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-control