NUVELO INC
Form 424B5
January 31, 2006
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Filed Pursuant to Rule 424(b)(5)
Registration Nos. 333-126591 and 333-131392

Prospectus supplement

(to prospectus dated August 3, 2005)

6,500,000 shares

Common stock

We are selling 6,500,000 shares of our common stock.

Our common stock is quoted on The Nasdaq National Market under the symbol NUVO. On January 30, 2006, the last reported sale price for our common stock was $16.03 per share.

	Per share	Total
Public offering price	$ 16.00	$ 104,000,000
Underwriting discounts and commissions	$ 0.96	$ 6,240,000
Proceeds to Nuvelo before expenses	$ 15.04	$ 97,760,000

We have granted the underwriters an option for a period of 30 days to purchase up to 975,000 shares to cover over-allotments, if any.

Investing in our common stock involves certain risks. See Risk factors beginning on page S-14 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.

JPMorgan **Deutsche Bank Securities**

Lehman Brothers

January 31, 2006

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Prospectus supplement

Prospectus

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

This prospectus supplement and the accompanying prospectus are part of a universal shelf registration statement on Forms S-3 that we filed with the Securities and Exchange Commission, or the SEC. Under the shelf registration process, we may sell any combination of debt securities, preferred stock and common stock in one or more offerings from time to time up to a total dollar amount, including an increase made pursuant to Rule 462(b) of the Securities Act of 1933, as amended, of $120,000,000, of which this offering is a part. In the accompanying prospectus, we provide you a general description of the securities we may offer from time to time under our shelf registration statement. This prospectus supplement describes the specific details regarding this offering, including the price, the amount of common stock being offered and the risks of investing in our common stock.

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein include important information about us, our common stock being offered and other information you should know before investing. To the extent information in this prospectus supplement is inconsistent with the accompanying prospectus or any of the documents incorporated by reference herein and therein, you should rely on this prospectus supplement. You should read both this prospectus supplement and the accompanying prospectus, together with the additional information about us described in the sections entitled Where you can find more information and Incorporation by reference. In addition, you should carefully consider the facts set forth under Risk factors beginning on page S-14 of this prospectus supplement and in the reports incorporated by reference herein before making an investment decision to purchase shares of our common stock.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus or that is contained in any free writing prospectus we may authorize to be delivered to you. We have not, and the underwriters have not, authorized anyone to provide you with additional or different information. We are not making an offer of these securities in any jurisdiction where the offer is not permitted. You should assume that the information in this prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. Unless the context otherwise requires, references to we or the company in this prospectus supplement and the accompanying prospectus mean Nuvelo, Inc. and its subsidiaries.

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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 dedicated to improving the lives of patients through the discovery, development and commercialization of novel acute cardiovascular and cancer therapies.

Our development pipeline includes three acute cardiovascular programs focused on alfimeprase, rNAPc2 and a thrombin inhibiting aptamer, as well as an emerging oncology pipeline.

Our lead cardiovascular development program is for alfimeprase, a novel, direct-acting thrombolytic agent, or blood clot dissolver, that is currently in Phase 3 clinical trials for the treatment of acute peripheral arterial occlusion, or PAO, and for the treatment of catheter occlusion. We also intend to expand this development program by initiating a Phase 2 clinical trial in the second half of 2006 to evaluate the potential of alfimeprase for the treatment of ischemic stroke and another Phase 2 clinical trial in 2007 to evaluate the potential of alfimeprase to treat deep venous thrombosis, or DVT. As provided in the collaboration and license agreement that we entered into on January 4, 2006, we granted Bayer HealthCare AG the right to commercialize alfimeprase outside the United States, while retaining the right to commercialize alfimeprase in the United States.

Our second cardiovascular development program is for recombinant nematode anticoagulant protein c2, or rNAPc2, an anticoagulant that inhibits the factor VIIa and tissue factor protease complex, which is responsible for initiating the blood clotting process. We recently completed a Phase 2a clinical trial with rNAPc2 in acute coronary syndrome, or ACS, and are currently enrolling patients in a subsequent Phase 2 trial intended to evaluate its potential use as a replacement for heparin, an anticoagulant, in patients with ACS.

Our third cardiovascular development program is in the preclinical stage and is focused on identifying an optimized thrombin inhibiting aptamer for potential use as a rapid-on/rapid-off anticoagulant for patients undergoing acute cardiovascular procedures, such as coronary artery bypass graft, or CABG, surgery.

In addition to these programs, we have an emerging oncology development pipeline. We are progressing a potent gastrointestinal epithelial growth factor, NU206, as a preclinical development candidate for the potential treatment of mucositis, which is a side effect of chemotherapy and radiation therapies received by cancer patients. NU206 is targeted to enter Phase 1 clinical development in the second half of 2006. We are also investigating the potential of rNAPc2 as a cancer therapy based on its apparent role in the cellular signaling of both metastasis and angiogenesis in a variety of cancers.

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Finally, we have a drug discovery effort focused on two research programs: the first investigating secreted proteins and the second investigating antibodies against cell surface proteins as potential cancer targets. Through these programs, we plan to further expand our pipeline and create additional partnering and licensing opportunities.

As of December 31, 2005, our cash, cash equivalents and short-term investments totaled approximately $70.3 million. In addition, in January 2006, following our entry into the alfimeprase collaboration and license agreement with Bayer, we received a $50.0 million up-front cash payment from Bayer. We expect that our operating expenses will increase significantly in 2006 as we intensify our alfimeprase Phase 3 clinical trial activity, increase expenditures under our alfimeprase manufacturing agreement with Avecia Ltd. and incur additional general corporate expenses. We expect our alfimeprase-related expenses will be offset to a substantial extent by cost-sharing and milestone payments that we expect to receive from Bayer.

Product pipeline

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

Products in development

Alfimeprase

Our lead product candidate, alfimeprase, is a thrombolytic agent with a novel mechanism of action. It is a modified and recombinant version of fibrolase, a naturally occurring enzyme that directly and rapidly degrades fibrin, the protein that provides the structural scaffold of blood clots. Thrombolytics currently on the market, such as alteplase (Activase), are plasminogen activators that work by activating plasminogen to form plasmin, which in turn degrades fibrin. In contrast, alfimeprase directly degrades fibrin, creating the potential for more rapid clot dissolution, or lysis. Alfimeprase is locally delivered at the site of the blood clot and is inactivated quickly by alpha-2 macroglobulin, a naturally occurring protein in the bloodstream. We believe

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this clearance mechanism limits the systemic activity of alfimeprase and implies that patients may experience fewer of the bleeding side effects associated with plasminogen activators.

Alfimeprase in acute peripheral arterial occlusion

The lead medical indication we are pursuing for alfimeprase is acute PAO. Acute PAO is a significant cause of morbidity in the United States, with estimates of over 100,000 cases reported annually. Acute PAO occurs when arterial blood flow is blocked to a distant part of the body, usually the leg, by a blood clot. Traditionally, surgical approaches have been used to treat acute PAO. However, thrombolytic agents such as Activase have been used as a less-invasive alternative, even though they have not been approved by the FDA to treat acute PAO. Studies have shown that current thrombolytic therapies can take 24 to 36 hours or more to restore flow to the blocked limb, with five to 16 percent of patients experiencing a major bleed and one to two percent of patients experiencing intracerebral hemorrhage. We believe alfimeprase has the potential to be a more effective agent than existing agents for use in treating acute PAO by reducing treatment time and the potential for bleeding side effects.

We completed our Phase 2 clinical trial in patients with acute PAO in the second quarter of 2004. This trial was an open label, dose-escalation study evaluating the safety and activity of alfimeprase. The trial enrolled 113 patients in multiple centers in the United States, Europe, Russia and other locations. The Phase 2 results indicate that alfimeprase has the potential to offer significant advances in the rapid resolution of a blood clot while minimizing potentially fatal side effects such as intracerebral hemorrhage and other bleeding complications. Analysis of the Phase 2 results showed that alfimeprase has the potential to partially or completely break up blood clots within four hours of initiation of dosing with rates of up to 76 percent and to restore arterial flow with rates of up to 60 percent. Up to 69 percent of study patients were able to avoid open vascular surgical intervention in the 30 days following treatment with alfimeprase. Among the 113 patients enrolled, there were no intracerebral hemorrhages or deaths at 30 days. There were seven major bleeding events reported, none of which were categorized as systemic bleeding events and only one of which was categorized by the investigator as possibly related to alfimeprase. Incidents of transient hypotension were also reported and were dose-related. Events associated with distal embolism were also noted. We do not believe that these events were more significant in number or severity than similar events associated with other therapies delivered by catheter to blood clots.

In April 2005, we commenced the first of two clinical trials in the alfimeprase Phase 3 acute PAO program, known as NAPA, or Novel Arterial Perfusion with Alfimeprase. This program consists of two overlapping trials that will include a total of 600 patients between the two trials. The first trial in this program, NAPA-2, is a randomized, double-blind study comparing 0.3 mg/kg of alfimeprase versus placebo in 300 patients. The trial is being conducted in over 100 centers worldwide. The study s primary endpoint is avoidance of open vascular surgery within 30 days of treatment. Open vascular surgery includes procedures such as surgical embolectomy, peripheral arterial bypass graft surgery and amputation, but does not include catheter-based procedures such as percutaneous angioplasty or stenting. A variety of secondary endpoints are also being evaluated, including safety endpoints such as the incidence of bleeding, as well as pharmacoeconomic endpoints such as length of hospital and intensive care unit stay. We expect to complete enrollment in the NAPA-2 trial in the second half of 2006.

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The second Phase 3 trial, NAPA-3, is the subject of a special protocol assessment, or SPA, agreement with the U.S. Food and Drug Administration, or FDA, and will essentially replicate the NAPA-2 trial. Under an SPA, the FDA provides guidance on the design of a trial prior to its initiation. We expect to begin enrollment in the NAPA-3 trial in early 2006.

We have been granted fast track designation by the FDA for alfimeprase in acute PAO. Fast track designation can potentially facilitate development and expedite review of biologics license applications. Fast track designation is reserved for new drugs that demonstrate the potential to address an unmet medical need and are intended for treatment of a serious or life-threatening condition. In addition, we have obtained orphan drug status for alfimeprase in the United States and Europe for the treatment of acute PAO, which may provide us with up to seven and ten years of market exclusivity in the United States and Europe, respectively, following market authorization.

Alfimeprase in catheter occlusion

We are also in late-stage clinical development for alfimeprase in catheter occlusion. Catheter occlusion is the obstruction of blood flow through a central venous catheter. It is estimated that about five million catheters are implanted in patients each year in the United States, and approximately 25 percent become occluded. Current treatment for catheter occlusion includes removal and replacement of the catheter, or treatment with alteplase (Cathflo Activase). Based on clinical trial evidence of alfimeprase s activity, we believe alfimeprase has the potential to restore flow to occluded catheters more rapidly than Cathflo Activase.

In the third quarter of 2004, we completed patient enrollment in a Phase 2 multi-center, double-blind, randomized study in 55 patients with occluded central venous catheters comparing three doses (0.3 mg, 1.0 mg and 3.0 mg) of alfimeprase against the approved dose of Cathflo Activase (2.0 mg). The alfimeprase 3.0 mg dose produced cumulative flow rates of 40 percent at five minutes after the first dose, 50 percent at 15 minutes after the first dose, 60 percent at 30 minutes and 120 minutes after the first dose, and 80 percent at 120 minutes after the second dose. This is compared to Cathflo Activase, which produced flow rates of zero percent at five minutes after the first dose, zero percent at 15 minutes after the first dose, 23 percent at 30 minutes after the first dose, 46 percent at 120 minutes after the first dose, and 62 percent at 120 minutes after the second dose. No major hemorrhagic events were reported in any treated patients and only one patient had a catheter-related infection.

In September 2005, we commenced the first of two multi-national trials in the alfimeprase Phase 3 catheter occlusion program, known as SONOMA, or Speedy Opening of Non-functional and Occluded catheters with Mini-dose Alfimeprase. The first trial is an efficacy study called SONOMA-2, which is a randomized, double-blind trial, comparing 3.0 mg of alfimeprase with placebo in 300 patients with occluded central venous catheters. Two-thirds of the patients will receive alfimeprase and the remainder will receive placebo. The study s primary endpoint is restoration of function to occluded central venous catheters at 15 minutes. We expect to complete enrollment in the SONOMA-2 trial in the second half of 2006.

The second study, known as SONOMA-3, will be an open label, single-arm trial evaluating alfimeprase in 800 patients. This study s primary endpoint is safety, although we will be evaluating efficacy in these patients as well. We expect to begin enrolling patients in this trial in the first half of 2006.

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Alfimeprase in stroke

In January 2006, we announced our intention to expand the alfimeprase development program and initiate a Phase 2 clinical trial in the second half of 2006 to study the potential of alfimeprase to treat patients with ischemic stroke. Each year, approximately 650,000 patients suffering from stroke are admitted into hospitals in the United States. Some of these patients have hemorrhagic strokes, which are characterized by the rupture of blood vessels in the brain and usually result in death. The large majority of stroke patients suffer from ischemic strokes, which are characterized by blood clots that prevent the flow of blood to the brain, thereby depriving the brain of oxygen. Depending on the location and severity of the blood clot, the most common consequence of ischemic stroke is loss of function, including paralysis.

Currently, the therapeutic options for patients with ischemic stroke are limited. Activase has been approved in the United States for treatment of ischemic stroke. Its use has been limited, however, by the requirement that patients receive it within three hours of onset of the stroke and by the increased bleeding risk associated with its use. We believe that alfimeprase has the potential to expand the treatment window for ischemic strokes due to its rapid and direct mechanism of action and its potential safety profile.

Alfimeprase in deep venous thrombosis

In January 2006, we also announced our intention to initiate a Phase 2 clinical program in 2007 to evaluate the potential of alfimeprase to treat patients suffering from DVT. Each year, approximately 300,000 patients are diagnosed with DVT in the United States. DVT is characterized by blood clots in the venous system of peripheral limbs, typically the legs. The consequences of DVT include pain and swelling of the affected limb and, in relatively rare circumstances, pulmonary embolism which can result in death.

Currently, very few DVT patients receive thrombolytics. DVT is rarely a life-threatening condition and, therefore, doctors are typically reluctant to administer thrombolytics, which expose DVT patients to significant bleeding risk. As a result, DVT patients generally receive anticoagulants intended to prevent further propagation of the blood clot and are told to limit activity until the blood clot resolves, often over a period of months. We believe alfimeprase has the potential to treat this patient population with a reduced bleeding risk because of its unique mechanism of action and its potential safety profile.

Alfimeprase license and collaboration agreements

In January 2006, we entered into a license and collaboration agreement with Bayer for the global development and commercialization of alfimeprase. Under this agreement, Bayer will commercialize alfimeprase in all territories outside the United States and will pay us tiered royalties ranging from a minimum of 15 percent to a maximum of 37.5 percent. We retain all commercialization rights and profits from alfimeprase sales in the United States. We are eligible to receive up to $385.0 million in milestone payments from Bayer, including a $50.0 million up-front cash payment that we have already received, up to $165.0 million in development milestones and $170.0 million in sales and commercialization milestones over the course of the agreement. In addition, Bayer will be responsible for 40 percent of the costs for global development programs. We will be responsible for 60 percent of the costs and will remain the lead for the design and conduct of the global development programs. Each party will bear its

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own expenses for any country-specific alfimeprase clinical trials it conducts, where the country-specific clinical trials are not part of the agreed global development program.

In October 2004, we obtained worldwide rights to develop and commercialize alfimeprase from Amgen, Inc. in exchange for the payment to Amgen of previously negotiated milestone payments and royalties. Future milestone payments under the license agreement could total as much as $35.0 million, although we currently cannot predict if or when any of these additional milestones will be achieved. Under our agreement with Bayer, we will continue to bear sole responsibility for these milestone payments and royalties owed to Amgen.

In June 2005, we entered into a development and validation agreement with Avecia for the scaled-up manufacturing process of alfimeprase. Under this agreement, Avecia will conduct process development and process validation work for the manufacture of alfimeprase, in accordance with FDA regulations. We are obligated to pay Avecia fees totaling £10.0 million for completion of this work, payable upon completion by Avecia of pre-negotiated milestones, of which £7.5 million had yet to be paid as of September 30, 2005. In December 2005, we amended the work program under our agreement with Avecia to provide that Avecia will conduct additional process development and process validation work in exchange for our payment of an additional £2.9 million.

rNAPc2

Our second drug candidate, rNAPc2, is a recombinant version of a naturally occurring protein that has anticoagulant properties. Specifically, rNAPc2 has been shown to block the factor VIIa and tissue factor protease complex, which is responsible for the initiation of the process leading to blood clot formation and has also been shown to play a role in both metastasis, or the secondary growth of cancer cells, and angiogenesis, or the formation of new blood vessels, as they relate to tumor growth. 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 cascade. By blocking the coagulation cascade before amplification of the coagulation process, rNAPc2 could prove to be more effective in treating patients with conditions such as ACS, or as a prophylactic against clot formation in conditions such as DVT. In addition, the novel mechanism of action of rNAPc2 offers the potential to have therapeutic utility in cancer.

ACS occurs when an atherosclerotic plaque ruptures in a coronary artery, which triggers the coagulation cascade and results 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, if severe, permanent heart muscle death. In the United States, ACS accounts for approximately 1.4 million hospital admissions annually. Patients with ACS are traditionally given aspirin and heparin, among other agents, to stabilize their medical condition. Recent guidelines also recommend the addition of the antiplatelet agent clopidogrel (Plavix) to the standard of 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 need for improved antithrombotic therapies.

rNAPc2, given alone or with standard therapy, may reduce the risk of subsequent heart attack or death in patients suffering from ACS. Unlike aspirin, heparin, and other 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,

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therefore, enable a multi-pronged attack at several points along the blood coagulation process. Alternatively, by stopping coagulation at the outset, rNAPc2 could also prove effective as a stand-alone therapy.

We licensed the worldwide rights for all indications of rNAPc2 and all of the rNAPc molecules owned by Dendreon Corporation in February 2004. The United States government may claim a non-exclusive right to use rNAPc2 with respect to the treatment of hemorrhagic fever. To date, rNAPc2 has been shown to be well tolerated in over 650 patients and healthy volunteers in several Phase 1 and 2 clinical studies.

In May 2005, we completed a Phase 2a double-blind, placebo-controlled clinical trial showing that rNAPc2 has an acceptable safety profile and is well tolerated in doses up to ten micrograms/kg in patients being treated for ACS, including unstable angina and non-ST segment elevation myocardial infarction. Results showed that treatment with rNAPc2, in addition to standard antithrombotic therapies in patients with ACS, resulted in a dose-related inhibition of thrombin generation without an increase in clinically significant bleeding. The difference in TIMI major or minor bleed rate was not statistically significant between the two treatment groups (4.3 percent in patients treated with rNAPc2 versus 2.5 percent in those treated with placebo). In addition, rNAPc2 suppressed prothrombin fragments one and two and prolonged the prothrombin time, both in a dose-related fashion.

Based on the encouraging safety results from the Phase 2a trial, we initiated a Phase 2 heparin-replacement trial with rNAPc2 in August 2005. The Phase 2 study is an open label study that is evaluating the efficacy and safety of rNAPc2 by reducing the dose of, and ultimately replacing, unfractionated heparin in patients being treated for ACS. The study will include 50 to 100 patients and is being conducted in approximately 25 centers across the United States and Canada. This trial is expected to complete enrollment in the first half of 2006.

In addition, we are planning to investigate the potential of rNAPc2 as a cancer therapy. The factor VIIa and tissue factor protease complex, which rNAPc2 inhibits, has been shown to play a role in the cellular signaling of both metastasis and angiogenesis in a variety of cancers. As an inhibitor of these processes, which are critical to the progression of a number of cancer types, rNAPc2 may have potential as a therapy for these cancers.

Thrombin inhibiting aptamer

We continue to pursue the development of a thrombin inhibiting aptamer under a collaboration agreement entered into with Archemix Corporation, a privately held biotechnology company located in Cambridge, Massachusetts, in January 2004. In September 2005, we concluded a Phase 1 clinical study for the first target molecule from this program, ARC183. This study evaluated the safety, tolerability, anticoagulation activity and titratability of ARC183 for potential use in acute cardiovascular settings such as CABG surgery. Preliminary results from the trial showed that administration of ARC183 resulted in a rapid onset of anticoagulation and demonstrated stable, dose-related anticoagulation activity and rapid self-reversal of drug effects after administration of the drug infusion ceased. However, the amount of drug needed to achieve the desired anticoagulation for use in CABG surgery resulted in a sub-optimal dosing profile. For that reason, we decided jointly with Archemix not to pursue further development of ARC183 and instead are pursuing an optimized thrombin inhibiting aptamer.

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Under the terms of our agreement, we paid Archemix an upfront fee of $3.0 million and paid all of the first $4.0 million of costs associated with development and commercialization. We and Archemix will equally share all such costs in excess of $4.0 million. We incurred $7.7 million in expenses for the upfront fee and related development costs in 2004 and $2.3 million for related development costs in the first nine months of 2005. Archemix is initially responsible for leading development and for all clinical development activities through the dosing of the first patient in a Phase 2 study. Thereafter, we and Archemix will agree on leadership of clinical development and commercialization activities. We are required to pay Archemix total development milestone payments of up to $11.0 million, including $10.0 million upon dosing of the first patient in a Phase 2 trial and $1.0 million upon the designation of any backup compound selected by both Archemix and us for IND-enabling studies. We currently cannot predict if or when any of these milestones will be achieved.

NU206

We expect to initiate a Phase 1 clinical program with NU206 in the second half of 2006. We plan to initially pursue NU206 as a supportive cancer therapy, specifically to treat radiation and chemotherapy-induced mucositis in the gastrointestinal tract. Research to date indicates that NU206 acts as a highly specific and potent stimulator of gastrointestinal epithelial cells. In addition, NU206 appears to be highly active in multiple animal models of gastrointestinal disease that could support clinical testing in additional indications.

In March 2005, we entered into a collaboration agreement with the Pharmaceutical Division of Kirin Brewery Company, Ltd., for the development and commercialization of NU206. Under this agreement, we received a $2.0 million upfront cash payment from Kirin in April 2005, and we will lead worldwide development, manufacturing and commercialization of the compound. All operating expenses and profits related to the development and commercialization of NU206 will be shared 60 percent by us and 40 percent by Kirin. If this agreement is terminated, or Kirin or we elect under certain circumstances to no longer actively participate in the collaboration, the relationship with respect to NU206 will convert from an expense and profit-sharing structure to a royalty-based structure.

Research programs

In addition to our clinical and development stage drug candidates, we have two ongoing drug discovery programs focused on the identification of novel human genes that encode proteins with therapeutic potential: the first program is focused on secreted proteins and the second on cancer antibody targets. Over the long-term, we intend to develop additional product opportunities from our ongoing discovery efforts. In addition to the development of internal therapeutic candidates, we intend to leverage these discoveries to create revenue-generating licensing and partnering arrangements.

The secreted protein program included a research program with Kirin and includes our internal discovery program. Our 2001 collaboration agreement with Kirin for the research and development of secreted proteins expired December 31, 2005, in accordance with its terms. We and Kirin are currently discussing the possibility of extending the term of this collaborative program, as we have previously. We and Kirin have already advanced several secreted protein candidates to more extensive studies to better define their therapeutic utility based upon early

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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.

The cancer 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.

Our strategy

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

Successfully develop and commercialize our lead drug candidate, alfimeprase. We are seeking to develop and commercialize our lead drug candidate, alfimeprase, for the treatment of acute PAO, catheter occlusion, and a variety of other thrombotic conditions, including stroke and DVT. As part of this strategy, in 2005 we initiated two pivotal Phase 3 clinical programs in acute PAO and in catheter occlusion. We have exclusive rights to this compound in the United States and in 2006 we entered into a significant development and collaboration agreement with Bayer for the development and commercialization of alfimeprase outside the United States.

Commercialize our hospital-based products in the United States. Rather than license other companies to commercialize our products in the United States, we plan to sell them ourselves through our own hospital-based sales force. We believe that the resources required to develop a sales and marketing organization to sell products to hospitals is manageable for a company of our size, and will allow us to capture more value from our clinical development successes. In 2005, we began to hire a marketing organization, which we plan to expand in 2006. Our marketing organization is currently performing market research and planning for the anticipated launch of alfimeprase.

Leverage our expertise in cardiovascular disease and oncology to advance our clinical development programs. We are primarily focused on the development of acute, hospital-based, cardiovascular drug candidates and oncology drug candidates. We believe this portfolio leverages our expertise in cardiovascular and oncology drug development, enabling us to pursue a more rapid path toward drug commercialization.

Build a diversified pipeline of product candidates. We are pursuing several drug development candidates in various stages of clinical and preclinical development. In addition, we seek to identify drug development candidates that have the potential to receive regulatory approval to treat a number of different indications, thereby further diversifying our risk by providing each drug candidate with a number of potential commercialization paths. We believe this strategy reduces our exposure to the impact of any single product failure, maximizes our potential returns from successful compounds, and increases our flexibility to eliminate programs we deem less promising. By broadening our portfolio across indications and products, we intend to increase the probability of clinical and commercial success. In addition, we focus on molecules that we believe have a greater chance of success due to the predictability of preclinical models used in their development.

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

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. On March 25, 2004, we reincorporated from Nevada to Delaware. Our principal executive offices are located at 201 Industrial Road, Suite 310, San Carlos, California 94070 and our telephone number is (650) 517-8000. Our world wide web address is http://www.nuvelo.com. We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information contained on our website and you should not consider it to be part of this prospectus supplement or the accompanying prospectus.

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The offering

Common stock we are offering	6,500,000 shares
Common stock to be outstanding after this offering	48,763,782 shares
Use of proceeds	The net proceeds to us from this offering will be approximately $97.3 million, after payment of underwriting discounts and commissions and estimated expenses of this offering, or approximately $111.9 million if the underwriters exercise their over-allotment option in full. We intend to use the net proceeds to us from this offering for general corporate purposes, including the advancement of our drug candidates in clinical trials, the development of a commercialization infrastructure, capital expenditures and to meet working capital needs. In addition, we must pay The Irvine Company the lesser of (i) ten percent of any amount raised in excess of $75.0 million or (ii) any remaining deferred rent obligation that we have to The Irvine Company. See Use of proceeds.
Nasdaq National Market Symbol	NUVO
Risk factors	See Risk factors beginning on page S-14 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 immediately after the closing of this offering is based on 42,263,782 shares of our common stock outstanding as of September 30, 2005, but excludes:

- an aggregate of 6,224,029 shares of our common stock issuable upon exercise of stock options outstanding as of September 30, 2005, granted under our 2004 Equity Incentive Plan, 2002 Equity Incentive Plan, 1995 Stock Option Plan, Non-Employee Director Stock Option Plan and Scientific Advisory Board/Consultants Stock Option Plan, and as of September 30, 2005, an aggregate of 823,539 shares of common stock issuable upon the exercise of stock options granted outside of any of our stock option plans, with exercise prices of all outstanding options ranging from $2.34 to $304.31 per share and a weighted average exercise price of $15.17 per share;

- an aggregate of 1,195,006 shares of common stock reserved for issuance pursuant to future award grants under our 2004 Equity Incentive Plan, based on options outstanding as of September 30, 2005;

- an aggregate of 259,470 shares of common stock issuable under our Employee Stock Purchase Plan as of September 30, 2005;

- an aggregate of 1,797,273 shares of our common stock issuable upon the exercise of warrants, with exercise prices ranging from $4.05 to $24.87 per share and a weighted average exercise price of $19.12 per share, outstanding as of September 30, 2005;

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$5.2 million of our common stock issuable at our option, to repay our convertible promissory note held by Affymetrix, Inc., including accrued interest as of September 30, 2005, at a conversion price based on 90 percent of the average price of our common stock over a ten-day period ending two days prior to conversion;

$7.5 million of our common stock issuable upon mutual agreement, to convert the remaining amount due on the promissory note under our line of credit with Dr. George Rathmann, including accrued interest, as of September 30, 2005, at a conversion price equal to the average price of our common stock over a 20-day period, ending two days prior to conversion, or, if in connection with an equity financing, at the offering price; and

up to $75.0 million of our common stock salable to Kingsbridge Capital Limited as of September 30, 2005, pursuant to the committed equity financing facility we entered into with Kingsbridge on August 4, 2005. Under this facility, we sold 653,103 shares for gross proceeds of $5.0 million in November 2005 and 1,186,297 shares for gross proceeds of $9.4 million in December 2005.

Unless otherwise stated, all information contained in this prospectus supplement assumes that the underwriters do not exercise their over-allotment option to purchase up to an additional 975,000 shares of common stock and all currency amounts are in United States dollars.

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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, 2002 through December 31, 2004 are derived from our audited consolidated financial statements for those periods. The summary data for the nine-month periods ended September 30, 2004 and September 30, 2005 is derived from our unaudited condensed 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 filings, you should read the section of this prospectus supplement entitled Incorporation by reference beginning on page S-54. 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 6,500,000 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,			Nine months ended September 30,	
Consolidated statement of operations data: (in thousands, except per share data)	**2002**	**2003**	**2004**	**2004**	**2005**
				(unaudited)	
Contract revenues	$ 25,554	$ 1,024	$ 195	$ 152	$ 362
Loss from continuing operations	(39,512)	(46,229)	(48,942)	(38,105)	(50,128)
Loss from discontinued operations, including loss on disposal	(5,466)	(3,958)	(3,547)	(1,402)	
Net loss	$ (44,978)	$ (50,187)	$ (52,489)	$ (39,507)	$ (50,128)
Basic and diluted net loss per share:					
Continuing operations	(5.48)	(2.19)	(1.59)	(1.25)	(1.23)
Discontinued operations	(0.76)	(0.18)	(0.11)	(0.05)	
Total basic and diluted net loss per share	$ (6.24)	$ (2.37)	$ (1.70)	$ (1.30)	$ (1.23)
Shares used in computation of basic and diluted net loss per share	7,220	21,054	30,874	30,427	40,727

	September 30, 2005	
	(unaudited)	
Consolidated balance sheet data:	**Actual**	**As adjusted**
Cash, cash equivalents and short-term investments	$ 75,530	$ 172,790
Working capital	51,480	148,740
Total assets	112,559	209,819
Current portion of debt obligations, excluding accrued interest	4,300	4,300
Non-current portion of debt obligations	8,871	8,871

Accumulated deficit	(306,176)	(306,176)
Total stockholders equity	64,047	161,307

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Risk factors

Investing 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 deciding to invest in our common stock. If any of the following risks actually occur, they may materially harm our business, financial condition, operating results and cash flow. As a result, the market price of our common stock could decline, and you could lose all or part of your investment. Additional risks and uncertainties that are not yet identified or that we think are immaterial may also materially harm our business, operating results and financial condition and could result in a complete loss of your investment.

Risks related to our business

Our near-term success is dependent on the success of our lead product candidate, alfimeprase, and we cannot be certain that it will receive regulatory approval or be successfully commercialized.

Alfimeprase is currently being evaluated in two Phase 3 clinical trials for the treatment of each of acute PAO and catheter occlusion and will require the successful completion of these or other planned Phase 3 clinical trials before we are able to submit a new drug application, or NDA, to the FDA for approval. If our Phase 3 or other clinical trials fail to demonstrate that alfimeprase is safe and effective, it will not receive regulatory approval. Even if alfimeprase receives FDA approval, it may never be successfully commercialized. We may also have inadequate financial or other resources to pursue this product candidate through the clinical trial process or through commercialization. In addition, prior to initiating our current Phase 3 trials for alfimeprase, we had never conducted a Phase 3 clinical trial, and we may be unable to successfully complete clinical trials involving the number of clinical sites and patients as planned for our alfimeprase Phase 3 clinical trials. If we are unable to successfully commercialize or obtain regulatory approval for alfimeprase, we may not be able to generate revenue, become profitable or continue our operations. One of our Phase 3 trials of alfimeprase, NAPA-3, is the subject of a special protocol assessment agreement with the FDA. Under this agreement, the FDA provides guidance on the design of a trial prior to its initiation. We have also been granted fast track designation by the FDA for alfimeprase in acute PAO. The special protocol assessment agreement and the fast track designation do not offer any assurance that alfimeprase will receive FDA approval, and the FDA is in no way constrained by the agreement or the designation in its ability to deny approval for alfimeprase.

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

We currently have two clinical stage drug candidates. All of our other potential products currently are in research or pre-clinical development, and revenues from the sales of any products 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 for any indication. We cannot predict whether we will be able to develop and commercialize any of our drug candidates successfully. If we are unable to obtain regulatory approval and successfully commercialize our potential products, our business, results of operations and financial condition will be affected in a materially adverse manner.

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Our clinical trials may not yield results that will enable us to obtain regulatory approval for our products.

We, and our collaborators, will only receive regulatory approval for a drug candidate if we can demonstrate in carefully designed and conducted clinical trials that the drug candidate is safe and effective. We do not know whether our current or any future clinical trials will demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals or will result in marketable products. Clinical trials are lengthy, complex and expensive processes with uncertain results. It will take us several years to complete our testing, and failure can occur at any stage of testing. To date, we have not successfully completed any Phase 3 clinical trials, and we have not completed all planned pre-clinical and Phase 1 clinical trials for each of our product candidates. The results we obtain in pre-clinical testing and early clinical trials may not be predictive of results that are obtained in later studies. We may suffer significant setbacks in advanced clinical trials, even after promising results in earlier studies. Based on results at any stage of clinical trials, we may decide to repeat or redesign a trial or discontinue development of one or more of our drug candidates. If we fail to adequately demonstrate the safety and efficacy of our products under development, we will not be able to obtain the required regulatory approvals to commercialize our drug candidates, and our business, results of operations and financial condition will be materially adversely affected.

Clinical trials are subject to continuing oversight by governmental regulatory authorities and institutional review boards, or IRBs, and must meet the requirements of these authorities in the United States and in foreign countries, including those for informed consent and good clinical practices. We may not be able to comply with these requirements and the FDA, a similar foreign authority, an IRB, or we may suspend or terminate clinical trials at any time.

Administering our drug candidates to humans may produce undesirable side effects. These side effects could interrupt, delay or halt clinical trials of our drug candidates and could result in the FDA or other regulatory authorities denying approval of our drug candidates for any or all targeted indications.

We rely on third parties, including contract research organizations and outside consultants, to assist us in managing and monitoring clinical trials. Our reliance on these third parties may result in delays in completing, or in failing to complete, these trials if they fail to perform with the speed and competency we expect.

If clinical trials for a drug candidate are unsuccessful, we will be unable to commercialize the drug candidate. If one or more of our clinical trials are delayed, we will be unable to meet our anticipated development or commercialization timelines. Either circumstance could cause the market price of our common stock to decline.

If we encounter difficulties enrolling patients in our clinical trials, our trials could be delayed or otherwise adversely affected.

Clinical trials for our drug candidates require that we identify and enroll a large number of patients with the disorder or condition under investigation. We, or our collaborators, may not be able to enroll a sufficient number of patients to complete our clinical trials in a timely manner.

Patient enrollment is affected by factors including:

design of the protocol;

the size of the patient population;