NUVELO INC
Form 424B5
March 03, 2004
Table of Contents

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Registration No. 333-112209

PROSPECTUS SUPPLEMENT

(To Prospectus dated February 5, 2004)

5,000,000 Shares

Common Stock

We are offering all of the 5,000,000 shares of common stock offered by this prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the symbol NUVO. On March 2, 2004, the last reported sale price for our common stock on the Nasdaq National Market was $13.21 per share.

Unless otherwise indicated, all per share amounts in this prospectus supplement give effect to a one-for-three reverse split of our common stock that became effective on February 23, 2004.

Investing in our common stock involves a high degree of risk. Before buying any shares you should carefully read the discussion of material risks of investing in our common stock under the heading Risk factors beginning on page S-9 of this prospectus supplement.

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

	Per share	Total
Public offering price	$13.00	$65,000,000
Underwriting discounts and commissions	$ 0.78	$ 3,900,000
Proceeds, before expenses, to us	$12.22	$61,100,000

The underwriters may also purchase up to an additional 750,000 shares of common stock from us at the public offering price, less the underwriting discounts and commissions, to cover over-allotments, if any, within 30 days from the date of this prospectus supplement. If the underwriters exercise the option in full, the total underwriting discounts and commissions will be $4,485,000, and the total proceeds, before expenses, to us will be $70,265,000.

The underwriters are offering the shares of common stock as set forth under Underwriting. Delivery of the shares will be made on or about March 8, 2004.

Sole Book-Running Manager

UBS Investment Bank

CIBC World Markets

Needham & Company, Inc.

JMP Securities

The date of this prospectus supplement is March 3, 2004.

Table of Contents

You should rely only on the information contained in or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not and the underwriters have not authorized anyone to provide you with information that is different from that contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. We are not offering to sell or seeking offers to buy shares of common stock in jurisdictions where offers and sales are not permitted. The information contained in this prospectus supplement or the accompanying prospectus is accurate only as of the date of this prospectus, regardless of the time of delivery of this prospectus or of any sale of our common stock. Unless the context otherwise requires, references to we, us or the company in this prospectus supplement and the accompanying prospectus mean Nuvelo, Inc. and its subsidiaries.

TABLE OF CONTENTS

Prospectus supplement

Prospectus

We own or have rights to use trademarks or trade names that we use in conjunction with the operation of our business. Nuvelo is a registered trade and service mark of ours. All other trademarks, service marks and trade names referred to in this prospectus supplement and the accompanying prospectus are the property of their respective owners.

CORPORATE INFORMATION

We were incorporated as Hyseq, Inc. in Illinois in 1992 and reincorporated in Nevada in 1993. On January 31, 2003, we merged with Variagenics, Inc., a publicly traded Delaware corporation based in Massachusetts, and, in connection with the merger, changed our name to Nuvelo, Inc. Our principal executive offices are located at 675 Almanor Avenue, Sunnyvale, California 94085 and our telephone number is (408) 215-4000. Our World Wide Web address is http://www.nuvelo.com. Information contained on our web site should not be considered to be part of this prospectus supplement or the accompanying prospectus.

Table of Contents

Prospectus supplement summary

This summary highlights information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before investing in our common stock. You should carefully read the entire prospectus supplement and the accompanying prospectus, including the Risk factors section, as well as the financial statements and the other information incorporated by reference herein before making an investment decision.

BUSINESS OVERVIEW

We are a biopharmaceutical company focused on the discovery, development and commercialization of novel products for acute cardiovascular indications and cancer. Our strategy is to focus on the clinical development of the drug candidates that we have partnered, in-licensed or discovered internally.

We currently have two drug candidates in clinical trials, and plan to have a third candidate enter clinical trials in the second half of 2004. Our lead drug candidate, alfimeprase, is a thrombolytic agent, or blood clot dissolver. Alfimeprase is currently in two separate Phase 2 clinical trials for the treatment of acute peripheral arterial occlusion (PAO) and catheter occlusion. Based on the current rate of enrollment, we project completing enrollment of the Phase 2 PAO trial in March or April of 2004 and, if the results of the Phase 2 trial are positive, we anticipate initiating a Phase 3 trial in this indication in the second half of 2004. We have obtained orphan drug status for alfimeprase in the United States for use in treating acute PAO. We are also currently conducting a Phase 2 multi-center, double-blind, randomized study in patients with occluded catheters. We project completing an interim analysis of the first 48 patients in March or April of 2004. We have a 50/50 cost/profit sharing collaboration in place with Amgen Inc. for the worldwide development and commercialization of alfimeprase.

Our second drug candidate is rNAPc2, which we recently in-licensed from Dendreon Corporation. rNAPc2 is a recombinant version of a naturally occurring protein that has anticoagulant properties resulting from its ability to block the Factor VIIa/Tissue Factor protease complex, which is responsible for the initiation of the process leading to blood clot formation. rNAPc2 is currently undergoing a Phase 2a double-blind, placebo controlled clinical trial for use in treating acute coronary syndromes (ACS), including unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI).

Our third drug candidate is ARC183, a novel thrombin inhibitor which we intend to develop for use in acute cardiac surgical procedures. We recently announced a collaboration agreement with Archemix Corporation for the development and commercialization of ARC183. We anticipate that an Investigational New Drug (IND) application for ARC183 will be filed in mid-2004. If an IND is accepted by the Food and Drug Administration (FDA), we expect that Phase 1 clinical trials will begin in the second half of 2004.

In addition to our clinical and development stage drug candidates, we have an ongoing discovery program that is focused on proprietary human genes encoding proteins that may have therapeutic applications. We intend to develop product opportunities from our ongoing discovery efforts by focusing on secreted proteins and antibody targets. The secreted protein program includes our collaboration with the pharmaceutical division of Kirin Brewery Company, Ltd. and our internal discovery program. Under our Kirin collaboration, we expect to complete the analysis of approximately 50 secreted protein genes in mouse models in the first half of 2004. We expect to leverage discoveries in these research programs to extend and expand our drug pipeline and to create revenue-generating licensing and partnering arrangements.

Table of Contents

OUR LEAD DRUG CANDIDATES

ALFIMEPRASE

Alfimeprase, our lead development candidate, is currently in two Phase 2 clinical trials in two distinct indications, acute PAO and catheter occlusion. Alfimeprase is a thrombolytic agent, or blood clot dissolver, with a novel mechanism of action. It is a modified and recombinant version of fibrolase, a naturally occurring enzyme that directly degrades fibrin, the protein which provides the structural scaffold of blood clots. Thrombolytics currently on the market such as urokinase (Abbokinase) or alteplase (Activase), are plasminogen activators that work by activating plasminogen to form plasmin which, in turn, degrades fibrin. In contrast, alfimeprase directly degrades fibrin, producing more rapid clot dissolution or lysis. Alfimeprase is locally delivered at the site of the blood clot and is inactivated quickly by a naturally occurring inhibitor in the bloodstream. This clearance mechanism limits the amount of drug in systemic circulation and associated side effects. Preclinical and early clinical data suggest that alfimeprase has the potential to lyse clots faster while also reducing the bleeding complications resulting from currently available agents.

Alfimeprase was identified through a research program at Amgen, who initiated the program with us in January 2002. The collaboration is a 50/50 cost/profit sharing arrangement with the parties sharing worldwide rights to alfimeprase. We are responsible for the clinical development activities and Amgen is responsible for manufacturing activities. Amgen will have the option to lead the commercialization in which both parties may participate.

Alfimeprase in Acute Peripheral Arterial Occlusion (PAO)

Our lead medical indication for alfimeprase is acute PAO. PAO is a significant cause of morbidity in the United States with over 100,000 cases reported annually. We have obtained orphan drug status on alfimeprase in the United States for this indication, which may provide us with seven years of market exclusivity in the United States. Acute PAO occurs when arterial blood flow is blocked to a distant part of the body, usually the leg, by a blood clot. Traditionally, bypass surgery and angioplasty have been used to treat acute PAO. However, thrombolytic agents such as urokinase (Abbokinase) or alteplase (Activase) have been increasingly used as a less-invasive alternative. We believe alfimeprase has the potential to be a more effective agent than existing agents for use in treating acute PAO by reducing the treatment time and potential bleeding side effects. We completed our Phase 1 trial on alfimeprase in the first quarter of 2003. This trial was a multi-center, open label, dose-escalation study to evaluate the safety and pharmacokinetics of alfimeprase, and was completed in 20 patients across 7 centers in the United States. The Phase 1 results showed that alfimeprase was well-tolerated with no confirmed drug-related adverse events reported. We initiated a Phase 2 program with alfimeprase in June 2003 in acute PAO.

In September 2003, we announced completion of a planned interim analysis of our Phase 2 trial with alfimeprase for acute PAO. The interim analysis was conducted on data from the first 36 patients enrolled in the trial. Following review of the patient data, the Data Safety and Monitoring Board (DSMB) and the Trial Steering Committee recommended that we continue to move forward with the trial in three doses. At an investigator meeting following the interim analysis, it was recommended that we concentrate on the two highest doses of alfimeprase. This change will result in 115 patients being treated. Based on the current rate of enrollment, we project completing enrollment of the Phase 2 PAO trial in March or April of 2004. If we successfully complete the Phase 2 trial and discussions with the FDA regarding the design of our planned Phase 3 trial, we expect to begin a Phase 3 PAO trial in the second half of 2004.

Table of Contents

Alfimeprase in catheter occlusion

Our second medical indication for alfimeprase is catheter occlusion. Catheter occlusion is the obstruction of blood flow through a central venous catheter by a blood clot. It is estimated that about five million catheters are implanted in patients each year in the United States, and approximately 20-25% become occluded. Current treatment for catheter occlusion includes invasive surgery to remove and replace the catheter, or treatment with Cathflo Activase (alteplase). Based on clinical trial evidence of alfimeprase s rapid lysis activity, we believe alfimeprase has the potential to rapidly restore blood flow to these occluded catheters.

We are currently conducting a Phase 2 multi-center, double-blind, randomized study in patients with occluded catheters comparing three doses of alfimeprase against the approved dose of Cathflo Activase. We expect to treat approximately 100 patients in this trial. We have recently increased the number of sites participating in the trial and, as a result, we have seen increased enrollment over the past few months. We project completing an interim analysis on the first 48 patients in March or April of 2004.

rNAPc2 (recombinant Nematode Anticoagulant Protein c2)

rNAPc2 is a recombinant version of a naturally occurring protein that has anticoagulant properties. Specifically, rNAPc2 has been shown to block the Factor VIIa/Tissue Factor protease complex, which is responsible for the initiation of the process leading to blood clot formation. Compared to other commercially available anticoagulants, which all exert their effects at later stages of the blood coagulation cascade, rNAPc2 is designed to block the first step in the clotting cascade, inhibiting coagulation before it starts. By blocking the coagulation cascade at such an early stage, rNAPc2 could prove to be safer and more effective in treating patients with conditions such as acute coronary syndrome or as a prophylactic against clot formation.

We recently licensed the worldwide rights for all indications of rNAPc2 and all of the rNAPc molecules owned by Dendreon. To date, rNAPc2 has been shown to be well-tolerated in over 500 patients and healthy volunteers in several Phase 1 and 2 studies. The indication that we are currently pursuing for rNAPc2 is acute coronary syndrome (ACS).

ACS, such as unstable angina (UA) and non-ST segment elevation myocardial infarction (NSTEMI), result when an atherosclerotic plaque ruptures in a coronary artery triggering the coagulation cascade and resulting in the formation of a blood clot. The clot blocks the flow of blood to the heart muscle depriving it of oxygen and causing chest pain and/or a heart attack. Worldwide, it is estimated that ACS accounts for more than 1.8 million hospital admissions annually. Patients with ACS are traditionally given aspirin and heparin to stabilize their medical condition. Recent guidelines also recommend the addition of the antiplatelet agent clopidogrel (Plavix) to standard care. However, based upon the significant number of patients with ACS who continue to experience poor outcomes such as recurrent angina, myocardial infarction or death, we believe there is a clear need for better antithrombotic therapy.

rNAPc2, given alone or with standard therapy, may significantly reduce the risk of subsequent heart attack or death in patients suffering from UA/NSTEMI. Unlike aspirin and heparin, or current antithrombotic agents, which all exert their effects at later stages of the blood coagulation cascade, rNAPc2 blocks the first step in the clotting cascade. A medical regimen that includes rNAPc2 could, therefore, enable a multi-pronged attack at several points along the blood coagulation process. Alternatively, by stopping coagulation before it starts, rNAPc2 could prove more effective even as a stand-alone therapy.

Table of Contents

A Phase 2a double-blind, placebo controlled clinical trial to determine a safe and effective dose of rNAPc2 in moderate to high-risk patients with UA/NSTEMI has been initiated. The study was planned to be conducted in three parts, each of which would investigate rNAPc2 in combination with current anticoagulant and antiplatelet therapies. Currently, the study is being reinitiated with the TIMI Study Group led by Dr. Eugene Braunwald of Brigham and Women s Hospital and Harvard Medical School. We plan to complete the Phase 2a study and further evaluate future clinical development based on the data from this trial.

Another Phase 2 dose-ranging study of rNAPc2 was conducted in 293 subjects undergoing elective, unilateral total knee replacement. The study examined the drug s potential to reduce the incidence of deep vein thrombosis (DVT), a condition whereby a blood clot (thrombus) develops in a deep vein, usually in the leg following orthopedic surgery. This proof-of-principle study demonstrated that rNAPc2 could provide effective antithrombotic efficacy with minimal effects on surgical hemostasis in a clinical setting which is associated with a high risk of thrombosis. We are currently evaluating other potential indications of rNAPc2 such as DVT prophylaxis.

A recently published preclinical study suggests that rNAPc2 may also be effective in the treatment of the Ebola virus infection. In addition, preclinical studies have shown that blocking the protease complex Factor VIIa/Tissue Factor prevents the growth of primary and metastatic tumors in animal models.

ARC183

ARC183 is a DNA aptamer, which is a single-stranded nucleic acid that forms well-defined three-dimensional shapes, allowing it to bind to thrombin with high affinity and specificity. The key advantage of ARC183 compared to other thrombin inhibitors is its rapid onset of action and short half-life, giving it the potential to be an ideal agent for medical procedures that require rapid resolution of anticoagulation or that require reversal of anticoagulation shortly after the procedure is completed.

We recently announced a collaboration agreement with Archemix, a privately held biotechnology company, located in Cambridge, Massachusetts, for the development and commercialization of ARC183. Our lead indication for ARC183 is as a thrombin inhibitor for use in coronary artery bypass graft (CABG) surgery.

According to the American Heart Association, more than 500,000 CABG procedures are performed in the United States annually. Currently, heparin is used to limit blood clotting in this indication, but is difficult to dose and can cause side effects such as bleeding and heparin-induced thrombocytopenia (HIT). Moreover, the effect of heparin must be reversed with the use of an antidote called protamine. Protamine is not approved by the FDA for reversal of heparin in CABG surgery and is associated with significant complications including hypotension, platelet dysfunction, complement activation and thrombus formation. We believe that there is a significant unmet medical need for a safe, fast-acting anticoagulant for use in CABG that is easier to administer, does not require a reversal agent and lacks the side effects such as bleeding and HIT.

ARC183 has shown potential in preclinical studies to be equally effective, with fewer side effects than heparin and protamine in combination. Due to its very short half-life, ARC183 is expected to lead to more predictable dosing as well as reduced incidence of bleeding side effects compared to heparin. We believe that ARC183 has the potential to replace current therapies and become the standard of care in cardiac surgical procedures. We are currently evaluating the potential for ARC183 for use in percutaneous intervention (PCI), such as angioplasty and stent placement, and non-coronary procedures, such as renal dialysis.

S-4

Table of Contents

We anticipate that an IND for ARC183 will be filed with the FDA in mid-2004. If our IND is accepted by the FDA, we expect to initiate Phase 1 clinical trials for use in CABG surgery in the second half of 2004.

CLINICAL PRODUCT PIPELINE

The following table summarizes key information about our current clinical product pipeline:

Drug candidate (technology)	Indication	Development status	Commercialization rights
alfimeprase (Fibrinolytic)	Acute Peripheral Arterial Occlusion	Phase 2	50/50 collaboration with Amgen
alfimeprase (Fibrinolytic)	Catheter Occlusion	Phase 2	50/50 collaboration with Amgen
rNAPc2 (Tissue Factor Inhibitor)	Acute Coronary Syndromes	Phase 2a	Nuvelo has exclusive commercialization rights
ARC183 (Thrombin-Inhibitor)	Coronary Artery Bypass Graft Surgery	IND anticipated to be filed mid-2004	50/50 collaboration with Archemix

RESEARCH AND DEVELOPMENT PROGRAMS

In addition to our clinical and development stage drug candidates, we have an ongoing discovery program focused on the identification of novel human genes that encode proteins with therapeutic potential. Over the long-term, we intend to develop additional product opportunities from our ongoing discovery efforts focused on secreted proteins and antibody targets.

The secreted protein program includes our collaboration with Kirin and our internal discovery program. Under our Kirin collaboration, we expect to complete the analysis of approximately 50 secreted protein genes in mouse models in the first half of 2004. We have already advanced several secreted protein candidates to more extensive studies to better define their therapeutic utility based upon early findings in initial mouse models. Within our internal secreted protein discovery program, we have developed a fast and efficient method of expressing human secreted proteins in mice. This program could significantly bolster our ability to identify which secreted proteins within our patent estate have the greatest potential for therapeutic use. We plan to test up to 55 secreted proteins with this internal program in 2004.

The antibody program is focused on screening our proprietary gene sequence collection to identify proteins located on the surface of tumor cells that could be targeted by therapeutic monoclonal antibodies. We are currently evaluating 18 targets in blood cancers and solid cancers. Of these 18, we have advanced 7 into in-vivo testing.

We expect to move the most promising internal drug candidates forward and potentially advance at least one of these into IND-enabling studies in 2004. In addition to the development of internal therapeutic candidates, we intend to leverage these discoveries to create revenue-generating licensing and partnering arrangements.

Table of Contents

OUR STRATEGY

We are focused on building a successful biopharmaceutical business and committed to creating a valuable product-focused company that leverages our drug discovery and development expertise. Key elements of our strategy are to:

Develop and successfully commercialize alfimeprase

We are seeking to develop and commercialize alfimeprase for the treatment of acute PAO and catheter occlusion. Alfimeprase is in Phase 2 clinical trials in these two indications, and we have an established collaboration with Amgen to facilitate its worldwide commercialization.

Progress our portfolio of cardiovascular clinical and development stage products

We have developed a portfolio of acute, hospital-based, cardiovascular drug candidates. We believe this portfolio leverages our established expertise in cardiovascular drug development, provides synergy with alfimeprase during both development and commercialization and enables us to pursue a more rapid path toward drug development.

Increase probability of commercial success

We are pursuing several drug development candidates simultaneously in order to reduce the impact of any single product failure. By broadening our product portfolio, we intend to increase the probability of clinical and commercial success. In addition, we focus on molecules that have a greater chance of success due to the predictability of preclinical models used in their development.

Opportunistically seek to license or acquire complementary products and technologies

We intend to supplement our internal drug discovery efforts through the acquisition of products and technologies that complement our development strategy. We continue to identify, evaluate and pursue the acquisition or licensing of strategically valuable product opportunities.

RECENT DEVELOPMENTS

On January 12, 2004, we entered into a worldwide collaboration agreement with Archemix to develop and commercialize thrombin inhibitor ARC183 for potential use in CABG surgery, PCI and other acute anticoagulant applications. We paid Archemix an upfront payment of $3.0 million and we will also pay a milestone payment upon initiation of the Phase 2 trial and a reimbursement of $1.0 million upon the designation of any backup compound. Under the terms of the agreement, Archemix will initially lead development and be responsible for all clinical development activities. As part of the transaction, we and Archemix will equally share all revenues and costs associated with the development and commercialization of ARC183 after we fund the first $4.0 million in research and development costs. We will have the option to lead commercialization efforts in which both companies may participate.

On February 4, 2004, we entered into a worldwide licensing agreement with Dendreon for Dendreon s novel anticoagulant, rNAPc2, and all other rNAPc molecules owned by Dendreon. Under the terms of the agreement, we paid Dendreon an upfront payment of $4.0 million ($500,000 in

cash and $3.5 million worth of Nuvelo common stock). In addition, we will pay to Dendreon milestone payments prior to and upon any commercialization, as well as royalties if and when we reach commercialization. Our license from Dendreon grants us exclusive worldwide rights to all indications for rNAPc products.

On February 4, 2004, we announced the appointment of Barry L. Zubrow, a former senior executive of The Goldman Sachs Group, Inc., to our board of directors. Mr. Zubrow replaced Thomas McCarter, who stepped down as a member of our board of directors effective February 3, 2004. Mr. Zubrow also replaced Mr. McCarter on our audit committee.

Table of Contents

The offering

Common stock we are offering	5,000,000 shares
Common stock to be outstanding after this offering	30,637,981 shares
NASDAQ National Market Symbol	NUVO
Use of proceeds	We are raising funds in this offering primarily for general corporate purposes, including current and future clinical trials of our lead drug candidate, alfimeprase, as well as other research and product development activities. See Use of proceeds.
Risk factors	See Risk factors beginning on page S-9 for a discussion of factors you should carefully consider before deciding to invest in shares of our common stock.

The number of shares of our common stock to be outstanding after this offering in the summary above is based on 25,637,981 shares outstanding as of January 31, 2004, and does not include, as of that date:

- an aggregate of 1,561,212 shares of our common stock reserved for issuance upon exercise of outstanding stock options granted under our 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan, Scientific Advisory Board/Consultants Stock Option Plan and the Variagenics, Inc. Amended 1997 Employee, Director and Consultant Stock Option Plan;
- an aggregate of 1,494,804 shares of common stock reserved for issuance pursuant to future option grants under these plans;
- an aggregate of 88,307 shares of common stock reserved for issuance under our Employee Stock Purchase Plan;
- an aggregate of 987,242 shares of common stock reserved for issuance upon the exercise of outstanding stock options granted outside of any of our stock option plans;
- warrants to purchase an aggregate of 1,887,325 shares of our common stock, with exercise prices ranging from $4.05 to $25.53 per share, and a weighted average exercise price of $17.76 per share;
- 519,181 shares of common stock issuable upon repayment of our note held by Affymetrix and 1,098,286 shares of common stock issuable upon mutual agreement to convert the promissory note under the Rathmann line of credit; and
- 263,296 shares issued on February 4, 2004 to Dendreon.

Unless otherwise stated, all information contained in this prospectus supplement assumes that our one-for-three reverse stock split has become effective and that the underwriters do not exercise their over-allotment option to purchase up to an additional 750,000 shares of common stock, and all currency amounts in this prospectus supplement are stated in US dollars.

Table of Contents

Summary consolidated financial data

The tables below present summary consolidated statement of operations and balance sheet data. The summary financial data for the years ended December 31, 2001 through December 31, 2003 are derived from our audited consolidated financial statements for those periods. This information is only a summary and should be read in conjunction with our historical consolidated financial statements and related notes contained in our annual reports, quarterly reports and recent current reports on file with the SEC incorporated by reference in this prospectus supplement and the accompanying prospectus. For more details on how you can obtain our SEC reports, you should read the section of this prospectus supplement entitled Incorporation by reference beginning on page S-43. Our consolidated statement of operations data includes the results of operations of Variagenics, Inc. from February 1, 2003. The as adjusted consolidated balance sheet data gives effect to the sale by us of 5,000,000 shares of our common stock in this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

	Year ended December 31,		
Consolidated statement of operations data:	**2001**	**2002**	**2003**
	(in thousands, except per share data)		
Revenue	$ 24,590	$ 26,433	$ 2,290
Research and development expenses	$ 46,506	$ 50,157	$ 33,084
General and administrative expenses	$ 13,452	$ 18,108	$ 17,223
Total operating expenses	60,783	70,368	51,532
Interest and other income	319	87	747
Net loss	$ (36,472)	$ (44,978)	$ (50,187)
Net loss per common share, basic and diluted	$ (6.77)	$ (6.23)	$ (2.38)
Shares used in computation of basic and diluted net loss per share	5,386	7,220	21,054

	December 31, 2003	
Consolidated balance sheet data:	**Actual**	**As adjusted**
	(in thousands)	
Cash, cash equivalents and short-term investments	$ 34,189	$ 94,714
Working capital	25,772	86,297
Total assets	57,809	118,334
Current portion of capital lease and line of credit obligations	4,741	4,741
Non-current portion of capital lease and line of credit obligations	8,871	8,871
Accumulated deficit	(203,559)	(203,559)
Total stockholders equity	22,701	83,226

Table of Contents

Risk factors

An investment in our common stock involves a high degree of risk. You should consider carefully the risk factors described below and all other information contained in or incorporated by reference in this prospectus supplement and the accompanying prospectus before making an investment decision. If any of the following risks actually occurs, our business, financial condition, operating results or cash flow could be harmed. As a result, the trading price of our common stock could decline, and you could lose all or part of your investment.

RISK RELATED TO OUR BUSINESS

We have not achieved profitability, have recent and anticipated continuing losses and may never become profitable.

For the years ended December 31, 2001, 2002 and 2003, we had net losses of $36.5 million, $45.0 million and $50.2 million, respectively. As of December 31, 2003, we had an accumulated deficit of $203.6 million.

All of our product candidates are in various stages of product development, and some are still in research or in early development. None of them are approved for sale. The process of developing biotherapeutics and related products will require significant additional research and development, preclinical testing, clinical trials and regulatory approvals. These activities, together with general administrative and other expenses, are expected to result in operating losses for the foreseeable future. To date, we have not generated any revenues from product sales. We do not expect to achieve significant product sales or royalty revenue for several years, and we may never do so. We expect to incur additional operating losses in the future, and these losses may increase significantly as we continue preclinical research and clinical trials, apply for regulatory approvals, develop our drug candidates, expand our operations and develop systems that support commercialization of our potential products. These losses, among other things, have caused and may cause our stockholders equity and working capital to decrease. We may not be successful in developing our drug candidates, obtaining regulatory approvals and commercializing our products, and our operations may not be profitable even if any of our drug candidates are commercialized. We may never generate profits and, as a result, the trading price of our common stock could decline. Moreover, utilization of our net operating loss carryforwards and credits may be subject to an annual limitation due to the change in ownership provisions of the Internal Revenue Code of 1986 and similar state law provisions. It is possible that certain transactions that we have entered into, including our merger with Variagenics that occurred in January 2003, when considered in connection with other transactions, may result in a change in ownership for purposes of these provisions.

Our relatively short operating history may affect our ability to execute our business strategy.

We have a short operating history. We commenced operations in the fourth quarter of 1994 with an initial business focused on gene discovery using our signature-by-hybridization platform and applications of our sequencing-by-hybridization technology, including the HyChip system. In 1998, we began to transition our business strategy from gene discovery to research and development of potential therapeutic protein candidates. As a company with a relatively short operating history, we face risks and uncertainties frequently encountered by companies in new and rapidly evolving markets, including:

Ø the implementation and successful execution of our business strategy and our sales and marketing initiatives;

Ø retention of current customers and collaborators and attraction of new customers and collaborators;

- our ability to respond effectively to competitive and technological developments related to our technologies, products and services;

- our ability to attract, retain and motivate qualified personnel; and

- our ability to effectively manage our anticipated growth.

If we fail to address these risks and uncertainties successfully, our business, results of operations, financial condition and prospects will be materially adversely affected.

We may face fluctuations in operating results.

Our operating results may rise or fall significantly as a result of many factors, including:

- the amount of research and development we engage in;

- the number of product candidates we have and their progress in research and preclinical studies;

- our ability to expand our facilities to support our operations;

- our ability to enter into new strategic relationships;

- the scope, duration and effectiveness of our collaborative arrangements;

- the costs involved in prosecuting, maintaining and enforcing patent claims;

- the possibility that others may have or obtain patent rights that are superior to ours;

- changes in government regulation; and

- release of successful products into the market by our competitors.

Excluding our three clinical and development stage drug candidates, our potential products currently are in research or preclinical development, and revenues from the sales of any products resulting from these efforts may not occur for several years, if at all. We also have a high percentage

of fixed costs such as lease obligations. As a result, we may experience fluctuations in our operating results from quarter to quarter and continue to generate losses. Quarterly comparisons of our financial results may not necessarily be meaningful, and investors should not rely upon such results as an indication of our future performance. In addition, investors may react adversely if our reported operating results are less favorable than in a prior period or are less favorable than those anticipated by investors or the financial community, which may result in a drop of our stock price.

We will need to raise additional capital, and such capital may be unavailable to us when we need it or not available on acceptable terms.

We will need to raise significant additional capital before we can become profitable. Financing may be unavailable when we need it or may not be available on acceptable terms. The unavailability of financing may require us to delay, scale back or eliminate expenditures for our research, development and marketing activities necessary to commercialize our potential biopharmaceutical products. We may also be required to grant rights to third parties to develop and market drug candidates that we would prefer to develop and market on our own, potentially reducing the ultimate value of these drug candidates that we could realize.

If we are unable to obtain additional financing when we need it, the capital markets may perceive that we may not be able to raise the amount of financing we desire, or on terms favorable to us, which may negatively affect the trading price of our common stock. Additional equity financings could result in

significant dilution of current stockholders equity interests. If sufficient capital is not available, we will delay, reduce the scope of, eliminate or divest one or more of our subsidiaries or our discovery, research or development programs. Any such action could significantly harm our business, financial condition and results of operations.

Our future capital requirements and the adequacy of our currently available funds will depend on many factors, including, among others, the following:

- Ø continued scientific progress in our research and development programs, including progress in our research and preclinical studies;
- Ø the cost involved in any facilities expansion to support research and development of our product candidates;
- Ø our ability to attract additional financing on favorable terms;
- Ø the magnitude and scope of our research and development programs, including development of product candidates;
- Ø our ability to maintain, and the financial commitments involved in our existing collaborative and licensing arrangements;
- Ø our ability to establish new collaborative relationships with other companies to share costs and expertise of identifying and developing drug candidates;
- Ø the cost of prosecuting and enforcing our intellectual property rights;
- Ø the cost of manufacturing our material for preclinical, clinical and commercial purposes;
- Ø progress in our clinical studies of alfimeprase;
- Ø the time and cost involved in obtaining regulatory approvals;
- Ø our need to develop, acquire or license new technologies or products;
- Ø competing technological and market developments;
- Ø future funding commitments to our subsidiary, Callida, and our ability to borrow funds from Affymetrix to fund our commitment, under the terms of the Affymetrix settlement;

- our ability to use our common stock to repay the outstanding note to Affymetrix and our line of credit from our Chairman, Dr. George B. Rathmann;
- legal and Nasdaq restrictions that impede our ability to raise funds from private placements of our common stock;
- future funding commitments to our collaborators;
- general conditions in the financial markets and in the biotech sector;
- the uncertain condition of the capital markets; and
- other factors not within our control.

Development of our products will take years, and our products require regulatory approval before they can be sold.

Excluding our three clinical and development stage drug candidates, our potential products currently are in research or preclinical development and revenues from the sales of any products resulting from these efforts may not occur for several years, if at all. We cannot be certain that any of our products will be

demonstrated to be safe and effective or that we will obtain regulatory approvals. In addition, any products that we develop may not be economical to manufacture on a commercial scale. Even if we develop a product that becomes available for commercial sale, we cannot be certain that consumers will accept the product. We cannot predict whether we will be able to develop and commercialize any of our drug candidates successfully. If we are unable to do so, our business, results of operations and financial condition will be affected in a materially adverse manner.

We do not yet have products in the commercial markets. We must demonstrate that our product candidates satisfy rigorous standards of safety and efficiency before the FDA and comparable agencies in foreign markets. We cannot apply for regulatory approval of our potential products until we have performed significant addition