

NephroGenex, Inc.
Form S-1/A
July 07, 2015

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As filed with the Securities and Exchange Commission on July 7, 2015

Registration No. 333-203530

SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Amendment No. 4
to

FORM S-1

REGISTRATION STATEMENT
UNDER THE SECURITIES ACT OF 1933

NephroGenex, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

2834
(Primary Standard Industrial
Classification Code Number)
3200 Beechleaf Court
Suite 900
Raleigh, NC 27604
(609) 986-1780

20-1295171
(IRS Employer
Identification No.)

(Address, including zip code, and telephone number,
including area code, of registrant's principal executive offices)

Pierre Legault
Chief Executive Officer
NephroGenex, Inc.
3200 Beechleaf Court
Suite 900
Raleigh, NC 27604
(609) 986-1780

(Name, address, including zip code, and telephone number,
including area code, of agent for service)

With copies to:

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Approximate date of commencement of proposed sale to public:

As soon as practicable after this Registration Statement becomes effective.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933 check the following box:

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

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 12b2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

(Do not check if a smaller reporting company)

CALCULATION OF REGISTRATION FEE

Title of each class of securities to be registered	Proposed Maximum Aggregate Offering Price⁽¹⁾⁽²⁾	Amount of Registration Fee⁽³⁾
Common Stock, \$.001 par value per share	\$ 17,250,000	\$2,004.45
Warrants to purchase shares of common stock ⁽⁴⁾		
Shares of common stock issuable upon exercise of the warrants	\$ 21,562,495	\$2,505.56
Total	\$ 38,812,495	\$4,510.01

(1) Estimated solely for the purpose of calculating the amount of registration fee pursuant to Rule 457(o) under the Securities Act, as amended.

(2) Pursuant to Rule 416, the securities being registered hereunder include such indeterminate number of additional securities as may be issuable to prevent dilution resulting from stock splits, stock dividends or similar transactions.

(3) Previously paid.

(4) No fee pursuant to Rule 457(g) under the Securities Act.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the Registration Statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell securities, and we are not soliciting offers to buy these securities, in any state where the offer or sale is not permitted.

PRELIMINARY PROSPECTUS

SUBJECT TO COMPLETION

DATED JULY 7, 2015

2,365,930 Shares of Common Stock

Warrants to Purchase 2,365,930 Shares of Common Stock

NephroGenex is offering 2,365,930 shares of common stock and warrants to purchase 2,365,930 shares of common stock (and the shares of common stock that are issuable from time to time upon exercise of the warrants). Each share of common stock is being sold together with one warrant to purchase one share of common stock. The warrants will have a per share exercise price of \$. The warrants are exercisable immediately and will expire five years from the date of issuance. Our common stock is listed on the NASDAQ Capital Market under the symbol "NRX." On July 2, 2015, the last reported sale price of our common stock on The NASDAQ Capital Market was \$6.34 per share. There is no established public trading market for the warrants, and we do not expect a market to develop. In addition, we do not intend to apply for a listing of the warrants on any national securities exchange.

We are an "emerging growth company" as that term is used in the Jumpstart Our Business Startups Act of 2012, and, as such, we have elected to take advantage of certain reduced public company reporting requirements for this prospectus and future filings.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page 8 of this prospectus for a discussion of information that should be considered in connection with an investment in our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Combined Per Share and Warrant	Total
Public Offering Price	\$	\$
Underwriting discounts and commissions ⁽¹⁾	\$	\$
Offering proceeds to us, before expenses	\$	\$

⁽¹⁾ We have agreed to reimburse the underwriters for certain expenses. See "Underwriting" beginning on page 132 of this prospectus.

We have granted a 45-day option to the representatives of the underwriters to purchase up to 354,889 additional shares of common stock at a purchase price of \$ per share and/or additional warrants to purchase up to 354,889 shares of common stock at a purchase price of \$0.01 per warrant to cover over-allotments, if any.

The underwriters expect to deliver the shares and warrants to purchasers in this offering on or about , 2015.

Aegis Capital Corp

The date of this prospectus is , 2015

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You should rely only on the information contained in this prospectus. Neither we nor any of the underwriters have authorized anyone to provide you with information different from, or in addition to, that contained in this prospectus or any free writing prospectus prepared by or on behalf of us or to which we may have referred you in connection with this offering. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. Neither we nor any of the underwriters is making an offer to sell or seeking offers to buy these securities in any jurisdiction where, or to any person to whom, the offer or sale is not permitted. The information in this prospectus is accurate only as of the date on the front cover of this prospectus, regardless of the time of delivery of this prospectus or of any sale of shares of our common stock or warrants, and the information in any free writing prospectus that we may provide you in connection with this offering is accurate only as of the date of that free writing prospectus. Our business, financial condition, results of operations and future growth prospects may have changed since those dates.

This prospectus includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. While we believe these industry publications and third-party research, surveys and studies are reliable, we have not independently verified such data.

For investors outside the United States: We have not and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the securities and the distribution of this prospectus outside the United States.

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PROSPECTUS SUMMARY

This summary provides an overview of selected information contained elsewhere in this prospectus and does not contain all of the information you should consider before investing in our common stock. You should carefully read this prospectus and the registration statement of which this prospectus is a part in their entirety before investing in our common stock, including the information discussed under "Risk Factors" and our financial statements and notes thereto that appear elsewhere in this prospectus. Unless otherwise indicated herein, the terms "we," "our," "us," or "the Company" refer to NephroGenex, Inc.

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, and in cases of acute kidney injury (AKI). 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 and recently completed the Phase 1 QT/QTc (TQT) cardiac safety study. In addition, we worked with the FDA to establish a new regulatory pathway for Pyridorin approval, as well as received support from the European Medicines Agency (EMA) regarding the pivotal Phase 3 program with Pyridorin in diabetic nephropathy.

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 entered into a Phase 3 program in 2014 termed the PIONEER trial which was agreed to by the U.S. Food and Drug Administration (FDA), with fast track designation, under a Special Protocol Assessment (SPA). This Phase 3 program is using an 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 our Phase 3 program compared to the traditional endpoint used in previous pivotal trials for diabetic nephropathy which is a 100% increase in SCr from baseline or end stage renal disease (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 are also studying the application of an intravenous formulation of Pyridorin to specific types of AKI in patients at increased risk and where pathogenic oxidative chemistries have been identified as a

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possible contributing factor to the severity of this condition. Our preclinical program has shown encouraging results in animal models of ischemia-reperfusion AKI including an observed treatment effect on post injury fibrosis. We expect to complete our preclinical program for an intravenous formulation of AKI in the third quarter of 2015.

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 ESRD; or (2) reduce the severity of AKI 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 AKI.

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

Our Strategy

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;

continued development of an intravenous formulation of Pyridorin for AKI, with an investigational new drug application (IND) filing and launch of the initial clinical study during the second half of 2015; and

deploying capital strategically to develop our portfolio of product candidates and create shareholder value.

Risks Relating to Our Business

We are a biopharmaceutical company, and our business and ability to execute our business strategy are subject to a number of risks of which you should be aware before you decide to buy our common stock. In particular, you should consider the risks discussed in the "Risk Factors" section of this prospectus and in the documents incorporated by reference, including, but not limited to, the following:

we have never been profitable, have no products approved for commercial sale and to date have not generated any revenue from product sales;

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we will require substantial additional funding beyond this contemplated offering to complete the development and commercialization of Pyridorin and to continue to advance the development of the intravenous formulation of Pyridorin, and such funding may not be available on acceptable terms or at all;

Pyridorin may not receive regulatory approval in a timely manner or at all;

we face competition from other biotechnological and pharmaceutical companies and our operating results will suffer if we fail to compete effectively;

we depend on third-party contractors for a substantial portion of our operations and may not be able to control their work as effectively as if we performed the function ourselves

we may be subject to delays in our clinical trials, which could result in increased costs and delays or limit our ability to obtain regulatory approval for our product candidates;

because the results of earlier studies and clinical trials of our product candidates may not be predictive of future clinical trial results, our product candidates may not have favorable results in future clinical trials, which would delay or limit their future development; and

we may be unable to maintain and protect our intellectual property assets, which could impair the advancement of our pipeline and commercial opportunities.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012. As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. See "Risk Factors - Risks Relating to Our Common Stock and this Offering - We are an 'emerging growth company' and will be able to avail ourselves of reduced disclosure requirements applicable to emerging growth companies, which could make our common stock less attractive to investors." These provisions include:

only two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;

reduced disclosure about our executive compensation arrangements;

no non-binding advisory votes on executive compensation or golden parachute arrangements; and

exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We may take advantage of these provisions until December 31, 2019. However, if certain events occur prior to December 31, 2019, including if we become a "large accelerated filer," our annual gross revenues exceed \$1.0 billion or we issue more than \$1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company before such date.

We have elected to take advantage of certain of the reduced disclosure obligations and may elect to take advantage of other reduced reporting requirements in future filings. As a result, the information that we provide to our stockholders may be different than the information

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you might receive from other public reporting companies in which you hold equity interests.

We refer to the Jumpstart Our Business Startups Act of 2012 in this prospectus as the "JOBS Act," and references in this prospectus to "emerging growth company" have the meaning associated with it in the JOBS Act.

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Notwithstanding the above, we are also currently a "smaller reporting company" meaning that we are not an investment company, an asset-backed issuer, or a majority-owned subsidiary of a parent company that is not a smaller reporting company and have a public float of less than \$75 million and annual revenues of less than \$50 million during the most recently completed fiscal year. In the event that we are still considered a smaller reporting company, at such time as we cease being an emerging growth company, the disclosure we will be required to provide in our SEC filings will increase, but will still be less than it would be if we were not considered either an emerging growth company or a smaller reporting company. Specifically, similar to emerging growth companies, smaller reporting companies are able to provide simplified executive compensation disclosures in their filings; are exempt from the provisions of Section 404(b) of the Sarbanes-Oxley Act requiring that independent registered public accounting firms provide an attestation report on the effectiveness of internal control over financial reporting; and have certain other decreased disclosure obligations in their SEC filings, including, among other things, only being required to provide two years of audited financial statements in annual reports.

Corporate Information

We were incorporated in the State of Delaware on May 25, 2004. Our principal executive offices are located at 3200 Beechleaf Court, Suite 900, Raleigh, NC 27604 and our telephone number is (609) 986-1780. Our website address is www.nephrogenex.com. The information contained on, or that can be accessed through, our website is not part of this prospectus.

We have obtained a registered trademark for Pyridorin in the United States. This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other company.

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THE OFFERING

Common stock offered by us	2,365,930 shares
Warrants offered by us	Warrants to purchase 2,365,930 shares of common stock. Each share of common stock is being sold together with one warrant to purchase one share of common stock. Each warrant will have an exercise price equal to \$, will be immediately exercisable and will expire on the fifth anniversary of the original issuance date.
Common stock to be outstanding after this offering	11,229,544 shares, or 13,595,474 shares if the warrants sold in this offering are exercised in full.
Over-allotment option	We have granted the underwriters a 45-day option to purchase up to 354,889 additional shares of our common stock at a purchase price of \$ per share and/or warrants to purchase up to 354,889 additional shares of common stock from us at a purchase price of \$0.01 per warrant.
Use of proceeds	We intend to use the net proceeds received from this offering for working capital and general corporate purposes. See "Use of Proceeds."
Risk Factors	See the section entitled "Risk Factors" beginning on page 8 of this prospectus for a discussion of factors you should carefully consider before deciding to invest in our common stock.
Nasdaq Capital Market symbol	NRX. We do not intend to list the warrants on The NASDAQ Capital Market, any other national securities exchange or any other nationally recognized trading system.

The number of shares of our common stock to be outstanding after this offering is based on 8,863,614 shares of our common stock outstanding as of March 31, 2015 and excludes as of such date:

1,271,321 shares of our common stock issuable upon the exercise of stock options, with a weighted average exercise price of \$4.16 per share;

15,500 shares of our common stock issuable upon the settlement of outstanding restricted stock units;

118,603 shares of our common stock issuable upon the exercise of outstanding warrants, with a weighted average exercise price of \$9.86 per share;

shares issuable upon exercise of warrants sold in this offering;

any shares of our common stock issuable upon exercise of the underwriters' over-allotment option; and

other shares of our common stock reserved for future issuance under our Amended and Restated 2007 Equity Incentive Plan, as amended.

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Unless otherwise indicated, all information contained in this prospectus assumes no exercise by the underwriters of their over-allotment option to purchase up to an additional 354,889 shares of our common stock or additional warrants to purchase up to 354,889 shares of our common stock.

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The following tables set forth a summary of our historical financial data as of, and for the periods ended on, the dates indicated. We have derived the statement of operations data for the years ended December 31, 2014 and 2013 from our audited financial statements incorporated by reference in this prospectus. We have derived the statement of operations data for the three months ended March 31, 2015 and 2014 and the balance sheet data as of March 31, 2015 from our unaudited financial statements incorporated by reference in this prospectus. The unaudited financial statements have been prepared on the same basis as our audited financial statements and include, in the opinion of management, all adjustments necessary for a fair presentation of the financial information set forth in those statements. You should read this data together with our financial statements and related notes appearing elsewhere in this prospectus and the sections in this prospectus entitled "Risk Factors," "Capitalization," "Selected Financial Data," and "Management's Discussion and Analysis of Financial Condition and Results of Operations." Our historical results for any prior period are not necessarily indicative of our future results.

	Years ended December 31,		Three months ended March 31,	
	2014	2013	2015 (unaudited)	2014 (unaudited)
(in thousands, except share and per share data)				
Statement of Operations Data:				
Expenses:				
Research and development	\$ 11,264	\$ 1,480	\$ 3,369	\$ 457
General and administrative	5,323	1,026	1,670	1,035
Total expenses	16,587	2,506	5,039	1,492
Loss from operations	(16,587)	(2,506)	(5,039)	(1,492)
Other income (expense):				
Change in value of preferred stock warrants	(140)	(3,417)		(140)
Interest expense	(140)	(383)	(143)	(78)
Interest income	47	1	9	10
Net loss	\$ (16,820)	\$ (6,305)	\$ (5,173)	\$ (1,700)
Net loss per share, basic and diluted	\$ (2.15)	\$ (19.71)	(0.58)	(0.37)
Weighted average shares outstanding, basic and diluted	7,827,519	319,882	8,863,103	4,587,498

	As of March 31, 2015 (Unaudited)	As Adjusted(1) (Unaudited)
(in thousands)		
Balance Sheet Data		
Cash and cash equivalents	\$ 16,362	\$ 29,817
Short-term investments	7,603	7,603
Total assets	25,109	38,564
Current portion of note payable	880	880

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Note payable, less current portion	5,897	5,897
Total liabilities	10,676	10,676
Total stockholders' equity	14,433	27,888

- (1) The as adjusted balance sheet data gives effect to our receipt of estimated net proceeds from this offering. A \$1.00 increase (decrease) in the assumed public offering price of \$6.34 per share, the last reported sale price of our common stock on the NASDAQ Capital Market on July 2, 2015, would increase (decrease) each of cash and cash equivalents, total assets and total stockholders' equity by \$2.2 million, assuming the number of shares offered by us as stated on the cover page of this prospectus remain unchanged and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable

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by us. Similarly, a one million share increase (decrease) in the number of shares offered by us, as set forth on the cover page of this prospectus, would increase (decrease) each of cash and cash equivalents, total assets and total stockholders' equity by \$6.0 million, assuming the public offering price of \$6.34 per share, the last reported sale price of our common stock on the NASDAQ Capital Market on July 2, 2015, remains the same, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the following risk factors, as well as the other information in this prospectus, including our financial statements and related notes, before deciding whether to invest in shares of our common stock, and the risk factors described in our periodic reports filed with the SEC which are incorporated by reference in the prospectus. The occurrence of any of the adverse developments described in the following risk factors could materially and adversely harm our business, financial condition, results of operations or prospects. In that case, the trading price of our common stock could decline, and you may lose all or part of your investment.

Risks Related to this Offering

There is no public market for the warrants to purchase shares of our common stock being offered in this offering.

There is no established public trading market for the warrants being offered in this offering, and we do not expect a market to develop. In addition, we do not intend to apply to list the warrants on any national securities exchange or other nationally recognized trading system, including The NASDAQ Capital Market. Without an active market, the liquidity of the warrants will be limited.

If you purchase our common stock in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing common stock in this offering will pay a price per share that substantially exceeds the net tangible book value per share of shares of our common stock based on the total value of our tangible assets less our total liabilities immediately following this offering. As a result, investors purchasing common stock in this offering will incur immediate dilution of \$3.86 per share, based on an assumed public offering price of \$6.34 per share (the last reported sale price of our common stock on the Nasdaq Capital Market on July 2, 2015) and our net tangible book value as of March 31, 2015. In the event that you exercise your warrants, you will experience additional dilution to the extent that the exercise price of the warrants is higher than the tangible book value per share of our common stock. For information on how the foregoing amounts were calculated, see "Dilution."

In addition, we have a significant number of stock options and warrants outstanding. To the extent that outstanding stock options or warrants, including the warrants offered in the prospectus, have been or may be exercised or other shares issued, you may experience further dilution.

Management will have broad discretion over the use of the net proceeds received by us in this offering and may apply them to uses that do not improve our operating results or the value of your securities.

Our management will have broad discretion in the application of the net proceeds we receive in this offering, including for any of the purposes described in the section of this prospectus entitled "Use of Proceeds," and you will not have the opportunity as part of your investment decision to assess whether our management is using the net proceeds appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business and cause the price of our common stock to decline. Pending their use, we may invest our net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our stockholders.

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A substantial number of shares of common stock may be sold in the market following this offering, which may depress the market price for our common stock.

Sales of a substantial number of shares of our common stock (including shares issued upon the exercise of options and warrants) in the public market following this offering could cause the market price of our common stock to decline. A substantial majority of the outstanding shares of our common stock are, and the shares of common stock sold in this offering upon issuance will be, freely tradable without restriction or further registration under the Securities Act of 1933, as amended.

Holders of our warrants will have no rights as a common stockholder until they acquire our common stock.

Until you acquire shares of our common stock upon exercise of your warrants, you will have no rights with respect to shares of our common stock issuable upon exercise of your warrants. Upon exercise of your warrants, you will be entitled to exercise the rights of a common stockholder only as to matters for which the record date occurs after the exercise date.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never declared or paid cash dividends on our capital stock. We anticipate that we will retain our earnings, if any, for future growth and therefore do not anticipate paying cash dividends in the future. As a result, only appreciation of the price of our common stock will provide a return to stockholders.

The warrants may not have any value.

The warrants sold in this offering will have an exercise price of \$ _____ per share and will expire on the fifth anniversary of the date they first become exercisable. In the event our common stock price does not exceed the exercise price of the warrants during the period when the warrants are exercisable, the warrants may not have any value.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock. We cannot assure you that we will be able to sell shares or other securities in any other offering at a price per share that is equal to or greater than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock or other securities convertible into or exchangeable for our common stock in future transactions may be higher or lower than the price per share in this offering.

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Risks Relating to Our Financial Position and Need for Additional Capital

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. 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 NDA or 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 or as a treatment for AKI will not increase.

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 PIONEER program for the treatment of diabetic nephropathy in patients with type 2 diabetes, and the preclinical and clinical development of an intravenous formulation of Pyridorin for AKI

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;

the ability of our product candidates to progress through clinical development successfully;

our need to expand our research and development activities;

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 enforce 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;

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the effect of competing drug candidates and new product approvals;

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.

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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 early 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 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 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 \$5.2 million and \$1.7 million for the three months ended March 31, 2015 and 2014, respectively. We had an accumulated deficit of approximately \$63.0 million as of March 31, 2015.

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, prepare for and begin the commercialization of any approved products, and add infrastructure and personnel to support our continuing product development efforts. We anticipate that any such losses could be significant for the next several years as we continue our Phase 3 clinical program of Pyridorin for the treatment of diabetic nephropathy in patients with type 2 diabetes, which we call the PIONEER 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, 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

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of future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues.

Borrowings under our credit facility may not be available to us to operate our business and successfully develop and commercialize our primary product candidate.

On November 20, 2014, we entered into a Loan and Security Agreement with East West Bank (East West) for a term loan (the Initial Term Loan) with an aggregate principal amount of \$7.0 million and, subject to the terms and conditions set forth in the agreement, a second term loan (the Second Term Loan) with an aggregate principal amount of \$5.0 million. As security for our obligations under the Loan Agreement, we granted East West a lien in substantially all of our assets, including owned and licensed intellectual property. At the Company's option, the Company could have borrowed the Second Term Loan on or before May 29, 2015, if the Company met certain clinical milestones. As of the date hereof, the Company has not met the clinical milestones for the Second Term Loan. However, the Company has made a proposal to East West to amend the clinical milestones necessary for incurrence of the Second Term Loan.

Our loan agreement contains customary affirmative and negative covenants, indemnification provisions and events of default. The affirmative covenants include, among others, covenants requiring us to maintain our legal existence and governmental approvals, deliver certain financial reports and maintain certain intellectual property rights. The negative covenants include, among others, restrictions on transferring or licensing our assets, changing our business, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, and creating other liens on our assets, in each case subject to customary exceptions. If we default under the Loan Agreement, East West may accelerate all of our repayment obligations and take control of our pledged assets, potentially requiring us to renegotiate the Loan Agreement on terms less favorable to us or to immediately cease operations. Further, if we are liquidated, East West has the right to repayment would be senior to the rights of the holders of our common shares to receive any proceeds from the liquidation. East West could declare a default under the Loan Agreement upon the occurrence of any event that East West interprets as a material adverse change as defined under the Loan Agreement, thereby requiring us to repay the loan immediately or to attempt to reverse the declaration of default through negotiation or litigation. Any declaration by our lender of an event of default could significantly harm our business and prospects and could cause the price of our common shares to decline. If we raise any additional debt financing, the terms of such additional debt could further restrict our operating and financial flexibility.

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 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 trials 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;

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

difficulties in identifying and randomizing 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 candidate 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 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 continue to emerge;

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

our ability to adhere to clinical trial 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 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.

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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.

NDA and MAA 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 in 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 with 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 and are enrolling patients for our Phase 3 PIONEER trial. In addition, we have successfully completed a QT/QTc (TQT) cardiac safety study. 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 studies and clinical trials, such as 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.

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, including delays or shortages in available drug product, 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, that include the age and condition of the patients and the stage and severity of disease, the nature of the protocol, the proximity of patients to clinical sites and the availability of effective treatments and/or availability of investigational treatment options 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;

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 subjects 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;

inability to obtain approval from regulatory authorities outside the United States to conduct a clinical trial in their respective country;

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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;

high screen fail 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 or vendor;

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.

Although the FDA has agreed to our endpoint for approval for the pivotal Phase 3 PIONEER program, other regulatory agencies outside the United States 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 one or more additional clinical trials in order to seek approval outside the United States.

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 other regulatory authorities may require us to perform. As such, any requirement by 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.

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.

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Pyridorin did not reach its primary endpoint in the intent to treat (ITT) population in the Phase 2b trial (PYR-210). However, in a prespecified subgroup of patients on stable long term standard of care, Pyridorin showed a dose-dependent treatment effect of approximately 50%. This subgroup is the 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 PIONEER trial is utilizing a new $\geq 50\%$ SCr increase event endpoint or ESRD. 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 PIONEER 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 connection with the sale of

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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.

In the European Union (EU), prescription drug pricing and reimbursement is subject to governmental control and reimbursement mechanisms used by private and public health insurers in the EU vary by member state. For the public systems, reimbursement is determined by guidelines established by the legislator or responsible national authority. As elsewhere, inclusion in reimbursement catalogues focuses on the medical usefulness, need, quality and economic benefits to patients and the health care system. Acceptance for reimbursement comes with cost, use and often volume restrictions, which can vary by member state. In those member states that impose price controls, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some member states, we or our partners may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies.

Some EU member states require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some member states, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our partners might obtain marketing approval for a product in a particular member state, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues that are generated from the sale of the product in that country. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, or if there is competition from lower priced cross-border sales, our profitability may be negatively affected.

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.

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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 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 find the manufacturing facilities of our future contract manufacturers acceptable 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 and are negotiating additional agreements with contract manufacturers for the production of the active pharmaceutical ingredients and the formulation 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 cGMP and other 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

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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 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 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;

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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.

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;

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

the extent to which our product candidates are approved for inclusion on formularies of hospitals and managed care organizations;

whether our product candidates are designated under physician treatment guidelines for the treatment of the indications for which we have received regulatory approval;

adverse publicity about our product candidates or favorable publicity about competitive products;

convenience and ease of administration of our product candidates;

potential product liability claims; and

countries accepting the EMA and FDA approvals without study conduct in their respective countries or among a patient population representative of their respective country.

If our product candidates are approved, but do not achieve an adequate level of acceptance by physicians, patients, the medical community and healthcare payors, sufficient revenue may not be generated from these products and we may not become or remain profitable. In addition, efforts to

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educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

We have no sales, marketing or distribution experience and we will have to invest significant resources to develop those capabilities or enter into acceptable third-party sales and marketing arrangements.

We have no sales, marketing or distribution experience. To develop sales, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that Pyridorin or any of our other product candidates will be approved. For product candidates where we decide to perform sales, marketing and distribution functions ourselves or through third parties, we could face a number of additional risks, including:

we or our third-party sales collaborators may not be able to attract and build an effective marketing or sales force;

the cost of securing or establishing a marketing or sales force may exceed the revenues generated by any products; and

our direct sales and marketing efforts may not be successful.

We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

We may not be successful in establishing and maintaining development and commercialization collaborations, which could adversely affect our ability to develop certain of our product candidates and our financial condition and operating results.

Because developing pharmaceutical products, conducting clinical trials, obtaining regulatory approval, establishing manufacturing capabilities and marketing approved products are expensive, we may seek to enter into collaborations with companies that have more experience. Additionally, if any of our product candidates receives marketing approval, we may enter into sales and marketing arrangements with third parties with respect to our unlicensed territories. If we are unable to enter into arrangements on acceptable terms, if at all, we may be unable to effectively market and sell our products in our target markets. We expect to face competition in seeking appropriate collaborators. Moreover, collaboration arrangements are complex and time consuming to negotiate, document and implement and they may require substantial resources to maintain. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements for the development of our product candidates.

When we collaborate with a third party for development and commercialization of a product candidate, we can expect to relinquish some or all of the control over the future success of that product candidate to the third party. For example, we may relinquish the rights to Pyridorin in jurisdictions outside of the United States. Our collaboration partner may not devote sufficient resources to the commercialization of our product candidates or may otherwise fail in their commercialization. The terms of any collaboration or other arrangement that we establish may not be favorable to us. In addition, any collaboration that we enter into may be unsuccessful in the development and commercialization of our product candidates. In some cases, we may be responsible for continuing preclinical and initial clinical development of a product candidate or research program under a collaboration arrangement, and the payment we receive from our collaboration partner may be insufficient to cover the cost of this development. If we are unable to reach agreements with suitable collaborators for our product candidates, we would face increased costs, we may be forced to limit the number of our product candidates we can commercially develop or the territories in which we commercialize them and we might fail to commercialize products or programs for which a suitable collaborator cannot be found. If we fail to achieve successful collaborations, our operating results and financial condition will be materially and adversely affected.

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The success of the company depends greatly on the success of Pyridorin's development in diabetic nephropathy, and the company's pipeline of product candidates beyond this lead indication is limited.

We are evaluating the application of an intravenous formulation of Pyridorin to specific types of acute renal injury in which pathogenic oxidative chemistries have been identified as likely causative factors in the onset, severity and progression of this condition. These include ischemia-reperfusion and contrast-dye-induced acute renal injury, which can arise in cardiac and vascular surgeries. However, the intravenous formulation of Pyridorin has never been evaluated in a clinical setting and there is no clinical evidence that the therapy will be effective in additional indications. Moreover, the completion of development, securing of approval and commercialization of an intravenous formulation of Pyridorin for additional indications will require substantial additional funding and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully advance any of these indications through the development process. Even if we receive FDA approval to market an intravenous formulation of Pyridorin for additional indications, we cannot provide assurance that this will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives.

If serious adverse events or other undesirable side effects are identified during the development of Pyridorin for one indication, we may need to abandon our development of Pyridorin for other indications.

Product candidates in clinical stages of development have a high risk of failure. We cannot predict when or if Pyridorin will prove effective or safe in humans or will receive regulatory approval. To date, the most common side effects observed in clinical trials of Pyridorin were a slight increase in diarrhea and constipation. New side effects could, however, be identified as we expand the size of our clinical trials and apply Pyridorin to other indications. If new side effects are found during the development of Pyridorin for any indication, if known side effects are shown to be more severe than previously observed or if Pyridorin is found to have other unexpected characteristics, we may need to abandon our development of Pyridorin for kidney disease in patients with type 2 diabetes and other potential indications. Additional or more severe adverse side effects with respect to Pyridorin may develop in future clinical trials, which could delay or preclude regulatory approval of Pyridorin or limit its commercial use.

Risks Relating to Our Business and Strategy

We face competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors in the United States, Europe and other jurisdictions, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical and generic drug companies and universities and other research institutions. Many of our competitors have greater financial and other resources, such as larger research and development staff and more experienced marketing and manufacturing organizations. Large pharmaceutical companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and manufacturing pharmaceutical products. These companies also have significantly greater research, sales and marketing capabilities and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. As a result of all of these factors, our competitors may succeed in obtaining patent protection and/or FDA approval or discovering, developing and commercializing drugs for the diseases that we are targeting before we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Some of the pharmaceutical and biotechnology companies we expect to compete with include AbbVie Inc., Bayer Corporation, Bristol-Meyers Squibb, Thrasos Therapeutics, Inc., Genkyotex S.A., Janssen Pharmaceutical, Inc., Pfizer Inc., Chemocentryx, Inc., Eli Lilly and Company, and

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Mitsubishi Tanabe Pharma. In addition, many universities and private and public research institutes may become active in our target disease areas. Our competitors may succeed in developing, acquiring or licensing on an exclusive basis, technologies and drug products that are more effective or less costly than Pyridorin or any other product candidates that we are currently developing or that we may develop, which could render our products obsolete and noncompetitive.

We believe that our ability to successfully compete will depend on, among other things:

- the results of our and our potential strategic collaborators' clinical trials and preclinical studies;
- our ability to recruit and randomize patients for our clinical trials;
- the efficacy, safety and reliability of our product candidates;
- the speed at which we develop our product candidates;
- our ability to design and successfully execute appropriate clinical trials;
- our ability to maintain a good relationship with regulatory authorities;
- the timing and scope of regulatory approvals, if any;
- our ability to commercialize and market any of our product candidates that receive regulatory approval;
- the price of our products;
- adequate levels of reimbursement under private and governmental health insurance plans, including Medicare;
- our ability to protect intellectual property rights related to our products;
- our ability to manufacture and sell commercial quantities of any approved products to the market; and
- acceptance of our product candidates by physicians and other health care providers.

If our competitors market products that are more effective, safer or less expensive or that reach the market sooner than our future products, if any, we may not achieve commercial success. In addition, the biopharmaceutical industry is characterized by rapid technological change. Because our research approach integrates many technologies, it may be difficult for us to stay abreast of the rapid changes in each technology. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Technological advances or products developed by our competitors may render our technologies or product candidates obsolete, less competitive or not economical.

We depend on third-party contractors for a substantial portion of our operations and may not be able to control their work as effectively as if we performed these functions ourselves.

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We outsource substantial portions of our operations to third-party service providers, including the conduct of preclinical studies and clinical trials, collection and analysis of data, and manufacturing. Our agreements with third-party service providers and CROs are on a study-by-study and project-by-project basis. Typically, we may terminate the agreements with notice and are responsible for the supplier's previously incurred costs. In addition, any CRO that we retain will be subject to the FDA's and EMA's regulatory requirements and similar standards outside of the United States and Europe and we do not have control over compliance with these regulations by these providers. Consequently, if these providers do not adhere to applicable governing practices and standards, the development and commercialization of our product candidates could be delayed or stopped, which could severely harm our business and financial condition.

Because we have relied on third parties, our internal capacity to perform these functions is limited to management oversight. Outsourcing these functions involves the risk that third parties may not perform to our standards, may not produce results in a timely manner or may fail to perform at all. Although we have

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not experienced any significant difficulties with our third-party contractors, it is possible that we could experience difficulties in the future. In addition, the use of third-party service providers requires us to disclose our proprietary information to these parties, which could increase the risk that this information will be misappropriated. There are a limited number of third-party service providers that specialize or have the expertise required to achieve our business objectives. Identifying,