part of our property.

BioStratum, Inc. (BioStratum) Grant Back License Agreement

In May 2007, we entered into a grant-back license agreement with BioStratum as part of our acquisition of certain of BioStratum's assets, including certain patent rights. The licensed patent rights include all patents and patent applications licensed by NephroGenex from BioStratum under an earlier, terminated license agreement between the parties. These rights include all patents owned or licensed by us with the exception of the patent applications that we license from VU. Under this agreement, we grant BioStratum an exclusive, sublicensable license and sublicense under those patent rights to make, have made, use, sell, offer for sale and import licensed products solely in Japan, Taiwan, Korea and China. The licensed products are Pyridorin or AGE inhibitor products that are covered by the licensed patents. As this license has been fully paid, there are no milestone payments under this agreement. In this agreement, we also agreed not to modify the Kansas or USC license agreements in a manner that would adversely affect BioStratum's rights.

The license grant to BioStratum was made solely to enable BioStratum to exercise its rights and perform its obligations pursuant to a license agreement with Kowa Company, Ltd. (Kowa) pursuant to which BioStratum granted Kowa an exclusive license (the Kowa Agreement) to manufacture and use licensed products in Japan, Taiwan, Korea, and China. The Kowa Agreement was terminated by Kowa on December 5, 2007.

After termination of the BioStratum grant-back license agreement for any reason other than assignment or transfer of the Kowa Agreement to NephroGenex, we are required to obtain the written consent of BioStratum to grant a license to any third party to develop, make, have made, use, sell, offer for sale, or import Licensed Products in Japan, Taiwan, Korea or China.

Manufacturing

We do not own or operate manufacturing facilities for the production of any of our product candidates, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently rely on third-party contract manufacturers for all of our required raw materials, active pharmaceutical ingredient (API) and finished product for our preclinical research and clinical trials, including the Phase 3 trials for Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes. In December 2013, we entered into a manufacturing agreement with Patheon Pharmaceuticals Inc. to manufacture pyridoxamine dihydrochloride, the API in Pyridorin. At our direction, Patheon will manufacture clinical trial material batches of pyridoxamine dihydrochloride capsules and placebo for our clinical supply. We do not have any current contractual relationships for the manufacture of commercial supplies of any of our product candidates if they are approved. If any of our products are approved by any regulatory agency, we intend to enter into agreements with a third-party contract manufacturer and one or more back-up manufacturers for the commercial

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production of those products. Development and commercial quantities of any products that we develop will need to be manufactured in facilities, and by processes, that comply with the requirements of the FDA and the regulatory agencies of other jurisdictions in which we are seeking approval. We currently employ internal resources to manage our manufacturing contractors.

The typical route for the chemical synthesis of Pyridorin (pyridoxamine) uses oxidative methods where the starting material is the readily and economically available pyridoxine (vitamin B6). Although such oxidative manufacturing methods are usable at a small scale, oxidative methods are not viable for large-scale production and commercialization. For example, the first step in the metabolism of pyridoxine is an enzymatic oxidation of the alcohol group to an aldehyde, thus converting pyridoxine to pyridoxal. The oxidative chemical synthetic parallels this by utilizing oxidizing agents such as manganese dioxide to convert pyridoxine to pyridoxal. However, the oxidation of pyridoxine is problematic at the scale required for commercial manufacturing for several reasons, including the need to rapidly remove large amounts of solid oxidants to minimize the potential for continuing oxidation reactions. Such overoxidation not only can convert pyridoxal to pyridoxic acid but can also lead to non-selective oxidation of the second hydroxymethyl group at the 5-position. Other difficulties can be encountered subsequent to the formation of pyridoxal. For example, in order to form the desired amine, pyridoxal is conveniently reacted with hydroxylamine to form an intermediate oxime that must be subsequently reduced. Hydroxylamine is a dangerous reagent to handle on an industrial scale due to its instability, its high reactivity and its toxicity. Reduction of the oxime is known and can be performed by methods such as using zinc. However, this is also an unfavorable reagent for large scale manufacturing. Reduction with hydrogen catalysts such as platinum or palladium is possible, but this route is expensive, difficult to control, and difficult to scale up. Over-reduction can lead to the generation of deoxy impurities that may be toxic anti-metabolites contaminating the API.

To overcome this barrier to commercialization, we have developed and patented a non-oxidative method for the synthesis of pyridoxamine and all of its intermediate compounds and salts. This method provides for large scale synthesis at a fraction of the price required using traditional oxidative methods. It also eliminates the safety and environmental hazards associated with these oxidative methods.

Government Regulation and Product Approval

Governmental authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, labeling, packaging, promotion, storage, advertising, distribution, marketing and export and import of products such as those we are developing. Our product candidates must be approved by the FDA through the NDA process before they may be legally marketed in the United States and by the EMA through the MAA process before they may be legally marketed in Europe. Our product candidates will be subject to similar requirements in other countries prior to marketing in those countries. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

United States Government Regulation

NDA Approval Processes

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (the FDCA) and implementing regulations. Failure to comply with the applicable U.S. requirements at any time during the product development process or approval process, or after approval, may subject an applicant to administrative or judicial sanctions, any of which could have a material adverse effect on us. These sanctions could include:

- refusal to approve pending applications;

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withdrawal of an approval;

imposition of a clinical hold;

warning letters;

product seizures;

total or partial suspension of production or distribution; or

injunctions, fines, disgorgement, or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

completion of nonclinical laboratory tests, animal studies and formulation studies conducted according to Good Laboratory Practices (GLPs) or other applicable regulations;

submission to the FDA of an IND, which must become effective before human clinical trials may begin;

performance of adequate and well-controlled human clinical trials according to Good Clinical Practices (GCPs) to establish the safety and efficacy of the proposed drug for its intended use;

submission to the FDA of a NDA;

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current Good Manufacturing Practices (cGMPs) to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and

FDA review and approval of the NDA.

Once a pharmaceutical candidate is identified for development, it enters the preclinical or nonclinical testing stage. Nonclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An IND sponsor must submit the results of the nonclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. Some nonclinical testing may continue even after the IND is submitted. In addition to including the results of the nonclinical studies, the IND will also include a protocol detailing, among other things, the objectives of the clinical trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated if the first phase lends itself to an efficacy determination. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin. A clinical hold may occur at any time during the life of an IND, and may affect one or more specific studies or all studies conducted under the IND.

All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with GCPs. They must be conducted under protocols detailing the objectives of the trial, dosing procedures, research subject selection and exclusion criteria and the safety and effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and progress reports detailing the status of the clinical trials must be submitted to the FDA annually. Sponsors also must timely report to FDA serious and unexpected adverse reactions, any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigation

brochure, or any findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the drug. An institutional review board, or IRB, at each institution participating in the clinical trial must review and approve the protocol before a clinical trial commences at that institution and must also approve the information regarding the trial and the consent form that must be

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provided to each research subject or the subject's legal representative, monitor the study until completed and otherwise comply with IRB regulations.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

Phase 1. The drug is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and elimination. In the case of some products for severe or life-threatening diseases, such as cancer, especially when the product may be inherently too toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

Phase 2. Clinical trials are performed on a limited patient population intended to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

Phase 3. Clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population at geographically dispersed clinical study sites. These studies are intended to establish the overall risk-benefit ratio of the product and provide an adequate basis for product labeling.

Human clinical trials are inherently uncertain and Phase 1, Phase 2 and Phase 3 testing may not be successfully completed. The FDA or the sponsor may suspend a clinical trial at any time for a variety of reasons, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to the submission of an IND, at the end of Phase 2 and before a NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date and for the FDA to provide advice on the next phase of development. Sponsors typically use the meeting at the end of Phase 2 to discuss their Phase 2 clinical results and present their plans for the pivotal Phase 3 clinical trial that they believe will support the approval of the new drug. If a Phase 2 clinical trial is the subject of discussion at the end of Phase 2 meeting with the FDA, a sponsor may be able to request a Special Protocol Assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim.

According to published guidance on the SPA process, a sponsor which meets the prerequisites may make a specific request for a SPA and provide information regarding the design and size of the proposed clinical trial. The FDA is supposed to evaluate the protocol within 45 days of the request to assess whether the proposed trial is adequate, and that evaluation may result in discussions and a request for additional information. A SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins. If a written agreement is reached, it will be documented and made part of the record. The agreement will be binding on the FDA and may not be changed by the sponsor or the FDA after the trial begins except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the drug was identified after the testing began.

Concurrent with clinical trials, sponsors usually complete additional animal safety studies and also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing commercial quantities of the product in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug and the manufacturer must develop methods for testing the quality, purity and potency of the

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drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its proposed shelf-life.

The results of product development, nonclinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests and other control mechanisms, proposed labeling and other relevant information are submitted to the FDA as part of a NDA requesting approval to market the product. The submission of a NDA is subject to the payment of user fees, but a waiver of such fees may be obtained under specified circumstances. The FDA reviews all NDAs submitted to ensure that they are sufficiently complete for substantive review before it accepts them for filing. It may request additional information rather than accept a NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing.

Once the submission is accepted for filing, the FDA begins an in-depth review. NDAs receive either standard or priority review. A drug representing a significant improvement in treatment, prevention or diagnosis of disease may receive priority review. The FDA may refuse to approve a NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. The FDA reviews a NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant. The FDA may refer the NDA to an advisory committee for review and recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations. Before approving a NDA, the FDA will inspect the facility or facilities where the product is manufactured and tested.

Expedited Review and Approval

The FDA has various programs, including Fast Track, priority review, and accelerated approval, which are intended to expedite or simplify the process for reviewing drugs, and/or provide for the approval of a drug on the basis of a surrogate endpoint. Even if a drug qualifies for one or more of these programs, the FDA may later decide that the drug no longer meets the conditions for qualification or that the time period for FDA review or approval will be shortened. Generally, drugs that are eligible for these programs are those for serious or life-threatening conditions, those with the potential to address unmet medical needs and those that offer meaningful benefits over existing treatments. For example, Fast Track is a process designed to facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases or conditions and fill unmet medical needs. Priority review is designed to give drugs that offer major advances in treatment or provide a treatment where no adequate therapy exists an initial review within six months as compared to a standard review time of ten months.

Although Fast Track and priority review do not affect the standards for approval, the FDA will attempt to facilitate early and frequent meetings with a sponsor of a Fast Track designated drug and expedite review of the application for a drug designated for priority review. Accelerated approval, which is described in Subpart H of 21 CFR Part 314, provides for an earlier approval for a new drug that is intended to treat a serious or life-threatening disease or condition and that fills an unmet medical need based on a surrogate endpoint. A surrogate endpoint is a laboratory measurement or physical sign used as an indirect or substitute measurement representing a clinically meaningful outcome. As a condition of approval, the FDA may require that a sponsor of a product candidate receiving accelerated approval perform post-marketing clinical trials.

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In the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was signed into law in July 2012, Congress encouraged the FDA to utilize innovative and flexible approaches to the assessment of products under accelerated approval. The law required the FDA to issue related draft guidance within a year after the law's enactment and also promulgate confirming regulatory changes. In June 2013, the FDA published a draft Guidance for Industry entitled, "Expedited Programs for Serious Conditions Drugs and Biologics" which provides guidance on FDA programs that are intended to facilitate and expedite development and review of new drugs as well as threshold criteria generally applicable to concluding that a drug is a candidate for these expedited development and review programs. In addition to the Fast Track, accelerated approval and priority review programs discussed above, the FDA also provided guidance on a new program for Breakthrough Therapy designation. A request for Breakthrough Therapy designation should be submitted concurrently with, or as an amendment to an IND. FDA has already granted this designation to around 30 new drugs and recently approved the first Breakthrough Therapy designated drug.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of the use of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND, and the submission date of a NDA, plus the time between the submission date of a NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for extension must be made prior to expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of a NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for a NDA, 505(b)(2) NDA or supplement to an approved NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

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Pediatric Exclusivity and Pediatric Use

Under the Best Pharmaceuticals for Children Act (BPCA) certain drugs may obtain an additional six months of exclusivity, if the sponsor submits information requested in writing by the FDA (a Written Request) relating to the use of the active moiety of the drug in children. The FDA may not issue a Written Request for studies on unapproved or approved indications or where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may not produce health benefits in that population.

We have not received a Written Request for such pediatric studies, although we may ask the FDA to issue a Written Request for such studies in the future. To receive the six-month pediatric market exclusivity, we would have to receive a Written Request from the FDA, conduct the requested studies in accordance with a written agreement with the FDA or, if there is no written agreement, in accordance with commonly accepted scientific principles, and submit reports of the studies. A Written Request may include studies for indications that are not currently in the labeling if the FDA determines that such information will benefit the public health. The FDA will accept the reports upon its determination that the studies were conducted in accordance with and are responsive to the original Written Request or commonly accepted scientific principles, as appropriate, and that the reports comply with the FDA's filing requirements.

In addition, the Pediatric Research Equity Act (PREA) requires all applications (or supplements to an application) submitted under section 505 of the FDCA (21 U.S.C. Section 355) for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral. It also authorizes the FDA to require holders of approved NDAs for marketed drugs to conduct pediatric studies under certain circumstances. In general, PREA applies only to those drugs developed for diseases and/or conditions that occur in both the adult and pediatric populations. Products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population.

As part of the FDASIA, Congress reauthorized both BPCA and PREA, which were slated to expire on September 30, 2012, and made both laws permanent.

Post-approval Requirements

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product may result in restrictions on the product or even complete withdrawal of the product from the market. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. In addition, the FDA may require testing and surveillance programs to monitor the effect of approved products that have been commercialized, and the FDA has the power to prevent or limit further marketing of a product based on the results of these post-marketing programs.

Any drug products manufactured or distributed by us pursuant to FDA approvals are subject to continuing regulation by the FDA, including, among other things:

- record-keeping requirements;
- reporting of adverse experiences with the drug;
- providing the FDA with updated safety and efficacy information;
- drug sampling and distribution requirements;
- notifying the FDA and gaining its approval of specified manufacturing or labeling changes; and

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complying with FDA promotion and advertising requirements.

Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and some state agencies for compliance with cGMP and other laws.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products. Future FDA and state inspections may identify compliance issues at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct.

From time to time, legislation is drafted, introduced and passed in Congress that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. In addition, FDA regulations and guidance are often revised or reinterpreted by the agency in ways that may significantly affect our business and our products. It is impossible to predict whether legislative changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to regulations of other countries governing clinical trials and commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of countries outside of the United States before we can commence clinical trials in such countries and approval of the regulators of such countries or economic areas, such as the European Union, before we may market products in those countries or areas. The approval process and requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from place to place, and the time may be longer or shorter than that required for FDA approval.

Under European Union regulatory systems, a company may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is compulsory for medicines produced by biotechnology or those medicines intended to treat AIDS, cancer, neurodegenerative disorders or diabetes and optional for those medicines which are highly innovative, provides for the grant of a single marketing authorization that is valid for all European Union member states. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessments report, each member state must decide whether to recognize approval. If a member state does not recognize the marketing authorization, the disputed points are eventually referred to the European Commission, whose decision is binding on all member states.

Reimbursement

Sales of our products will depend, in part, on the extent to which the costs of our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly challenging the prices charged for medical products and services. Additionally, the containment of healthcare costs has become a priority of federal and state governments and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. If these third-party payors do not consider our products

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to be cost-effective compared to other therapies, they may not cover our products after approved as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (the MMA) imposed new requirements for the distribution and pricing of prescription drugs for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which will provide coverage of outpatient prescription drugs. Part D plans include both stand-alone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for our products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. A plan for the research will be developed by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures will be made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our products to be cost-effective compared to other available therapies, they may not cover our products as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010 (collectively, the ACA), enacted in March 2010, is expected to have a significant impact on the health care industry. ACA is expected to expand coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, among other things, ACA is expected to expand and increase industry rebates for drugs covered under Medicaid programs and make changes to the coverage requirements under the Medicare Part D program. We cannot predict the impact of ACA on pharmaceutical companies, as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions which has not yet occurred. In addition, some members of the U.S. Congress have been seeking to overturn at least portions of the legislation and we expect they will continue to review and assess this legislation and alternative health care reform proposals. Any legal challenges to ACA, as well as Congressional efforts to repeal ACA, add to the uncertainty of the legislative changes enacted as part of ACA.

In addition, in some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country

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to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally tend to be significantly lower.

Legal Proceedings

From time to time, we are involved in various legal proceedings arising in the ordinary course of our business. We are not presently a party to any legal proceedings the outcome of which, if determined adversely to us, would individually or in the aggregate have a material adverse effect on our business, operating results or financial condition.

Facilities

Our corporate headquarters and clinical development operations are located in Research Triangle Park, North Carolina where we lease and occupy approximately 3,100 square feet of space. The lease for our office expired in December 2013 and is currently leased on a month-to-month basis. We intend to enter into a long-term lease in the near future. We believe that our facility is suitable and adequate for our current needs.

Employees

As of March 17, 2014, we had 6 employees, of which all are involved in our drug development operations and in general and administrative functions. None of our employees are represented by a labor union and we consider our employee relations to be good. In addition, we are or have engaged with a sizable number of consultants and companies that provide expertise in each of the key functions involved with the development of Pyridorin, including in the fields of regulatory, non-clinical, clinical and CMC. In addition, from time to time, we consult with scientific and clinical advisors.

The Company's Internet address is www.nephrogenex.com. The Company's annual reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, are available free of charge through the Investor Relations section of our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC. The SEC maintains an internet site that contains our public filings with the SEC and other information regarding the Company, at www.sec.gov. These reports and other information concerning the Company may also be accessed at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The contents of these websites are not incorporated into this Annual Report. Further, our references to the URLs for these websites are intended to be inactive textual reference only.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012. We will remain an "emerging growth company" until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenues of $1 billion or more; (ii) December 31, 2019; (iii) the date on which we have issued more than $1 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission. We refer to the Jumpstart Our Business Startups Act of 2012 herein as the "JOBS Act," and references herein to "emerging growth company" shall have the meaning associated with it in the JOBS Act.

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Item 1A. RISK FACTORS

Except for the historical information contained herein or incorporated by reference, this report and the information incorporated by reference contains forward-looking statements that involve risks and uncertainties. These statements include projections about our accounting and finances, plans and objectives for the future, future operating and economic performance and other statements regarding future performance. These statements are not guarantees of future performance or events. Our actual results could differ materially from those discussed in this report. Factors that could cause or contribute to these differences include, but are not limited to, those discussed in the following section, as well as those discussed in Part II, Item 7 entitled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere throughout this report and in any documents incorporated in this report by reference.

You should consider carefully the following risk factors, together with all of the other information included or incorporated in this report. If any of the following risks, either alone or taken together, or other risks not presently known to us or that we currently believe to not be significant, develop into actual events, then our business, financial condition, results of operations or prospects could be materially adversely affected. If that happens, the market price of our common stock could decline, and stockholders may lose all or part of their investment.

Risks Relating to Our Financial Position and Need for Additional Capital

We have never been profitable. Currently, we have no products approved for commercial sale, and to date we have not generated any revenue from product sales. As a result, our ability to reduce our losses and reach profitability is unproven, and we may never achieve or sustain profitability.

We have never been profitable and do not expect to be profitable in the foreseeable future. We have not yet submitted any product candidates for approval by regulatory authorities in the United States or elsewhere for our lead indication, the treatment of diabetic nephropathy in patients with type 2 diabetes, or any other indication. We have incurred net losses in each year since our inception, including net losses of $6.3 million and $2.9 million for the years ended December 31, 2013 and 2012, respectively. We had an accumulated deficit of approximately $41.0 million as of December 31, 2013. Our working capital and cash and cash equivalents as of December 31, 2013 were $(14.7) million and $2.1 million, respectively.

To date, we have devoted most of our financial resources to our corporate overhead and research and development, including our drug discovery research, preclinical development activities and clinical trials. We have not generated any revenues from product sales. We expect to continue to incur losses for the foreseeable future, and we expect these losses to increase as we continue our development of, and seek regulatory approvals for, Pyridorin, which is our lead product candidate, and our other product candidates, prepare for and begin the commercialization of any approved products, and add infrastructure and personnel to support our product development efforts and operations as a public company. We anticipate that any such losses could be significant for the next several years as we begin our Phase 3 clinical program of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, which we call the Pyridorin program, and related activities required for regulatory approval of Pyridorin and pursuing an intravenous formulation of Pyridorin for AKI in clinical trials. If Pyridorin or any of our other product candidates fails in clinical trials or does not gain regulatory approval, or if our product candidates do not achieve market acceptance, we may never become profitable. As a result of the foregoing, we expect to continue to experience net losses and negative cash flows for the foreseeable future. These net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when,

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or if, we will be able to achieve profitability. In addition, our expenses could increase if we are required by the FDA or the EMA, to perform studies or trials in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates. The amount of future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues.

We will require substantial additional funding, which may not be available to us on acceptable terms, or at all, and, if not so available, may require us to delay, limit, reduce or cease our operations.

We are currently advancing Pyridorin through clinical development for diabetic nephropathy and an intravenous formulation of Pyridorin for AKI through preclinical development. Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is expensive. We will require substantial additional future capital in order to complete clinical development and commercialize Pyridorin, and to conduct the research and development and clinical and regulatory activities necessary to bring other product candidates to market. If the FDA or EMA requires that we perform additional nonclinical studies or clinical trials, our expenses would further increase beyond what we currently expect and the anticipated timing of any potential New Drug Application (NDA) or Marketing Authorization Application (MAA) would likely be delayed. Further, there can be no assurance that the costs to obtain regulatory approval of Pyridorin as a treatment for diabetic nephropathy in patients with type 2 diabetes will not increase.

We intend to use substantially all of the net proceeds from our recently completed initial public offering to fund (i) the continued clinical development of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, including our anticipated Phase 3 trial and (ii) further development of an intravenous formulation of Pyridorin for AKI. Any remaining amounts will be used for general corporate purposes, general and administrative expenses, capital expenditures, working capital and prosecution and maintenance of our intellectual property. As such, our net proceeds from our recently completed initial public offering will not be sufficient to complete clinical development of any of our product candidates. Accordingly, we will continue to require substantial additional capital to continue our clinical development and commercialization activities. Because successful development of our product candidates is uncertain, we are unable to estimate the actual funds we will require to complete research and development and commercialize our products under development.

The amount and timing of our future funding requirements will depend on many factors, including but not limited to:

- the progress, costs, results of and timing of our Phase 3 Pyridorin program for the treatment of diabetic nephropathy in patients with type 2 diabetes, and the clinical development of an intravenous formulation of Pyridorin for AKI;
- the willingness of the EMA or other regulatory agencies outside the U.S. to accept our Phase 3 Pyridorin program, as well as our other completed and planned clinical and nonclinical studies and other work, as the basis for review and approval of Pyridorin in the European Union for the treatment of diabetic nephropathy in patients with type 2 diabetes;
- the outcome, costs and timing of seeking and obtaining FDA, EMA and any other regulatory approvals;
- the number and characteristics of product candidates that we pursue, including our product candidates in preclinical development;
- the ability of our product candidates to progress through clinical development successfully;
- our need to expand our research and development activities;

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the costs associated with securing and establishing commercialization and manufacturing capabilities;

market acceptance of our product candidates;

the costs of acquiring, licensing or investing in businesses, products, product candidates and technologies;

our ability to maintain, expand and defend the scope of our intellectual property portfolio, including the amount and timing of any payments we may be required to make, or that we may receive, in connection with the licensing, filing, prosecution, defense and enforcement of any patents or other intellectual property rights;

our need and ability to hire additional management and scientific and medical personnel;

the effect of competing technological and market developments;

our need to implement additional internal systems and infrastructure, including financial and reporting systems; and

the economic and other terms, timing of and success of our existing licensing arrangements and any collaboration, licensing or other arrangements into which we may enter in the future.

Some of these factors are outside of our control. Based upon our currently expected level of operating expenditures, we believe that we will be able to fund our operations into 2016. This period could be shortened if there are any significant increases in planned spending on development programs or more rapid progress of development programs than anticipated. We do not expect our existing capital resources to be sufficient to enable us to complete the commercialization of Pyridorin, if approved, or to initiate any clinical trials or additional development work needed for any of our other product candidates, other than as described above. Accordingly, we expect that we will need to raise additional funds in the future.

We may seek additional funding through a combination of equity offerings, debt financings, government or other third-party funding, commercialization, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements. Additional funding may not be available to us on acceptable terms or at all. In addition, the terms of any financing may adversely affect the holdings or the rights of our stockholders. In addition, the issuance of additional shares by us, or the possibility of such issuance, may cause the market price of our shares to decline.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail one or more of our research or development programs. We also could be required to seek funds through arrangements with collaborative partners or otherwise that may require us to relinquish rights to some of our technologies or product candidates or otherwise agree to terms unfavorable to us.

We have a limited operating history and we expect a number of factors to cause our operating results to fluctuate on a quarterly and annual basis, which may make it difficult to predict our future performance.

We are a development stage pharmaceutical company with a limited operating history. Our operations to date have been limited to developing our technology and undertaking preclinical studies and clinical trials of our product candidates. We have not yet obtained regulatory approvals for any of our product candidates. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a longer operating history or approved products on the market. Our financial condition and operating results have varied significantly in the past and are expected to continue to significantly fluctuate from quarter-to-quarter or year-to-year due to a variety

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of factors, many of which are beyond our control. Factors relating to our business that may contribute to these fluctuations include:

- any delays in regulatory review and approval of our product candidates in clinical development, including our ability to receive approval from the FDA and the EMA for Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes based on our Phase 3 Pyridorin program, and our other completed and planned clinical and nonclinical studies and other work, as the basis for review and approval of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes;

- delays in the commencement, enrollment and timing of clinical trials;

- difficulties in identifying and treating patients suffering from our target indications, and kidney disease in patients with type 2 diabetes in particular;

- the success of our clinical trials through all phases of clinical development, including our Phase 3 trial of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes;

- potential side effects of our product candidates that could delay or prevent approval or cause an approved drug to be taken off the market;

- our ability to obtain additional funding to develop our product candidates;

- our ability to identify and develop additional product candidates;

- market acceptance of our product candidates;

- our ability to establish an effective sales and marketing infrastructure directly or through collaborations with third parties;

- competition from existing products or new products that may emerge;

- the ability of patients or healthcare providers to obtain coverage or sufficient reimbursement for our products;

- our ability to adhere to clinical study requirements directly or with third parties such as contract research organizations (CROs);

- our dependency on third-party manufacturers to manufacture our products and key ingredients;

- our ability to establish or maintain collaborations, licensing or other arrangements;

- the costs to us, and our ability and our third-party collaborators' ability to obtain, maintain and protect our intellectual property rights;

costs related to and outcomes of potential intellectual property litigation;

our ability to adequately support future growth;

our ability to attract and retain key personnel to manage our business effectively; and

potential product liability claims.

Accordingly, the results of any quarterly or annual periods should not be relied upon as indications of future operating performance.

Our recurring losses from operations may raise substantial doubt regarding our ability to continue as a going concern.

Our recurring losses from operations may raise substantial doubt about our ability to continue as a going concern. There is no assurance that sufficient financing will be available when needed to allow us

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to continue as a going concern. The perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations.

Risks Relating to Regulatory Review and Approval of Our Product Candidates

We cannot be certain that Pyridorin will receive regulatory approval, and without regulatory approval we will not be able to market Pyridorin.

Our business currently depends entirely on the successful development and commercialization of Pyridorin. Our ability to generate revenue related to product sales, if ever, will depend on the successful development and regulatory approval of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes or an intravenous formulation of Pyridorin for AKI.

We currently have no products approved for sale and we cannot guarantee that we will ever have marketable products. The development of a product candidate and issues relating to its approval and marketing are subject to extensive regulation by the FDA in the United States, the EMA in Europe and regulatory authorities in other countries, with regulations differing from country to country. We are not permitted to market our product candidates in the United States or Europe until we receive approval of a NDA from the FDA or a MAA from the EMA, respectively. We have not submitted any marketing applications for any of our product candidates.

NDAs and MAAs must include extensive preclinical and clinical data and supporting information to establish the product candidate's safety and effectiveness for each desired indication. NDAs and MAAs must also include significant information regarding the chemistry, manufacturing and controls for the product. Obtaining approval of a NDA or a MAA is a lengthy, expensive and uncertain process, and we may not be successful in obtaining approval. The FDA and the EMA review processes can take years to complete and approval is never guaranteed. If we submit a NDA to the FDA, the FDA must decide whether to accept or reject the submission for filing. We cannot be certain that any submissions will be accepted for filing and review by the FDA. Regulators of other jurisdictions, such as the EMA, have their own procedures for approval of product candidates. Even if a product is approved, the FDA or the EMA, as the case may be, may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and Europe also have requirements for approval of drug candidates with which we must comply prior to marketing in those countries. Obtaining regulatory approval for marketing of a product candidate in one country does not ensure that we will be able to obtain regulatory approval in any other country. In addition, delays in approvals or rejections of marketing applications in the United States, Europe or other countries may be based upon many factors, including regulatory requests for additional analyses, reports, data, preclinical studies and clinical trials, regulatory questions regarding different interpretations of data and results, changes in regulatory policy during the period of product development and the emergence of new information regarding our product candidates or other products. Also, regulatory approval for any of our product candidates may be withdrawn.

We have completed three Phase 2 trials for Pyridorin. Before we submit a NDA to the FDA or a MAA to the EMA for Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, we must successfully conduct two Phase 3 trials. In addition, we must complete other nonclinical and clinical studies, such as a thorough QT interval (TQT) clinical study, two nonclinical carcinogenicity studies and a nonclinical cardiac safety study. We cannot predict whether our future trials and studies will be successful or whether regulators will agree with our conclusions regarding the preclinical studies and clinical trials we have conducted to date.

If we are unable to obtain approval from the FDA, the EMA or other regulatory agencies for Pyridorin and our other product candidates, or if, subsequent to approval, we are unable to successfully commercialize Pyridorin or our other product candidates, we will not be able to generate sufficient revenue to become profitable or to continue our operations.

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Any statements in this document indicating that Pyridorin has demonstrated preliminary evidence of efficacy are our own and are not based on the FDA's or any other comparable governmental agency's assessment of Pyridorin and do not indicate that Pyridorin will achieve favorable efficacy results in any later stage trials or that the FDA or any comparable agency will ultimately determine that Pyridorin is effective for purposes of granting marketing approval.

Although the FDA has agreed to our endpoint for approval, other regulatory agencies outside the United States, such as the EMA, may not agree to our proposed endpoint for approval of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, in which case we would need to complete an additional clinical trial in order to seek approval outside the United States.

The EMA and regulatory authorities in other countries in which we may seek approval for and market Pyridorin may require additional nonclinical studies and/or clinical trials prior to granting approval. It may be expensive and time consuming to conduct and complete additional nonclinical studies and clinical trials that the EMA and other regulatory authorities may require us to perform. As such, any requirement by the EMA or other regulatory authorities that we conduct additional nonclinical studies or clinical trials could materially and adversely affect our business, financial condition and results of operations. Furthermore, even if we receive regulatory approval of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, the labeling for Pyridorin in the United States, Europe or other countries in which we seek approval may include limitations that could impact the commercial success of Pyridorin.

Delays in the commencement, enrollment and completion of clinical trials could result in increased costs to us and delay or limit our ability to obtain regulatory approval for Pyridorin and our other product candidates.

Delays in the commencement, enrollment and completion of clinical trials could increase our product development costs or limit the regulatory approval of our product candidates. We do not know whether any future trials or studies of our other product candidates will begin on time or will be completed on schedule, if at all. The start or end of a clinical study is often delayed or halted due to changing regulatory requirements, manufacturing challenges, required clinical trial administrative actions, slower than anticipated patient enrollment, changing standards of care, availability or prevalence of use of a comparative drug or required prior therapy, clinical outcomes or financial constraints. For instance, delays or difficulties in patient enrollment or difficulties in retaining trial participants can result in increased costs, longer development times or termination of a clinical trial. Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the size of the patient population, the eligibility criteria for the clinical trial, the age and condition of the patients, the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites and the availability of effective treatments for the relevant disease.

A product candidate can unexpectedly fail at any stage of preclinical and clinical development. The historical failure rate for product candidates is high due to scientific feasibility, safety, efficacy, changing standards of medical care and other variables. The results from preclinical testing or early clinical trials of a product candidate may not predict the results that will be obtained in later phase clinical trials of the product candidate. We, the FDA or other applicable regulatory authorities may suspend clinical trials of a product candidate at any time for various reasons, including a belief that subjects participating in such trials are being exposed to unacceptable health risks or adverse side effects. We may not have the financial resources to continue development of, or to enter into collaborations for, a product candidate if we experience any problems or other unforeseen events that delay or prevent regulatory approval of, or our ability to commercialize, product candidates, including:

- inability to obtain sufficient funds required for a clinical trial;

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inability to reach agreements on acceptable terms with prospective CROs and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;

negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours, leading to a decision or requirement to conduct additional preclinical testing or clinical trials or abandon a program;

serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;

inability to obtain approval from institutional review boards (IRBs), to conduct a clinical trial at their respective sites;

conditions imposed by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;

delays in enrolling research subjects in clinical trials;

high drop-out rates of research subjects;

inadequate supply or quality of product candidate components or materials or other supplies necessary for the conduct of our clinical trials;

greater than anticipated clinical trial costs;

poor effectiveness of our product candidates during clinical trials;

unfavorable FDA or other regulatory agency inspection and review of a clinical trial site;

failure of our third-party contractors or investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;

delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our technology in particular; or

varying interpretations of data by the FDA and similar foreign regulatory agencies.

Clinical failure can occur at any stage of clinical development and we have never conducted a Phase 3 trial or submitted a NDA or MAA before. The results of earlier clinical trials are not necessarily predictive of future results and any product candidate we or our potential future collaborators advance through clinical trials may not have favorable results in later clinical trials or receive regulatory approval.

Clinical failure can occur at any stage of our clinical development. Clinical trials may produce negative or inconclusive results, and we or our collaborators may decide, or regulators may require us, to conduct additional clinical trials or nonclinical studies. In addition, data obtained from trials and studies are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may delay, limit or prevent regulatory approval. Success in preclinical studies and early clinical trials does not ensure that subsequent clinical trials will generate the same or similar results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. A

number of companies in the pharmaceutical industry, including those with greater resources and experience than us, have suffered significant setbacks in Phase 3 clinical trials, even after seeing promising results in earlier clinical trials.

Pyridorin did not reach its primary endpoint in the intent to treat (ITT) population in the Phase 2b study (PYR-210). However, in a subgroup of patients on stable long term standard of care, Pyridorin showed a dose dependent treatment effect of approximately 50%. This subgroup is the

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patient population that will be studied in the Phase 3 program. Subgroup analysis carries the inherent risk that the results may not be repeatable in a subsequent trial. It is possible that the treatment effect observed in this subgroup of PYR-210 may not repeat in our Phase 3 trials.

Pyridorin has demonstrated a promising treatment effect in Phase 2 clinical trials using a rate of change in SCr endpoint. The Phase 3 trial will utilize a new 50% SCr increase event endpoint. While there is a strong correlation between the rate of change of SCr and the 50% SCr increase event endpoint, no clinical trials have been conducted using this new endpoint. We cannot assure you that our Pyridorin program will achieve positive results using this new endpoint.

In addition, the design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well-advanced. We may be unable to design and execute a clinical trial to support regulatory approval. Further, clinical trials of potential products often reveal that it is not practical or feasible to continue development efforts.

If Pyridorin is found to be unsafe or lack efficacy, we will not be able to obtain regulatory approval for it and our business would be harmed. For example, if the results of our Phase 3 Pyridorin program do not achieve the primary efficacy endpoints or demonstrate expected safety, the prospects for approval of Pyridorin would be materially and adversely affected.

In some instances, there can be significant variability in safety and/or efficacy results between different trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in composition of the patient populations, adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. We do not know whether any Phase 2, Phase 3 or other clinical trials we or any of our potential future collaborators may conduct will demonstrate the consistent or adequate efficacy and safety that would be required to obtain regulatory approval and market Pyridorin. If we are unable to bring Pyridorin to market, or to acquire other products that are on the market or can be developed, our ability to create long-term stockholder value will be limited.

Our product candidates may have undesirable side effects which may delay or prevent marketing approval, or, if approval is received, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales.

Pyridorin targets a broad range of pathogenic oxidative chemistries, including advanced glycation end-products, toxic carbonyls, and reactive oxygen species that develop in patients with diabetes and are considered a principal causative factor in the development and progression of diabetic microvascular disease. Unforeseen side effects from any of our product candidates could arise either during clinical development or, if approved, after the approved product has been marketed. The most common side effects observed in clinical trials of Pyridorin were a slight increase in diarrhea and constipation. No patients were withdrawn from the study for these side effects. Additional or unforeseen side effects from these or any of our other product candidates could arise either during clinical development or, if approved, after the approved product has been marketed.

The range and potential severity of possible side effects from systemic therapies is significant. The results of future clinical trials may show that Pyridorin causes undesirable or unacceptable side effects, which could interrupt, delay or halt clinical trials, and result in delay of, or failure to obtain, marketing approval from the FDA and other regulatory authorities, or result in marketing approval from the FDA and other regulatory authorities with restrictive label warnings.

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If any of our product candidates receives marketing approval and we or others later identify undesirable or unacceptable side effects caused by such products:

- regulatory authorities may require the addition of labeling statements, specific warnings, a contraindication or field alerts to physicians and pharmacies;
- we may be required to change instructions regarding the way the product is administered, conduct additional clinical trials or change the labeling of the product;
- we may be subject to limitations on how we may promote the product;
- sales of the product may decrease significantly;
- regulatory authorities may require us to take our approved product off the market;
- we may be subject to litigation or product liability claims; and
- our reputation may suffer.

Any of these events could prevent us or our potential future collaborators from achieving or maintaining market acceptance of the affected product or could substantially increase commercialization costs and expenses, which in turn could delay or prevent us from generating significant revenues from the sale of our products.

Reimbursement decisions by third-party payors may have an adverse effect on pricing and market acceptance. If there is not sufficient reimbursement for our products, it is less likely that they will be widely used.

Market acceptance and sales of Pyridorin or any other product candidates that we develop, if approved, will depend on reimbursement policies and may be affected, among other things, by future healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will cover and establish payment levels. We cannot be certain that reimbursement will be available for Pyridorin or any other product candidates that we develop. Also, we cannot be certain that reimbursement policies will not reduce the demand for, or the price paid for, our products. If reimbursement is not available or is available on a limited basis, we may not be able to successfully commercialize Pyridorin or any other product candidates that we develop.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) changed the way Medicare covers and pays for pharmaceutical products. The legislation established Medicare Part D, which expanded Medicare coverage for outpatient prescription drug purchases by the elderly but provided authority for limiting the number of drugs that will be covered in any therapeutic class. The MMA also introduced a new reimbursement methodology based on average sales prices for physician- administered drugs. Any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain in the United States. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The United States and several other jurisdictions are considering, or have already enacted, a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access to healthcare. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. We expect to experience pricing pressures in

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connection with the sale of Pyridorin and any other products that we develop, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative proposals.

In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act (collectively, ACA) became law in the United States. The goal of ACA is to reduce the cost of health care and substantially change the way health care is financed by both governmental and private insurers. While we cannot predict what impact on federal reimbursement policies this legislation will have in general or on our business specifically, the ACA may result in downward pressure on pharmaceutical reimbursement, which could negatively affect market acceptance of Pyridorin or any future product candidates. In addition, some members of the U.S. Congress have been seeking to overturn at least portions of the legislation and we expect they will continue to review and assess this legislation and alternative health care reform proposals. We cannot predict whether new proposals will be made or adopted, when they may be adopted or what impact they may have on us if they are adopted.

If we do not obtain protection under the Hatch-Waxman Act and similar legislation outside of the United States by extending the patent terms and obtaining data exclusivity for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of Pyridorin and our other product candidates, if any, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In the event that we are unable to obtain any patent term extensions, the issued patents for methods of using Pyridorin are expected to expire in June 2024 assuming they withstand any challenge.

If we market products in a manner that violates healthcare fraud and abuse laws, or if we violate government price reporting laws, we may be subject to civil or criminal penalties.

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal healthcare laws, commonly referred to as "fraud and abuse" laws, have been applied in recent years to restrict certain marketing practices in the pharmaceutical industry. Other jurisdictions such as Europe have similar laws. These laws include false claims and anti-kickback statutes. If we market our products and our products are paid for by governmental programs, it is possible that some of our business activities could be subject to challenge under one or more of these laws.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, or causing to be made, a false statement to get a false claim paid. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service covered by Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers or formulary managers on

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the other. Although there are several statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Most states also have statutes or regulations similar to the federal anti-kickback law and federal false claims laws, which apply to items and services covered by Medicaid and other state programs, or, in several states, apply regardless of the payor. Administrative, civil and criminal sanctions may be imposed under these federal and state laws.

Over the past few years, a number of pharmaceutical and other healthcare companies have been prosecuted under these laws for a variety of promotional and marketing activities, such as: providing free trips, free goods, sham consulting fees and grants and other monetary benefits to prescribers; reporting inflated average wholesale prices that were then used by federal programs to set reimbursement rates; engaging in off-label promotion; and submitting inflated best price information to the Medicaid Rebate Program to reduce liability for Medicaid rebates.

If the FDA and EMA and other regulatory agencies do not approve the manufacturing facilities of our future contract manufacturers for commercial production, we may not be able to commercialize any of our product candidates.

We do not intend to manufacture the pharmaceutical products that we plan to sell. We currently have agreements with contract manufacturers for the production of the active pharmaceutical ingredients and the formulation of sufficient quantities of drug product for our Phase 3 trial of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes and the other trials and nonclinical studies that we believe we will need to conduct prior to seeking regulatory approval. However, we do not have agreements for commercial supplies of Pyridorin or any of our other product candidates and we may not be able to reach agreements with these or other contract manufacturers for sufficient supplies to commercialize Pyridorin if it is approved. Additionally, the facilities used by any contract manufacturer to manufacture Pyridorin or any of our other product candidates must be the subject of a satisfactory inspection before the FDA or the regulators in other jurisdictions approve the product candidate manufactured at that facility. We are completely dependent on these third-party manufacturers for compliance with the requirements of U.S. and non-U.S. regulators for the manufacture of our finished products. If our manufacturers cannot successfully manufacture material that conform to our specifications and current good manufacturing practice requirements of any governmental agency whose jurisdiction to which we are subject, our product candidates will not be approved or, if already approved, may be subject to recalls. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured the product candidates, including:

- the possibility that we are unable to enter into a manufacturing agreement with a third party to manufacture our product candidates;
- the possible breach of the manufacturing agreements by the third parties because of factors beyond our control; and
- the possibility of termination or nonrenewal of the agreements by the third parties before we are able to arrange for a qualified replacement third-party manufacturer.

Any of these factors could cause the delay of approval or commercialization of our product candidates, cause us to incur higher costs or prevent us from commercializing our product candidates successfully. Furthermore, if any of our product candidates are approved and contract manufacturers fail to deliver the required commercial quantities of finished product on a timely basis and at commercially reasonable prices and we are unable to find one or more replacement manufacturers capable of production at a substantially equivalent cost, in substantially equivalent volumes and quality and on a timely basis, we would likely be unable to meet demand for our products and could lose

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potential revenue. It may take several years to establish an alternative source of supply for our product candidates and to have any such new source approved by the government agencies that regulate our products.

Even if our product candidates receive regulatory approval, we may still face future development and regulatory difficulties.

Our product candidates, if approved, will also be subject to ongoing regulatory requirements for labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market information. In addition, approved products, manufacturers and manufacturers' facilities are required to comply with extensive FDA and EMA requirements and requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to current Good Manufacturing Practices (cGMPs). As such, we and our contract manufacturers are subject to continual review and periodic inspections to assess compliance with cGMPs. Accordingly, we and others with whom we work must continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production and quality control. We will also be required to report certain adverse reactions and production problems, if any, to the FDA and EMA and other similar agencies and to comply with certain requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. Accordingly, we may not promote our approved products, if any, for indications or uses for which they are not approved.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, it may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

issue warning letters;

mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;

require us or our potential future collaborators to enter into a consent decree or permanent injunction, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;

impose other administrative or judicial civil or criminal penalties;

withdraw regulatory approval;

refuse to approve pending applications or supplements to approved applications filed by us or our potential future collaborators;

impose restrictions on operations, including costly new manufacturing requirements; or

seize or detain products.

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Risks Relating to the Commercialization of Our Products

Even if approved, our product candidates may not achieve broad market acceptance among physicians, patients and healthcare payors, and as a result our revenues generated from their sales may be limited.

The commercial success of Pyridorin, if approved, will depend upon its acceptance among the medical community, including physicians, health care payors and patients. The degree of market acceptance of Pyridorin or future product candidates will depend on a number of factors, including:

limitations or warnings contained in our product candidates' FDA-approved labeling;

changes in the standard of care or availability of alternative therapies at similar or lower costs for the targeted indications for any of our product candidates;

limitations in the approved clinical indications for our product candidates;

demonstrated clinical safety and efficacy compared to other products;

lack of significant adverse side effects;

sales, marketing and distribution support;

availability of reimbursement from managed care plans and other third-party payors;

timing of market introduction and perceived effectiveness of competitive products;

the degree of cost-effectiveness;

availability of alternative therapies at similar or lower cost, including generics and over-the-counter products;

enforcement by the FDA and EMA of laws and rulings that prohibit the illegal sale of pyridoxamine as a dietary supplement;